Bone health in adults with epilepsy

by

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Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

The systematic review on the effect of vitamin D on bone health in adults epilepsy was co-authored by Dr. Heba Tallah Mohammed; she contributed to the choice of quality assessment scales, the quality assessment of the included studies as well as edits in the body of the text. The text for the systematic review has also been copy-edited by Joe Petrick for clarity and comprehension. Chao Dong Hu and Maheen Farooqi contributed as second reviewers in the study selection process.

The thesis as a whole has received edits from Dr. Tejal Patel.

Abstract

Epilepsy has been associated with an increased fracture risk by various studies in the literature. This is attributed to the decreased bone mineral density (BMD) linked to the anti-epileptic drugs (AEDs) that are used to control seizures. As increasing age is also associated with decreasing BMD, older adults with epilepsy are at particular risk for fracture. There is no consensus on managing this risk and many epilepsy care guidelines do not address the risk at all. This is understandable considering the lack of adequate research on counteractive measures in this specific population. Moreover, though a prevailing theory explains the observed decreased BMD to be a result of AEDs reducing active vitamin D levels, the efficacy of vitamin D supplementation as a protective measure does not have robust evidence nor is there an agreed upon treatment regimen. The proposed project will aim to fill the gaps in the research and establish groundwork for future research on prevention and treatment by: examining the existing literature on vitamin D supplementation for bone health in adults with epilepsy; investigating the prevalence of osteoprotective behaviours and their impact on fracture occurrence in older Canadian adults with and without epilepsy; and determining the prevalence of vitamin D supplementation in the older adult Canadian epileptic population.

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List of Abbreviations

25-OHD	25-hydroxycholecalciferol
Ad-SOS	Amplitude-dependent speed of sound ultrasound
AEDs	Anti-Epileptic Drugs
ALP	Alkaline Phosphatase
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BRFSS	Behavioral Risk Factor Surveillance System
CCHS	Canadian Community Health Survey
CFI	Canadian Foundation for Innovation
CIHR	Canadian Institute for Health Research
CRDCN	Canadian Research Data Centre Network
DXA	Dual-energy X-ray absorptiometry
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Care Excellence
NPHS	National Population Health Survey
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PTH	Parathyroid hormone
PWE	People with epilepsy
SIGN	Scottish Intercollegiate Guidelines Network
SPA	Single Photon Absorptiometry
SSHRC	Social Sciences and Humanities Research Council
WHO	World Health Organization

1. Introduction

1.1 Epilepsy and Epilepsy-related Injuries

Epilepsy is one of the most common neurological diseases in the world, affecting approximately 50 million people globally: between 4 to 10 per 1000 people[1]. Each year, an estimated 2.4 million people are diagnosed with epilepsy; infants and the elderly are at particular risk[1,2]. Idiopathic epilepsy, that is epilepsy with no clear underlying cause, accounts for 60% of all diagnosed epilepsy, therefore a decline in the incidence rate is unlikely until both all etiologies and their respective preventive measures are established[1]. Although Canadian estimates are not available, the overall economic impact associated with epilepsy in Europe was calculated to be €15.5 billion in the year 2004[3]. In the United States new cases of epilepsy are associated with $362 million in costs for the first year of treatment and nearly $2 billion annually for existing cases[4]; according to 2015 estimates, Canada's population is approximately 10% of the United States' population and so the estimated Canadian cost could be in the tens of millions of dollars, a considerable amount [5,6].

One contributor to the costs associated with epilepsy is injury resulting from falls caused by seizures. People living with epilepsy have a 2–6 times greater risk of fracture; hip fractures notably are 2–3 times higher in both men and women with epilepsy[7]. According to a meta-analysis of 3 case-control, 1 cross-sectional and 8 cohort studies, the relative risk of fracture in individuals with epilepsy is 2.2 times that of those without. Of importance is the fact that while 35% of the documented fractures were seizure related,

the remainder were due to other factors, particularly a significant decrease in bone mineral density (BMD) in patients with epilepsy[8]. Low BMD scores correlate with more fragile bones and, therefore, to fractures upon impact after a fall. One way to reduce the risk of injury by seizure-related falls is to minimize the occurrence of seizures.

Although surgery is a treatment option in patients with epilepsy, it is typically only recommended to patients who do not respond to pharmacotherapy[9]. Even then approximately one third of patients with refractory epilepsy would not be eligible candidates[10] as other factors like age, type of seizures and comorbidities are also taken into consideration[11]. Currently, there is no cure for epilepsy, only treatment. Anti-epileptic drugs (AEDs) are fairly successful in fulfilling this purpose and are able to control seizures in up to 70% of patients[2]. Moreover, a review by Schmidt and Loscher found that two thirds of patients continued to use AEDs even after epileptic surgery[12] and a cohort study of 615 individuals post-epileptic surgery found that of 365 that were "seizure-free", only 28% were no longer taking AEDs[13]. AEDs are integral to the treatment of epilepsy. Unfortunately, AEDs are associated with reductions of BMD.

1.2 Anti-Epileptic Drugs and Bone Health

It is estimated that 20–65% of patients using AEDs develop osteopenia[7]. Both osteopenia and osteoporosis are defined by decreased bone density in comparison to healthy controls. According to the World Health Organization (WHO), osteopenia is characterized by a BMD that is 1–2.5 standard deviations below that of a sex and race-matched healthy 30 year old whereas osteoporosis is more severe with a BMD of 2.5 or more standard deviations lower[14]. Using Dual-energy X-ray absorptiometry (DXA)

measurements, which measures total bone mineral content of most trabecular bone including spine and ribs and can accurately detect a 5% change, 38–60% of 143 patients aged 18–89 treated with AEDs in tertiary epilepsy clinics would be classified as having osteopenia or osteoporosis[15–19].

This observed decrease in BMD in patients with epilepsy can be attributed to a number of factors outside of AEDs, several of which are associated with institutionalization: poor diet, lack of exercise and lack of sun exposure. However, after controlling for confounding factors a decline in BMD associated with AED use still exists[16]. Within a meta-analysis of 94 cohort and 72 case control studies investigating 80 risk factors for fracture among adults, an analysis of 3 case-control and 2 prospective cohort studies of participants taking AEDs indicated that among participants aged 35 years and older AED use was associated with an increased fracture risk of 2.64 relative to those not on AEDs[20]. Overall meta-analysis of all studies indicated that AED use was consistently high risk for fractures related to bone mass loss whether the data was analyzed by study design and quality, age and sex of participants, fracture site or other study characteristics[20]. Longer use of AEDs appears to correlate with increasing risk of fracture: 12 or more years on AEDs results in a 4.15 relative risk of fracture compared to the 1.09 relative risk for less than 2 years of use; each year was associated with a 9% increase in relative risk according to an 8 year case control study of 40,485 patients with epilepsy with a median age of 39.1 years[21]. In a population-based pharmacoepidemiological case-controlled study of 124,655 patients with an average age of 43.44 years who had sustained a fracture in the year 2000, when data was unadjusted all AED use was associated with an increased fracture risk[22]. After controlling for confounding variables, such as prior facture or comorbidity with other

conditions, carbamazepine, oxcarbazepine, clonazepam, phenobarbital were still significantly associated with any fracture; fracture risk associated with use of the remaining AEDs was in the same range, however due to low statistical power (e.g. 22 cases on ethosuximide compared to 1,804 on carbamazepine) they were not considered statistically significant[22]. Moreover, fracture risk at any location was found to be significantly higher when the AEDs in question were enzyme-inducing [22].

1.3 Bone Loss: Overview

Bone remodeling is the ongoing process of bone formation and resorption. Osteoblasts are responsible for the formation of bone while osteoclasts are responsible for resorption[23]. There is a balance between these opposing activities that is carefully regulated by several factors, including, calcium, vitamin D and PTH. Bone loss occurs when there is an imbalance in this process resulting in more bone resorption than formation and thus net bone loss.

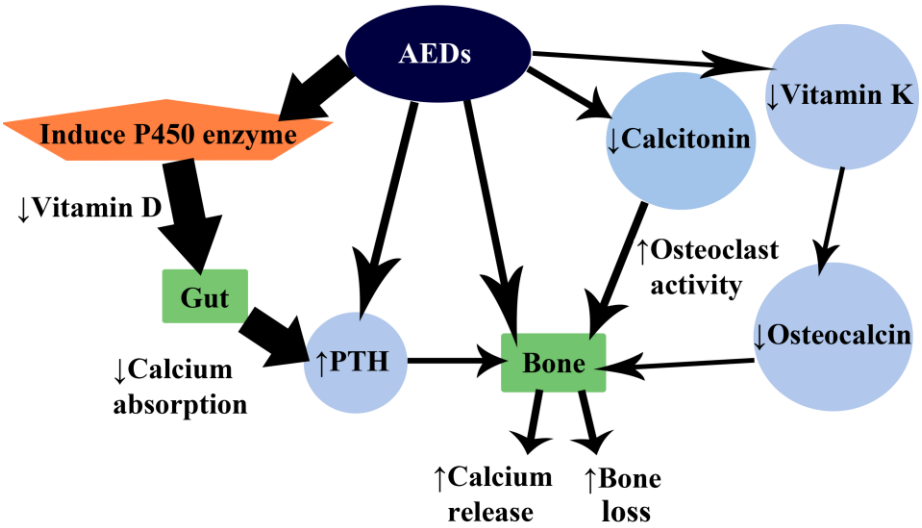
Calcium accounts for 1–2% of body weight and 99% of it is mineralized in tissue, particularly bone and teeth where it provides rigidity and structure. Circulating blood holds some of the remaining 1% of total body calcium. The plasma concentration of calcium is under strict homeostasis. Hypocalcemia would lead to increased release of calcium from bones to regain balance, therefore resulting in bone loss[24]. Parathyroid hormone (PTH) is one of the controlling factors of calcium homeostasis. Continuously enhanced levels of PTH increase the release of calcium from bones and, again, result in bone loss[25,26]. Hypophosphatemiahinders formation of the sites where new bone is made post-puberty[27].

Low serum calcium and phosphate are also partly responsible for osteomalacia: softening of the bone that, too, is characterized by low BMD and that facilitates fracture after injury[28,29]. In a study of 1105 women aged 43–80 years in which 99% of participants were post-menopausal, increased bone turnover was associated with rapid bone loss; high bone turnover is also thought to be associated with increased fracture risk independent of BMD[30].

1.4 Bone Loss: Proposed AED Mechanisms

The mechanism by which AED use leads to a decline in bone health is not straightforward (see Figure 1). AEDs are associated with several bone metabolism abnormalities including hypocalcemia, hyperparathyroidism, hypophosphatemia and increased bone turnover[15].

