Geographical Differences and Twenty-Year Changes in the Prevalence of Osteoporosis and Fractures in Canadians: the Canadian Multicenter Osteoporosis Study and the Canadian Longitudinal Study on Aging

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"This thesis is dedicated to positive change
in a world full of opportunity" [1]

[1] https://www.yumpu.com/en/document/read/33284198/athis-thesis-is-dedicated-to-positive-change-in-a-world-full-of-

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CONTRIBUTION OF AUTHORS

The MSc Candidate (Nazila Hassanabadi) wrote the initial draft of all sections of this thesis. Under the guidance of the thesis supervisor (Dr. Suzanne Morin) and senior statistician (Claudie Berger), the candidate prepared the data application protocol for data access to the Canadian Multicentre Osteoporosis Study data, conducted all analyses using the Canadian Longitudinal Study on Aging and the Canadian Multicentre Osteoporosis Study data, and drafted the manuscripts. Dr. Morin supervised all aspects of the projects, revised the drafts and was responsible for the study results. Claudie Berger oversaw the statistical analysis and revised the manuscript. Dr. Morin, Claudie Berger and the Candidate had access to the data and vouched for the validity of the data. Drs. Alexandra Papaioannou, Angela M Cheung, Elham Rahme, William D Leslie, and David Goltzman helped with results interpretation and gave critical feedback on both manuscripts. All authors approved the final manuscripts.

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ABBREVIATIONS

25(OH)D: 25-hydroxy vitamin D

AB: Alberta

ADL: Activities of daily living

AFF: Atypical femur fractures

BC: British Columbia

BMD: Bone mineral density

BMI: Body mass index

BP: Bisphosphonate

CaMos: Canadian Multicentre Osteoporosis Study

CCDSS: Canadian Chronic Disease Surveillance System

CCHS-HA: Canadian Community Health Survey - Healthy Aging

CI: Confidence Interval

CIHI: Canadian Institute for Health Information

CIHR: Canadian Institutes of Health Research

COPD: Chronic obstructive pulmonary disease

CLSA: Canadian Longitudinal Study on Aging

CVA: Cerebrovascular accident

DOES: Dubbo Osteoporosis Epidemiology Study

DMO: Densité minérale osseuse

DXA: Dual-energy x-ray absorptiometry

EFPIA: European Federation of Pharmaceutical Industry Associations

ELCV: Étude longitudinale canadienne sur le vieillissement

EU: European Union

FLS: Fracture Liaison Services

FOM: Fractures ostéoporotiques majeures

FRAX: Fracture risk assessment tool

FRQs: Fonds de Recherche du Québec – santé

GLOW: Global Longitudinal Study of Osteoporosis in Women

HT: Hormone therapy

IKT: Integrated knowledge translation

IMC: Indice de masse corporelle

IOF: International Osteoporosis Foundation

IQR: Interquartile ranges

ISCD: International Society for Clinical Densitometry

LSC: Least Significant Change

LSI: Life Space Index

MB: Manitoba

MOF: Major osteoporotic fractures

NHANES: National Health and Nutrition Examination Survey

NL: Newfoundland and Labrador

NS: Nova Scotia

ON: Ontario

ONJ: Osteonecrosis of the jaw

OPUS: Osteoporosis and Ultrasound study

OR: Odds ratio

PHAC: Public Health Agency of Canada

PTH: Parathyroid hormone

QC: Quebec

QOL: Quality of life

RA: Rheumatoid arthritis

RANKL: Receptor activator of nuclear factor kappa-B ligand

RI-MUHC: Research Institute of the McGill University Health Centre

RSBO: Réseau de recherche en santé buccodentaire et osseuse

SERM: Selective estrogen receptor modulator

SD: Standard deviation

TUG: Timed up and go

US: United States

WHI: Women's Health Initiative

WHO: World Health Organization

ABSTRACT

Osteoporosis is a major public health concern that brings long-term disability and excess mortality. Studies have shown that bone mineral density (BMD) and fracture rates have changed over time, and these parameters differ across and within countries. Data are lacking on changes in BMD, fracture rates, and management of osteoporosis in the last decades in Canada, and whether there are differences in the prevalence of osteoporosis and fractures across provinces. The Canadian Multicentre Osteoporosis Study (CaMos) and the Canadian Longitudinal Study on Aging (CLSA), two population-based longitudinal cohorts recruited twenty years apart, provide valuable information about skeletal health determinants in Canadians.

This scholarly work consists of two projects. Firstly, using baseline data from the CLSA and CaMos cohorts, our objectives were to compare age- and sex-specific BMD, prevalent fracture patterns between cohorts, and anti-osteoporosis treatment use among individuals at high-risk for fracture over a twenty-year period. Secondly, using baseline data from CLSA, we aimed to describe sex-specific BMD and prevalent major osteoporotic fractures (MOF) patterns across Canadian provinces and to determine the association between physical performance measures and these outcomes.

In the first project, we compared the baseline data of participants 50-85 years from CaMos (N=6,479; 1995-1997) and the CLSA comprehensive cohort (N=19,534; 2012-2015). We documented that CaMos participants on average were older than in CLSA and that they also had lower mean height, body mass index (BMI), weight, and a higher prevalence of smoking than their cohort counterparts. In regression analyses, the mean BMD at the femoral neck was higher in CLSA than in CaMos while the odd for MOF was lower in CLSA compared to CaMos. In women

at high-risk for fractures, the use of anti-osteoporosis treatment was higher in CLSA, while in men, use of anti-osteoporosis treatment was very low, with no significant difference between cohorts.

In the second project, we used the baseline data of 10,716 women and 10,511 men aged 50-85 years participating in the CLSA comprehensive cohort. We observed the lowest mean BMI in British Columbia (BC) and the highest in Newfoundland and Labrador (NL). The prevalence of osteoporosis was 5.2 % in women and 0.9 % in men and did not differ significantly between provinces. Adjusted linear regression analysis demonstrated significant differences in hip BMD across provinces; women and men from BC and Alberta (AB), and women from Manitoba (MB) and Nova Scotia (NS) had lower, while men from NS had higher adjusted BMD than Ontario ([ON]: reference). Adjusted Odds Ratios for prevalent MOF were significantly lower in women and men from BC compared to ON. While physical performance measures varied between provinces and were associated with BMD and fractures, adjusting for physical performance measures did not explain the observed geographical variations.

Through the study of two large cohorts, we documented changes in BMD and fracture rates in Canadians over the last two decades and the existence of geographical differences in these parameters. Furthermore, we noted the persistence of a care gap in women and in men at high-risk for fractures. The etiology of these differences is multifactorial and the result of unmeasured individual and societal factors such as lifestyle changes and access to healthcare. Increasing awareness of osteoporosis and fracture prevalence and how these parameters vary across jurisdictions can inform skeletal healthcare delivery throughout Canada.

RÉSUMÉ

L'ostéoporose est un problème important de santé publique important. La densité minérale osseuse (DMO) et les taux de fractures ont changé au fil du temps, et ces paramètres diffèrent d'un pays à l'autre et au sein du même pays. Il existe un manque de données sur les changements dans la DMO, les taux de fractures et la prise en charge de l'ostéoporose au cours des dernières décennies au Canada, et sur les différences dans la prévalence de l'ostéoporose et des fractures entre les provinces. L'Étude canadienne multicentrique sur l'ostéoporose (CaMos) et l'Étude longitudinale canadienne sur le vieillissement (ELCV), deux cohortes longitudinales recrutées à vingt ans d'intervalle, fournissent des informations sur les déterminants de la santé squelettique chez les Canadiens.

En utilisant les données des cohortes ELCV et CaMos, nous avons comparé la DMO selon l'âge et le sexe, le taux de fractures prévalentes entre les deux cohortes, ainsi que l'utilisation des traitements anti-ostéoporotiques chez les personnes à risque élevé de fracture. Ensuite, en utilisant les données de l'ELCV, nous avons décrit la prévalence de l'ostéoporose et des fractures ostéoporotiques majeures (FOM) dans les provinces canadiennes et déterminé l'association des mesures de la performance physique avec ces variables.

Nous avons comparé les données des participants de 50 à 85 ans de CaMos (N = 6 479 ; 1995-1997) et de l'ELCV (N = 19 534 ; 2012-2015). Nous avons observé que les participants de CaMos étaient en moyenne plus âgés que ceux de l'ELCV et qu'ils avaient également une taille, un indice de masse corporelle (IMC), un poids et une prévalence de tabagisme plus élevés que ceux de l'ELCV. Dans les analyses de régression, la DMO au col fémoral était plus élevée dans l'ELCV que celle dans CaMos, tandis que le taux de FOM était plus faible dans l'ELCV par rapport à CaMos. Chez les femmes à haut risque de fractures, le recours à un traitement anti-ostéoporotique

était plus élevé dans l'ELCV, tandis que chez les hommes, le recours aux traitements anti-ostéoporotiques était très faible, sans différence significative entre les cohortes.

Dans le deuxième projet, nous avons utilisé les données de 10 716 femmes et 10 511 hommes âgés de 50 à 85 ans participant de la cohorte ELCV. Nous avons observé l'IMC moyen le plus bas en Colombie-Britannique (CB) et le plus élevé au Terre-Neuve-et-Labrador (T.-N.-L.). La prévalence de l'ostéoporose était de 5,2 % chez les femmes et de 0,9 % chez les hommes et ne différait pas significativement entre les provinces. Nous avons démontré des différences significatives dans la DMO entre les provinces; les femmes et les hommes de la CB et de l'Alberta, et les femmes du Manitoba et de la Nouvelle-Écosse avaient une DMO ajustée plus faible, alors que les hommes de la NE avaient une DMO ajustée plus élevée que ceux de l'Ontario (ON : référence). Les rapports des cotes ajustés pour les FOM étaient significativement plus faibles chez les femmes et les hommes de la CB par rapport à l'ON. Alors que les mesures de la performance physique variaient entre les provinces et étaient associées à la DMO et aux fractures, l'addition de ces mesures aux modèles de régression n'expliquait pas les variations géographiques observées.

Nous avons donc documenté les changements dans la DMO et les taux de fractures ostéoporotiques au cours des deux dernières décennies et l'existence de différences géographiques dans ces paramètres. De plus, nous avons noté la persistance d'un écart thérapeutique chez les femmes et chez les hommes à risque élevé de fractures. L'étiologie de ces différences résulte entre autres de facteurs individuels et sociétaux tels que le niveau d'éducation, les changements des habitudes de vie au fil du temps et l'accès aux soins de santé. Une sensibilisation accrue à la prévalence de l'ostéoporose et des fractures et à la façon dont ces paramètres varient d'une juridiction à l'autre peut éclairer la prestation des soins partout au Canada.

CHAPTER 1
BACKGROUND

1.1 Osteoporosis

1.1.1 Definition

Osteoporosis is a common and major public health concern, often under-diagnosed (1, 2). This medical condition is characterized by chronic deterioration of bone architecture and accelerated loss of bone mass (3-5). Impaired bone microarchitectural structure increases fragility and predisposes the skeleton to fractures (6). Although the term "osteoporosis" was first introduced in France in the 1820s and entered the English terminology by 1885, its definition varied among researchers, medical dictionaries, and books for many years. Eventually, in 1993, an international consensus was achieved at an international conference held in Hong Kong: "a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" (7, 8). The International Society for Clinical Densitometry (ISCD) and the World Health Organization (WHO) have defined osteoporosis as the decline in bone mineral density (BMD) by equal or more than 2.5 standard deviations from the average of young healthy women (T-score ≤ -2.5) (9, 10). In clinical practice, BMD, measured at the lumbar spine and the hip, has robust ability to predict fractures (11). Osteoporosis is classified into two main categories: primary osteoporosis and secondary osteoporosis. Primary osteoporosis is considered as the most common form of the disease, and is a consequence of aging and sex hormone deficiency throughout life in both men and women (12). Secondary osteoporosis is defined as bone loss and increase bone fragility caused by underlying diseases and medication use such as glucocorticoids (13).

1.1.2 Bone mineral density measurement

In the absence of a typical fragility fracture, the gold standard for osteoporosis diagnosis is the measurement of BMD at the lumbar spine and proximal femur by dual-energy X-ray

absorptiometry (DXA) (10, 14). Bone densitometer machines are produced by different manufacturers, of which GE Lunar and Hologic are the two most common types. While they have similar specifications, they have differences in terms of methods of deriving energy beams, calibration techniques and ways of analyzing the scans mainly due to their manufacturer-specific intrinsic processing (15) (16). During the DXA scanning, the x-ray beams not absorbed by the bone are detected on the other side of the body while patient is lying on the table. The higher mineral content of the bone, the less energy detected. The radiation energy per pixel (picture element) is detected and converted into areal density. Values for BMD is presented as g/cm^2 and converted into values related to the average individual peak bone mass (T-score=patient's BMD–population peak BMD/standard deviation of population peak BMD) or to the bone mass related to the individual's age (z-score=patient's BMD–population age related BMD/standard deviation of population age related BMD) (17). For the purpose of osteoporosis diagnosis in individuals older than 50 years, BMD is expressed in T-score standard deviation values in relation to a 20–29 years old healthy woman, and is calculated from the Third National Health and Nutrition Examination Survey (NHANES III) reference values for white women (14, 18). The Canadian Multicenter Osteoporosis Study (CaMos) has provided age- and skeletal site-specific reference norms for men and women based on the results of peak bone mass measurements in young participants (youth cohort); these differ from those accrued in the NHANES dataset (19). Routine screening for osteoporosis by BMD in the general population is not yet recommended as it is not cost-effective from a socioeconomic standpoint (20). In Canada, the 2010 clinical practice guidelines for the diagnosis and management of osteoporosis recommend that men and women age ≥ 65 years and adults < 65 years with clinical risk factors for osteoporosis and fracture be screened with BMD (21, 22).

Reduced bone density is a major risk factor for fragility fracture (23). The cortical and trabecular bone play a key role in determining the mechanical competence of bone and the risk for fracture. When the trabecular plates of bone (number of trabeculae, trabecular thickness, and connectivity) are lost, the architecturally weakened bone is prone to fractures. BMD measurement is a surrogate marker of bone strength; for each SD decrease in BMD, the fracture risk increases approximately two fold (24, 25). Due to the importance of the BMD, most risk assessment paradigms incorporate BMD for fracture prediction (26). However, BMD has low sensitivity (30-50 %) when used alone for fracture prediction, as most fragility fractures occur in patients who do not meet the BMD criteria for osteoporosis (9, 27, 28).

1.1.3 Epidemiology and disease burden

The population is aging worldwide. Globally, the number of individuals 65 years and older increased from 6 % in 1990 to 9 % in 2019 (29). This rise is projected to continue and reach 16 % by 2050; so that by 2050, 1 in 6 individuals in the world will be 65 years or older, up from 1 in 11 in 2019. In Canada, it is estimated that by 2031, at least one in every four Canadians will be 65 or older (30). As the population is aging, the number of older adults with chronic age-associated diseases such as osteoporosis is expected to increase (2, 31). Osteoporosis affects approximately 200 million people across the world, of which 54 million are estimated to be in the United States (US) (32). In the US, the National Health and Nutrition Examination Survey (NHANES) 2013–2014 study demonstrated that the prevalence of osteoporosis (defined as a T-score of ≤ -2.5 at femoral neck, lumbar spine, or either) in adults aged ≥ 50 years varied between 10 % and 17 % in women and 3 % to 5 % in men depending on the skeletal site measured (33). The Canadian Multicentre Osteoporosis Study (CaMos) estimated the prevalence of osteoporosis (based on lumbar spine T-score of ≤ -2.5) to be 12.0 % in women and 2.9 % in men ≥ 50 years (34).

Osteoporosis is associated with fractures often termed fragility fractures, of which those of the hip, vertebral, humerus and wrist are commonly referred to as major osteoporotic fractures (MOF) (35). Fragility fractures bring a substantial burden to healthcare systems, individuals, and society (36); they are associated with significant reduction in health-related quality of life (QOL), mobility, activities of daily living (ADL), and survival (31, 37). Hip and vertebral fractures reduce autonomy, cause long-term disability, and increase costs to society and individuals (4, 5, 38-41). Worldwide osteoporosis-associated costs were estimated at US $34.8 billion in 1998 and anticipated to rise dramatically by 2050 to US $131.5 billion (42). The cost of fragility fractures in 27 countries of the European Union (EU) has been estimated to be CAN $54.4 billion in 2010, equal to 26,300 life years lost (35). In Canada, the estimated burden of osteoporosis was $4.6 billion in 2016 compared to $2.3 billion in 2008 (43). Annually osteoporosis is the cause of more than 9 million fractures worldwide, equivalent to one fragility fracture every 3 seconds (35). On average, 1 in 3 women and 1 in 5 men older than 50 years, will experience at least one osteoporotic fracture in their lifetime (44). CaMos documented the prevalence of vertebral fractures on spine radiographs in women and men aged ≥ 50 years combined to be 16.4 % (95 % Confidence Interval [CI] 15.4 -17.4) (45). Using provincial administrative health data of fiscal year 2015-16, the Canadian Chronic Disease Surveillance System (CCDSS) of the Public Health Agency of Canada (PHAC) reported that 2.2 millions (12 %) Canadians 40 years and older were living with osteoporosis and that 1.8 million Canadians had suffered a fracture at major osteoporotic sites (2). Approximately 30,000 hip fractures occur annually in Canada; more than one quarter occur in men, and three quarters are in men and women aged 75 and older (46, 47).

1.1.3.1 Geographical variations in osteoporosis, BMD, and fractures

1.1.3.1.1 Variations in osteoporosis and BMD

The risk of osteoporosis and fractures varies worldwide, by geographic location, sex, race/ethnicity and socioeconomic status (48, 49). In a report by International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA), the prevalence of osteoporosis (T-score $\leq$ -2.5 at the femoral neck) in adults 50 years and older in the European Union was highest in Germany with 6.1 % of the total population (6.6 % in men and 22.6 % in women 50 years and older). In this report, the prevalence of osteoporosis varied from 5.7 % in Slovakia to 6.9 % in Greece, Italy and Sweden in men , and 19.3 % for Bulgaria to 23.4 % for Italy in women (50). The prevalence of osteoporosis documented by BMD T-score has been reported as being highest in Scandinavian countries than in other European countries (51). Using the Osteoporosis and Ultrasound study (OPUS) data, Paggiosi et al. described the proximal femur BMD in European women aged 60 to 69 years to be significantly higher compared to that for US women (European women 14.2 % vs. US women 7.1 %, P-value < 0.001) (52). In Canada, the CaMos study reported modest differences in BMD and in the prevalence of osteoporosis between Canadian provinces (53, 54). Indeed, the highest age-standardized mean total hip BMD was documented in Saskatoon, Toronto, and Kingston in both men and women, while the lowest age-standardized mean BMD was in Halifax (women) and in Quebec (men). Similarly, the prevalence of osteoporosis (defined by BMD T-score ≤ -2.5 at any site) varied across provinces and was the highest in Quebec in both men and women. The provinces with the lowest prevalence of osteoporosis did not necessarily have the highest prevalence of fracture.