Figure 1. Mechanisms of anti-epileptic drugs (AEDs) acting on bone



PTH = parathyroid hormone**,** heavier weight arrows represent prevalent AED induction pathway

Other identified mechanisms that vary by drug are direct action on bone and interference with vitamin K metabolism, which promotes calcium integration into bone[25,31]. Of particular concern is enhanced conversion of active vitamin D to an inactive metabolite caused by AEDs that induce hepatic cytochrome P450 enzymes: carbamazepine, oxcarbazepine, phenobarbital, phenytoin and topiramate[25]. A suggested mechanism is that the decrease in biologically active vitamin D results in decreased calcium absorption in the gut, leading to hypocalcemia and increased circulating parathyroid hormone which in turn promotes bone turnover (Figure 1). For this reason, vitamin D supplementation is decidedly appealing as a countermeasure or, perhaps, a preventative measure. However, this potential mechanism does not explain all observed phenomena, such as the decreased BMD found in patients taking valproate, an enzyme inhibitor rather than inducer[15]. A cross-sectional study examining the effect of long term AED therapy, 4 enzyme-inducing AEDs and 6 non-enzyme-inducing AEDs, on bone density in 42 ambulatory adult patients with a mean age of 33 found that both enzyme-inducing and non-enzyme-inducing AEDs were associated with decreases in BMD. There was a propensity for enzyme-inducing AEDs to yield lower spine, total hip, femoral neck and total body BMDs, but these differences were not statistically significant[18].

Newer non-enzyme-inducing AEDs are available. However some have still been linked to a detrimental effect on bone, though not necessarily by the same pathway as enzyme-inducing AEDs. For example, levetiracetam[32] and lamotrigine[33] have been linked to decreased bone health in human studies and zonisamide[34] in rats. Moreover, the choice of AED by prescriber is based upon efficacy and tolerability in patients and is often influenced by past experience, recommendation by colleagues and affordability for patient[35].

Monotherapy, treatment with one drug, is ideal, but polytherapy, treatment with multiple drugs, is necessary for refractory epilepsy. Polytherapy is associated with a higher risk of bone metabolism abnormalities than monotherapy[18]. Prescription data from 2004 to 2009 in Norway of an average of 44,611 patients on at least one AED found that carbamazepine and lamotrigine were the most commonly used in those aged 20–59 while carbamazepine and phenobarbital, both enzyme-inducing, were most commonly used in those aged 60–102, a subgroup that is already at increased risk for osteoporosis and fractures. It should be noted that 18% of the population studied were on polytherapy and that 61% of the polytherapy was a combination of a non-enzyme-inducer paired with an enzyme-inducing AED[36]. An Italian database encompassing 289 general practitioners in the Caserta region analyzed over the years 2005 to 2011 found that phenobarbital and valproic acid, both associated with decreased BMD, were the most commonly prescribed AEDs for new incidences of epilepsy[37]. According to an analysis of an anonymous demographic and medical database compiled from general practitioners and specialists throughout Germany, of 43,712 adult patients using AEDs from 2010–2012, the top 4 drugs in use were valproate, levetiracetam, carbamazepine and lamotrigine[38]. Manitoba data from 1998 to 2013 found that among people with epilepsy, phenytoin, carbamazepine, valproic acid and lamotrigine were the top four AEDs in use; the top two are hepatic enzyme-inducing AEDs and the third is an enzyme-inhibitor[39]. An American study using national Veteran Health Administration, pharmacy and Medicare data on 72,358 patients 66 years and older found that between the years 1998 and 2004, the majority (67%) of those with newly diagnosed epilepsy were treated with phenytoin, followed by gabapentin (11%), carbamazepine (8.5%) and valproic acid (5.6%)[40]. Though newer AEDs with better side effect profiles are

in use, the older AEDs associated with metabolic bone disease via the hepatic enzyme-induction pathway are still highly prescribed, particularly in the older population that is more vulnerable to osteoporosis and fracture.

1.5 Bone Health: Osteoprotective Measures for the General Population

Regardless of the exact underlying mechanisms, there is a considerable amount of evidence indicating a relationship between AED use and reduction in BMD which has the capacity to lead to bone disease and, ultimately, fractures. Thus, counteracting this effect by improving BMD is a clear cut approach to reducing AED associated fractures. Genetics are thought to moderate up to 80% of the peak bone mass of an individual. However 20% or more depend on lifestyle factors. Prospective interventional studies in youth have demonstrated the beneficial effects of both calcium intake and exercise on BMD[41]. As peak bone mass is achieved in early adulthood, the main determining factor for bone health in adults and the elderly is bone loss and the prevention thereof.

Exercise has been found to continue to be of benefit to bones in older age. Cross-sectional studies have calculated an 8% greater BMD in individuals under 50 years of age who participate in exercise programs as compared to matched controls and a 6% difference in those over 50[42]. Longitudinal studies derived more modest results: a 2% increase in BMD in adults under 50 associated with exercise and a 1% increase for those over 50 years old[42].

Calcium and vitamin D, a main proponent of normal calcium metabolism, also continue to be valuable to bone health in older age. A three year study in adults aged 65

and older found that calcium and vitamin D supplementation moderately reduced bone loss in the femoral neck, spine and total body and also reduced the incidence of non-vertebral fractures[43]. A meta-analysis of 29 randomized trials in people aged 50 and over had similar findings: depending on whether study outcomes were fracture risk or BMD based, calcium and vitamin D supplementation were associated with a 12% decrease in fracture risk or 0.54% reduction in the rate of bone loss at the hip and a 1.19% decrease at the spine as compared to those not taking supplements[44]. A Cochrane review of the literature up to December 2012 included 53 medical trials and 91,791 participants over 65 years old that investigated fracture outcomes with vitamin D supplementation or vitamin D and calcium supplement combination treatment as compared to placebo control or calcium supplementation only control[45]. This review concluded that though there was high quality evidence for combined vitamin D and calcium supplementation reducing the risk of any type of fracture, there was also high quality evidence that vitamin D supplementation alone, in doses no higher than 800 IU, was unlikely to prevent fractures[45]. Beneficial findings of vitamin D supplementation appear to be at more robust doses; doses of 1800–4000 IU have been suggested[44–46].

Exercise as well as calcium and vitamin D intake have shown to enhance bone health to some degree in normal adults in research. The application of this research to the general population requires both the advocacy of these osteoprotective behaviours by health care professionals as well as guidelines on recommended amounts of exercise and supplementation for health care professionals to follow.

1.6 Bone Health: Recommendations for the General Adult Population

Osteoporosis Canada cites Canada's Physical Activity Guide, stating that all adults, including those over 65 years, should participate in 30 minutes or more of moderate to vigorous intensity physical activity for 5 days a week or more. Moderate activity is classified as activity during which one would not be able to sing. Vigorous activity is classified as activity during which one would be able to neither talk nor sing. Strength training, such as weight lifting, and balance training, such as dancing or Tai Chi, are suggested. Weight-bearing physical activity is emphasized: that is, activity in which bones and muscles of the legs and trunk work against gravity. Examples of weight-bearing physical activities are walking, jogging, step aerobics, dancing, stair climbing, soccer, basketball, volleyball and other sports that involve running or jumping. Cycling and swimming are not considered weight-bearing physical activity[47]. Physical activity is recommended by Osteoporosis Canada specifically to slow the rate of bone loss as well as to strengthen muscles to prevent falls.

Health Canada recommends 600 IU or 15 μg of vitamin D per day for adults up to 70 years of age and 800 IU or 20 μg for adults older than 70[48]. It is estimated that a young white person will obtain 1000 IU or 25 μg of vitamin D from 4 minutes ultraviolet B radiation on 25% of the body surface. Older individuals or people with darker skin can need up to 18 minutes of exposure for the same results: per day, this is enough exposure to accumulate over time to a significant amount of ultraviolet B radiation which can result in detrimental effects to skin[49]. Moreover, sun exposure can also be influenced by geographical location, season, and ambulatory status and so it is difficult to quantify an ideal exposure time or to guarantee adherence from non-ambulatory patients[50]. Canadians are considered to be at risk for vitamin D insufficiency or deficiency particularly during

winter months, but possibly during the summer as well due to geographical location[49]. There are vitamin D-fortified products on the market; in Canada only cow's milk and margarine are required to be fortified. The vitamin D content does not transfer well to dairy products made from fortified milk, such as yogurt and cheese[48]. Calcium is generally acquired through dietary intake: Health Canada recommends between 1000–1200 mg of calcium per day for adults depending on age and gender[48].

Diet can prove insufficient for acquiring all necessary nutrients and, as mentioned above, acquiring an optimal amount of vitamin D via sunlight can be difficult, particularly for Canadians. Supplementation therefore becomes a simple alternative to ensure a fixed intake of both vitamin D and calcium. However, in the case of calcium supplementation, adverse effects such as kidney stones, gastrointestinal issues and, potentially, increased cardiovascular mortality have been observed[51]. The American Society for Bone and Mineral Research states that calcium supplements should only be used when adequate calcium cannot be obtained through the diet[52]. Unfortunately, high dairy intake is less tolerable in older adults and for many of them supplementation becomes necessary[51].

1.7 Bone Health: Recommendations for Adults with Epilepsy

Guidelines offered by the American Epilepsy Society do not mention bone health or treatments for AED associated bone loss except for a link to a paper on the treatment of new onset epilepsy by French *et al.* that notes vitamin D levels are affected by AED use[53,54]. A drug safety update in 2009 in the U.K. warned about the "adverse effect on bones" of AEDs. The drugs specified in this safety update were carbamazepine, phenytoin, primidone, phenobarbital and valproate. At risk patients were identified: "those who are immobilised

for long periods, those who have inadequate sun exposure, those with inadequate dietary calcium intake." Vitamin D supplementation was recommended only for those considered at risk; no dosage recommendations were made[55].

The International League Against Epilepsy offers the National Institute for Health and Care Excellence (NICE) epilepsy guideline which, as of a new addition in 2012, denotes that a high level of vigilance must be taken for adverse effects of AEDs, such as bone health issues. However, outside of this brief mention, the guideline has no specific recommendations[56]. Instead, it is stated that blood tests, such as those for bone metabolism, should be taken into consideration to determine any comorbidities or if there is just cause, but these blood tests are not recommended to be conducted regularly unless clinically indicated[56].

Bone health is not mentioned by Epilepsy Canada. However, the epilepsy management guideline of Critical Care Services Ontario recommends screening for osteopenia and osteoporosis for patients on AED therapy. Full blood count, electrolytes, liver enzymes, vitamin D levels, and other tests of bone metabolism are indicated every 2–5 years for adults taking enzyme-inducing AEDs[10]. There are no treatment recommendations stated except for post-menopausal women, who are recommended to avoid enzyme-inducing AEDs and take daily vitamin D and calcium supplements[10].

The Scottish Intercollegiate Guidelines Network (SIGN) epilepsy guideline also has a section specifically on bone health. It states that patients taking AEDs should receive dietary and other lifestyle advice to reduce the risk of osteoporosis. Bone health in post-menopausal women with epilepsy is highlighted, though once again there are no specific

treatment recommendations[57]. A randomized control trial attempting to implement the SIGN epilepsy guidelines was conducted in 2003, the year of its previous draft publication. Encompassing 38 general practices over 3,000 square miles, adherence to the guideline was poor[58].