1.1.3.1.2 Variations in fractures

Worldwide, the prevalence of hip fractures has been reported to vary between countries (49). The highest rates of hip fractures are documented in women compared to men (with an average ratio of 2:1) and in North America, Europe and Oceania compared with Asia, Middle East and Latin America (49, 55). In the systematic review by Kanis and coll., Denmark, Sweden, Austria, and Norway had the highest rates of hip fracture, and Nigeria, South Africa, and Ecuador had the lowest rates(56). Dhanwal and coll. reported a wide geographic variation in the incidence of hip fracture across different regions of the world the lowest hip fracture risk in Latin America and Africa, intermediate risk in Kuwait, China, Hong Kong and Iran, and the highest risk in North Europe and the US, and lowest in Latin America and Africa (57). In Latin America, studies have shown a prevalence of hip fracture of 4 to 36.2 for every 10,000 people (58). A study of women aged 50 or older in five Latin American countries (Porto Rico, Brazil, Colombia, Argentina and Mexico) found that the prevalence of vertebral fractures was similar to that of some parts of Europe and China (Beijing) (59). The prevalence of fractures not only differs between countries, but within regions of countries (40). Variation in inter-regional rates of fractures was recognized previously in the US, Europe, and Latin America (57). CaMos documented the presence of geographic variation of fractures between Canadian provinces (53). They also identified that the pattern of geographic variation in incident and prevalent low-trauma fracture were similar in both men and women; the highest rates of fracture was seen in Ontario and the lowest in Quebec.

1.1.3.1.3 Etiology of variations

The etiology for such variations is considered to be multifactorial and associated with a combinations of factors including population specific characteristics, race/ethnicity, income, urban residence, latitude, environmental factors, as well as public healthcare services provision (40, 57,

58). Cauley et al. noted that the 8–10 % higher BMD in men from Tobago compared to that from the US was associated with both race/ethnicity difference and urban lifestyle in the US. In Canada, the prevalence of osteoporosis among Canadians aged 25 years or older from CaMos was reported to be twice higher in White women than in Chinese women. The prevalence of fractures was also higher in White women compared to Chinese women and differences ranged from 5.3 % (95 % CI: 3.9; 6.8) for MOF in the younger age group to 14.5 % (9.2; 19.7) for any fractures in women 50+ years (60). Using the population-based Manitoba BMD Program registry of women aged 40 years or older, it has been documented that Asian and Black women have lower risk for MOF compared to White women (61).

A comprehensive evaluation of the fracture risk between developed and less developed countries suggested that a higher socioeconomic status within a country is associated with higher hip fracture rates than less developed regions (49). Socioeconomic status affects diet which then will impact anthropometric parameters (height and weight), bone mass and nutritional status. Nutritional deficit during certain period of life (specifically during childhood and adolescence) has led to a lower BMD in South Korean men than in men from Hong Kong (62). Geographic differences of vitamin D deficiency (defined as <75 nmol/l) varied across the world, ranged around 50 % in Thailand and Malaysia to 90 % in Japan and South Korea (49). The increasing height in wealthy countries compared to low-income countries leads to lower hip fracture rates and better bone mass (63). However, in a study of population fracture registry of women 50+ from Manitoba the decrease in MOF was reported to be related to improvements in BMD over time rather than other factors such as increasing BMI in the population (64).

Difference in osteoporosis or/and hormone therapy may also contribute to the differences in BMD between the US and other countries (65). Urbanization in more developed countries, has led to

lower physical activity, reliance on cars and buses instead of walking or cycling, increase in hard surfaces, sitting in chairs rather than on the floor, and many other changes might help to explain the large differences in hip fracture rates in genetically similar populations living in different countries. CaMos study suggested a combined model of age, BMD, falls and prior fractures as a good predictor of geographic variation of fractures in both men and women (53). However, CaMos models were limited by the absence of ascertainment of variables such as vitamin D level and physical function measures.

1.1.3.2 Secular changes in BMD and fractures

BMD and fractures rates have changed over time in different parts of the world. There are reports of declining age-standardized fractures incidences in many countries over the last decade with similar trends in fragility fractures.

Identifying changes in BMD trajectory is essential to the understanding of prevention of osteoporosis and fracture in the population. In the US, secondary analysis of the NHANES data, demonstrated a decreasing trend in age-adjusted mean femoral neck BMD from 2005 to 2014 (66) (32). Age-adjusted mean BMD from 2005 to 2016 significantly decreased from 0.780 g/cm^2 to 0.771 g/cm^2 in women, and from 0.864 g/cm^2 to 0.832 g/cm^2 in men. In Canada, a significant annual linear increase of 0.52 % in BMD at the femoral neck was documented using the large Manitoba BMD registry data of women aged 50 years and older from 1996-2006 (64).

A secular decline in hip fracture risk has been reported in Europe, US and Canada over the second half of the 20th century, while an increase in these rates was detected in Asian countries such as Japan, China, Mexico and Taiwan (40) (49, 67). For example, in Belgium, age-adjusted incidence of hip fractures significantly decreased by 0.34 % and 1.12 % per year in men and women respectively (68). Similarly in Denmark a decline in the incidence rate of hip fractures was

observed, 20 % in men and 22 % in women from 1997 to 2006 (69). Analysis of data from the United Kingdom revealed that subsequent major and subsequent hip fractures declined -0.19 % and -0.17 % (from 1999 to 2012 respectively (70). In the US, data from the late 1990s and extending through the mid-2000s suggested that age-adjusted rates of hip fractures were declining (71). In Canada, age-standardized rates of hip fracture rates have decreased in both sexes from 1985 to 2005 (72). The major osteoporotic fracture rates have also decreased linearly from 1996 to 2006 in a large population-based cohort in Manitoba (64). The age-specific hip fracture rates over a 21-year period decreased by 31.8 % in women (from 118.6 to 80.9 fractures per 100,000 person-years) and by 25.0 % in men (from 68.2 to 51.1 fractures per 100,000 person-years) (36). The largest decrease in the percentage of hip fracture was observed in 55-64 years age group (36). Recently, PHAC has shown that despite an increase in the absolute number of fractures (at any fracture sites: hip, forearm, humerus, pelvic and spine) from 2000–2001 to 2015–2016, the age-standardized annual hip and forearm fracture rates have decreased while those of humerus fracture have remained stable and of pelvic and spine fractures have increased (2).

The actual causes of observed changes in fracture risk were considered to be multifactorial, including changes in obesity rates, anti-osteoporosis medications (40), birth cohort and period effects (73), changes in medical care, insurance coverage and reimbursement for DXA, improvement in BMD, and nutrition (33). Although, in the Manitoba cohort study, the decline in the hip fracture rates was thought to be explained by improvements in BMD, and not change in osteoporosis treatment and obesity (64). Other authors have reported that decline in testing and treatment for osteoporosis, change in the use of postmenopausal hormone therapy, vitamin D supplementation, changing patterns of physical activity, urbanization, and greater overall longevity have also led to changes in country-specific fracture rates. (73, 74).

1.1.4 Clinical risk factors for osteoporosis and fractures

Although osteoporosis is more common in women and in older individuals, it can affect people of all ages. A wide range of clinical risk factors associated with osteoporosis have been identified in the literature (58, 75). The presence of these risk factors varies significantly across populations (76, 77); the more risk factors one person has, the greater their risk for low bone mass and fractures (2). Overall, the risk of osteoporosis is higher in postmenopausal women (2, 49, 75) because of the accelerated bone resorption due to the loss of protective estrogens (78).

Osteoporosis risk factors are often divided into two categories: modifiable and non-modifiable (79). Non-modifiable risk factors are older age, female sex, personal history of fragility fracture ethnicity and genetics (2, 12, 80-82). Modifiable risk factors are low body mass index (BMI), low body weight (below 60 kg), major weight loss (more than 10 % of body weight documented at age 25), low appendicular lean mass (83), physical inactivity (especially resistance and high-impact activities) (84), smoking (85), excessive alcohol intake (more than three standard drinks per day) (86), and inadequate dietary calcium and vitamin D (87).

Other risk factors associated with secondary osteoporosis include medical conditions and long-term use of specific medications (2). The most common medical conditions associated with osteoporosis include rheumatologic and autoimmune disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, multiple sclerosis), endocrine and hormonal disorders (hyperthyroidism, hypogonadism, hyperparathyroidism, diabetes mellitus, growth hormone deficiency and acromegaly), malabsorption disorders (e.g., celiac disease, inflammatory bowel disease, chronic liver diseases), renal disorders (e.g., chronic kidney disease), and some hematological disorders (e.g., multiple myeloma, beta thalassemia major) (2, 12, 80). Glucocorticoid is the leading medication causing drug-induced osteoporosis (12). Other

medications associated with higher risk of osteoporosis include thyroid hormone, hypogonadism-inducing agents, thiazolidinediones, alpha adrenergic blockers, antidepressants, anticonvulsants, narcotic and opioid medications, immunosuppressive therapy, antiretroviral therapy, heparin, loop diuretics, proton pump inhibitors, aluminum-containing antacids (2, 12, 80).

Independent from BMD, there are other clinical risk factors associated with fracture risk (88). Similar to osteoporosis, the prevalence of osteoporotic fractures rates increase with age and is higher in women (2, 49, 75). In both women and men, from the age of 50 years the fracture risk doubles with every decade mainly due to the decline in BMD as well as the increase in other clinical risk factors (86). Previous fragility fracture doubles the risk of a second fracture in both men and women (89). Excessive alcohol consumption (≥3 units per day) increases the risk of a fracture by 40 % due to poor nutritional status and direct effects on osteoblasts and parathyroid hormone levels (88). Similarly, an increased fracture risk has been reported in individuals with history of cigarette smoking (90). Glucocorticoid use (≥3 months) impairs bone formation, calcium absorption and muscle weakness and therefore increase the risk of falls and fractures (91, 92). History of hip fracture in parents is associated with an increased risk of fracture (93). Ethnicity (Caucasian and Asian), low level of education, low socioeconomic and living status, and genetics are identified in the literature as other risk factors for osteoporotic fractures (35, 49, 75, 81). Secondary risk factors, including disorders and medications that make the bone more fragile and/or effect balance (increasing risk of falling), and inadequate calcium and vitamin D intake influence bone remodelling and increased risk of fracture (88).

Falls are an important and independent predictor for fractures and the leading cause of the majority of hip fractures (94). Falls are the cause of 80 % percent of axial skeleton fractures and 50 % of those who fall will do so repeatedly (95). Physical function and mobility can also affect the risk

for fracture. Inactivity or load-bearing physical activity and muscle activity decrease mechanical load on the bone and muscle and therefore reduce bone remodeling and tension on bone. The risk for hip fractures have been shown to be 50 % higher in women who sit down for > 9 h/day compared to those who sit for <6 h/day (88). Physical performance measures (chair stand time, walking speed, grip strength) and muscle indices (appendicular lean mass), are known to predict fracture risk independently from other risk factors (94).

1.2 Management of osteoporosis

1.2.1 Fracture risk assessment

The suboptimal performance of bone mineral density as the sole predictor of fracture risk and treatment decision making has led to the development of fracture risk prediction algorithms (96). Fracture risk assessment tools are established to estimate fracture risk by combining multiple risk factors for fracture including demographic and physical characteristics, personal and family history, other health conditions, and medication use to create risk assessment tools (96, 97). The three tools that have been independently validated are Fracture risk assessment tool (FRAX®), Garvan Fracture risk calculator, and QFractureScores-2016 (26).

The FRAX® was launched in 2008 and has been the most widely studied tool incorporated into clinical practice guidelines (1, 7). This tool is distinguished from others because it can directly be calibrated to fracture incidence rates in the target population and considers death as a competing risk (26). The FRAX® score is a computer-based risk assessment tool and was developed to calculate the 10-year probability of major osteoporotic fractures (MOF: hip, clinical spine, humerus or wrist fracture) and hip fractures by considering well-established and independent variables related to skeletal fracture risk (97). The variables entered in FRAX calculator include individuals' demographic data (age, gender, body mass index (BMI), alcohol intake, and current

smoking), important clinical risk factors (fracture history, parental hip fracture, glucocorticoids use, rheumatoid arthritis or RA, and secondary osteoporosis), and BMD at the femoral neck as an optional input variable **(**98**,** 99**)**. As fracture probability differs markedly in different regions of the world, FRAX® is calibrated to those countries where the epidemiology of fracture and mortality rates is known (7). FRAX® has been validated in 64 countries, including Canada, and yearly almost 6 million FRAX calculations are done (1, 7). Despite the fact that FRAX is well accepted worldwide, there are limitations to the use of FRAX since it does not currently include important risk factors such as falls (97); recency of fracture, number of prior fractures, and biomarkers (97). The Garvan fracture risk calculator was created using the data from the Dubbo Osteoporosis Epidemiology Study (DOES) initiated in 1989 to calculate 5- and 10-year fracture probability nomograms were constructed using age, sex, body weight, history of prior fractures after age 50 years, history of falls in the previous 12 months, and femoral neck BMD (optional) (96). The QFractureScores was created using the largest prospective database for osteoporotic fracture prediction, more than 2 million women and men age 30–85 years from England and Wales (96). The QFractureScores estimates the probability of 1- and 10-year of any osteoporotic fracture (hip, wrist, spine, or humerus) and hip fracture risk using the numerous risk factors including age, sex, ethnicity, height, weight, smoking status, alcohol consumption, previous fracture, parental osteoporosis or hip fracture, living in a nursing or care home, history of falls, medical history and medication history. Both Garvan fracture risk calculator and QFractureScores are not used frequently in Canada.

Management guidelines, designed specifically according to each country's need, were developed to lessen osteoporosis-related fractures worldwide (22, 100, 101). The goal of treatment is to decrease fracture risk and bone loss, and if applied to high-risk populations, can result in up to 60

% reductions in fracture risk (5, 97). It is important to consider that not all treatment options are appropriate for everybody, and each option has its risks, benefits, and limitations (97). Canadian clinical practice guidelines recommend initiating treatment in men and women who have sustained a hip or vertebral fracture or multiple fractures, in those who have a FRAX® score of ≥ 20 % for a major osteoporotic fracture and in individuals with low BMD T-scores and other clinical risk factors such as use of anti-hormonal therapies, frequent falls and inflammatory conditions (21).

1.2.2 Lifestyle modification

Healthy bones necessitate having a balanced nutrition and adequate calcium and vitamin D intake, engaging in regular physical activity (resistance training exercises), and avoiding smoking and excessive alcohol consumption (100). A diet with sufficient micronutrients, including vitamin D (1000–2000 IU per day), calcium (1000–1300 mg per day), magnesium and vitamin K, has been linked to increased bone strength (2). Many older adults cannot reach target serum levels of vitamin D with diet alone (79): this can safely and inexpensively be treated with vitamin D supplements (85, 102).

Exercise is one of the few strategies can improve multiple fracture risk factors at any stage of life by maintaining bone structure through mechanical loading (100). Well-controlled supervised resistance and high-impact training exercises can improve multiple fall-related risk factors in older women (103). Resistance training programs are the most effective strategies to improve muscle strength and function, balance (104) and gait to reduce the risk of falling (87). Systematic reviews of trials of exercise or physical therapy found a 13 % reduction in the risk of falls (1, 102). Resistance exercises are effective both as a single intervention and as part of a multicomponent treatment (104). Considering the different mechanisms of action regarding medication and exercise on bone, it is reasonable to expect that combining exercise and medication could be more

effective in decreasing osteoporotic fracture risk than either alone (78, 105). Smoking and alcohol are linked to reduction in bone density through different mechanisms. The decrease in bone density can be the result of smoking and alcohol itself or other risk factors associated with them (2).

1.2.3 Pharmacologic therapy

A number pharmacologic options are available in Canada, both antiresorptive and anabolic agents and with a diverse dosing frequencies and routes of administration (22). All therapies available in Canada have been associated with reduction in the risk of vertebral fractures in menopausal women with osteoporosis, while some prevent hip and nonvertebral fractures. Generally, depending on the medication and the level of adherence, pharmacologic therapy reduces the risk of vertebral fracture by 30 % to 70 %.

Antiresorptive medications are the mainstay of fracture prevention (106) and include bisphosphonates (BPs), monoclonal antibody to receptor activator of nuclear factor kappa-B ligand (RANKL), hormone therapy (HT), selective estrogen receptor modulator (SERMs), and calcitonin (107). Romozosumab and Teriparatide are two anabolic medications for osteoporosis treatment in Canada (22).

BISPHOSPHONATES (BPs) – Today, BPs are considered first-line therapy for osteoporosis, due to their low cost, ability to increase BMD and reduce osteoporosis-related fracture risk (3, 12). The first bisphosphonate, alendronate, has been the most commonly used bisphosphonates since it became available in 1995 (7). While bisphosphonates act similar, they are available in multiple formulations: oral tablets (alendronate, risedronate, and ibandronate), effervescent tablets (alendronate), combined with vitamin D (alendronate), immediate release or delayed release (risedronate), and intravenous injections (zoledronic acid and ibandronate). Bisphosphonates have been associated with the rare complications like osteonecrosis of the jaw (ONJ) and atypical femur

fractures (AFF), and each formulation has its own specific adverse side effects; oral bisphosphonates are associated with upper gastrointestinal discomfort (including heartburn, indigestion, esophageal erosion, and esophageal ulcer), and IV bisphosphonates associated with acute phase injection reactions (fever, muscle aches). AFF and ONJ are associated with the cumulative exposure of the bisphosphonates and it is now recommended that duration of therapy be limited to 3 to 5 years, after which a drug holiday should be instituted. The concerns around AFF and ONJ have worsened the care gap in osteoporosis; clinicians and patients are less likely to initiate or continue therapy even in the presence of high fracture risk. Educational measures are being developed.

DENOSUMAB – Denosumab is a human monoclonal antibody indicated as first-line therapy for individuals at high risk for fractures, patients unable to tolerate oral therapy, women with breast cancer, and men with prostate cancer receiving androgen deprivation therapy. Denosumab is effective in increasing BMD at the lumbar spine and total hip, and decreasing the relative risk of vertebral fractures, nonvertebral fractures and hip fractures (12). Denosumab is available in a subcutaneous injectable formulation and is generally well tolerated. Adverse effects associated with denosumab are hypersensitivity, musculoskeletal pain, hypercholesterolemia, hypocalcemia (in patients with creatinine clearance < 30 mL/min), ONJ, and AFF (rare).