An accepted treatment of bone health in patients with epilepsy taking AEDs has not been established. In fact, not all epilepsy guidelines acknowledge the risk of bone metabolism abnormalities caused by AEDs. Moreover, those guidelines that do caution against the negative effects of AEDs on the bone do not specify any recommendations to deal with this possibility, presumably leaving it to the individual clinician's discretion. A common treatment would be supplementation of vitamin D or calcium or both, although there is no agreed upon standard dose. This is concerning, as evidence shows that the recommended doses of vitamin D are not high enough to be clinically relevant even in people without epilepsy[44–46]. As far back as 1998, the lack of guidelines for treating bone metabolism disease in epilepsy has been criticized, with suggestion for up to 2 times the typically prescribed doses of vitamin D supplementation[59]. This suggestion was in turn scrutinized for not going into greater detail, ignoring age, AED type and other factors[60]. A study in 2001 looking at the practice patterns of neurologists found that only 28% of neurologists treating adults with epilepsy evaluated their patients for bone disease and only 7% prescribe prophylactic calcium or vitamin D. Of those that find evidence of bone disease, 37% treat with calcium or vitamin D, 57% refer to a specialist and 7% take no action[61]. With insufficient guidelines, the majority of neurologists do not appear to monitor bone health in their adult patients with epilepsy. For those that do, there is an apparent variability in their professional response to a diagnosis of bone disease.

There is insufficient literature with recommendations to treat or prevent reduced BMD in individuals with epilepsy. Of the existing literature, there is a particular focus on women, especially post-menopausal women. This is to be expected: despite a similar rate of bone loss in men and women starting from the mid-30s, as women approach menopause they begin to lose bone at a rate of 2–3 percent higher per year than men [62]. Women are also at greater risk for fracture than men at any age and at age 50 and above the disparity is such that the lifetime risk for hip, forearm or vertebral fractures in white women is 39.7% compared to 13.1% in white men[63]. Penovich *et al.* recommended DXA scans of the spine and hip in at-risk women be collected and repeated every 2 years or if a fracture occurs[64]. Dietary counselling and supplementation to meet daily needs divided into 2–3 doses per day for optimal absorption were also recommended [64]. However, a case note review and patient questionnaire by Kampman *et al.* in 2005 demonstrated that despite local recommendations of 800 IU vitamin D and 1,500 mg calcium in women with epilepsy on carbamazepine, phenobarbital, phenytoin or primidone, less than 5% of women treated with enzyme-inducing AEDs were informed of this[65]. Kampman *et al.* concluded that awareness of the issue of bone health in patients on AEDs among neurologists and patients had not increased compared to a survey completed in 1995[65]. Again, it is important note that the recommended vitamin D dose is much lower than doses that have proved to be clinically relevant and even these lower recommendations were not being followed.

1.8 Bone Health: Current Osteoprotective Behaviours in Individuals with Epilepsy

Although there is not much research in the area, one study investigating vitamin D and calcium supplementation in adults with epilepsy using the patient database at the

Veteran Affairs Medical Center in Lexington, Kentucky found that between October 1998 and March 2007, 4.9% of their sample, whose mean age was 55.7 years, had documented calcium and vitamin D supplement usage while taking AEDs[66]. Alternatively, another American survey completed by 260 adult patients from an epilepsy clinic, whose mean age was 41.9 years, found that 25.4% reported regular calcium and vitamin D supplement usage[67]. In comparison, between 2007 and 2009, 31% of Canadians aged 6 to 79 years old reported taking a vitamin D supplement and between 2005–2006[68], 37% of Americans aged 1 year or older reported taking a vitamin D supplement[69]. Considering the disparity in American findings, an accurate reflection of vitamin D use in Canadian adults with epilepsy is needed. Previous estimates do, however, indicate that vitamin D supplementation may be low in this especially vulnerable group.

A study investigating exercise, diet and other health behaviours in adults with epilepsy using data from the 2005 California Health Interview Survey concluded that the diet and exercise behaviours of Californian adults with epilepsy were comparable to the general population and under the levels recommended by experts[70]. This was confirmed by a study using 2005 Canadian Community Health Survey (CCHS) data that demonstrated no difference in physical activity between those with epilepsy and those without between the ages of 12 to 39 years[71]. This excluded adults at higher risk of developing osteoporosis. A second study using 2001 to 2005 CCHS data addressed physical activity in several chronic conditions. According to this study, individuals with epilepsy were 1.4 times more likely to be physically inactive than the general population; the population of interest included those 12 years and over and trends in age groups were not investigated[72]. A clinical study comparing 35 epilepsy patients to 36 controls found that physical fitness as measured by

walking, knee-dips, pelvis elevations and flexibility was significantly lower in the epileptic group at every test. Moreover, body mass index was significantly higher in the epileptic group[73]. Importantly, all studies used data collected from 2005 and earlier. These studies also did not address potential differences in physical activity between age groups and did not place a particular emphasis on the older population which is at increased risk of osteoporosis. In fact, one of the stated studies excluded this subpopulation

1.9 Summary

Epilepsy is a common and costly condition to the health care system and those personally afflicted. Injuries, particularly fractures, are associated not only with seizures themselves but also the medications used to control seizures. This is of particular concern in adults: both the osteoporosis clinical practice guidelines and the National Osteoporosis Foundation cite individuals 50 years of age and over to be at increased risk for osteoporosis and fracture as compared to younger individuals[74,75]. As underlying mechanisms of the decline in BMD associated with AED use are not yet delineated, the best corrective and preventative therapy is to enhance bone health. Known strategies to improve bone health in the general adult population consist of physical exercise and adequate calcium and vitamin D. Unfortunately these strategies have not been well studied in adults with epilepsy despite abundant evidence of the relationship between decreased bone health and AEDs. A comprehensive evaluation of the effect of vitamin D supplementation in particular on bone in adults with epilepsy would not be remiss, in light of the vitamin's hypothesized central role in the mechanism many AEDs are suggested to act through.

A consensus on the management of metabolic bone diseases in patients with epilepsy has not been reached. Although there exists an Ontario guideline for epilepsy that acknowledges the issue and puts forth some recommendations for managing the potential for developing bone disease, particularly in post-menopausal women, these instructions are not thorough. Moreover, follow up studies conducted in other countries do not inspire confidence in the adherence to such guidelines. As such, it is crucial to determine the current dietary choices, physical activity, sun exposure and vitamin D supplement use in the adult Canadian epileptic population, a group that is vulnerable to bone loss from both increasing age as well as the medication necessary for seizure control. Knowledge of current osteoprotective behaviours in the epileptic population would be reflective of current epilepsy health care in Canada and could possibly support any future alterations in treatment guidelines. It could also be used to guide strategies to improve rates of these protective lifestyle behaviours, perhaps through increasing accuracy of sample size estimation for future research.

2 The Research Purpose

2.1 Research Questions

The overall purpose of this project was to build a firm foundation regarding the issue of decreased bone health in individuals with epilepsy. Specifically this project aimed to determine the current state of osteoprotective measures in people with epilepsy. To accomplish this, there are three main research questions to address.

1. What is the effect of vitamin D supplementation on bone health in adults with epilepsy?
2. What is the current level of osteoprotective behaviours in the adult epileptic Canadian population and how does this compare to those without epilepsy?
3. What is the current prevalence of vitamin D supplementation in Canadian adults over 50 years old with epilepsy?

2.2 Research Projects

To address the stated research questions, three projects are proposed.

1. A systematic review on the effect of vitamin D supplementation on bone health in adults with epilepsy
2. A secondary data analysis investigating the calcium and vitamin D intake, physical activity and sun exposure as well as number of fractures in the adult Canadian population
3. A survey on vitamin D supplementation as well as other inquiries regarding behaviours that impact bone health, epilepsy medication use and awareness of the potential negative effect of AEDs on bone health.

3 Systematic Review

3.1 Rationale

As mentioned above, there is no consensus on the use of vitamin D supplementation specifically in people with epilepsy or the doses that would be recommended in this population. Recommended doses for the general population vary from 600–800 IU depending on age[48]. Systematic reviews have found that these doses are too low to be clinically relevant[44,45]. Considering the pathway that links enzyme-inducing AEDs to decreased bone health implicates reduced vitamin D levels[25], efficacy and treatment regimen of vitamin supplementation may differ in people with epilepsy. Thus, the effect of vitamin D treatment on bone health warrants an investigation in people with epilepsy.

3.2 Objective

To investigate the effect of vitamin D treatment on bone health in adults with epilepsy in the existing literature as measured by outcomes such as bone turnover markers, bone mineralization and fracture occurrence.

3.3 Methodology

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines[76]. Prior to commencement of the literature search, Prospero, the Cochrane Library and the Joanna Briggs Institute Library of Systematic Reviews were searched for any reviews on the topic of epilepsy[77–79]. No similar systematic reviews were found.

3.3.1 Databases

Medline, PubMed, Scopus, Embase databases for articles from 1946 to 2015. Health Canada's Clinical Trial Database, Cochrane Clinical Trials, Clinical Trials.gov, EU Clinical Trials, International Pharmaceutical Abstracts and Google were also searched to reduce publication bias. The grey literature procedure of Godin *et al.* was followed when searching Google[80]. The references of all full articles retrieved after passing the first stage of screening were reviewed as well. See Appendices A and B for a complete list of keywords and search terms.

3.3.2 Study Selection:

Studies were eligible for inclusion if they met the following criteria: studies on adult (≥18 years old) patients with epilepsy using at least one AED, a vitamin D supplement intervention and some form of bone health outcome measure (e.g. multiple bone turnover markers or bone mineralization). We excluded studies on children because of the rapid change in bone associated with growth before maturity has been reached. Studies had to demonstrate that a measured change is attributable to a vitamin D intervention. If a combination intervention of calcium and vitamin D was used a calcium-only control arm in the study was required for it to be eligible for inclusion. Only completed studies with original data were eligible: publications summarizing previously published studies were excluded and for eligible studies with overlapping patients the study with a larger sample size was kept.

Studies were excluded if the extent of their outcome measures were to evaluate serum vitamin D levels and/or serum calcium levels alone with no bone outcome measure. Reviews, letters and case studies were also excluded. Studies that were not published in English were excluded.

All studies were screened by at least two members of the research team (HF plus either CDH or MF; see Acknowledgement). Discrepancies were discussed by all three reviewers until agreement was reached.

3.3.3 Data Extraction:

The following data were extracted from eligible studies: authors, publication year, study location, study methodology, sample details (number of participants, sex, age, years of AED use), intervention details (dosing regimen, study length) and outcome measurements (bone turnover markers, bone mineralization).

3.3.4 Quality Assessment:

The methodological quality of included studies was independently assessed by two reviewers (HF & HM; see Acknowledgements) using a modification of the Newcastle-Ottawa Scale for nonrandomized studies[81,82] and the Cochrane Collaboration Tool Risk of bias assessment for randomized studies[83]. The modified Newcastle-Ottawa Scale includes items on statistical methods, confounding effects and reporting of data to assess methodological bias and excludes items on cohort follow-up, which are not relevant to

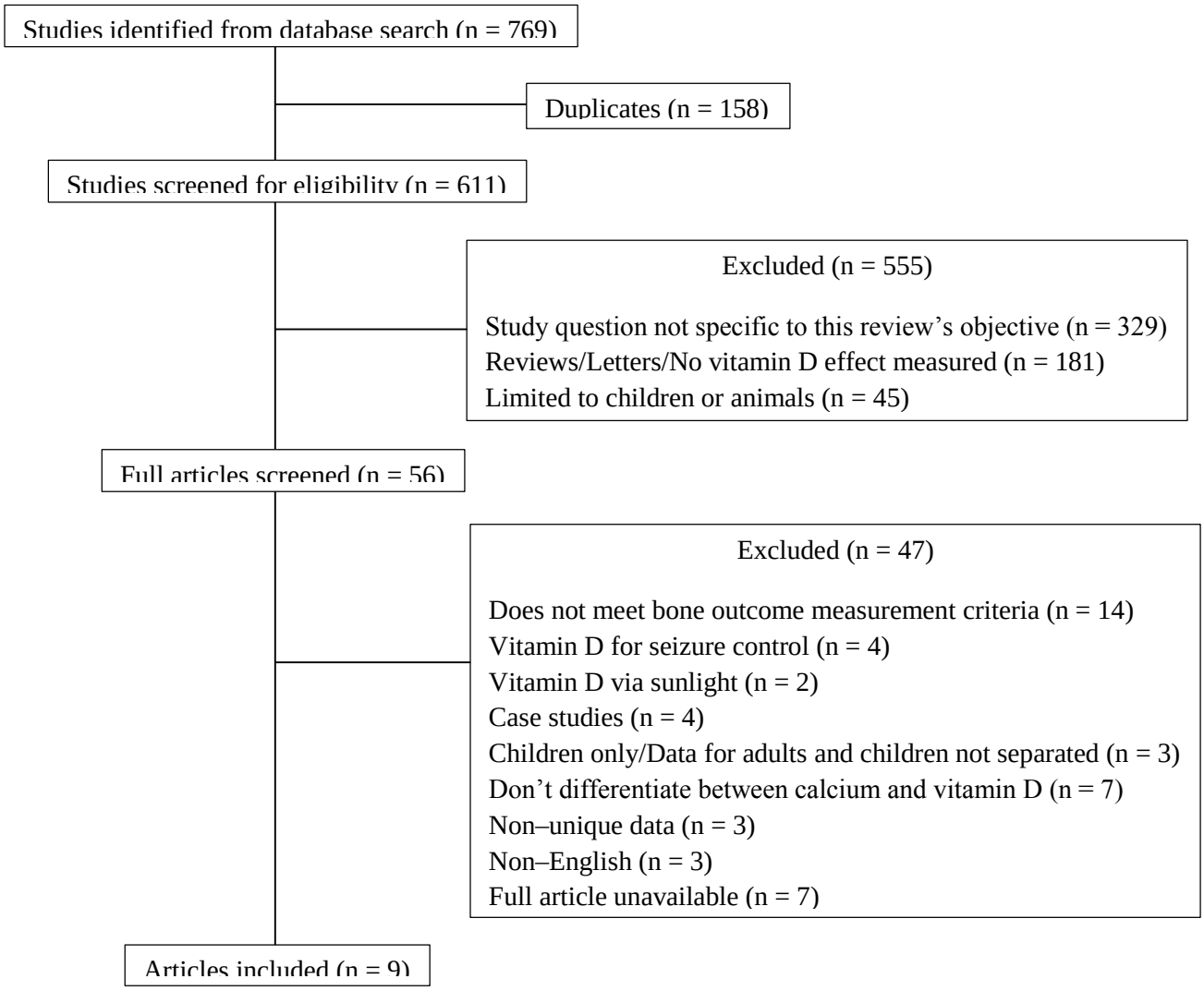
studies included in this review; it also uses a more sensitive 4-point scale of assessment (0–3 points per category) rather than the all or nothing scoring system of the original.

3.4 Results

3.4.1 Search Results

Searches returned 769 articles; after removing duplicates 611 remained. Fifty-six articles were retrieved for full-text review after the initial screen based on title and abstract (kappa coefficient of 0.905, standard error of 0.031); of these studies nine met all eligibility criteria (kappa coefficient of 0.827, standard error of 0.096) (see Figure 2 and Appendix C).

Figure 2. PRISMA Flow Diagram



3.4.2 Studies Selected

Four randomized trials and five non-randomized, quasi-experimental studies were eligible for this review[84–92]. Ages of participants ranged from 18 years to 92 years. All studies included both males and females; proportion of female patients ranged from 17%–73%. Sample size ranged from 6 to 226. Study length ranged from 1 month to 12 months. Several AEDs were used by patients in the studies: phenobarbital, phenytoin, primidone,

carbamazepine, valproate, topiramate, lamotrigine, gabapentin, clonazepam (see Appendix C). Only one of the nine studies investigated patients who were taking non enzyme-inducing AEDs[88]. One of the nine studies restricted its patients with epilepsy to those who had evidence of osteopenia and at least one documentation of hypocalcemia[85],while two recruited patients with increased amount of osteoid or an increase in the osteocytic osteolysis[86,89]. Post-vitamin D intervention data in the study conducted by Offermann and colleagues is visually represented thus the authors' own descriptions of results are used to compensate for lack of measurement values[90].

3.4.3 Bone Health Indicators

Outcomes reported by different studies varied: five studies reported serum vitamin D (25-hydroxycholecalciferol, 25-OHD)[85–87,90,91], eight studies reported serum calcium and alkaline phosphatase (ALP) levels[84–87,89–92], four serum parathyroid hormone (PTH) levels[84,85,89,90], four inorganic phosphate[85,86,89,92] and six reported on bone mineralization [84–86,88,89,91] (Appendix C). Of the seven studies that measured alkaline phosphatase, one of them stated explicitly that the bone-specific isoenzyme was measured[87] while six measured total serum alkaline phosphatase.

3.4.4 Quality Assessment

The methodological quality of included studies indicated all were of at least adequate quality (each scoring 50% or higher on the scales used), with randomized controlled trials consistently scoring higher (Appendices D and E). The mean rating for

randomized controlled trials was 4.5 out of a possible total of 6 using the Cochrane Collaboration tool[93] while the non-randomized, quasi-experimental studies had a mean rating of 15.4 out of a possible 21 in the modified Newcastle-Ottawa Scale[82]. Descriptions of outcomes measured are provided in Appendix F.

3.4.5 Baseline (pre-intervention) Findings

Before examining changes in bone health after vitamin D administration, some studies compared the initial state of bone health indicators in people with epilepsy with that of those without epilepsy. These measures included serum 25-OHD, serum calcium, serum ALP, serum PTH, serum phosphorus and bone mineralization.

3.4.5.1 Serum 25-OHD

Six studies investigated serum 25-OHD levels (Table 1)[85–88,90,91]. Of the three that made comparisons to controls, two found the mean serum 25-OHD levels of patients with epilepsy to be significantly lower[85,91]. Offermann and colleagues noted that 90.5% of patients with epilepsy had serum 25-OHD levels below 15 ng/mL, as opposed to 69.2% of controls[90]. Mikati and colleagues found that 34% of their patients with epilepsy had serum 25-OHD levels below 10 ng/mL and 46% were between 10 to 20 ng/mL[88], while Pedrera and colleagues found that 36% of their patients with epilepsy had serum 25-OHD levels below 15 ng/mL[91]. These patients would be considered either vitamin D deficient or insufficient[88,90,91].

3.4.5.2 Serum Calcium

In the six studies that compared serum calcium in people with epilepsy to controls, all found that the mean levels were lower in patients with epilepsy, (Table 1)[84,85,89–92]. This difference was statistically significant in three studies[85,89,91]. In Offermann's study this difference was not significant but it was noted that 71.6% of their epilepsy patients had subnormal serum calcium levels (below 2.25 mmol/L or 9.00 mg/dl) as compared with 50.0% of controls[90]. Sherk & Snape did not state if the difference was significant; their groups with epilepsy had a mean serum calcium level at or below 9.00 mg/dl while the control groups had higher means (9.6 mg/dl and 9.9 mg/dl for males and females respectively)[92]. All other studies, whether differences between controls and patients were significant or not, had mean serum levels above 9.00 mg/dl.

3.4.5.3 Serum ALP

All six studies that compared ALP in patients and controls found that mean serum ALP levels were elevated in the patients with epilepsy (Table 1)[84,85,89–92]. Five studies found this difference to be statistically significant[84,85,89–91]; Sherk & Snape did not state if this difference was significant[92].

3.4.5.4 Serum PTH

Four studies that investigated PTH reported that the mean serum PTH levels of patients with epilepsy was higher than that of controls[85,89–91], a difference that was statistically significant in two studies (Table 1)[85,91]. Offermann and colleagues noted that 83.2% of patients with epilepsy had serum PTH levels above 110 pg/mL as compared to

79.2% of controls[90] and Pedrera and colleagues found that 17% of the patients with epilepsy had serum PTH levels that were above upper accepted limits[91].

3.4.5.5 Serum Inorganic Phosphate/Phosphorous

Of the three studies that investigated inorganic phosphate/phosphorous [85,89,92], two found that patients with epilepsy differed significantly from the control group (Table 1)[85,89], with one study finding that inorganic phosphate/phosphorous levels were significantly higher[89] and the other significantly lower[92]. Sherk & Snape noted that the observed levels were considered clinically normal and did not stated any significant difference[92].