HORMONE THERAPY (HT), SELECTIVE ESTROGEN RECEPTOR MODULATOR (SERMS) – Before the Women's Health Initiative (WHI – 1991), HT with estrogen-progesterone was the cornerstone of the pharmacological treatment of osteoporosis in postmenopausal women. Since WHI demonstrated that the estrogen-progestin combination was associated with an increased risk for cardiovascular events, stroke, venous thromboembolism, and invasive breast cancer, the use of HT in the treatment of osteoporosis became limited (12). The use of raloxifene is indicated

as the first-line therapy in women at risk of vertebral fracture only; however, it may also be used in women at risk for vertebral fractures and developing breast cancer, and in higher-risk patients during a bisphosphonate holiday. Despite raloxifene's benefits, it may cause vaginal bleeding, hot flashes, dyslipidemia, venous thromboembolism, stroke, and cardiovascular disease.

ROMOZOSUMAB – Romosozumab is a humanized monoclonal antibody that inhibits sclerostin in skeletal tissue (12). Romosozumab lower risk of new vertebral fracture up to 73%, and increase BMD at the lumbar spine, total hip, and femoral neck up to 13% (12). However, the use of Romosozumab for osteoporosis treatment is limited due to a higher rate of serious adverse cardiovascular events compared with other available medications.

PARATHYROID HORMONE ANALOGUES – Teriparatide is a recombinant human parathyroid hormone (PTH) analogue and is indicated as the initial treatment in postmenopausal women at high risk for fracture, and patients unable to take oral medications. Teriparatide result in an increase in vertebral, femoral, and total-body BMD and a reduction in the number of new vertebral and non-vertebral fractures (12). Due to the potential risk of osteosarcoma, teriparatide is contraindicated in patients with Paget's disease, unexplained alkaline phosphatase elevations, prior skeletal radiotherapy, primary or metastatic bone malignancy, and hypercalcemic disorders (e.g., primary hyperparathyroidism).

1.2.4 Treatment gap

Despite notable advances in our understanding of the pathogenesis and treatment of osteoporosis, and the availability of effective drugs to prevent fractures, there is evidence suggesting that many patients who should receive pharmacological therapy are either not prescribed these medications or if prescribed medication, refuse to take it (73, 108, 109). Overall, less than 30 % of patients with fractures are subsequently diagnosed with osteoporosis, and less than half of those receive

treatment (110). In many cases, in those in whom the treatment is started, adherence to the treatment in many cases is very low (20 %) after one year (111, 112).

With the introduction of bisphosphonates in the 1990s, an increase in the number of patients using bisphosphonates was noted over time. However, since 2007-2008, a decline in bisphosphonate use was observed in the US and European countries (73), whether in individuals at high-risk for fracture or not. In a retrospective observational cohort study in the US, a decline in osteoporosis medication use from 40 % to 21 % in individuals with hip fracture between 2001 and 2011 has been reported (113). In a study using a commercial US insurance claims database of 97,169 people with incident hip fracture and mean age of 80.2 years (SD 10.8), initiation of osteoporosis medication declined from 9.8 % in 2004 to 3.3 % in 2015 (114).

Similar low treatment rates after a MOF have been documented in the Global Longitudinal Study of Osteoporosis in Women (GLOW; a prospective observational practice-based study in postmenopausal women from the US, Canada, Europe, and Australia) (115). In the first-year follow-up, among 1,075 women aged 55 years and older with an incident fracture, only 17 % had started with anti-osteoporosis medications, 15 % of participants with any single MOF and 35 % of those with multiple fractures.

Despite improvements in the treatment of osteoporosis in Canada, care gap exists in the management of osteoporosis and fragility fractures in both men and women. This gap was documented in the CaMos population (116, 117). Among 5,566 women in CaMos, the percentage of women with fragility fractures who did not receive pharmacotherapy was 55-60 % during 10 years of follow up. In men the percentage of those with clinical fragility fracture who received bisphosphonates was very suboptimal, increased from 0.5 % to 9.5 % in 5 years. According to the recent PHAC findings, in 2014-2015 only less than one fifth of individuals with MOF received

an osteoporosis diagnosis, screened with by DXA or prescribed an anti-osteoporosis medication in the year following a fracture (2).

Certain factors have been found to be associated with a reduced likelihood of being prescribed osteoporosis medication following a fracture and include older age and male sex; while pre-fracture use of anti-osteoporotic medication and calcium, prior diagnosis of osteoporosis, and site of fracture (spine fracture > multiple fractures > hip fracture) were strongly associated with medication use post-fracture (73, 115). The possible underlying causes for 'The Osteoporosis Treatment Gap' have been explored in the literature and found to be multifactorial; safety concerns about medication, misunderstanding of the benefit/risk ratio, inadequate access to appropriate investigation and treatment, and lack of structured post-fracture care (115) (73). The fear of rare, but serious, side effects of osteoporosis medication, particularly ONJ and AFF, highlight the need for improved education of health-care professionals and patients and clearer communication of the benefits and risks (114). Furthermore, osteoporosis is managed by many diverse specialties, which means there is a loss of clarity over who is responsible for the overall management of affected patients, and incomplete alignment of national and international guidelines, creates confusion in regards to the osteoporosis management plan.

Fracture Liaison Services (FLS), or specialized multidisciplinary care models, have been designed to improve the care gap in the management of osteoporosis and secondary fracture prevention (114, 118).

CHAPTER 2
RATIONALE & OBJECTIVES

2.1 Study rationale

Previously the Canadian Multicentre Osteoporosis Study (CaMos) has provided invaluable insight in the epidemiology of osteoporosis and fractures among Canadians (54). CaMos was a population-based cohort study of 9,423 women and men recruited between 1995 and 1997 examining osteoporosis and fracture risk in community-dwelling Canadians. In CaMos, participants aged 25 years and older were recruited through random telephone numbers from within 50 km of nine study centers across Canada. Data collection included an in-person interviewer-administered questionnaire (IAQ), and physical measurements. CaMos found that Canadians from different geographic regions experienced different prevalence of osteoporosis and fractures, and this regional variation in the prevalence of osteoporosis (by BMD T-scores ≤ -2.5) was related to underlying differences in the distribution of BMD. In CaMos, regions with a high prevalence of men and women with BMD T-score ≤ -2.5 did not have a correspondingly high rate of fracture. The lowest mean total hip BMD (g/cm^2) were in Quebec (men) and Halifax (women); whilst the highest age-standardized incidence of low-trauma fracture was in Calgary in men and women respectively. In CaMos, the consideration of clinical and individuals risk factors for fractures, in addition to BMD, increased the concordance between regions of high estimated risk with regions with high rates of fracture. CaMos concluded that the difference in fracture rates was not related to a specific factor but to a comprehensive assessment of fracture risk, including age, BMD, falls, prior fracture, and radiographic vertebral fractures.

However, CaMos baseline data were collected over twenty years ago. More recent studies have demonstrated that BMD and fractures rates have changed differently over time in many jurisdictions, and differently in men and women. A secular decline in fracture risk rates was reported in Europe and the US over the second half of the 20th century, while an increase in these

rates was detected in Asian countries such as Japan, China, Taiwan. It is unknown whether there have been any changes in BMD and fracture rates in Canada in the last 20 years, and if so, what variables are associated with these changes. With the introduction of treatment guidelines and pharmacological treatment options in recent years, it is worth exploring the care gap and whether individuals at high-risk for fractures receive appropriate osteoporosis management.

The Canadian Longitudinal Study on Aging (CLSA) is an ongoing longitudinal study in Canada started in 2012 to recognize and share determinants of healthy ageing in Canadians 45-85 years in two different cohorts: the tracking cohort and the comprehensive cohort (54). In the comprehensive cohort of CLSA, 14,777 men and 15,320 women were recruited using provincial health registries and random digit dialling sampling frames from a 25-50 km radius of the 11 data collection sites. Data was through a 90-minute face-to-face in-home interview and in-person visit for physical assessments at one of the CLSA data collection sites. The CLSA collected data can support nationwide examination of skeletal health such as physical performance measures, bone mineral density (BMD), vitamin D levels and other determinants.

2.2 Study objectives

The objectives of this study include:

1. Compare age- and sex-specific BMD and prevalent fracture patterns at entry into the CaMos and the CLSA cohorts and determine whether different patterns have emerged over a 20-year period
2. Compare vitamin D and calcium supplements and anti-osteoporosis medication use over time and determine how the treatment care gap has evolved in those at high-risk for fracture

3. Describe sex-specific BMD and prevalent fracture patterns across geographical regions in Canada and explore the effect of different skeletal determinants on these outcomes.

CHAPTER 3

MANUSCRIPT 1: VARIATION IN BONE MINERAL DENSITY AND FRACTURES OVER 20 YEARS AMONG CANADIANS: A COMPARISON OF THE CANADIAN MULTICENTER OSTEOPOROSIS STUDY AND THE CANADIAN LONGITUDINAL STUDY ON AGING

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3.1 Abstract

Background: Data are lacking on the change in bone mineral density (BMD), fractures, and osteoporosis (OP) treatment in Canada over time.

Methods: We explored sex-specific differences in femoral neck BMD (FN-BMD), prevalent major osteoporotic fractures (MOF) in men and women 50-85 years from Canadian Multicenter Osteoporosis Study (CaMos, N=6,479; 1995-1997) and Canadian Longitudinal Study on Aging (CLSA, N=19,534; 2012-2015). We created linear and logistic regression models to compare femoral neck and fracture risk between cohorts, adjusting for age and other important covariates. Among participants with prevalent MOF, we compared the use of calcium and vitamin-D supplements (SUP), hormone therapy (HT), and bisphosphonates (BP).

Results: Mean (SD) age in CaMos (women 65.5 [8.5]; men 65.1 [8.7]) was higher than in CLSA (women 63.3 [9.0]; men 64.2 [9.1]). CaMos participants had lower mean height and BMI, and a higher prevalence of smoking than those of CLSA. Adjusted linear regression models (estimates; 95%CI) demonstrated lower FN-BMD (g/cm^2) in CaMos women (-0.017; -0.021 to -0.014) and men (-0.006; -0.011 to 0.000), while adjusted Odds Ratios (95%CI) for prevalent MOF were higher in CaMos women (1.99; 1.71 to 2.30) and men (2.33; 1.82 to 3.00) compared to CLSA. In women with prevalent MOF, HT use was not different in CaMos vs CLSA (43.3% vs 37.9%), but SUP use (32.0% vs 48.3%) and BP use (5.8% vs 17.3%) were lower in CaMos participants. In men, comparisons yielded inconclusive results.

Conclusion: Higher BMD and lower risk of fractures were noted in the CLSA participants as compared to CaMos participants, even after adjusting for multiple covariates. We noted a concurrent improvement in anti-osteoporosis treatment, though the care gap remains particularly elevated in men.

Key words: Aging, Bone mineral density, CaMos, CLSA, Trend

3.2 Introduction

Osteoporosis, a chronic age-associated disease (1, 2), is characterized by an increased propensity to fracture caused by a loss of bone strength (3, 4). Osteoporosis-related fractures increase the likelihood of subsequent fractures and bring a substantial burden to the healthcare system (5) (6). As the population is aging, it is projected that by 2031, at least one in every four Canadians will be 65 or older (7), and as a result, age-associated diseases like osteoporosis are expected to also increase over time. The high prevalence of osteoporosis and the associated fractures make this condition a major public health issue.

During the past decades, international variations in osteoporosis and osteoporotic fracture rates have been reported, with temporal trends that differ between populations (8-10). In the US, the analysis of National Health and Nutrition Examination Survey (NHANES) data demonstrated that the prevalence of osteoporosis (T-score<-2.5) among people aged 50 years and older declined between 1988 and 2006, stabilized from 2005 to 2010, and then increased in 2014 (11-13). The mean bone mineral density (BMD) at the femoral neck among US men and women aged 30 years and older was stable for the first three NHANES cycles from 2005 to 2010, and significantly decreased after 2014 (11).

Hip fracture rates appeared to have plateaued or decreased in the last two decades in many developed countries, following a rise in preceding years; however, in the developing world, age- and sex-specific fracture rates are still rising (9). Decreasing trends in hip fracture rates were observed in North America, Europe, and Oceania, and increasing rates were detected in Asian countries such as Japan, China and Taiwan (14, 15). The prevalence of hip fractures in the elderly population from the NHANES cohort increased in both men and women from 1986-2005 to 2005-2010 (16, 17).

Due to significant advances in osteoporosis management over the past 50 years, including the widespread availability of effective pharmacological therapies, osteoporosis is no longer considered an inevitable consequence of ageing (18, 19). Country-specific clinical guidelines have been developed worldwide and provide osteoporosis management guidance to reduce fracture risk (20-22).

The magnitude of change in BMD, fracture rates, and anti-osteoporosis care in the last decades amongst the general population in Canada is not well described. The Canadian Multicentre Osteoporosis Study (CaMos) (baseline 1995-97) and the Canadian Longitudinal Study on Aging (CLSA, baseline 2012-15) are two large population-based longitudinal cohorts in Canada providing valuable information about skeletal health determinants of Canadians. Using baseline data from the CLSA and CaMos cohorts, we aimed to compare age- and sex-specific BMD, prevalent fracture patterns between the two cohorts separated by a 20 -year period, and to compare the use of vitamin D and calcium supplements and anti-osteoporosis medications between cohorts to determine how the treatment care gap has evolved in individuals at high-risk for fracture.

3.3 Methods

3.3.1 Data source and study population

This study was performed using the baseline data from the CaMos (23) and CLSA cohorts (24). CaMos is a longitudinal population-based cohort study of 6,539 women and 2,884 men who were recruited between 1995 and 1997 to examine osteoporosis and fracture risk in community-dwelling Canadians (23). Participants aged 25 years and older were recruited through a random telephone-based sampling frame from within 50 km of one of nine study centers (Vancouver in British Columbia; Calgary in Alberta; Saskatoon in Saskatchewan; Toronto, Hamilton, and Kingston in Ontario; Quebec City in Quebec; Halifax in Nova Scotia; and St John's in Newfoundland and

Labrador). Data collection included an in-person interviewer-administered questionnaire, and physical measurements. Exclusion criteria were being unable to communicate in English, French, or Chinese, and institutionalized individuals.

CLSA is an ongoing longitudinal study in Canada started in 2012 to recognize determinants of healthy ageing in Canadian 45-85 years in two different cohorts: tracking cohort and comprehensive cohort; the latter constituting the study population of this analysis (24). In the CLSA comprehensive cohort, 14,777 men and 15,320 women were recruited using provincial health registries and random digit dialling sampling frames from 25-50 km radius of the 11 centers (Data Collection Site: Victoria, Vancouver, and Surrey in British Columbia; Calgary in Alberta; Winnipeg in Manitoba; Hamilton and Ottawa in Ontario; Montreal and Sherbrooke in Quebec; Halifax in Nova Scotia; St. John's in Newfoundland and Labrador). Data were collected through a 90-minute face to face in-home interview and in-person visit for physical assessments at one of the CLSA data centers. The exclusion criteria were being a resident of Northwest Territories, Nunavut, Yukon, or federal First Nations reserves, being a full-time member of the Canadian Armed Forces, living in institutions, inability to respond in English or French, and having cognitive impairment. Potential participants were evaluated for cognitive impairment through telephone screening tools designed specifically for the CLSA.

This study was conducted using baseline data of men and women aged 50 to 85 years from CaMos and CLSA (Supplemental Figure 3.1). We used the data of participants without missing BMD measurement as well as other covariates; including 4,608 women and 1,871 men from CaMos, and 9,583 women and 9,951 men from the comprehensive cohort in CLSA.

3.3.2 Variables

3.3.2.1 Bone mineral density

We used BMD measured at the femoral neck for this analysis. In CaMos, BMD was measured at baseline using dual-energy X-ray absorptiometry (DXA) from Hologic (7 centers), or Lunar manufacturers (2 centers). Machine calibration was done daily. Daily and weekly quality assurance tests were performed. Lunar data were converted into equivalent Hologic values by standard methods. Cross-calibration was performed across centres. More details regarding quality control have been published previously (25).

In CLSA, BMD measurements were done using Hologic densitometers at all centers (26). Appropriate quality control and cross-calibration of DXA machines were performed within and between centers using standard operating procedures. Local quality controls were done daily using a Spine Phantom (i.e. a tool for standardization and quality control in spinal bone mineral measurements (119)), and weekly using the Whole-Body Phantom. Once a year, cross-calibrations across all densitometers were done with the Gold Standard Traveling Phantoms.

In order to assess cross-calibration between CLSA and CaMos densitometers, we followed the International Society for Clinical Densitometry (ISCD) recommendation for the Least Significant Change (LSC) for quality assurance between the DXA Scanners used in both cohorts (27). In CaMos, since the comparisons of the measurements on the Hologic densitometers used in Quebec City were stable over time, no longitudinal corrections were ever required. Therefore, we used the CaMos spine phantom for cross-calibration purposes between the CaMos and CLSA densitometers. We scanned the CaMos phantom 30 times on each of two Hologic densitometers: the CaMos densitometer still in use in Quebec City and a CLSA densitometer located in Hamilton.

As the differences between densitometers were within the threshold limit of 1.5% (28), no adjustment was required.

3.3.2.2 Osteoporosis, fractures, and anti-osteoporosis treatment

Osteoporosis was defined as the presence of a femoral neck T-score equal to -2.5 or less. We generated femoral neck BMD T-scores using the young normal values from the NHANES III BMD of white women 20-29 years old (29).

Fractures were defined as prevalent self-reported major osteoporotic fractures (MOF; hip, clinical spine, wrist and humerus) that occurred with low trauma (standing height or less) during adult life. In CaMos, we selected fractures that occurred after the age of 18 years, while in CLSA, the fracture variable was derived from the Osteoporosis (OST) module asking specifically for fractures occurring in adult life. We generated 10-year fracture risk probabilities for MOF and hip fractures using the femoral neck T score (NHANES III BMD of women 20-29 years old as per ISCD recommendations) and clinical risk factors using the Canadian FRAX® tool (29).

According to most clinical practice guidelines, pharmacotherapy is recommended in those at high-risk for fractures, including men and women with a prevalent MOF, a FRAX probability for MOF of ≥ 20 % over the next 10 years, or those with osteoporosis with a BMD T-score ≤-2.5 (20, 21, 30). We defined participants with any of these characteristics as being at high-risk for fracture and documented the proportion of men and women who appropriately received supplemental calcium, vitamin D and anti-osteoporosis medication to reduce fracture risk at entry into the cohorts.

3.3.2.3 Anthropometric measurements

In CaMos, weight (kg) and height (cm) were measured using portable scale and carpenter's ruler respectively during the DXA measurement visit or at the time of the interview if no DXA scans were scheduled. In CLSA, weight (kg) and height (cm) were measured twice using a 140-10 Healthweigh digital physician scale and Seca 213 stadiometer respectively (31, 32). We used the average of weight and height measurement in this study. For both cohorts, body mass index (BMI) was calculated by dividing the weight in kg by height (in metre) square.

3.3.2.4 Other variables

Other explanatory variables were selected based on literature review and their availability in both CaMos and CLSA datasets. The variables considered were ethnicity (white or other), level of education (holding or not at least a high school diploma), smoking (current smoker or non-smoker, as used in FRAX), alcohol consumption in the past 12 months divided in two categories (less than 3 servings /day or 3 or more servings/day). Vitamin D and calcium supplements intake on a regular basis as well as any use of glucocorticoids, bisphosphonates, raloxifene, and hormone therapy (women only), were derived from the Drugs and Medication questionnaire in CaMos and In-Home Questionnaire (Version 4.0) in CLSA. Of note, etidronate and alendronate were approved for the treatment of osteoporosis in 1995 (CaMos baseline) and risedronate in 2000 in Canada.

3.3.3 Statistical methods

All analyses were stratified by sex. The prevalence of osteoporosis and MOF was further stratified by age groups. Descriptive statistics were generated using means and standard deviations (SD) or medians and interquartile ranges (IQR), and frequency and percentages as appropriate. Standard tests (chi-square, student t-test and analysis of variance) were used to compare categorical and continuous variables between cohorts.

Differences between cohorts were assessed by including the cohort membership (CaMos vs. CLSA) as an independent variable in regression models. Linear regression models were created to estimate the differences in femoral neck BMD between cohorts using CLSA as the reference. We first created unadjusted linear models looking at the association of femoral neck BMD with cohort membership. Multiple linear regression models were then fit with each covariable. The covariables meeting statistically significance ($p<0.05$) were included in the fully adjusted models. Age, BMI and height were included in the fully adjusted linear models regardless of significance. Logistic regressions were used to examine the associations of the cohort membership with MOF. Similar strategy as above was applied. We further adjusted the final model with femoral neck BMD.

Since the CLSA is known to have participants with a higher education level than the Canadian population (24), we studied the effect of education on the prevalence of osteoporosis in both cohorts. To do so, we used logistic regressions for the prevalence of osteoporosis stratified by sex and age groups, looking at cohort, post-secondary education (yes/no) and the interaction of cohort with post-secondary education. Sensitivity analyses were done using data from participants of White ancestry only.

All statistical analyses were performed using statistical R software (Version 1.2.5033© 2009-2019 RStudio, Inc). A 2-sided p-value of <0.05 was considered significant.

3.4 Results

3.4.1 Baseline characteristics

The total number of eligible participants from both cohorts was 26,013 (CaMos: 4,608 women and 1,871 men; CLSA: 9,583 women and 9,951 men) (Supplemental Figure 3.1), and their characteristics are shown in Table 3.1. In general, participants from CaMos were older (mean [SD] age in CaMos: women; 65.5 [8.5] and men; 65.1 [8.7]) than participants from CLSA (women; 63.3

[9.0] and men; 64.2 [9.1]). They also had lower mean height, weight, and BMI than those from CLSA. The prevalence of current smokers in CaMos was significantly higher in both women (13.5% vs 7.0%) and men (15.8% vs 8.5%). The percentage of women and men with post-secondary education was lower in CaMos than CLSA. Individuals who self-identified as White constituted over 92% of both cohorts.

3.4.2 Osteoporosis and bone mineral density

Prevalence of osteoporosis are presented by sex and age groups in Figure 3.1. In all sex and age group categories, the prevalence of osteoporosis was significantly higher in CaMos compared to CLSA with differences between cohorts in women ranging from 2.3% (50-64 years) to 16.1% (75-85 years) and in men from 0.3% (50-65 years) to 4.6% (75-85 years). The logistic regression models for the prevalence of osteoporosis showed that the interactions between cohort and education were not significant in women for all age groups (data not shown). Because of the smaller sample size in CaMos men, we could only look at the interaction between cohort and post-secondary education in men 75-85 years old, which was not significant. Therefore, we did not further stratify our results by education level.

Participants from CaMos had significantly lower mean (SD) femoral neck T-score (women; -1.4 [1.0], men; -0.6 [1.0]) than CLSA (women; -1.1 [1.0], men; -0.4 [1.0]). As expected, unadjusted estimates (95% CI) for femoral neck BMD were lower in CaMos in both women (-0.032 g/cm^2 [-0.036; -0.028]) and men (-0.024 g/cm^2 [-0.030; -0.018]) than CLSA (Figure 2). Adjusting for age, BMI, height, and other important covariates decreased the differences between the cohorts. However, estimates remained significantly lower in CaMos women (-0.017 g/cm^2 [-0.021; -0.014]) and men (-0.006 g/cm^2 [-0.011; 0.000]), compared to CLSA.

3.4.3 Major osteoporosis fracture

The prevalence of MOF by sex and age groups are presented in Figure 3.1. In all sex and age groups, the prevalence of MOF was higher among CaMos participants compared to CLSA except for men aged 75-85 years where there was no statistical difference.

Unadjusted Odds Ratios (OR, 95% CI) for prevalent MOF were significantly higher in women and men from CaMos compared to CLSA (Figure 3.3**)**. After adjusting for covariates, ORs for prevalent MOF remained significantly higher in CaMos than CLSA in both women (OR 1.99 [1.71, 2.30]) and in men (OR 2.33 [1.82, 3.00]).

As sensitivity analyses, the regression models on BMD and fractures were performed on participants of white ancestry only. Results were similar to previous findings in both the linear regression for BMD and logistic regression for fractures.

3.4.4 Anti-osteoporosis treatment use in participants at high-risk for fracture

The proportion of participants at high-risk for fractures was higher in CaMos than CLSA in both women and men, except for men in whom there was no difference between groups when defined based on a high FRAX probability (Table 3.2). As can be seen in Figure 3.4, in women, use of supplements and bisphosphonates was significantly lower in CaMos for every category of high-risk definition. Overall, the use of hormone therapy did not differ between women from CaMos (35.6%) compared to CLSA (37.4%) at high-risk for fractures (either categories). In men, the comparisons of supplements and anti-osteoporosis treatment use were inconclusive, mainly due to the small number of men at high-risk for fractures.

3.5 Discussion

We have documented higher BMD values and lower risks of fractures in the CLSA participants compared to the participants of CaMos, recruited 20 years apart, even after adjusting for important covariates. This is in agreement with reports from other developed countries where BMD has increased and fracture rates have decreased over the last decades. We also noted improvement in anti-osteoporosis treatment over time in high-risk for fractures, nevertheless, the care gap remains elevated, specifically in men.

Changes over time in BMD measurements are also documented in many countries. In a study examining BMD in older US adults between 2005 and 2014 from the National Health and Nutrition Examination Survey, there was some evidence of a decline in femur neck BMD between 2005-2006 and 2013-2014, but not in lumbar spine BMD. Changes in the risk factors that could be examined, such as BMI, smoking, milk intake, did not explain the femur neck BMD trends (12). In Canada, a significant annual linear increase of 0.52% in BMD at the femoral neck was documented using the large Manitoba BMD registry data of women aged 50 years and older from 1996-2006 (33). The temporal increases in BMI, obesity, and osteoporosis treatment did not explain these changes. We noted that BMD was higher in the CLSA participants as compared to the CaMos cohort, supporting an improvement in bone mass in Canadians over a 20- year period. Although we also documented that age, height, BMI, smoking, alcohol consumption, level of education, supplement and anti-osteoporosis medication use were different between cohorts, adjusting for these variables did not explain the differences between cohorts.

Secular changes in major osteoporotic fractures have been documented previously in various countries. The overall incident rate of fragility fractures has been predicted to increase in many countries (18, 34), mainly due to the impending aging trajectory (8). However, the trends in osteoporotic fracture rates had been reported to differ between population depending on the

fracture site. In Denmark, data from 1995 to 2010 showed a general decline in the incidence rate of major osteoporotic fractures in both men and women 50+ adults (8). Similarly, the trend in Italy from 2007 to 2014 revealed an overall decline in the incidence rate of hip fractures in older women (34). In the US, Medicare and the National Inpatient Survey data indicated a decline in hip fracture incidence between 1985 and 2012 (12). A recent study using the UK Clinical Practice Research Datalink with a 20-year follow-up time (1990–2012) revealed stable overall sex-specific fracture incidence, though this varied by fracture sites with radius-ulna fracture becoming less frequent in women and hip fractures rising in men. (35). We found that the prevalence of major osteoporotic fractures in both women and men, except in men aged 75-85 years, were lower in CLSA compared to CaMos. These results were consistent with the data from the study of the Manitoba BMD registry of women aged 50 years and older, which documented a decline in major osteoporotic fractures from 1996-2006, attributed to a secular increase in BMD, rather than changes in anti-osteoporosis treatment or in BMI (33). It was also recently demonstrated using Canadian national administrative data, that the age-standardized annual hip and forearm fracture rates decreased, humeral fracture rates relatively stabilized, and spine fracture rates increased over the study period 2000–01 to 2015-16 (2). The basis for the stabilization and often reduction in fracture rates in industrialized countries remains uncertain. Although an improvement in BMD has been considered as the major factor contributing to reductions in osteoporotic fracture rates (33), other factors like greater rates of osteoporosis treatment, change in lifestyle, introduction of new anti-osteoporosis medication (bisphosphonates), increasing prevalence of obesity, and alterations in tobacco consumption might also contribute (6, 18). Period and birth cohort effects have been studied in a nationwide hip fracture study in Sweden and Denmark and found to have an impact on fracture rates (36). In general, population health indices and life expectancy at birth in developed countries have improved, and access to healthcare throughout the lifespan has expanded

over many decades. Over the past half-century, there have been rapid and marked advancements in pharmacological interventions for osteoporosis (37). However, evidence suggests that only a minority of patients at high-risk for fractures receive screening or treatment known to reduce fracture risk (38).

We documented that there have been improvements in anti-osteoporosis pharmacotherapy in women in the last 2 decades. The introduction of bisphosphonate and clinical practice guidelines after the CaMos baseline (1995-1997) could possibly explain this improvement since etidronate and alendronate were approved for the treatment of osteoporosis in 1995 and risedronate in 2000. However, the care gap (discrepancy between the provided and recommended treatment) is still remarkably high. Regardless of the definition of the high-risk category, only about 20% of CLSA women at high-risk for fracture were being treated with bisphosphonates. This was similar to the findings PHAC report where less than 20% of Canadians with MOF received an osteoporosis diagnosis, underwent a BMD test or received a prescription for an osteoporosis-related medication (2). Our sample number of men at high-risk for fracture prevented us from adequately comparing both cohorts. Nevertheless, our results support the previous evidence that there is a larger care gap in men than in women.

The main strengths of this study include the large sample size and comprehensiveness of CaMos and CLSA. The quality control of densitometers within and between cohorts and similar ascertainment of bone health outcomes are other strengths. Also, both cohorts had similar ethnic admixtures, with the majority of their participants with white ethnic backgrounds, which allowed us to compare cohorts directly. There are some limitations in this study. The CLSA was designed to study healthy aging, while CaMos was designed to study osteoporosis. The difference in the design and objectives of these two studies may have affected participants' characteristics and results may be subject to selection and healthy participant biases. Individuals with prevalent

fractures or osteoporosis might have been more likely to participate in CaMos than healthy adults, while the CLSA may have been more attractive to healthy adults. Even though we could adjust for multiple factors, selection bias remains a concern and our results should be interpreted with this limitation in mind. This analysis was performed on CaMos and CLSA participants, regardless of the participant's ethnic/racial background. To control for the possible effect of ethnicity/race on bone mineral density and prevalent fractures rates, a sensitivity analysis using data of participants of white ancestry was performed. Finally, as similar sampling weights did not exist for both cohorts, the sampling weights could not be applied. To compensate for the difference in sampling strategy between both cohorts, we presented the prevalence by sex and age groups.

In conclusion, higher BMD values and lower risk of fractures were noted in the CLSA participants 50 years and older as compared to the participants of CaMos. An improvement in anti-osteoporosis treatment was noted over a 20-year period in women at high-risk for fracture and may provide some insight into the improvement in BMD and fractures over time. The care gap, however, remains high, particularly in men.

Data availability statement

The datasets generated for this article were generated by the Canadian Longitudinal Study of Aging; researchers apply for data access by following the procedure outlined here: *www.clsa-elcv.ca*. Questions regarding access the datasets should be directed to *ac.vcle-aslc@ssecca*.

3.6 Ethics approval

This study was approved by the Research Institute of the McGill University Health Centre (RI-MUHC) Research Ethics Board (Ethics Certificate No. 2019-4926).

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The opinions expressed in this manuscript are the author's own and do not reflect the views of the Canadian Longitudinal Study on Aging.

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3.8 Authors' contributions

SNM conceived the study and secured funding for this study. NH and CB conducted the data analysis and drafted the initial manuscript supervised by SNM. AP, AMC, ER, WDL and DG helped with results interpretation, and gave critical feedback on the manuscript. All authors approved the final manuscript.

3.9 Conflicts of interest

Authors report no conflict of interest.

3.10 Tables

Table 3.1 Baseline characteristics by cohort

	Women		Men	
	CaMos (n=4,608)	CLSA (n=9,583)	CaMos (n=1,871)	CLSA (n=9,951)
Age (years) - Mean (SD)	**65.5 (8.5)**	**63.3 (9.0)**	**65.1 (8.7)**	**64.2 (9.1)**
Height (cm) - Mean (SD)	**159.4 (6.3)**	**161.6 (6.5)**	**173.0 (6.9)**	**175.3 (7.0)**
Weight (kg) - Mean (SD)	**69.0 (13.4)**	**72.5 (15.7)**	**81.8 (13.2)**	**86.9 (15.4)**
Body mass index (kg/m^2)- Mean (SD)	**27.1 (5.0)**	**27.8 (5.8)**	**27.3 (3.8)**	**28.2 (4.5)**
Smoking (current) - N (%)	**620 (13.5)**	**674 (7.0)**	**296 (15.8)**	**848 (8.5)**
Alcohol (>= 3 drink/day) - N (%)	**42 (0.9)**	**305 (3.2)**	**131 (7.0)**	**898 (9.0)**
Ethnicity (White) - N (%)	**4433 (96.2)**	**8889 (92.8)**	1757 (93.9)	9241 (92.9)
Postsecondary degree - N (%)	**2038 (44.2)**	**7343 (76.6)**	**965 (51.6)**	**7978 (80.2)**
Calcium supplement use (past month)- N (%)	**2216 (48.1)**	**4203 (43.9)**	**486 (26.0)**	**1513 (15.2)**
Vitamin D supplement use (past month)- N (%)	**1614 (35.0)**	**5982 (62.4)**	**419 (22.4)**	**3811 (38.3)**
Bisphosphonate use- N (%)	**110 (2.4)**	**582 (6.1)**	**3 (0.2)**	**103 (1.0)**
Hormone therapy use (ever) - N (%)	**2231 (48.4)**	**3212 (33.5)**	**-**	**-**
FRAX probability for MOF (%) - Mean (SD)	**10.6 (7.5)**	**9.7 (6.6)**	**5.4 (3.1)**	**5.5 (3.1)**
FRAX probability for hip fracture (%) - Mean (SD)	**2.6 (4.7)**	**1.8 (3.6)**	**1.2 (2.0)**	**1.1 (1.8)**
Femoral Neck BMD (g/cm^2) - Mean (SD)	**0.691(0.119)**	**0.723(0.114)**	**0.791(0.125)**	**0.816(0.125)**
Prevalent MOF - N (%)	**503 (10.9)**	**594 (6.2)**	**103 (5.5)**	**266 (2.7)**
Prevalent Any fracture - N (%)	**1158 (25.1)**	**1855 (19.4)**	**355 (19.0)**	**1113 (11.2)**
Osteoporosis (T-Score ≤ -2.5 at femoral neck) - N (%)	**562 (12.2)**	**478 (5.0)**	**38 (2.0)**	**87 (0.9)**

In bold: statistically significant differences (P Value ≤ 0.05 in ANOVA and Chi-squared test) by cohorts
* Calculated with BMD
**Calculated using NHANESIII data for women
Non-weighted results

Table 3.2. CaMos and CLSA participants with baseline characteristics that meet the definition of high-risk for fracture

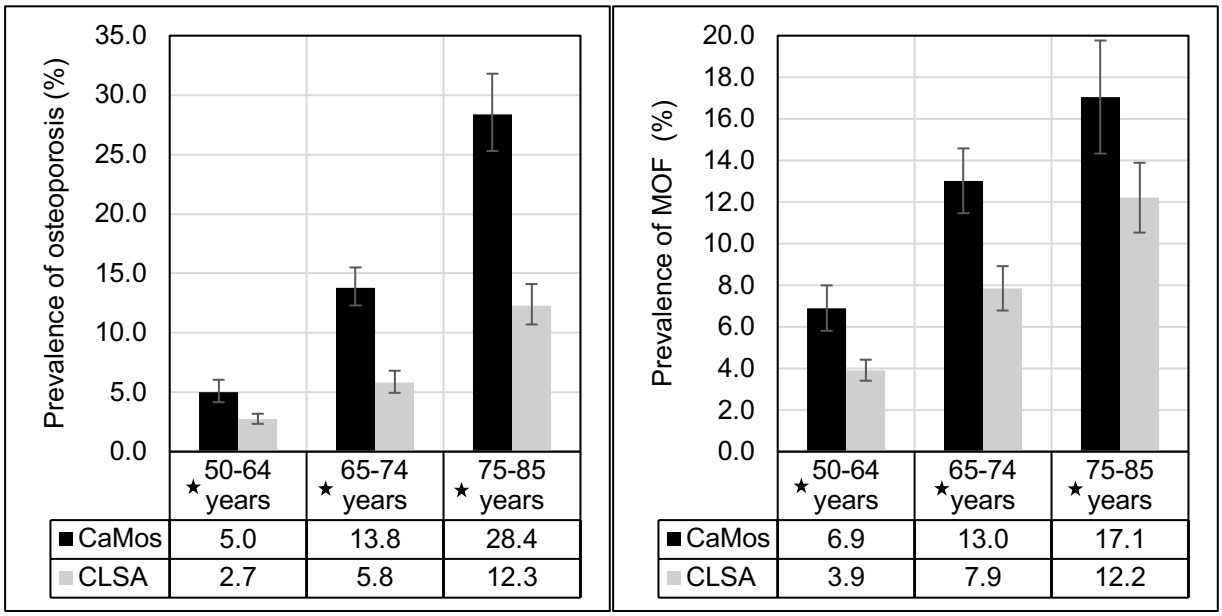
	Women		Men	
	CaMos (n=4,608)	CLSA (n=9,583)	CaMos (n=1,871)	CLSA (n=9,951)
FRAX probability for MOF ≥ 20% - N (%)	**430 (9.3)**	**684 (7.1)**	12 (0.6)	44 (0.4)
With prevalent MOF - N (%)	**503 (10.9)**	**594 (6.2)**	**103 (5.5)**	**266 (2.7)**
Osteoporosis (T-Score ≤ -2.5 at femoral neck) - N (%)	**562 (12.2)**	**478 (5.0)**	**38 (2.0)**	**87 (0.9)**
High-risk for fracture – either of the following: FRAX probability for MOF ≥ 20% With prevalent MOF Osteoporosis (T-Score ≤ -2.5 at femoral neck)	**562 (12.2)**	**478 (5.0)**	**38 (2.0)**	**87 (0.9)**