Table 1. Biochemical bone turnover markers in controls and in patients with epilepsy

Study Serum 25-OHD (ng/mL)	Controls (baseline)	Patients (baseline)	P-value	Patients (post-intervention)	P-value
Hahn & Halstead, 1979	19.2±1.6	8.6±0.8	<0.001	62.6±9.3	<0.001
Hoikka *et al.*, 1982	—	5.2±1.5	—	33.4±14.8	<0.01
Krishnamoorthy *et al.*, 2010	—	24.36±3.42	—	31.53±3.27	<0.001
Offermann *et al.*, 1979	7.3	6.9	NS	—	NS
Pedrera *et al.*, 2000	31.2±8.6	22.0±12.1	<0.0001	88±25	<0.0001
Serum calcium (mg/dL)					
Christiansen *et al.*, 1973	9.90±0.35	9.56±0.33	<0.001	9.59	NS
Hahn & Halstead, 1979	9.65±0.11	9.08±0.16	<0.01	9.49±0.18	<0.02
Hoikka *et al.*, 1982	—	9.38±0.48	—	9.50±0.52	NS
Krishnamoorthy *et al.*, 2010	—	9.24±0.31	—	9.93±0.26	<0.001
Mosekilde *et al.*, 1977	10.084±0.036	9.932±0.068	<0.05	10.028±0.048	NS
Offermann *et al.*, 1979	8.96	8.68	NS	—	NS
Pedrera *et al.*, 2000	9.6±0.4	9.2±0.4	NS	—	NS
Sherk & Snape, 1977	9.6^{M} 9.9^{F}	8.8^{M} 9.0^{F}	—	9.2^{M} 9.2^{F}	$<0.01^{M}$ 0.25^{F}
Serum ALP (IU/L)					
Christiansen *et al.*, 1973	5.1±1.4[a]	8.1±2.6[a]	<0.001	7.8[a]	NS
Hahn & Halstead, 1979	65±5	138±23	<0.01	118±19	<0.02
Hoikka *et al.*, 1982	—	245±82	—	185±46	<0.05
Krishnamoorthy *et al.*, 2010	—	81.92±19.63[c]	—	54.77±11.53[c]	<0.001
Mosekilde *et al.*, 1977	147±4	198±11	<0.01	165±9	<0.01
Offermann *et al.*, 1979	30	42	<0.01	—	NS
Pedrera *et al.*, 2000	94±36	185±52	<0.0001	118±35	<0.0001
Sherk & Snape, 1977	$3.0^{b, M}$ $3.4^{b, F}$	$5.0^{b, M}$ $4.9^{b, F}$	—	$4.3^{b, M}$ $3.8^{b, F}$	$<0.01^{M}$ $<0.01^{F}$
Serum PTH (pg/mL)					
Hahn & Halstead, 1979	4.5±0.6 µL Eq/mL	10.4±1.6 µL Eq/mL	<0.001	6.3±0.8 µL Eq/mL	<0.05
Mosekilde *et al.*, 1977	67.5±2.2	61.8±7.1	NS	59.3±7.2	NS
Offermann *et al.*, 1979	203	243	NS	—	NS
Pedrera *et al.*, 2000	36.7±9.6	52.7±15.6	<0.0001	35.7±14.9	<0.0001
Inorganic phosphate/phosphorous (mg/dL)					
Hahn & Halstead, 1979	3.82±0.13	3.27±0.18	<0.02	3.70±0.16	<0.02
Hoikka *et al.*, 1982	—	3.10±0.37	—	3.25±0.40	NS
Mosekilde *et al.*, 1977	3.65±0.06	3.90±0.12	<0.01	3.65±0.12	<0.05
Sherk & Snape, 1977	4.0^{M} 3.7^{F}	3.4^{M} 3.8^{F}	—	3.2^{M} 3.8^{F}	—

Values in table are given as mean[90,92], mean±standard deviation[84,86–88,91] or mean±standard error[85,89]; NS=not significant, a=King-Armstrong units, b=Bodansky units, c = bone-specific isoenzyme, F=female subjects, M=male subjects

3.4.5.6 Bone Mineralization

The five studies that investigated bone mineralization found that bone mineralization was lower in those with epilepsy compared to controls[84,85,88,89,91].

Bone Mineral Content

Christiansen and colleagues found that the initial bone mineral content (BMC) of patients with epilepsy (87±16% of the calculated normal value) was significantly lower ($p<0.001$) than in those without epilepsy[84].

Bone Mass

Hahn & Halstead found that in patients with epilepsy forearm bone mass was significantly lower ($p<0.02$) than in controls: 81.7±4.7 % of age-sex norm in epilepsy patients vs. 101.4±2.1% in controls[85].

Bone Mineral Density

Mikati and colleagues found that BMD was significantly lower ($p<0.05$) at all sites in patients with epilepsy both compared to their own age, sex and ethnicity-matched non-epileptic controls and the manufacturer's database age-matched control values[88]. T scores for lumbar spine (-0.87±1.06), total hip (-0.58±0.93), femoral neck (-0.70±0.97), trochanter (-0.5±0.94) and 1/3 radius (-0.85±1.05) were compared to zero; a score below zero denoted a mean BMD less than the mean from the manufacturer's database[88].

Ultrasound

Pedrera and colleagues found that amplitude-dependent speed of sound measurements of non-dominant hands were significantly lower ($p<0.0001$) in patients with epilepsy (1926±104 m/s) than in controls (2036±74 m/s)[91].

Biopsy

Mosekilde and colleagues conducted quantitative morphometric analyses of biopsies in their patients with epilepsy, providing a more in-depth picture of bone health. Those with epilepsy initially had more uncalcified bone than controls as measured by relative osteoid volume (4.8±0.4% in patients vs. 2.1±0.3% in controls, $p<0.01$), osteoid surface (28.1±1.4% vs. 13.9±1.3%, $p<0.01$) and mean width of osteoid seams (12.2±0.4µm vs. 8.9±0.3µm, $p<0.01$)[89]. Patients with epilepsy also had increased bone resorption as measured by resorption surfaces (6.3±0.3% vs. 3.8±0.2%, $p<0.01$) and mean volume of periosteocytic lacunes (71.9±1.9µm2 vs. 52.0±0.7µm2, $p<0.01$) than did controls[89]. The percentage of trabecular bone surface active in bone mineralization was also significantly higher (24.7±1.2% vs. 13.5±1.3%, $p<0.01$) in patients than in controls[89].

3.4.6 Post-vitamin D Intervention

3.4.6.1 Serum 25-OHD

The five studies that measured changes in serum 25-OHD levels after vitamin D intervention noted an increase[85–87,90,91], of which four were statistically significant (Table 1)[85–87,91]. Offermann and colleagues noted a seasonal change in serum 25-OHD that appeared to be dose-dependent in individuals taking vitamin D supplements, such that higher dosed groups experienced larger, though not significant, increases[90].

3.4.6.2 Serum Calcium

Six of the eight studies that measured changes in serum calcium levels after vitamin D intervention noted an increase[84–87,89,92]; three studies reported statistically significant findings (Table 1)[85,87,92]. Offermann and colleagues noted a seasonal change in serum calcium that appeared to be dose-dependent in individuals taking vitamin D supplements[90].

3.4.6.3 Serum ALP

Seven of the eight studies that measured change in ALP found a decline in serum levels after vitamin D administration[84–87,89,91,92], of which six were statistically significant (Table 1)[85–87,89,91,92].

3.4.6.4 Serum PTH

Of the four studies that measured change in serum PTH, two found a significant decrease after vitamin D administration[85,91] while two did not observe any change (Table 1)[89,90]. Offermann and colleagues noted that vitamin D administration lowered the frequency of abnormal PTH levels in their patients[90].

3.4.6.5 Serum Inorganic Phosphate/Phosphorous

In two of the four studies that measured serum inorganic phosphate/phosphorous a significant change was seen after treatment, an increase in one study[85] and a decrease in the other (Table 1)[89].

3.4.6.6 Bone Mineralization

Six studies investigated bone mineralization and all observed some positive changes after vitamin D treatment[84–86,88,89,91], though of these one study found a change in bone morphology but not BMD[86].

Bone Mineral Content

When comparing patients with epilepsy taking enzyme-inducing AEDs for at least one year who also took 350 mg/day of calcium combined with 2000 IU/day of vitamin D2 to a control group without epilepsy on the same regimen, BMC had increased significantly ($p<0.001$) by 4.9% above baseline values, whereas there was no significant change in controls[84].

Bone Mass

At a dose of 4000 IU per day (2000 IU twice daily) of vitamin D3 for 4 months, a significant increase of 4.6% ($p<0.02$) in forearm bone mass from baseline was observed in patients taking enzyme-inducing AEDs for more than two years[85].

Bone Mineral Density

When measuring BMD with DXA, Mikati and colleagues found that after 12 months of either 400 IU or 4000 IU daily vitamin D2 administration BMD at all sites remained significantly lower than in controls as well as relative to the manufacturer's database values[88]. BMD of patients in the low dose arm did not change significantly from baseline however patients in the high dose arm of the study had a significant increase in BMD at several sites: lumbar spine ($p<0.03$), total hip ($p<0.02$), and 1/3 radius (3 of 5 sites, $p<0.04$)[88]. Though significant, this increase was less than 1% from baseline. Patients in the

low dose arm of the study were significantly older than those in high dose arm ($p<0.01$) and their duration of AED therapy was also significantly longer ($p<0.04$)[88]. These researchers conducted linear regression and stated that age and AED duration did not appear to influence the results in the two treatment arms[88]. Hoikka and colleagues measured BMD using the gamma ray attenuation method and found no statistically significant difference from baseline in patients with epilepsy after 6 months treatment with 2000IU daily vitamin D2[86].

Ultrasound

Pedrera and colleagues found that ultrasound measurements of non-dominant hands increased significantly ($p<0.0001$) from baseline (1926±104 m/s to 2000.1±98 m/s) one month after a single administration of 120,000 IU of vitamin D3[91].

Biopsy

After taking 9000 IU vitamin D2 daily for nine months, patients with epilepsy in Mosekilde's study had a decrease in uncalcified bone from baseline measured by biopsy[89]. Specifically, relative osteoid volume (4.8±0.4% at baseline vs. 2.2±0.3% post-treatment, $p<0.02$), osteoid surface (28.1±1.4% vs. 21.8±1.6%, $p<0.01$) and mean width of osteoid seams (12.2±0.4μm vs. 8.9±0.7μm, $p<0.01$) decreased significantly from baseline and both relative osteoid volume and mean width of osteoid seams were no longer significantly higher than controls[89]. The percent of osteoid surfaces remained significantly higher than controls ($p<0.01$) even after vitamin D treatment[89]. Bone resorption as measured by resorption surfaces (6.3±0.3% vs. 4.8±0.4%) and mean volume of periosteocytic lacunes (71.9±1.9μm2 vs. 53.1±1.7μm^2) also decreased significantly after treatment (both $p<0.01$);

however, while the difference in the mean volume of periosteocytic lacunes between patients and controls were no longer significantly different, the resorption surfaces remained significantly elevated in patients with epilepsy than in controls ($p<0.05$)[89]. After vitamin D treatment, the percentage of trabecular bone surface active in bone mineralization was also significantly decreased in patients (24.7±1.2% vs. 13.0±0.9%, $p<0.01$) and was no longer significantly different from that of controls[90]. The biopsies of patients treated with 6 months of 2000 IU daily vitamin D2 showed a significant ($p<0.02$) decrease in relative osteoid volume (9.0±5.6% pre-treatment vs. 4.0±2.1% post-treatment); Hoikka and colleagues noted that five of the sample of nine' values returned to a normal range[86].

3.4.7 Bone Health Indicators in Patients with Epilepsy Treated with Calcium Alone vs. Calcium + Vitamin D

Two studies used a calcium control of either 390 mg[84] or 1000 mg[87] daily in the patient groups such that one group with epilepsy received calcium only and another group with epilepsy received calcium as well as vitamin D supplementation[84,87].

3.4.7.1 Serum 25-OHD

Serum levels of vitamin D decreased significantly in individuals with epilepsy treated with 1000 mg of calcium daily for 90 days (Table 2)[87]. Patients treated with 1000 mg calcium and an additional 400 IU daily of 25-OHD for 90 days had a significant increase in vitamin D serum levels (Table 2)[84].