In bold: statistically significant differences (P Value ≤ 0.05 in Chi-squared test) by cohorts
Non-weighted results
MOF: low trauma fractures of the hip, clinical spine, wrist and humerus

3.11 Figures

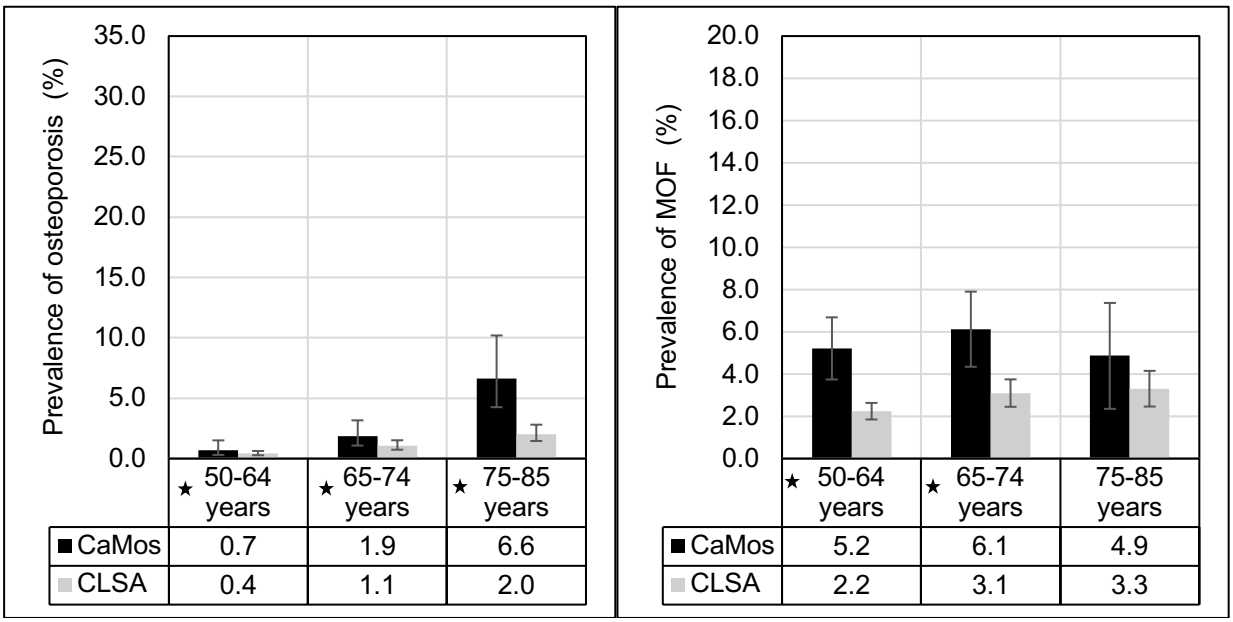
Figure 3.1. Prevalence of osteoporosis and major osteoporotic fractures (MOF) (%, CI) by sex and age group

A. Women



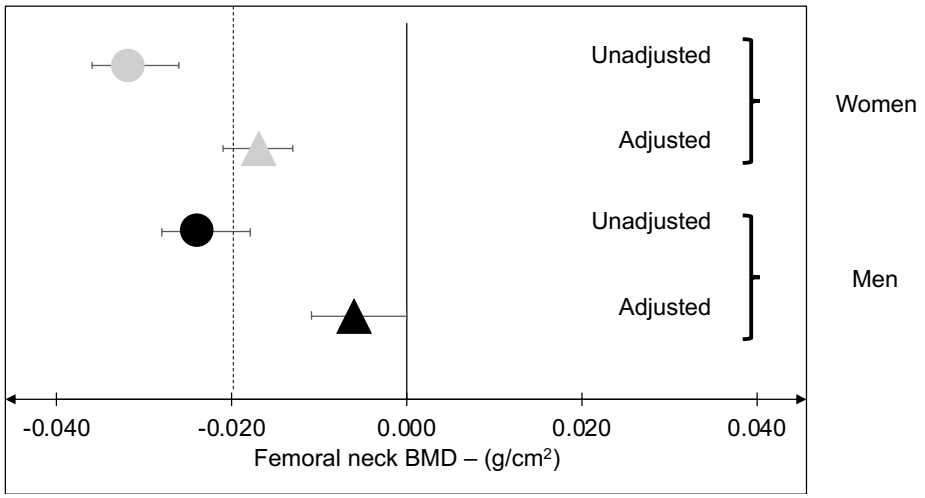
* Statistically significant by cohort (P<0.05)
Osteoporosis: defined as femoral neck T-score ≤ -2.5
MOF: low trauma fractures of the hip, clinical spine, wrist and humerus

B. Men



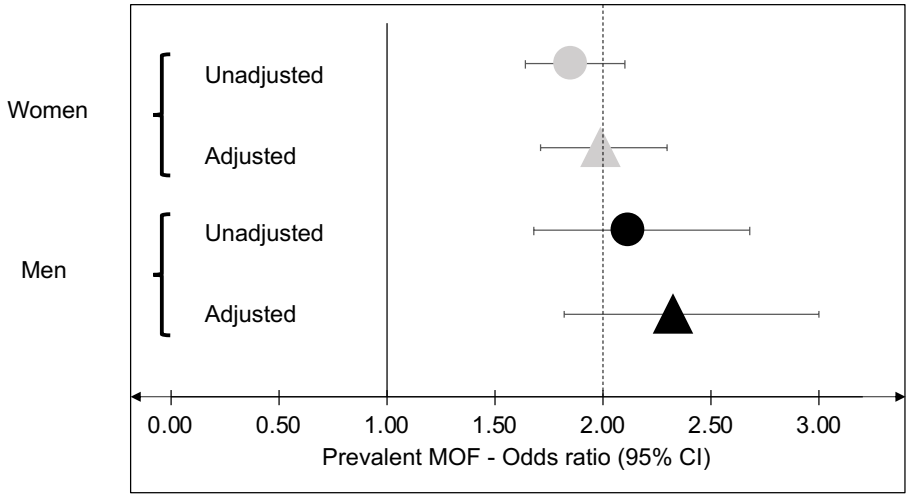
* Statistically significant by cohort (P<0.05)
Osteoporosis: defined as femoral neck T-score ≤ -2.5
MOF: low trauma fractures of the hip, clinical spine, wrist and humerus

Figure 3.2. Unadjusted and adjusted femoral neck bone mineral density (BMD) estimates (95% CI) for cohort membership – CaMos vs. CLSA (reference)



Grey triangle (adjusted model in women): adjusted for age, BMI, height, smoking, calcium and vitamin D supplement, corticosteroid, bisphosphonates, raloxifene, hormone therapy
Solid triangle (adjusted model in men): adjusted for age, BMI, height, smoking, calcium supplement, corticosteroid, bisphosphonates
All associations were statistically significant (P<0.05).
Non-weighted results.

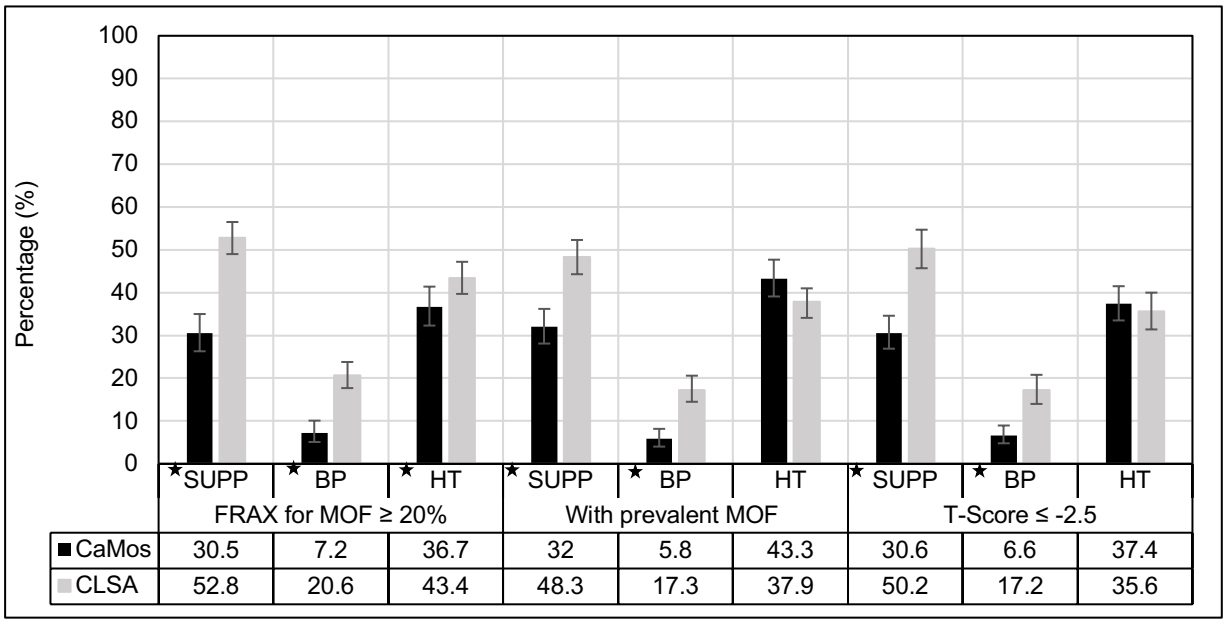
Figure 3.3. Unadjusted and adjusted Odds Ratios (95% CI) for major osteoporotic fractures (MOF) according to cohort membership – CaMos vs. CLSA (reference)



Grey triangle (adjusted model in women): adjusted for age, BMI, height, calcium and vitamin D supplement, corticosteroid, bisphosphonates, BMD at femoral neck, education, alcohol, ethnicity
Solid triangle (adjusted model in men): adjusted for age, BMI, height, calcium supplement, bisphosphonates, BMD at femoral neck, education
All associations were statistically significant (P<0.05).
Non-weighted results.

Figure 3.4. Anti-osteoporosis treatment use (%, CI) in participants at high-risk for fracture

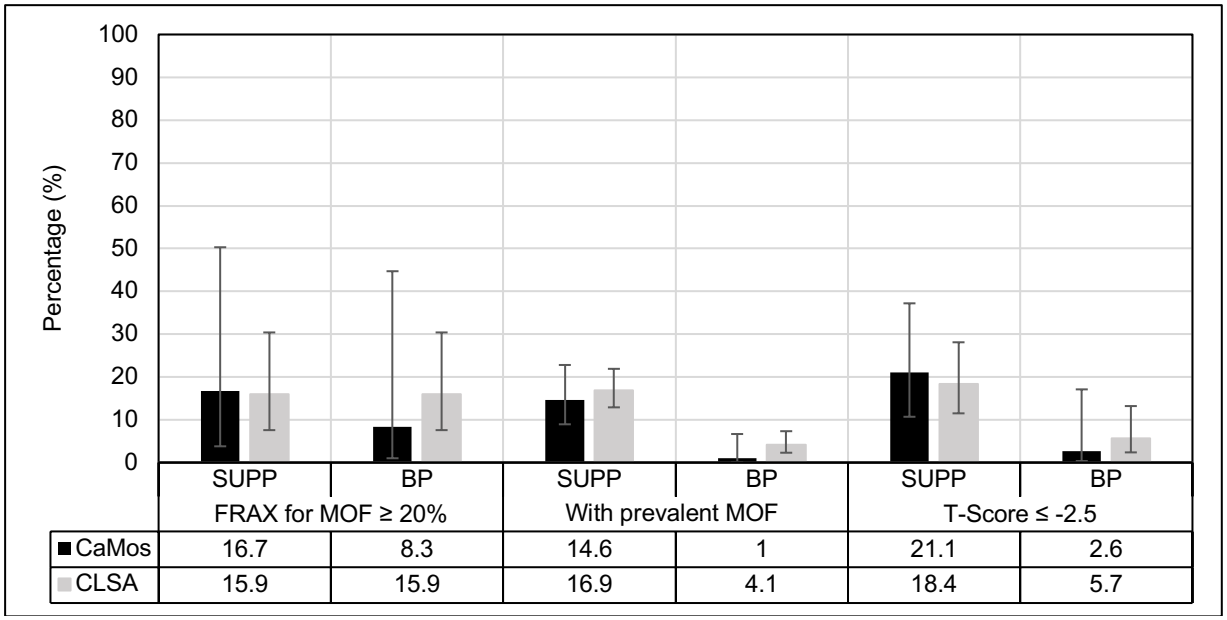
A. Women



	FRAX for MOF ≥ 20%			With prevalent MOF			T-Score ≤ -2.5		
	SUPP	BP	HT	SUPP	BP	HT	SUPP	BP	HT
CaMos	30.5	7.2	36.7	32	5.8	43.3	30.6	6.6	37.4
CLSA	52.8	20.6	43.4	48.3	17.3	37.9	50.2	17.2	35.6

SUPP: supplement (calcium and vitamin D); BP (bisphosphonates); HT (hormone therapy)
T-score at femoral neck, Non-weighted results
* Statistically significant comparisons between CLSA and CaMos (P Value ≤ 0.05 in Chi-squared test)

A. Men

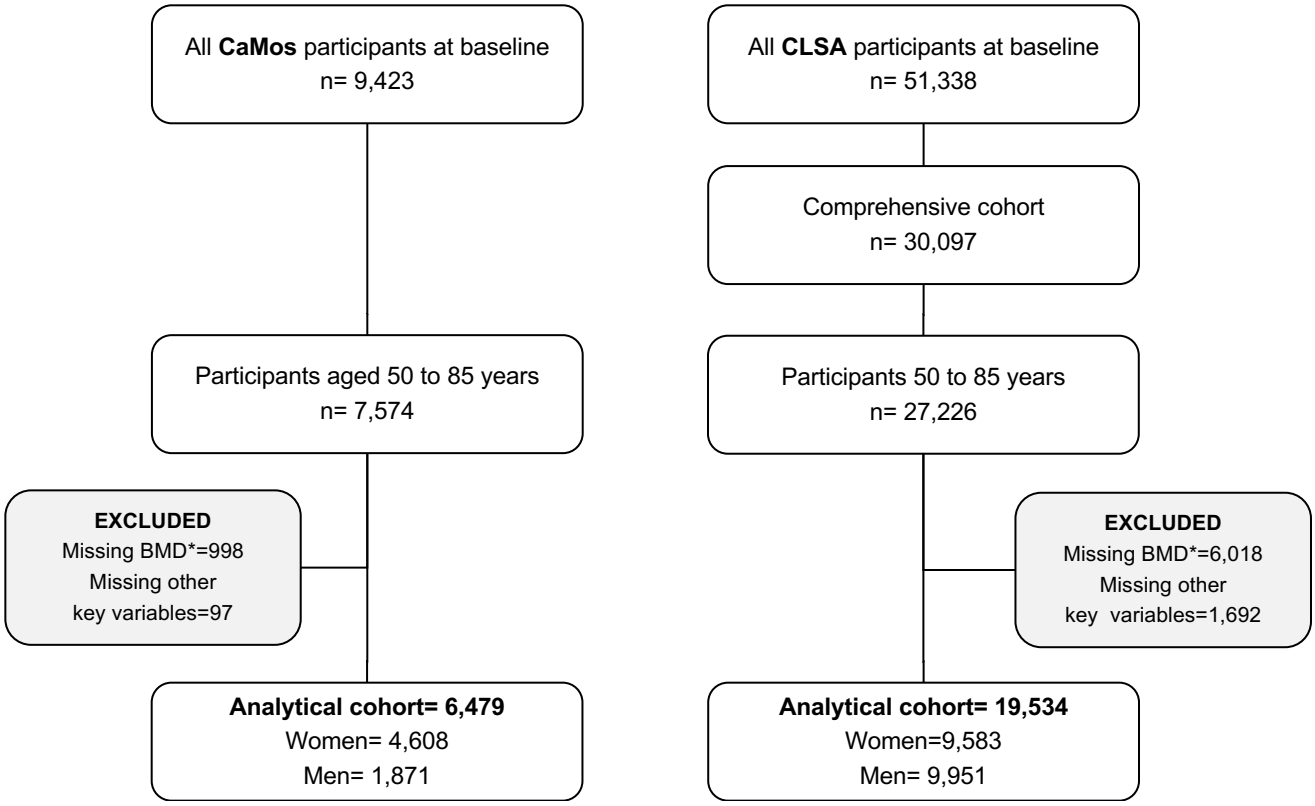


	FRAX for MOF ≥ 20%		With prevalent MOF		T-Score ≤ -2.5	
	SUPP	BP	SUPP	BP	SUPP	BP
CaMos	16.7	8.3	14.6	1	21.1	2.6
CLSA	15.9	15.9	16.9	4.1	18.4	5.7

SUPP: supplement (calcium and vitamin D); BP (bisphosphonates);
T-score at femoral neck, Non-weighted results
All comparisons between CLSA and CaMos were **not** statistically significant (P Value ≥ 0.05 in Chi-squared test)

3.12 Supplemental Material

Supplemental Figure 3.1. Study design and population



***** BMD at femoral neck

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CHAPTER 4
BRIDGING

In previous chapter, the study was conducted with the objectives of comparing age- and sex-specific bone mineral density (BMD), prevalent fracture, and anti-osteoporosis medications between the CaMos and the CLSA cohorts to see whether different patterns have emerged over a 20-year period. We documented higher BMD values and lower risks of fractures in the CLSA participants 50 years and older compared to the participants of CaMos. We also noted improvement in anti-osteoporosis treatment in women at high-risk for fractures; nevertheless, the care gap remains elevated, specifically in men over the same period.

CaMos previously has found that Canadians from different geographic regions experienced the different prevalence of osteoporosis and fractures, and this regional variation in the prevalence of osteoporosis was related to underlying differences in the distribution of BMD. It is unclear if these variances in the prevalence of osteoporosis and fractures across Canada persist and whether they can be explained by differences in clinical risk factors such as falls, physical function or vitamin D status; factors not ascertained systematically in the CaMos cohort. In the next chapter, we conducted our project with the objective of comparing sex-specific BMD and prevalent fracture patterns across geographical regions in Canada and exploring the effect of different skeletal determinants on these outcomes.

CHAPTER 5

MANUSCRIPT 2: GEOGRAPHIC VARIATION IN BONE MINERAL DENSITY AND PREVALENT FRACTURES IN CANADIAN LONGITUDINAL STUDY ON AGING

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5.1 Abstract

Background: The prevalence of osteoporosis and fractures differs across countries and regions. We aimed to describe sex-specific total hip bone mineral density (BMD), and prevalent major osteoporotic fractures (MOF) variations between Canadian provinces.