3.4.7.2 Serum Calcium

Patients receiving 390 mg of calcium daily for three months with or without 2000 IU of vitamin D2 did not see a significant change in serum calcium levels post-treatment (Table 2)[84]. Patients receiving 1000 mg of calcium daily for 90 days had significant decrease in serum calcium levels while those receiving additional 25-OHD had a significant increase in serum calcium levels (Table 2)[87].

3.4.7.3 Serum ALP

In Christiansen's study, both groups did not see a significant change after treatment (Table 2)[84]. On the other hand, although Krishnamoorthy's study reported a significant decrease in serum ALP levels in the 1000 mg calcium with 400IU vitamin D daily treatment arm, a significant increase was detected in the calcium-only treatment arm (Table 2)[87].

3.4.7.4 Bone Mineral Content

Both epileptic treatment groups saw an increase in BMC from baseline, but this change was only significant in individuals treated with vitamin D supplement along with calcium (Table 2)[84].

Table 2. Comparison between calcium alone and calcium plus vitamin in patients with epilepsy.

Study	**Calcium-only**		**P-value**	**Calcium + Vitamin D**		**P-value**
Serum 25-OHD (ng/mL)	**Baseline** (mean±SD)	**Post-intervention** (mean±SD)		**Baseline** (mean±SD)	**Post-intervention** (mean±SD)	
Krishnamoorthy *et al.*, 2010	25.19±5.98	19.76±5.35	<0.001	24.36±3.42	31.53±3.27	<0.001
Serum calcium (mg/dl)						
Christiansen *et al.*, 1973	9.56±0.33	9.57	NS	9.56±0.33	9.59	NS
Krishnamoorthy *et al.*, 2010	9.30±0.36	8.80±0.38	<0.001	9.24±0.31	9.93±0.26	<0.001
ALP (IU/L)						
Christiansen *et al.*, 1973	8.1±2.6[a]	8.1[a]	NS	8.1±2.6[a]		
Krishnamoorthy *et al.*, 2010	78.83±11.04	101.75±9.56[b]	<0.001	81.92±19.63[b]	54.77±11.53	<0.001
BMC						
Christiansen *et al.*, 1973	87±16 % of normal mean	100.1±3.6% of baseline	NS	87±16% of normal mean	103.7±4.9% of baseline	<0.001

a=King's Armstrong unit, b = bone-specific isoenzyme, NS=non-significant [84,87]

3.5 Discussion

Our systematic review is the first to investigate the effect of vitamin D supplementation on bone health in adults with epilepsy who take AEDs. Bone health has been found to be compromised in people with epilepsy, particularly those taking enzyme-inducing AEDs which decrease biologically active vitamin D levels. Increased fractures and decreased BMD have been found in this population[15]; this review addresses the impact of supplementing this decreased vitamin D in patients to manage this adverse effect. All outcomes assessed in this review (Appendix F) showed some change, typically an improvement, after vitamin D supplementation.

At baseline considerable proportion of adults with epilepsy were either vitamin D deficient or insufficient. Vitamin D deficiency has been classified as having a 25-OHD level of <10 ng/mL[94]; the World Health Organization classifies insufficiency as a 25-OHD level of <20 ng/mL[95]. However, more recent research has classified vitamin D deficiency as a 25-OHD level of <20 ng/mL and insufficiency as <30 ng/mL[94]. In the studies reviewed, patients with epilepsy had lower serum levels of vitamin D, up to twofold, than did controls[84,85,89–92]. Three of five studies had patients in the vitamin D deficient category by either convention with levels <9 ng/mL at baseline[85,86,90]; the other two studies had patients with baseline vitamin D levels between 22–25 ng/mL[87,91] which is insufficient according to newer research[94] but is considerably higher. A possible explanation for this discrepancy is geographical location: the two studies with higher baseline vitamin D levels in patients took place in India[87] and Spain[91] as compared to the three studies taking place in Germany[90], Finland[86] and the USA[85]. The main source of vitamin D is sunlight which varies by geographical location and by time of year which may also be a possible reason for observed differences[96]. It is important to note that of the two studies with higher baseline vitamin D levels in patients, the one study that compared to controls without epilepsy found that patients had significantly lower levels[91].

Although some studies found patients with epilepsy to have significantly lower serum calcium at baseline as compared to controls, the majority of patients with epilepsy still had serum calcium levels that fell into the normal range (a range of 8.7–9.9mg/dL in the included studies as compared to the approximate 8.9–10.4 mg/dL normal range for adults[97]). This is not unusual. Vitamin D deficiency with normal serum calcium is typical[98]. The mechanisms of calcium homeostasis exist to maintain normal serum calcium; this

normal serum calcium may come at the expense of other abnormalities such as elevated PTH or increased release of calcium from the bone (degradation).

Vitamin D treatment increased serum 25-OHD and calcium levels, though not always significantly. This has also been found in other studies (that did not meet the eligibility criteria for this review) investigating vitamin D treatment purely to correct vitamin D levels in patients with epilepsy[99,100]. In two of four studies, serum levels of the bone turnover marker inorganic phosphate/phosphorous were found to be significantly different, either higher or lower, in patients as compared to controls pre-vitamin D treatment and were normalized by a statistically significant amount post-treatment; the normalization of this bone turnover marker post-treatment suggests that vitamin D was positively effecting bone health[85,89].

In the studies reviewed, people with epilepsy typically had elevated levels of ALP and PTH at baseline, both of which can accompany low serum vitamin D[98]. The normal range of ALP is wide and varies greatly depending on age and sex (around 37–222U/L to encompass the ranges for adults aged 18 years and older)[101]. Many of the included studies did find baseline ALP levels in patients that were likely higher than the normal range, however this is difficult to ascertain when not looking at the individual and the range appropriate for their age and sex. Post-vitamin D treatment, these elevated levels tended to decrease, particularly serum ALP, after vitamin D treatment. Several case reports of people with epilepsy on long-term AED therapy also noted elevated ALP levels[102].

Both ALP and PTH are considered bone turnover markers and their elevated levels can indicate abnormal bone formation[101,103]. However, PTH levels that do not fall within the

normal range may occur for a number of reasons, thus this hormone's usefulness in determining bone health is more limited than other measures. Evidence showed an association between elevated ALP levels and risk of deteriorating bone condition. A prospective study on 512 post-menopausal women found that elevated serum bone ALP at baseline was significantly associated with osteoporotic fractures[104]. A systematic review of 134 reports to investigate using bone turnover markers to assess osteoporotic status found moderate correlations between high ALP levels and low BMD scores and that elevated ALP levels might indicate a need for osteoporosis screening[105].

In our review, patients with epilepsy generally had elevated ALP levels as compared to controls without epilepsy. That finding along with the reported association between elevated ALP and decreased bone health suggest that ALP levels could be used as an indicator that vitamin D supplementation is required. It may also be possible to determine the range at which ALP levels are a concern and treatment should be started. To our knowledge this avenue has not been explored and further investigation is recommended.

It is important to note that ALP has a number of sources including bone and liver. Considering that AEDs are inducers of hepatic enzymes, elevated ALP may be an indicator of liver health rather than bone health. However, hepatotoxicity is a rare side effect of AED therapy and is often idiosyncratic and not dose-dependent, therefore, raised total serum ALP levels may not necessarily be indicative[106]. Of the six studies included in this review that investigated serum ALP, the one study that measured bone-specific ALP observed a reduction post-vitamin D treatment similar to other studies that measured total ALP[87]. Another study measured leucin arylamidase, a liver enzyme whose elevation indicates

damage, and concluded from the normal levels that both the initially raised ALP observed only in patients taking AEDs as well as the non-significant decrease in ALP post-vitamin D treatment were a result of the bone isoenzyme[90]. Pedrera and colleagues measured alanine aminotransferase and gamma-glutamyl transferase, markers of liver health, in their study and found that unlike ALP there were no differences in either of these markers between controls and patients at baseline and that they did not change post-vitamin D treatment despite reduction in ALP[91]. Therefore, an elevated ALP without a coinciding rise in gamma-glutamyl transferase indicates a bone-specific origin[103]. Hahn and Halstead measured total ALP but concluded, based on their previous study that the reduction in ALP seen after vitamin D treatment was due to the bone isoenzyme[85]. We must consider that the ALP changes observed in these studies were noted post-vitamin D intervention, while AED use remained constant; likely these changes in ALP were of bone origin rather than liver. Regardless, if ALP measurements were used in clinical practice as an indication that vitamin D treatment is necessary, measurement of the bone-specific ALP would be more convincing evidence than total ALP.

The effect of vitamin D treatment on bone mineralization was difficult to ascertain because different measures (i.e., BMD, BMC, hand ultrasounds and biopsies) were used to determine this bone health outcome. However, all six studies that investigated bone mineralization found some positive change in at least one measure used[84,86,88,89,91,99]. The studies varied from 1 to 12 months, so duration of supplementation may be a confounding factor. For example, of the two studies that investigated BMD, a six month intervention with vitamin D supplementation did not see a significant change[86] while a 12 month intervention did[88]. On the other hand, that 6 month intervention did find significant

improvements in bone morphology which may suggest that some bone mineralization measurements need a longer period of treatment to yield observable results[86].

Another potential confounder is dosing. Pedrera and colleagues used a single 120,000 IU dose of vitamin D and observed significant improvements[91]. Mikati and colleagues administered lower doses of either 400 or 4000 IU daily and noted no changes in BMD in their low-dose treatment arm[88], which is consistent with research that has found doses below 800 IU to be of little effect[44–46]. The high-dose arm in Mikati's study was within a range suggested to be effective[88].

Mikati found a less than 1% increase in total hip BMD after 12 months of vitamin D treatment ($p<0.02$)[88] which was comparable to the results seen in male patients with epilepsy treated for 12 months with the bone loss drug risedronate[107]. A clinical trial that investigated larger supplement dosing of 1,000–1,500 mg calcium and 500–750 IU vitamin D daily paired with placebo or 35 mg risedronate weekly in 27 male veterans with epilepsy found a small but significant decrease of <2% from baseline in total body BMD in the placebo arm after two years as compared to a non-significant increase of <0.085% in the risendronate arm[107]. In this study the difference in efficacy between supplementation alone or with pharmacotherapy was not significant[107]. It is important to note that participants with subnormal serum calcium and vitamin D were excluded from the study, which may have had implications on the usefulness of calcium or vitamin D supplementation treatment in improving BMD[107]. The study was excluded from this review due to an inability to differentiate the effect of vitamin D from the effect of calcium supplementation in the combined treatment[107]. Similarly, it is important to note that Mikati's study is the

only one in our review that included patients who were taking non-enzyme-inducing AEDs, though the authors noted that the majority were taking enzyme-inducing AEDs[88]. This may have influenced the results as the effect of vitamin D intervention may be different in patients taking non-enzyme inducing AEDs as compared to patients taking enzyme-inducing AEDs which have been linked to decreased vitamin D.