Methods: We used baseline data of 21,227 Canadians (10,716 women, 10,511 men) aged 50 years and older participating in the Canadian Longitudinal Study on Aging (2012-2015). Linear and logistic regression models were used to examine associations between the province of residence and total hip BMD, and self-reported MOF, stratified by sex and adjusted for important covariates.

Results: The mean (SD) age of participants was 63.9 (9.1) and it did not differ between provinces. The mean Body Mass Index (BMI; kg/m^2) was lowest in British Columbia (BC; 27.4 [5.0]) and highest in Newfoundland and Labrador (NL; 28.8 [5.3]). Women and men from BC had the lowest mean total hip BMD (g/cm^2), and the lowest prevalence of MOF. Alberta (AB) (12.0%) had the highest proportion of participants reporting recent falls, while Manitoba (MB; 8.4%) had the fewest. Linear regression demonstrated significant differences in total hip BMD; women and men from BC and AB, and women from MB and Nova Scotia (NS) had lower, while men from NS had higher adjusted total hip BMD than ON. Adjusted Odds Ratios (95% confidence intervals) for prevalent MOF were significantly lower in BC women (0.50; 0.37-0.69) and men (0.35; 0.22-0.57) compared to ON. Results were similar when restricting the analyses to participants who claimed White race/ethnicity.

Conclusion: Geographical variations in total hip BMD and the prevalence of MOF between provinces persisted after adjusting for important covariates. These observed variations are likely associated with unmeasured individual, social and environmental factors.

Keywords: osteoporosis, bone mineral density, fracture, CLSA, Canada

5.2 Introduction

The population is aging worldwide; globally, the number of individuals 65 years and older has increased from 6% in 1990 to 9% in 2019. (1). As the population is aging, the number of older adults with chronic diseases such as osteoporosis is expected to increase (2, 3). Osteoporosis, a common and major public health concern (3, 4), is characterized by chronic deterioration of bone architecture which increases bone fragility and predisposes to fractures (5-8). Fragility fractures bring a substantial burden to the healthcare system, individuals, and society (9); decrease independence and cause long-term disability (6, 7, 10-13).

The risk of osteoporosis and fractures varies worldwide by geographic location, sex, race/ethnicity and socioeconomic status (14, 15). Worldwide, the highest rates of hip fractures were documented in the US and Northern Europe (Sweden and Norway) (16). The International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA) have reported the prevalence of osteoporosis (defined as a T-score $\leq$ -2.5 at the femoral neck on bone mineral density [BMD]) in adults 50 years and older to vary within the European Union, with Germany having the highest percentage of individuals with osteoporosis (17). Within country geographical difference in BMD and osteoporosis was previously documented in other countries including US (18), Mexico (19), and Canada (20).

The Canadian Multicentre Osteoporosis Study (CaMos, 1995-1997) demonstrated that Canadians from different geographic regions experience different rates of fractures and prevalence of osteoporosis (20). The lowest mean BMD (measured at the total hip) was documented in men in Quebec and in women in Nova Scotia, while the highest rates of fracture were in Ontario and the lowest in Quebec (20). It is unclear if these variances in the prevalence of osteoporosis and fractures across Canada persist, and whether they can be explained by differences in clinical risk

factors such as falls, physical function or vitamin D status; factors not ascertained systematically in the CaMos cohort.

The Canadian Longitudinal Study on Aging (CLSA) is an ongoing large population-based longitudinal cohort that aims to study determinants of healthy aging and has obtained a vast array of information on its fifty-one thousand participants. Using baseline data from CLSA (2012-2015), our objectives were to describe sex-specific BMD, and prevalence of osteoporosis and of major osteoporotic fractures (MOF) in Canadians across provinces, and to determine if physical performance measures were associated with these outcomes.

5.3 Methods

5.3.1 Data source and study population

Between 2012 and 2015, 30,097 women and men between the age of 45 and 85 were recruited in the CLSA comprehensive cohort. This cohort was recruited using provincial health registries and random digit dialing sampling frames. The inclusion criteria were age between 45-85 years and living within 25-50 km radius of the 11 data collection sites (Victoria, Vancouver, and Surrey in British Columbia; Calgary in Alberta; Winnipeg in Manitoba; Hamilton and Ottawa in Ontario; Montreal and Sherbrooke in Quebec; Halifax in Nova Scotia; St. John's in Newfoundland and Labrador). Data were acquired through a face-to-face in-home interview and in-person visit for physical assessments. Residents of the Canadian territories (Northwest, Nunavut, and Yukon), residing in federal First Nations reserves, full-time member of the Canadian Armed Forces, living in institutions, unable to respond in English or French, or those having cognitive impairment were excluded. Signed informed consent was obtained from every study participant. Ethics approval for the present study was granted through the Research Institute of the McGill University Health

Centre (2019-4926). For this analysis, we included 21,227 participants (10,716 women and 10,511 men) aged 50 to 85 years with a valid BMD measurement at the total hip (Figure 4.1).

5.3.2 Variables

5.3.2.1 Geographical regions

The exposure variable was geographical region defined as the participants' province of recruitment (proxy for residence) of British Columbia (BC), Alberta (AB), Manitoba (MB), Ontario (ON), Quebec (QC), Nova Scotia (NS), and Newfoundland and Labrador (NL).

5.3.2.2 Anthropometric measurement

Weight in kg and shoeless standing and sitting height in centimeter (cm) were measured twice using a 140-10 Healthweigh digital physician scale and Seca 213 stadiometer respectively (21, 22). We used the average of weight and height measurement in this study. Body mass index (BMI) was calculated from dividing the weight in kg by height (in metre) square.

5.3.2.3 Bone mineral density

Bone mineral density was measured at the total hip, using an Hologic Discovery A™ dual-energy X-ray absorptiometry (DXA) densitometer (23). Appropriate quality controls were done within and between data collecting centres using standard operating procedures. Local quality controls were done daily using a Spine Phantom, and weekly using the Whole-Body Phantom. Once a year, cross-calibrations across all densitometers was done with the Gold Standard Traveling Phantoms. Between-center differences were within the threshold limit of 1.5% (personal communication September 2020) (24).

5.3.2.4 Osteoporosis, fractures and falls

Osteoporosis was defined as the presence of a T-score $\leq$ -2.5 at femoral neck. We generated femoral neck BMD T-scores using the young normal values from the National Health and

Nutrition Examination Survey (NHANES) III BMD of white women 20-29 years old (25). Prevalent fractures were defined as self-reported major osteoporotic fractures (MOF; hip, clinical spine, wrist and humerus) that occurred during adult life. The fracture variable was derived by combining two questions: "Have you ever broken a bone in your adult life that resulted from a minor fall or low level of injury (e.g., a simple fall from standing height)?" (OST_5/ OST_BONE) and "What type of fracture(s)?" (OST_6/ OST_FRAC_COM). We derived the fall variable from the Falls (FAL) module in the maintaining contact questionnaire (MCQ version 2.7, FAL_1/ FAL_12MN_MCQ) where the participants were asked about any falls over the past 12 months, in which they hurt themselves enough to limit some of their normal activities.

5.3.2.5 Physical performance measures

The physical performance measures in CLSA included the following tests: hand grip strength, timed-up-and-go (TUG), chair rise and standing balance (22). Tests were performed according to the CLSA standard operating procedures (26-30).

The hand grip strength is a measure of isometric muscle strength in the upper extremity (31). Dominant hand grip strength was measured in the CLSA using the Tracker Freedom® Wireless Grip Dynamometer (26). The average of three measurements in kilogram (kg) was used in this study. A mean measurements of 32.3 kg (24.2 kg in women, 41.2 kg in men) have been seen in healthy Canadian aged 60 to 79 years (32). Since 7% of the participants had missing values for grip strength, we also created a categorical variable with quartiles of grip strength with a fifth category including the participants with missing values.

The TUG test was developed as a mean of measuring functional mobility and balance in the elderly (31) . The TUG test measured the time in seconds it took for the participants to rise from a standard armchair, walk to a line on the floor 3 metres away, turn around, return to the chair, and sit down

again (28). Therefore, a faster TUG score indicated a better performance. On average, healthy individuals between the ages of 60-80 years complete the TUG in 8-10 seconds (33).

The chair rise test measures lower limb strength and balance (31). Participants were asked to stand up and sit down from a standard chair as quickly as possible five times in a row, with arms folded across the chest (30). The time in seconds from the initial sitting position (prior to the first stand) to the final standing position (at the end of the fifth stand) was recorded. The age matched norms for chair rise test are 11.4 seconds and 14.8 seconds for 60-69 and 70-79 age groups, respectively (34).

The standing balance test measured an individual's static balance (31). An average of 53-55 second has been observed in healthy individuals aged 60 to 80 years (33). Participants were asked to position one meter from a wall, stand on one foot for as long as possible (60 seconds maximum) while first lifting the dominant leg to the calf level (29). This test was measured in seconds and was repeated in both legs. The best of the two scores was categorized as “good performance” i.e. 60 sec, and “poor performance” i.e. <60 sec in this study.

5.3.2.6 Other variables

Other explanatory variables were selected based on literature review and their availability in CLSA. Smoking was categorized as current smoker or non-smoker, and alcohol consumption in the past 12 months was divided in two categories (less than 3 servings /day or 3 or more servings/day). Other variables considered were level of education (holding or not at least a high school diploma), annual household income (above and below 100K), employment status (currently employed or not), marital status (living with a partner or not), and history of hip fracture in parents (yes, no). In women, use of hormone therapy (HT, ever vs never) and menopausal status were ascertained from the Women Health modules. The Life-Space Index (LSI) measured the functional

performance and functional status and ranged between 0 and 120, with a higher score reflecting a better functional status (35).

We combined comorbidities known to increase the risk for osteoporosis or fragility fractures and categorized them as no comorbidities, 1-3 comorbidities, or 4 or more comorbidities. These conditions included rheumatoid arthritis, osteoarthritis, neurological disease, dementia, stroke/CVA, epilepsy, cardiovascular disease, hypertension, cancer, asthma or COPD, chronic kidney disease, hyper or hypothyroidism, malabsorption syndromes, diabetes, and depression or anxiety.

The use of vitamin D and calcium supplements within the last month were obtained from In-Home Questionnaire (Version 4.0). Serum total 25-hydroxy vitamin D (25(OH)D) was measured using the Liaison (Diasorin Incorporated) assay and was reported in nmol/L. The detection limits for this chemiluminescent immunoassay technology were 10 nmol/L to 375 nmol/L.

We generated 10-year fracture risk probabilities for MOF and hip fractures using the femoral neck T score (NHANES III BMD of women 20-29 years old as per International Society for Clinical Densitometry [ISCD] recommendations) and clinical risk factors using the Canadian Fracture Risk Assessment Tool (FRAX®) (25).

5.3.3 Statistical methods

Descriptive statistics were generated using means and standard deviations (SD) or medians and interquartile ranges (IQR), and frequency and percentages as appropriate. Standard tests (chi-square, student t-test and analysis of variance) were used to compare categorical and continuous variables between province. Visual inspection of histograms and quantile-quantile plot (qqplot) showed that all continuous variables were normally distributed except FRAX scores (MOF and

hip). The FRAX scores were not log-transformed since they are used solely to classify the participants in those at risk of fracture or not (36). Pearson, spearman and chi-square tests were used to assess the strength of the relationship between variables.

All regression models were stratified by sex. Linear regression models were created to estimate the differences in total hip BMD between the provinces using Ontario as the province of reference. We first created unadjusted linear models looking at association of BMD values with province of residence. Multiple linear regression models were then fit with province, age and each covariable, among which grip strength was included as a categorical variable. The covariables meeting significance ($p<0.05$) were included in the fully adjusted models. Age, BMI, and height were included in the fully adjusted linear models regardless of significance. Finally, multiple linear regression models were used to estimate BMD explained by the province of residence after controlling for the potential confounding variables. Models including grip strength as continuous variable (i.e., excluding participants with missing values for grip strength), showed similar results, and therefore are not presented. Logistic regressions were used to examine the associations of the province of residence with MOF. Similar strategy as above was applied. We further adjusted the final model with femoral neck BMD.

We explored the stability of our results by conducting further sensitivity analyses using CLSA analytic weights (version 1.2), and data from participants reporting White ancestry only (91.8% of the cohort). All statistical analyses were performed using statistical R software (Version 1.2.5033© 2009-2019 RStudio, Inc). A 2-sided p-value of <0.05 was considered significant.

5.4 Results

5.4.1 Baseline characteristics

We identified 21,227 participants aged 50 years or more with available total hip BMD measurements at baseline (Figure 4.1), including 10,716 women and 10,511 men from the following seven Canadian provinces: BC (4,260), AB (2,163), MB (2,274), ON (4,684), QC (4,143), NS (2,178), and NL (1,525). Baseline characteristics of the participants stratified by the province of residence are shown in Table 4.1. The mean (standard deviation, SD) age of the participants was 63.9 (9.1) years and did not differ significantly between provinces. The participants in QC had the lowest mean height (165.7 cm [9.3]) and participants in BC had the highest mean height (169.8 cm [9.5]), while participants in BC and NL had respectively the lowest and highest mean BMI (BC: 27.4 kg/m^2 [5.0]; NL: 28.8 kg/m^2 [5.3]). The proportion of current smokers significantly varied between provinces and was highest in QC (10.2 %). Vitamin D supplement use was lowest in NL (42.8 %) and highest in AB (65.4 %). Although the level of 25(OH)D varied significantly between provinces, the mean 25(OH)D level in all provinces were above the sufficient level of 50 nmol/L. The proportion of participants having a FRAX MOF > 20 % was lowest in QC (3.3 %) and highest in MB (4.8 %) and the proportion of those who reported a fall in the previous 12 months varied by province from 8.4 % (MB) to 12.0 % (AB).

All measures of physical performance varied between provinces (Table 4.2), but the means for grip strength, TUG, chair rise and median for balance were within the normal range for healthy individuals. Mean (SD) grip strength varied from 33.6 kg (10.8) in MB to 35.9 kg (12.1) in NL. The proportion of participants with a value of 60 seconds for the balance test, i.e., the best score that could be obtained, varied from 30.7% (AB) to 50.9% (BC).

5.4.2 Osteoporosis, BMD, and prevalent fractures

The prevalence of osteoporosis and the mean total hip BMD (g/cm^2) by province of residence are presented in Figure 3.2. The prevalence of osteoporosis was 5.2 % in women and 0.9 % in men and did not differ significantly between provinces. Although not statistically significant, we found the highest prevalence of osteoporosis in MB women (6.6%) and NL men (1.3%) and the lowest in NS in both women (4.0%) and men (0.5%).

The mean total hip BMD significantly differed between provinces, and the lowest was noted in BC in both women and men. Unadjusted and fully adjusted estimates for total hip BMD by province of residence are presented in Table 4.3. Unadjusted estimates demonstrated that women from all provinces, except NL, had a lower total hip BMD than women from Ontario (reference) with statistically significant differences ranging from -0.012 g/cm^2 (MB, QC) to -0.023 g/cm^2 (BC). Adjusting for co-variables did not change the associations except for the province of QC where the estimate (95% confidence interval) for total hip BMD changed from -0.012 g/cm^2 (-0.020; -0.004) to -0.004 g/cm^2 (-0.010; 0.003). In men, unadjusted total hip BMD estimates for BC, AB and QC were lower than Ontario as opposed to men from NS who had total hip BMD higher than Ontario. Adjusted estimates remained similar in all provinces except for QC where the results changed from statistically significant to non-significant (-0.014 g/cm^2 [-0.022; -0.005] to 0.001 g/cm^2 [-0.007; 0.009]). While physical performance measures varied between provinces, adjusting for physical performance measures did not explain the observed geographical variations (Table 4.3).

The proportion of participants with prevalent MOF are presented in Figure 3.1. The differences between provinces were statistically significant in both sexes, with women and men from BC having the lowest proportion of prevalent MOF (4.1 % and 1.3 % respectively). Adjusted Odds

Ratios (CI: 95% confidence intervals) for prevalent MOF were significantly lower in women from BC (0.50 [0.37; 0.69]), and men from BC (0.35 [0.22; 0.57]) compared to that from Ontario (Table 4.4). Similar to the linear regression analyses, adjusting for physical performance measures did not explain the odds ratio variations between provinces. Analyses in the subgroup with self-reported White ancestry only or using CLSA sampling weights yielded similar results to those of the main analysis.

5.5 Discussion

Our findings support significant variations in sex-specific BMD and self-reported major osteoporotic fracture patterns across Canadian provinces in the population aged 50 years and older. Although a higher prevalence of osteoporosis (lower BMD) is typically associated with higher fracture rates (14, 15), we noted that women and men in BC not only had the lowest BMD estimates, but also the lowest odds of fracture. These results are consistent with findings from CaMos twenty years ago, in which, the regional variation in the prevalence of low BMD was not concordant with the regional variation in prevalent fracture in men or women (20). We were unable to further explain these regional variations by adding novel variables collected as part of the CLSA study into our models, such as physical function.

We noted the prevalence of osteoporosis in CLSA cohort (women: 5.2 %, men 0.9 %) was lower than previous reports in Canada. Osteoporosis in CaMos was defined by lumbar spine or femoral neck BMD T-score ≤ -2.5 in women and men 50 years and older, including participants above 85 years, which may account for the higher prevalence of osteoporosis of 18.8% and 6.2% in women and men, respectively (20). Due to the absence of lumbar BMD measurements in CLSA dataset, osteoporosis prevalence was defined using femoral neck BMD only, as is recommended by ISCD (37). According to the 2015-16 Public Health Agency of Canada (PHAC) report, the latest

prevalence of osteoporosis was 18.9 % in women and 4.4 % in men (3). PHAC used linked health administrative databases for men and women aged 40 years and older to determine the prevalence of osteoporosis and the incidence of fractures in Canadian over 15 years (2000–2001 to 2015–2016); in this report, the prevalence is essentially dependent on the reporting of osteoporosis by clinicians in medical records or billing claims. The methodology and age group considered in the PHAC report may contribute for the differences in the reported prevalence compared to our results. For total hip BMD, we observed in CLSA the lowest BMD in women (-0.023 g/cm^2) and men (-0.025 g/cm^2) from BC. In CaMos the lowest age-standardized means were in QC (men) and NS (women).

Studies have shown that the prevalence of fractures not only differs between countries, but within regions of countries (12, 18, 19). Dhanwal et al. found a north-south gradient pattern of fractures in the US and Europe (16), with northern regions having a higher rate of hip fractures. Additionally, they documented regional variations in vertebral fracture prevalence among Latin American countries; Brazil (1.7%), Argentina (14.5%), and Mexico (15.7%). In Canada, geographical variation in the prevalence of fractures was also documented in CaMos (20). While we were able to demonstrate the presence of geographical variation in the prevalence of fractures across the Canadian provinces, we found the CLSA pattern to be different and the magnitude of the prevalence of fracture to be lower than that from CaMos. In CLSA, we found that the lowest proportions of fracture were in BC women (4.1%) and men (1.3%), and the highest, in women from NS (8%) and men from MB (4.5%). As compared to the CaMos findings where the lowest prevalence of fractures were observed in QC women (5.8%) and men (3.4%) and the highest in women (13.5%) and men (7.3%) from Kingston (ON).

Owing to the availability of physical performance measures in the CLSA dataset (chair rise, grip strength, balance test, and TUG), we were able to investigate fracture risk by physical measures in this cohort. These measures have been shown to predict major osteoporotic fractures independently of traditional clinical risk factors and BMD (38). For example, one leg standing time <10 seconds has been shown to be associated with 76% increased risk of major osteoporotic fractures in older women after adjusting for age, height, and weight (39). TUG also can predict falls and other geriatric outcomes in older adults independently (40). While we established that each of these measures were associated with BMD estimates and fracture risk, adding the variables to our models did not further explained the observed geographical variations.

The causes for these variations are generally considered to be multifactorial and likely associated with a combination of risk factors including population specific characteristics, income, place of residence (urban vs rural), environmental factors, as well as healthcare services utilization (12, 15, 16, 41-43). Vitamin D deficiency with threshold level of below 50 nmol/L is associated with higher risks of fractures and bone loss, and have been reported to vary by age (lower levels in childhood and the elderly), ethnicity (lower in European Caucasians compared with non-Caucasians), and regions (44). Previously CaMos found the prevalence of vitamin D deficiency in adults aged 50-70 years to be 17.7% in women and 22.3% in men (45). We found the prevalence of vitamin D deficiency to be lower (10.6%) in 50-85 years in the CLSA comprehensive cohort. The lower prevalence of vitamin D deficiency probably reflects the higher proportion of people who take vitamin D supplement in CLSA, similar to CaMos findings in where the level of 25(OH)D increased over the 10-year follow-up of CaMos, due in part to an increase intake of vitamin D supplement (46). Adjusting for vitamin D level in our regression analysis, did not significantly affect the result.

Some studies justified in part these variations by differences in ethnicity of the study populations. Cauley et al. explained the higher BMD in men from Tobago compared to that from the US by difference in ethnicity admixture (15). A registry based cohort study of women aged 40 years or older from Manitoba, has documented that Asian and Black women have lower risk for MOF than other ethnicities (47). Canadians self-identified as Chinese and Whites in the CaMos Study differed on a number of important risk factors for osteoporosis and fractures including height, BMI, calcium intake, tea consumption, falls, and BMD (48). In CLSA, 92% of the cohort self-identified as White and the remainder reported various ethnic backgrounds (Black, Asian, South East Asian, etc.); our results were similar when we restricted the analysis to the subgroup of individuals of White ancestry only.

The main strengths of this study include the large sample size, the population sampling methods, and the comprehensiveness of the variables. Quality controls and cross-calibration of DXA machines, performed within and between centers using standard operating procedures, ensured comparability of BMD measurement within centers. In CLSA, the participants had to be able to communicate and give written consent in either French or English (30), which may have resulted in a cohort that under-represents people with lower levels of literacy in French or English or those with certain health conditions such as hearing problems (49). However, the CLSA cohort profile, including response rates, selected sociodemographic, lifestyle and health status characteristics, have been shown to be comparable with estimates from the Canadian Community Health Survey–Healthy Aging (CCHS-HA) and the Canadian census data (49). Also, the weighted prevalence estimates for chronic conditions were aligned with the nationally representative sources.

Although CLSA comprehensive cohort is a national sample of the Canadian population; it only represents Canadians living 25-50 km around large cities in 7 out of ten Canadian provinces and

the majority is comprised of individuals of White ethnic background. Because of the cross-sectional nature of our data, we were not able to evaluate the temporality of the risk factors and did not have data on incident fractures. Like any observational studies, selection bias is a potential limitation leading to possibility of residual confounding since there are a wide range of individual, social and environmental factors known to be determinants of musculoskeletal health that were not available in the dataset.

In conclusion, findings from this study support the existence of geographical variations in BMD and prevalent fractures between provinces. Although, physical performance measures (chair rise, grip strength, balance test, TUG) were strongly associated with BMD and fracture prevalence in the CLSA cohort, their addition to regression models did not explained the observed variations. Other unmeasured factors likely explain some of the observed geographical variations. Better understanding of geographical variations would be helpful in the optimization of osteoporosis management strategies.

5.6 Data availability statement

The datasets generated for this article were generated by the Canadian Longitudinal Study of Aging; researchers apply for data access by following the procedure outlined here: *www.clsa-elcv.ca*. Questions regarding access the datasets should be directed to *ac.vcle-aslc@ssecca*.

5.7 Ethics approval

This study was approved by the Research Institute of the McGill University Health Centre (RI-MUHC) Research Ethics Board (Ethics Certificate No. 2019-4926).

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The opinions expressed in this manuscript are the author's own and do not reflect the views of the Canadian Longitudinal Study on Aging.

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5.9 Authors' contributions

SNM conceived the study and secured funding for this study. NH and CB conducted the data analysis and drafted the initial manuscript supervised by SNM. AP, AMC, ER, WDL and DG helped with results interpretation, and gave critical feedback on the manuscript. All authors approved the final manuscript.

5.10 Conflicts of interest

Authors report no conflict of interest.

5.11 Tables

Table 5.1. Baseline characteristics by province of residence

	BC (n=4,260)	AB (n=2,163)	MB (n=2,274)	ON (n=4,684)	QC (n=4,143)	NS (n=2,178)	NL (n=1,525)	Total (n=21,227)	P-value*
Age (years) – Mean (SD)	64.(9.3)	63.8 (9.1)	64.0 (9.1)	64.1 (9.2)	63.7 (8.9)	64.1 (8.8)	63.7 (8.9)	63.9 (9.1)	0.218
Sex (Women) – N (%)	2174 (51.0)	1069 (49.4)	1159 (51.0)	2331 (49.8)	2144 (51.7)	1079 (49.5)	760 (49.8)	10716 (50.5)	0.384
Height (cm) – Mean (SD)	169.8 (9.5)	169.6 (9.6)	168.1 (9.4)	168.8 (9.6)	165.7 (9.3)	168.3(10.0)	168.1 (9.0)	168.2 (9.6)	<0.001
Body mass index (kg/m^2) – Mean (SD)	27.4 (5.0)	28.1 (5.4)	28.7 (5.9)	28.1 (5.2)	27.7 (5.1)	28.6 (5.3)	28.8 (5.3)	28.1 (5.3)	<0.001
Smoking (Current smoker) – N (%)	265 (6.2)	159 (7.4)	184 (8.1)	370 (7.9)	421 (10.2)	159 (7.3)	125 (8.2)	1683 (7.9)	<0.001
Alcohol (3 or more drinks/day) – N (%)	307 (7.2)	97 (4.5)	105 (4.6)	307 (6.6)	289 (7.0)	133 (6.1)	58 (3.8)	1296 (6.1)	<0.001
Education (Post-secondary degree/ Diploma) – N (%)	3407 (80.0)	1762 (81.5)	1711 (75.2)	3553 (75.9)	3077 (74.3)	1709 (78.5)	1293 (84.8)	16512 (77.8)	<0.001
Employment (Currently employed) – N (%)	1616 (37.9)	837 (38.7)	874 (38.4)	1736 (37.1)	1404 (33.9)	785 (36.0)	547 (35.9)	7799 (36.7)	<0.001
Number of comorbidities – N (%)									0.004
No comorbidities	863 (20.3)	414 (19.1)	433 (19.0)	878 (18.7)	862 (20.8)	367 (16.9)	297 (19.5)	4114 (19.4)	
1-3 comorbidities	2697 (63.3)	1377 (63.7)	1508 (66.3)	3078 (65.7)	2632 (63.5)	1382 (63.5)	976 (64.0)	13650 (64.3)	
4+ comorbidities	445 (10.4)	221 (10.2)	236 (10.4)	480 (10.2)	343 (8.3)	186 (8.5)	145 (9.5)	2056 (9.7)	
History of hip fracture in parents – N (%)	572 (13.4)	295 (13.6)	352 (15.5)	646 (13.8)	502 (12.1)	295 (13.5)	218 (14.3)	2880 (13.6)	0.010
Corticosteroid use (3 months or more) – N (%)	251 (5.9)	100 (4.6)	103 (4.5)	232 (5.0)	164 (4.0)	99 (4.5)	76 (5.0)	1025 (4.8)	0.007
Calcium supplement (past month) – N (%)	1346 (31.6)	776 (35.9)	553 (24.3)	1257 (26.8)	1528 (36.9)	455 (20.9)	349 (22.9)	6264 (29.5)	<0.001

Vitamin D supplement (past month) – N (%)	2097 (49.2)	1415 (65.4)	1041 (45.8)	2509 (53.6)	1919 (46.3)	994 (45.6)	652 (42.8)	10627 (50.1)	<0.001
25(OH)D (nmol/L) – Mean (SD)	90.8 (36.9)	102.0 (44.0)	87.6 (36.7)	94.7 (37.2)	85.8 (34.1)	89.5 (34.5)	86.0 (32.7)	91.0 (37.0)	<0.001
FRAX score (MOF) – Mean (SD)	7.6 (5.7)	7.7 (5.7)	7.9 (6.3)	7.9 (5.7)	7.7 (5.3)	7.4 (5.4)	7.6 (5.4)	7.7 (5.6)	0.004
FRAX score (hip) – Mean (SD)	1.5 (3.0)	1.4 (3.1)	1.6 (3.7)	1.5 (2.9)	1.4 (2.7)	1.3 (2.6)	1.4 (2.3)	1.5 (2.9)	0.002
Falls (past 12 months) – N (%)	427 (10.0)	259 (12.0)	192 (8.4)	472 (10.1)	471 (11.4)	219 (10.1)	141 (9.2)	2181 (10.3)	0.002

BC=British Columbia; AB=Alberta; MB=Manitoba; ON=Ontario; QC=Quebec; NS=Nova Scotia; NL= Newfoundland and Labrador.
Number of missing values for: body mass index=12, smoking=1, alcohol=8, education=34, employment=209, comorbidities=1,407, 25(OH)D=1,862, history of hip fracture in parents=785, falls=253, corticosteroid use=599, calcium supplement=276, vitamin D supplement=278.
Non-weighted results.
* ANOVA and Chi-squared test

Table 5.2. Physical performance by province of residence

	BC (n=4260)	AB (n=2163)	MB (n=2274)	ON (n=4684)	QC (n=4143)	NS (n=2178)	NL (n=1525)	Overall (n=21227)	P-value*
Grip strength (max-kg) – Mean (SD)	35.5 (11.7)	35.3 (11.6)	33.6 (10.8)	35.4 (12.0)	35.1 (11.4)	34.8 (11.8)	35.9 (12.1)	35.1 (11.6)	<0.001
Timed-up-and-go (sec) – Mean (SD)	9.6 (2.4)	9.5 (2.0)	9.7 (2.2)	9.5 (2.2)	9.5 (1.9)	8.8 (2.0)	9.8 (2.0)	9.5 (2.1)	<0.001
5 Chair rises (sec) – Mean (SD)	13.3 (3.6)	11.9 (3.2)	13.8 (3.8)	13.4 (3.5)	13.7 (3.9)	12.3 (3.3)	15.4 (3.4)	13.4 (3.7)	<0.001
Balance test (Good performance) – N (%)	2168 (50.9)	665 (30.7)	801 (35.2)	1491 (31.8)	1586 (38.3)	684 (31.4)	666 (43.7)	8061 (38.0)	<0.001

BC=British Columbia; AB=Alberta; MB=Manitoba; ON=Ontario; QC=Quebec; NS=Nova Scotia; NL= Newfoundland and Labrador.
Number of missing values for: grip strength=1,483, timed-up-and-go=80, chair rise=563, balance test=728.
Non-weighted results.
* ANOVA and Chi-squared test

Table 5.3. Unadjusted and adjusted estimates (95% confidence intervals) for total hip bone mineral density (BMD, g/cm^2) by province of residence

Estimates g/cm^2 (95% CI)	Women N=9,319			Men N= 8,905		
	Unadjusted	*Adjusted Model 1	**Adjusted Model 2	Unadjusted	***Adjusted Model 1	****Adjusted Model 2
BC	**-0.023 (-0.031, -0.016)**	**-0.021 (-0.028, -0.015)**	**-0.022 (-0.029, -0.016)**	**-0.025 (-0.034, -0.017)**	**-0.018 (-0.026, -0.011)**	**-0.020 (-0.028, -0.012)**
AB	**-0.018 (-0.027, -0.008)**	**-0.017 (-0.025, -0.009)**	**-0.018 (-0.026, -0.010)**	**-0.022 (-0.032, -0.012)**	**-0.022 (-0.031, -0.012)**	**-0.023 (-0.032, -0.013)**
MB	**-0.012 (-0.021, -0.002)**	**-0.014 (-0.022, -0.007)**	**-0.014 (-0.022, -0.006)**	0.001 (-0.009, 0.012)	0.002 (-0.007, 0.012)	0.003 (-0.006, 0.012)
QC	**-0.012 (-0.020, -0.004)**	-0.003 (-0.009, 0.004)	-0.004 (-0.010, 0.003)	**-0.014 (-0.022, -0.005)**	0.003 (-0.005, 0.010)	0.001 (-0.007, 0.009)
NS	**-0.013 (-0.023, -0.004)**	**-0.012 (-0.020, -0.004)**	**-0.013 (-0.021, -0.005)**	**0.013 (0.003, 0.024)**	**0.013 (0.003, 0.023)**	**0.010 (0.001, 0.020)**
NL	0.003 (-0.007, 0.014)	-0.003 (-0.012, 0.006)	-0.001 (-0.011, 0.008)	0.011 (-0.000, 0.023)	0.006 (-0.004, 0.016)	0.006 (-0.004, 0.017)
ON	Reference					

BC=British Columbia; AB=Alberta; MB=Manitoba; ON=Ontario; QC=Quebec; NS=Nova Scotia; NL= Newfoundland and Labrador.
Non-weighted results
* adjusted for age, height, body mass index (BMI), smoking, life space index, comorbidities, education, hormone replacement therapy (HRT)
** adjusted for age, height, body mass index (BMI), smoking, life space index, comorbidities, education, hormone replacement therapy (HRT) AND physical performance measures (TUG, chair rise, balance, and hand grip strength)
*** adjusted for age, height, body mass index (BMI), smoking, life space index, comorbidities, marital status, level of income, vision
**** adjusted for age, height, body mass index (BMI), smoking, life space index, comorbidities, marital status, level of income, vision, AND physical performance measures (TUG, chair rise, balance, and hand grip strength)
In bold: statistically significant estimates (P-value $\leq$ 0.05)

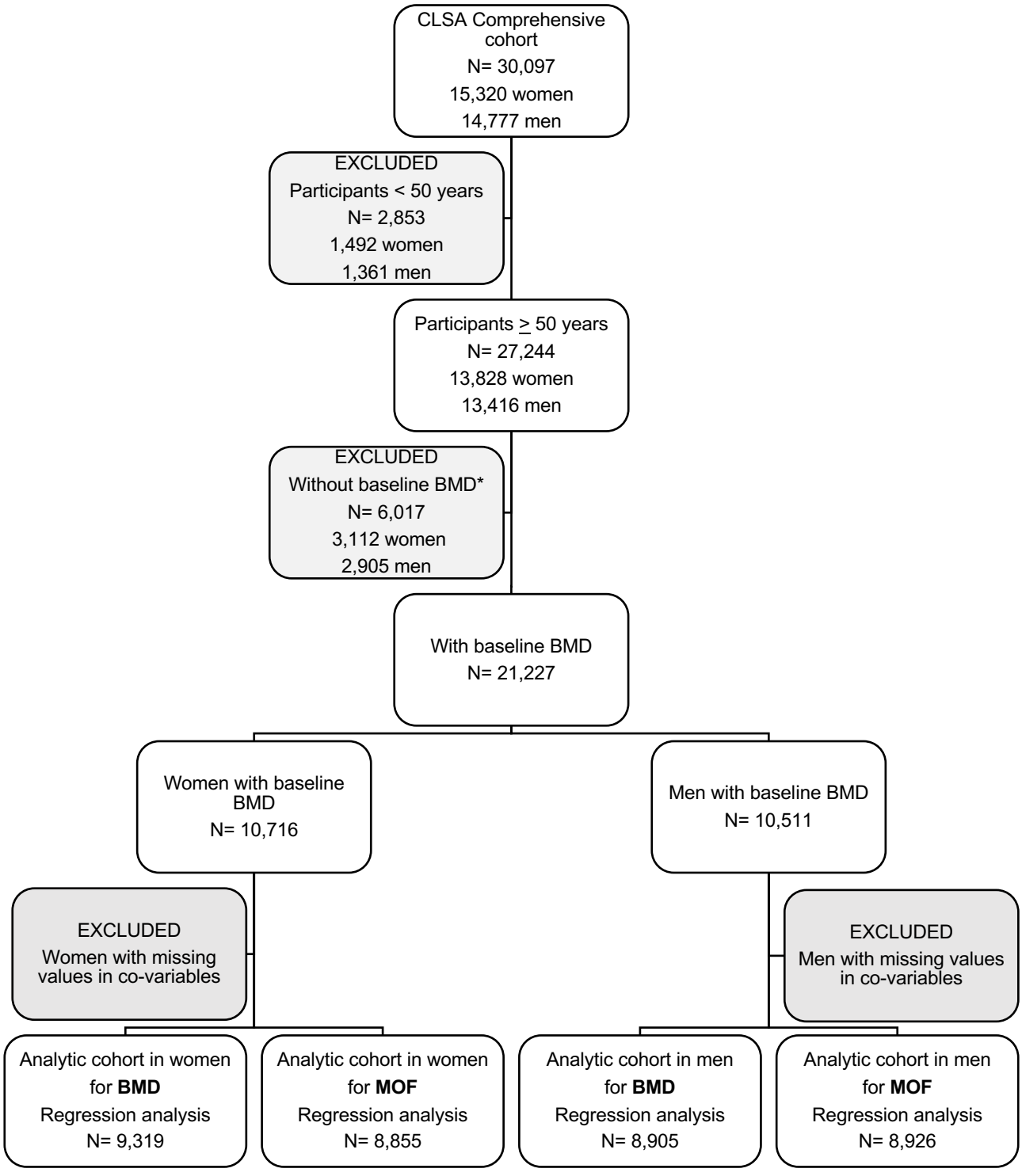
Table 5.4. Unadjusted and adjusted odds ratio (OR) with 95% confidence intervals for prevalent MOF by province of residence in women and men