Although all patients with epilepsy in the reviewed studies were 18 years of age or older, participants' age, the AED(s) taken and the treatment history varied considerably. Hahn & Halstead restricted their participants to patients with epilepsy who had evidence of osteopenia and at least one documentation of hypocalcemia, which may have played a role in the significant increase seen in forearm bone mass observed after vitamin D treatment, a bone health indicator not measured in the other reviewed studies[85]. Similarly both studies that used biopsies restricted their patient groups, which may have limited the reproducibility of their results in all patients with epilepsy[86,89].

Moreover, the heterogeneity of study methodologies make findings difficult to generalize. Different types of vitamin D supplementation — e.g., D2, D3, 25-OHD — introduced yet another possible confounder. We found no relationship between the type of vitamin D administered and its efficacy in treating bone health, nor can we draw conclusions on the optimal length of treatment with vitamin D. Christiansen et al.'s follow-up study to their 1973 investigation used a similar protocol but compared 25-OHD and vitamin D3 treatment, rather than the original vitamin D2 treatment, in people with epilepsy using phenobarbital and phenytoin[108]. In this later study, Christiansen and colleagues did not find significant changes in BMD unlike in their first study. Although their

more recent study did not have a calcium-only control arm with which to compare the effect of the vitamin D and calcium combination treatment, therefore excluding it from this review, the authors concluded that the lack of observable effect on bone health was attributable to the type of vitamin D treatment used[108]. Two subsequent randomized, double-blinded trials testing calcium paired with 4000 IU/day of vitamin D2 or D3 for 6 months in patients with epilepsy found no difference in patients using carbamazepine[109] but found that only vitamin D2 treatment was effective in patients using phenobarbitone and primidone[110]. Whether this means that only some types of vitamin D treatments are effective in improving bone health in people with epilepsy taking AEDs or whether this has implications on which specific AEDs are responsive to vitamin D treatment is not known. Further studies are warranted.

Taking calcium, vitamin D or both is frequently recommended to maintain bone health. A Cochrane systematic review of 53 trials with participants 65 years of age or older found stronger evidence for combined calcium and vitamin D treatment than for vitamin D alone with respect to fracture outcome[45]. On the other hand, a meta-analysis of 29 trials with participants 50 years of age or older found evidence for both calcium treatment alone or combined calcium and vitamin D treatment in fracture outcome[44]. Both reviews noted that doses of vitamin D above 800 IU are necessary for observable outcomes and the Cochrane review which found less favourable evidence for vitamin D treatment did not include any trials with doses over 800 IU[44,45]. Although the low vitamin D doses perhaps concealed possible benefits of vitamin D treatment in these reviews, calcium appears to be the more effective supplement to maintain bone health in the general population. However,

for patients with epilepsy vitamin D plays a significant role in the mechanism that links many AEDs to bone health.

Seven of the nine studies in our review assessed vitamin D treatment without the addition of calcium and found that bone health generally appeared to improve[85,86,88–92]. The remaining two studies evaluated the efficacy of combined vitamin D and calcium supplements relative to that of calcium-only treatment[84,87]. Including vitamin D in treatment appeared to provide some benefit. One study found that calcium treatment alone significantly decreased serum calcium levels and increased already elevated ALP in patients whereas combination treatment significantly increased serum calcium levels and decreased serum ALP[87]. The second study found no significant change in BMC in the calcium-only arm but found significantly higher BMC after combined treatment[84]. Despite being conducted 37 years apart by different researchers using different protocols and vitamin D supplement types, both studies support the use of vitamin D supplementation in people with epilepsy. Although evidence on the value of vitamin D supplementation on preventing fractures among the general adult population is limited, it appears to improve bone health in epileptic patients taking AEDs. It is worth noting that one of these studies used a low dose of 400 IU vitamin D yet still found significant results[87]. It is possible that the addition of calcium supplementation may have played a role in this. The dose of vitamin D, with or without calcium, necessary to see improvements in bone health is not yet known though doses of 800 IU have been suggested when used in combination with calcium[44] and doses of 1800–4000 IU have been suggested when used[46].

More standardized intervention studies (dosing, duration, outcomes) are needed to evaluate the effectiveness of vitamin D on bone health in adults with epilepsy. The methodological quality of the reviewed studies ranged from medium to low risk of bias. The major concern between studies was a lack of replication. The effect of vitamin D treatment on bone mineralization suffers the most from a lack of standardized protocol and it is, arguably, the most important outcome of bone health as it is a better measure than bone turnover markers such as ALP and PTH. Findings linking vitamin D with bone health improvement are not fully conclusive. Many concerns have not been addressed, including the type of vitamin D used, the dose and duration of intake. There is also a lack of research on vitamin D supplementation in people with epilepsy that investigates fracture outcomes. Vitamin D intervention studies for bone health in the general population[44,45] as well as osteoporosis drug studies in the general population[111,112] tend to focus on fracture outcomes. Fracture outcome may be of more clinical significance when considering efficacy of a treatment targeting bone health.

Only nine studies met our eligibility criteria and they were methodologically heterogeneous and conducted over a span of four decades. Consequently, it is difficult to determine the efficacy of vitamin D supplements to improve bone health in patients with epilepsy. Our review found some evidence that vitamin D supplementation may be beneficial to bone health in patients with epilepsy. Therefore, long-term studies that include comparable dosing schedules of vitamin D (preferably >1800 IU daily), bone turnover markers, BMD measurement and fracture outcomes are recommended to clarify the clinical role vitamin D supplements play in bone health management in patients taking AEDs.

4 Secondary Data Analysis

4.1 Rationale

BMD peaks in early adulthood and begins to decline with age. At a certain point this decline becomes clinically relevant due to its ability to predict fracture occurrence[113,114]. Many AEDs have been associated with a detrimental effect on bone, including decreased BMD and this reduction appears to worsen with increasing years of AED use[8,21,22]. Although BMD is one of the better predictors of fracture risk it is not the only one. Along with increasing age, particularly those aged 50 and older, women have also been found to have a higher risk of fracture than men[62,63,74,75]. Among older adults with epilepsy, there is an accumulation of risk: AED use and age as well as being biologically female for approximately 50% of this population. There is also the risk of falling associated specifically with seizure occurrence which increases opportunity for injury and fracture occurrence, particularly when paired with compromised BMD.

Considering that in Canada 1.2 billion dollars was spent on osteoporotic fractures in the 2007–2008 fiscal year alone, the management of osteoporosis and bone health in general is of great importance[115]. Strategies to improve bone health include osteoprotective behaviours such as weight-bearing physical activity that stresses bone and muscle as well as calcium and vitamin D intake[42,45,47].

Due to the increased risk of fracture in people with epilepsy, ideally this would be reflected in the population by an increase in the participation of osteoprotective

behaviours. Two studies using Canadian Community Health Survey (CCHS) data have found either no difference or that people with epilepsy are less active than the general population[71,72]. One of these studies investigated Canadians aged 12–39 years old, excluding older adults who are more vulnerable to decreased bone health[71], while the other investigated the entire survey population of Canadians aged 12 years and older[72]. Neither study differentiated between children and adults.

This study investigates osteoprotective behaviours in the adult Canadian population with and without epilepsy using the 2010 CCHS and focusing on adults aged 50 and older who are particularly vulnerable to declining bone health. Weight-bearing activity is compared to a younger subgroup of adults (aged 18–49 years old) as a baseline to note changes in physical activity that occur with age and general decline in health (energy, mobility, strength) rather than due to epilepsy status. Motivation to exercise will also be evaluated as an underlying factor for actual participation. Unlike previous studies, this study will also consider food choices made based on calcium content or osteoporosis concern as well as the amount of sun exposure (vitamin D) experienced and fracture occurrence.

4.2 Objectives

Primary Objectives:

1. To investigate among those aged 50 and older with and without epilepsy, differences in osteoprotective behaviours:
    a. Weight-bearing physical activity

i. Is there a difference compared to younger adults (aged 18–49)?

ii. Is there a difference in motivation to exercise?

b. Dietary choices related to bone health

c. Vitamin D and calcium supplement use

d. Sun exposure

Secondary Objectives:

2. To investigate, where possible, any gender differences in osteoprotective behaviours.
3. To investigate fracture occurrence in adults with epilepsy as compared to those without

4.3 Hypothesis

The frequency of physical activity in older adults with epilepsy will be lower than that found in an analysis of the CCHS 2005 data (mean of exercising 82.5 times in three months)[71], due an older subsample (50 years and older compared to 12–39 years old). Frequency of physical activity in individuals with epilepsy will be similar to or less than that of those without epilepsy, as has been found in an analysis of the CCHS 2005 data[71] and the CCHS 2003 data[72].

4.4 Methodology

This study is a secondary database analysis of a cross-sectional survey.

4.4.1 Survey

The CCHS is a cross-sectional survey that collects health-related data from Canadians aged 12 and over in all provinces and territories. The survey is calculated to be representative of 97% of the Canadian population aged 12 and over; as of 2007, the survey is conducted on an annual basis[116]. In the 2010 the Public Health Agency of Canada sponsored the addition of several questions, including epilepsy prevalence[117,118]. Moreover, the survey consistently addresses questions of nutrition, physical activity, sun exposure and fractures. Therefore the survey data collected from 2010 is of interest in examining the patterns of behaviours that are favourable to bone health in adults with epilepsy.

The CCHS has been validated. Most of the CCHS variables originate from the National Population Health Survey (NPHS); this includes sections on physical activity, sun exposure and injuries[117,119]. The NPHS was developed through literature research and specialist consultation from Statistics Canada, Health Canada, provincial ministries of health and academic researchers. The NPHS questionnaire was approved by Statistics Canada and an Advisory Committee with representatives from provincial ministries of health, Health Canada, Public Health Agency of Canada, Statistics Canada and other government departments and specialists[119].

4.4.2 Data Extracted

Data were extracted for adult participants (aged 18 and older). Forty-seven items from the CCHS survey was extracted. For a detailed list of variables and how they relate to

the concepts of epilepsy, physical activity, sun exposure and bone-related dietary choices, see Appendix A (Table 9). For examples of wording of CCHS questions, see Appendix A (Table 10). Fracture data were also extracted as a bone health outcome. Demographic data (age and gender) were considered due to their independent effects on bone health[74]. Ambulatory status was considered for its potential limiting effects on other variables, particularly physical activity.

4.4.3 Derived Variables

Ambulatory status: Participants were considered non-ambulatory if they answered "no" to any one of questions 14 and 15 or "yes" to any one of questions 16–18 or 20 in the Health Utilities Index section of the survey (see Appendix A, Table 10). These items evaluated the participant's mobility with questions asking if participants are usually able to walk around the neighbourhood without difficulty and without mechanical support, are able to walk at all, require the help of another person to walk or require a wheelchair.

Frequency of weight-bearing activity: Activities included were walking for exercise, walking to work/school, popular/social dance, home exercises, ice hockey, ice skating, in-line skating, jogging, exercise class/aerobics, skiing/snowboarding, baseball/softball, tennis, weight-training, volleyball, soccer and basketball. Bicycling and swimming were excluded as they are not considered weight-bearing activities. Gardening, golfing and fishing were excluded due to tendency to be low-effort. The number of times participants reported engaging in these activities for the past 3 months was summed up.