OR (95% CI)	Women N=8,855			Men N=8,926		
	Unadjusted	*Adjusted Model 1	**Adjusted Model 2	Unadjusted	***Adjusted Model 1	****Adjusted Model 2
BC	**0.51 (0.38, 0.69)**	**0.53 (0.40, 0.72)**	**0.50 (0.37, 0.69)**	**0.34 (0.21, 0.54)**	**0.34 (0.21, 0.55)**	**0.35 (0.22, 0.57)**
AB	0.77 (0.55, 1.08)	0.72 (0.50, 1.02)	0.71 (0.50, 1.02)	0.71 (0.45, 1.14)	0.71 (0.45, 1.14)	0.71 (0.43, 1.16)
MB	1.03 (0.77, 1.39)	1.18 (0.87, 1.62)	1.19 (0.87, 1.62)	1.19 (0.81, 1.76)	1.26 (0.85, 1.88)	1.29 (0.86, 1.93)
QC	**0.72 (0.55, 0.95)**	0.77 (0.58, 1.03)	0.77 (0.58, 1.03)	0.79 (0.55, 1.13)	0.80 (0.55, 1.16)	0.76 (0.51, 1.12)
NS	1.09 (0.80, 1.49)	1.31 (0.95, 1.80)	1.32 (0.95, 1.83)	**0.41 (0.23, 0.73)**	**0.51 (0.28, 0.91)**	0.59 (0.33, 1.07)
NL	0.92 (0.64, 1.33)	0.95 (0.65, 1.38)	0.96 (0.65, 1.40)	0.73 (0.43, 1.22)	0.74 (0.44, 1.25)	0.76 (0.44, 1.30)
ON	Reference					

BC=British Columbia; AB=Alberta; MB=Manitoba; ON=Ontario; QC=Quebec; NS=Nova Scotia; NL= Newfoundland and Labrador.
Non-weighted results
* adjusted for age, height, body mass index (BMI), comorbidities, femoral neck BMD, history of calcium usage in previous month, life space index, history of corticosteroid use, history of hip fractures in parents, number of falls in the past 12 months, and osteoporosis diagnosis
** adjusted for age, height, body mass index (BMI), comorbidities, femoral neck BMD, history of calcium usage in previous month, life space index, history of corticosteroid use, history of hip fractures in parents, number of falls in the past 12 months, and osteoporosis diagnosis AND physical performance measures (TUG, chair rise, and balance)
*** adjusted for age, height, body mass index (BMI), comorbidities, femoral neck BMD, history of calcium usage in previous month, level of income, and osteoporosis diagnosis
**** adjusted for age, height, body mass index (BMI), comorbidities, femoral neck BMD, history of calcium usage in previous month, level of income, and osteoporosis diagnosis AND physical performance measures (TUG, chair rise, and balance)
In bold: statistically significant odds ratios (P-value ≤ 0.05)

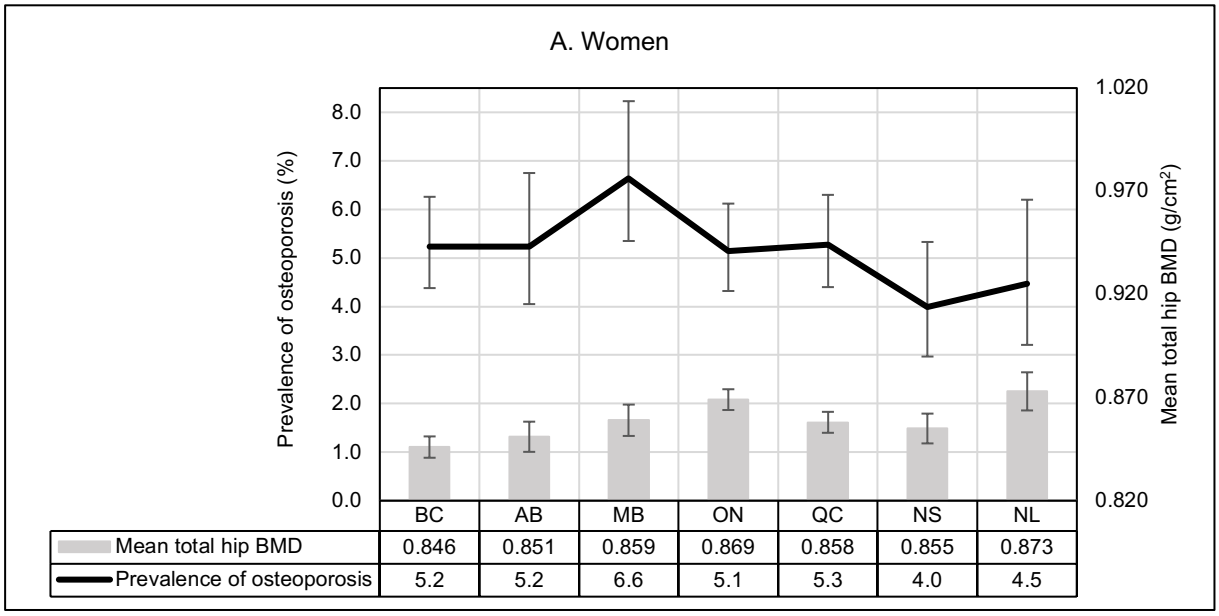
5.12 Figures

Figure 5.1. Flowchart of the participants



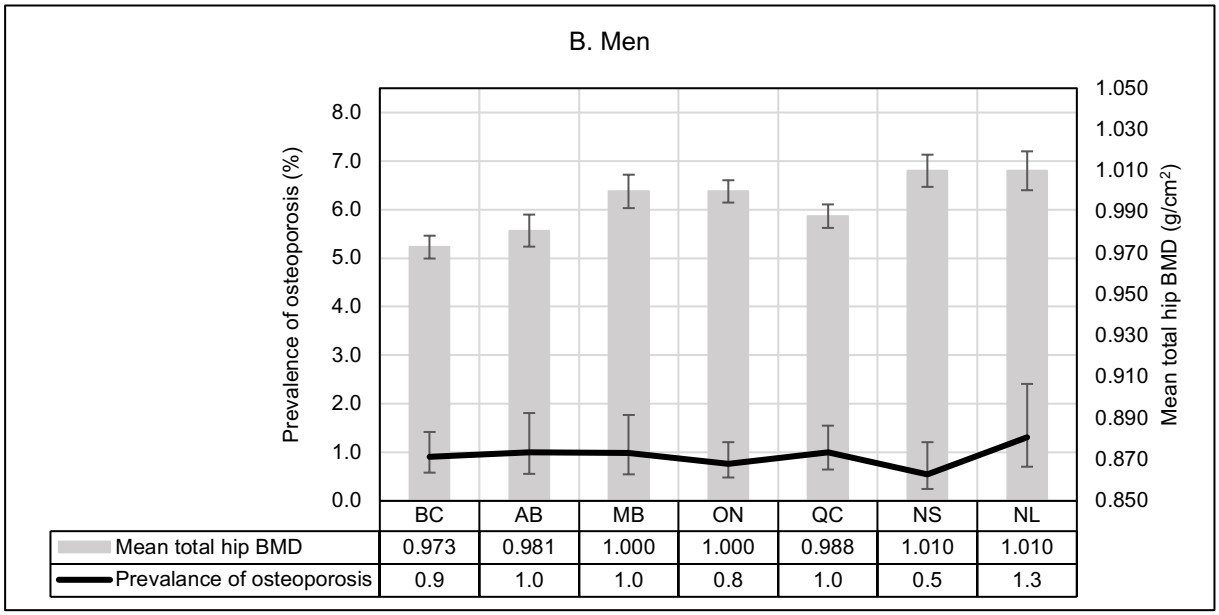
* BMD at total hip

Figure 5.2. Proportion of osteoporosis (Femoral neck T-score ≤ -2.5) and mean total hip bone mineral density (BMD, g/cm^2) in women and men



	BC	AB	MB	ON	QC	NS	NL
Mean total hip BMD	0.846	0.851	0.859	0.869	0.858	0.855	0.873
Prevalence of osteoporosis	5.2	5.2	6.6	5.1	5.3	4.0	4.5

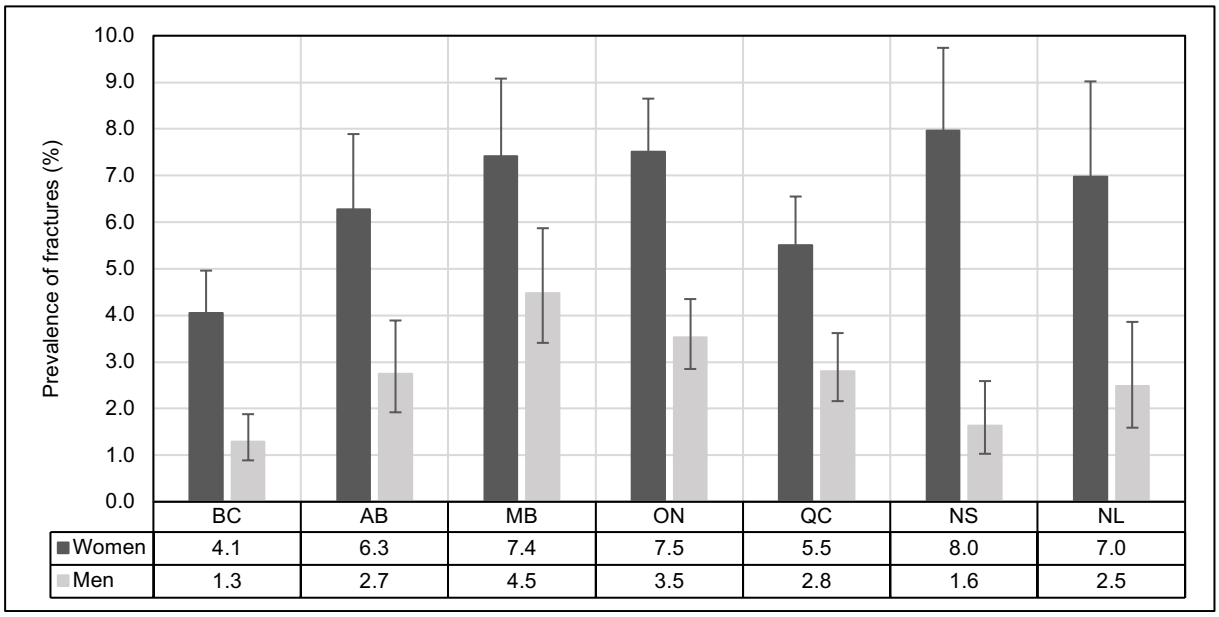
BC=British Columbia; AB=Alberta; MB=Manitoba; ON=Ontario; QC=Quebec; NS=Nova Scotia; NL= Newfoundland and Labrador.
Comparison of prevalence of osteoporosis between provinces: P Value ≥ 0.05 in Chi-squared test
Comparison of mean total hip BMD between provinces: P Value < 0.05 in ANOVA
Non-weighted.



	BC	AB	MB	ON	QC	NS	NL
Mean total hip BMD	0.973	0.981	1.000	1.000	0.988	1.010	1.010
Prevalance of osteoporosis	0.9	1.0	1.0	0.8	1.0	0.5	1.3

BC=British Columbia; AB=Alberta; MB=Manitoba; ON=Ontario; QC=Quebec; NS=Nova Scotia; NL= Newfoundland and Labrador.
Comparison of prevalence of osteoporosis between provinces: P Value ≥ 0.05 in Chi-squared test
Comparison of mean total hip BMD between provinces: P Value < 0.05 in ANOVA
Non-weighted.

Figure 5.3. Proportion of major osteoporotic fractures (MOF) in women and men



	BC	AB	MB	ON	QC	NS	NL
Women	4.1	6.3	7.4	7.5	5.5	8.0	7.0
Men	1.3	2.7	4.5	3.5	2.8	1.6	2.5

BC=British Columbia; AB=Alberta; MB=Manitoba; ON=Ontario; QC=Quebec; NS=Nova Scotia; NL= Newfoundland and Labrador.
Differences between provinces were statistically significant in both women and men (P-value $\leq$ 0.05 in Chi-squared test)
Non-weighted.

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CHAPTER 6
DISCUSSION

6.1 General discussion

As the population is aging, more Canadians will be living with chronic age-associated diseases such as osteoporosis (2, 31, 120), bringing a substantial burden to healthcare systems, individuals, and society (36, 43). Over the past decades, overtime change and geographical variations in osteoporosis and osteoporotic fracture rates have been documented in many countries (40, 121, 122). In this thesis, we first assessed the changes in BMD, fractures rates, and anti-osteoporosis treatment use in Canada over the past two decades. We then explored the patterns in osteoporosis, BMD, and fracture rates between Canadian provinces. Our results identified a higher mean BMD and lower fracture rates in the more recent cohort, consistent with improved musculoskeletal health in older Canadians over time. We also demonstrated significant variations in sex-specific BMD and self-reported major osteoporotic fracture across Canadian provinces, with BC having both the lowest mean BMD and the lowest fracture rates. Although our results may be limited by selection bias and unmeasured individual, social and environmental factors, they are in keeping with similar findings documented in other countries.

The limitations of the projects were thoroughly discussed in the corresponding manuscripts. The first issue was the generalizability of our results. Both cohorts' participants represent Canadians living around large cities and of predominantly White ethnic background. To control for the possible effect of ethnicity/race on our outcomes of bone mineral density and fractures rates, we conducted a sensitivity analysis keeping only data from participants of White ancestry; results remained unchanged. We also confirmed that the cohorts' profiles, including response rates, selected sociodemographic, lifestyle and health status characteristics, were shown to be comparable with estimates from other nationally representative sources (123); we believe our results are overall representative of the Canadian elder population.

We also considered selection and healthy participants biases because: firstly, the difference in the design and objectives of cohorts studies would have affected the participants' interest in participating in the studies and baseline characteristics and our results consequently; secondly, due to a wide range of individuals, social and environmental factors known to be determinants of musculoskeletal health but not measured in the datasets, our results were subject to the possibility of residual confounding. To compensate for the possible differences in sampling strategy between both cohorts, we presented the prevalence by sex and age groups. Also, it has been shown that the weighted prevalence estimates for chronic conditions were aligned with the nationally representative sources.

Finally, because of the cross-sectional nature of our data, we were not able to evaluate the temporality of the risk factors and did not have data on incident fractures. As follow up data for the CLSA become available, further analyses documenting fracture rates over time will be performed.

Despite the development of very efficient osteoporosis management strategies, guidelines, and services in recent years, we documented that the osteoporosis treatment gap in individuals at high-risk for fractures has remained elevated. The reasons for this gap include lack of identification by clinicians of patients at high-risk for fractures, underestimation of fracture risk by both clinicians and patients, concerns about adverse effects and costs of medication, uncertainty about the duration of therapy, insufficient knowledge of the disease and its management. More specifically, concerns about harms associated with long term bisphosphonate use have led to cessation or lack of initiation of effective therapies. As the rate of osteoporosis and fractures differ across countries, also do access to healthcare, BMD testing, use of anti-osteoporosis medication, socioeconomic status and patient values.

6.2 Future work and perspectives

The first step toward optimized osteoporosis care and reducing the burden of osteoporosis is to have a comprehensive understanding of the disease pathophysiology and epidemiology. The following steps should focus on exploring the barriers in osteoporosis management and improving identifying high-risk individuals. Initiatives concentrating on research-focused solutions, and clinical and research expertise with the lived experience of the patient voice, are needed to help policy makers create adaptable practices in all provinces (124). All elements of the future initiatives should function synergistically and be guided by clinicians, scientists, and patient advocates, and supported by governance. Future works should also focus on gaining more understanding of the osteoporosis risk factors, underlying causes, variations, medication accessibility, and region-specific factors. This understanding would navigate the health care delivery to be better tailored to each province's needs, and aligned with province resources. The fact that the osteoporosis treatment gap has remained high, means that only small proportions of high-risk individuals are identified and treated.

While efforts should be put into increasing adherence to treatment guidelines and osteoporosis management strategies, there is also a need for improvement in the current risk assessment tools and the development of newer tools. Earlier detection of an individual at high risk for developing osteoporosis or early intervention has been shown to be associated with less morbidity and mortality (125, 126). Many novel tools have been designed and introduced during the past few years which focus on either individual genetic factors such as polygenic risk scores (127), or advanced technologies such as artificial intelligence (128). Polygenic risk scores aggregate many small effects of alleles across the human genome to estimate the risk of a disease (127), such as osteoporosis. Indeed, most of the genetic risk of osteoporosis is imparted by common genetic

variants, each of which has a small effect, but taken together, explains five-fold more variance in bone density in the population than non-genetic clinical risk factors. Furthermore, combining high level imaging technologies with these novel risk factors and using artificial intelligence to discover unidentified risk factors using large datasets could increase the sensitivity and specificity of the assessment tools.

As new advances in the field of artificial intelligence, machine learning models have shown promising capacity in osteoporosis diagnosis or fracture detection. Fracture risk prediction tools and risk factor identification are additional promising lines of research. These innovations in a field where human capacity and judgment play an important role are impressive while the standardized protocol is still under development. Future work should focus on finding the domains in which artificial intelligence may assist the care, whether prevention, diagnosis or management of osteoporosis and fracture.

Despite the emphasis that should be put on increasing knowledge and evidence-based practice, the application of knowledge has remained a key issue. Collaborative models of health research like integrated approaches (e.g. integrated knowledge translation, IKT) and patient and public engagement have been suggested as possible strategies to improve the relevance, impact, and efficiency of research (129). These strategies have been created due to a failure to address ongoing variations in practice, and to develop effective and efficient evidence-based healthcare services. The patient engagement could be both in IKT and health research. The IKT adopts meaningful collaborative connections in the team including researchers and knowledge users. The main goal is to find solutions for the key logistical and translational barriers imposing the care gap, to deliver care based on contextual, cultural, and social realities, and to get acceptable outcomes both for the healthcare (those delivering the care) and patients (those receiving the care). However, the

evidence for the effectiveness of these models is limited, future works should evaluate the practicality of these models.

Finally, our results support the importance of characterizing bone health predictors in populations of different backgrounds to tailor the development of population-specific fracture prevention strategies. Increasing awareness of osteoporosis and its consequences depends on effective communication between patients and all professionals involved in their care, which could be possible through increased public awareness and engagement.

6.3 Conclusion

We documented changes in BMD and fracture rates among Canadians over the last two decades and the existence of geographical differences in these parameters. Our study provides evidence of the ongoing care gap in individuals at high-risk for fractures. A greater understanding of underlying causes and increasing awareness of how bone health parameters vary across the country will help to plan the most effective strategies for effective healthcare delivery for the prevention and treatment of osteoporosis.

CHAPTER 7
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