Duration of weight-bearing activity: For the weight-bearing activities above, participants reported the time interval spent each time when participating in the activity. Four time intervals were available to choose from with a ranking from 1 to 4: 1 indicated 1–15 minutes spent on the activity, 2 indicated 16–30 minutes, 3 indicated 31 minutes to 1 hour, 4 indicated more than 1 hour. Using these values, the mean of each participant's total reported duration of time spent on weight-bearing activities was calculated; if a participant reported participating in more than one activity, the reported duration spent doing each of those activities would be averaged. Mean duration was then re-sorted into the four categories: 1 indicated mean scores of 1.00–1.99, 2 indicated 2.00–2.99, 3 indicated 3.00–3.99 and 4 indicated scores of 4.00.

4.4.4 Statistical Analyses

Chi square, Mann-Whitney, Kruskal-Wallis, T-test and ANOVA were used to make comparisons between four subgroups: those aged 50 and older with epilepsy, those aged 50 and older without epilepsy, 18–49 year olds with epilepsy, 18–49 year olds without epilepsy. Significance testing conducted on all four subgroups underwent further analysis to determine where significant differences were occurring; pairwise testing was used for Kruskal-Wallis and the Sheffe post-hoc analysis was used for ANOVA. Comparisons were made on the amount and duration of physical activity and sun exposure as well as the prevalence of bone-related dietary choices. The number of fractures were compared and were used as an outcome for regression modeling. Age, gender, physical activity and sun exposure were used as explanatory variables in a model for fracture occurrence to test if these osteoprotective behaviours are significant predictors of an actual bone health

outcome. See Appendix I for full statistical analysis outline. All values presented are weighted by scaling the weights provided by Statistics Canada. No analyses had unweighted frequencies of less than 5 in accordance with Statistics Canada's disclosure regulations.

4.5 Results

4.5.1 Baseline Demographics

The CCHS 2010 sample consisted of an unweighted total of 56,210 adult participants (18 years and older) who responded to the questions concerning epilepsy. Of these 56,210 there were 318 adults with epilepsy, 161 of whom were aged 50 years and older. The prevalence of epilepsy in the CCHS 2010 sample was 0.6% for all adults, 0.6% for those 18–49 years old and 0.5% for those 50 years and older, which is within the 0.4%–1.0% global prevalence range (Table 3)[1]. The gender distribution among those 18–49 years old with epilepsy was 51.7% male vs. 48.3% female and 47.9% male vs. 52.1% female for those without epilepsy; among those 50 years and older it was 43.0% male vs. 57.0% female for those with epilepsy and 49.9% vs. 50.1% for those without. The mean age of adults (18 years and older) with epilepsy was 42.78±16.63 years and without epilepsy was 44.02±19.00 (mean ± standard deviation) years; for those 50 years and older the mean age was 59.30±9.34 years for those with epilepsy and 63.43±10.28 years for those without epilepsy (Table 3).

There was no significant difference in the gender distribution between those with and without epilepsy (Table 3). Among those aged 50 years and older, people with epilepsy (PWE) were significantly ($p<0.001$) younger than those without in this sample. This significant difference did not exist in the younger subgroup of people aged 18–49 years old nor when the entire CCHS sample (aged 12 years and older) was analyzed. Among those 50 years and older, there was no difference in ambulatory status between PWE and those without. However, between the ages of 18–49 years old, 7.9% of PWE were non-ambulatory compared to 0.1% of those without epilepsy: this difference was significant ($p<0.0001$).

Table 3. Demographics, CCHS 2010

Characteristic	**18–49 years old**		**50 years and older**	
Attribute	With Epilepsy (N=157)	Without Epilepsy (N=25,088)	With Epilepsy (N=161)	Without Epilepsy (N=30,804)
Gender (%)				
Male	51.7	47.9	43.0	49.9
Female	48.3	52.1	57.0	50.1
Age (years)				
Mean (SD)	34.95 (9.536)	34.01 (9.390)	59.30[a] (9.341)	63.43[a] (10.277)

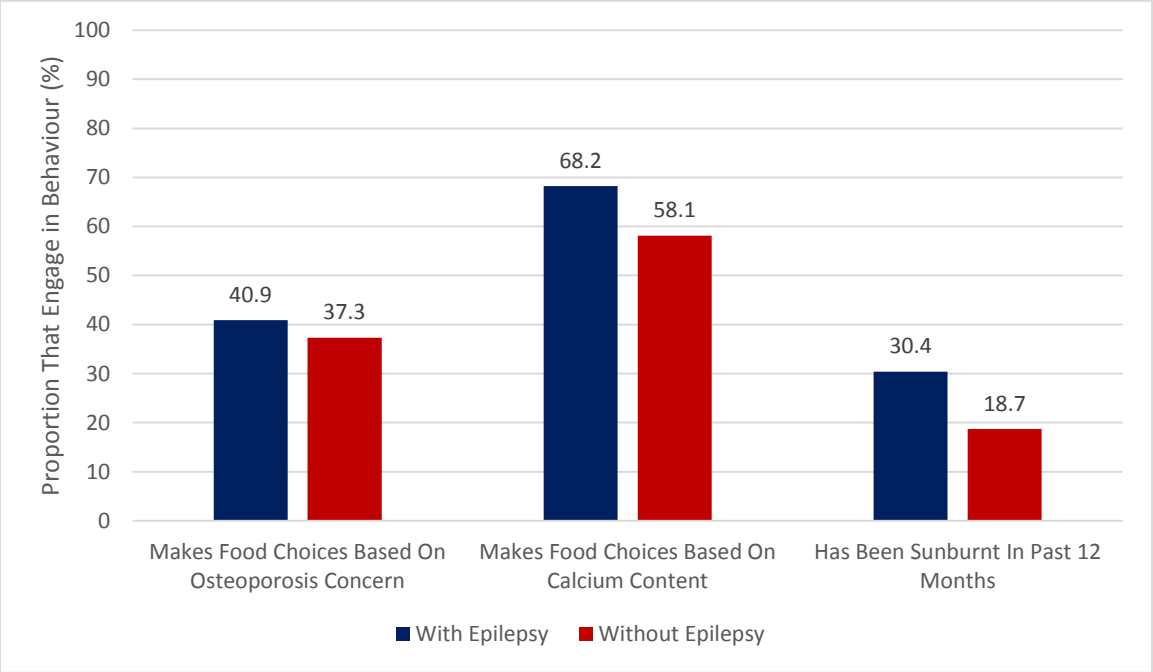
% = Chi square, years = T-test, a = $p<0.001$ between groups

4.5.2 Food Choices

Although the CCHS does collect information on general vitamin and mineral supplement use, it does not collect information on calcium and vitamin D specifically. Dietary information collected is limited to fruit and vegetable consumption and dietary choices; dairy information is not collected. Our questions regarding vitamin D and calcium

intake could not be answered. Therefore dietary food choices were used as an indirect measure. Among those 50 and older, there was no significant difference between the proportion of PWE who made food choices based on calcium content or osteoporosis concern compared to those without epilepsy (Figure 3).

Figure 3. Lifestyle behaviours in those 50 years and older, CCHS 2010

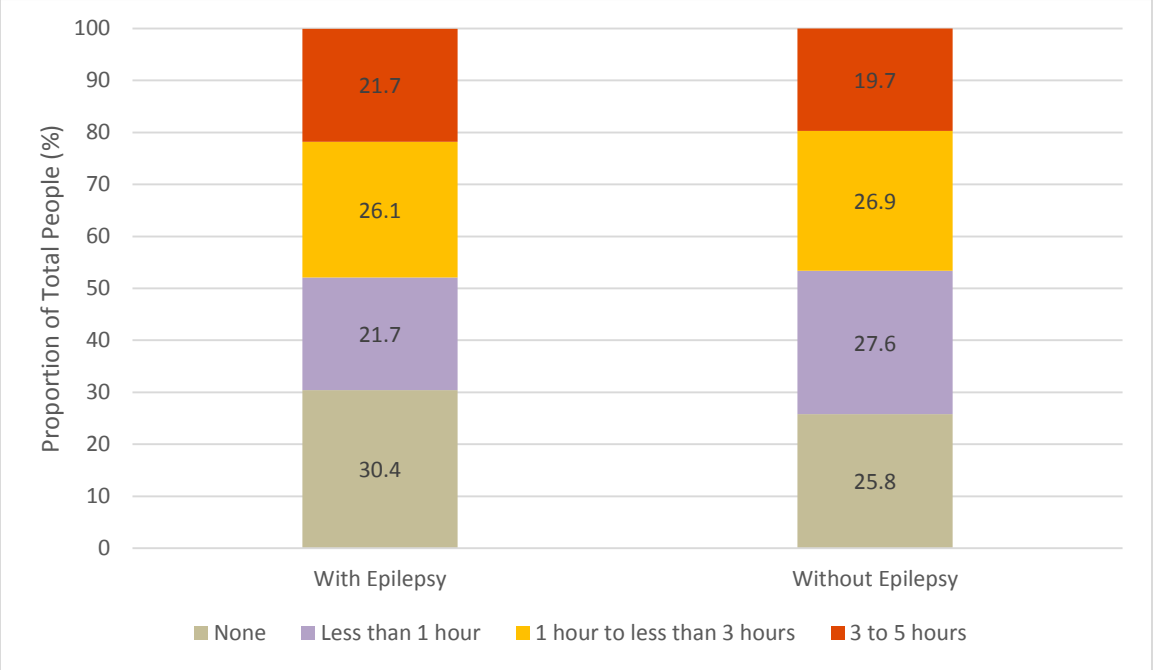


Chi square, p = NS

4.5.3 Sun Exposure

Among those 50 and older, there was no significant difference in sun exposure between PWE and those without, as measured by time intervals spent in the sun. (Figure 4). There was also no significant difference in reported sun burns (Figure 3).

Figure 4. Time spent in sun in a normal day by those 50 years and older, CCHS 2010



Chi square, p = NS for all analyses

4.5.4 Weight-bearing Activity – Participation

Among those 50 and older there was no significant difference in reported participation in at least one weight-bearing activity in the past 12 months based on epilepsy status (Table 4). Among people without epilepsy who were 50 years and older, significantly ($p<0.0001$) more women reported participating in at least one weight-bearing activity than men. This difference was not observed among PWE who were 50 years and older. Among the 18–49 year olds there was no significant difference in reported participation in at least one weight-bearing activity in the past 12 months based on epilepsy status (Table 4); people who were not ambulatory were excluded from this

analysis due to the higher amount of non–ambulatory people in the 18–49 year old PWE subgroup.

Among those 18–49 years old, PWE reported participating in significantly ($p<0.001$) less types of weight-bearing activities than those without. However 18–49 year old PWE participated in significantly ($p<0.025$) more types of activities than their older counterparts. Similarly, among people without epilepsy, the younger subgroup participated in significantly ($p<0.0001$) more types of activities than the older subgroup. Although PWE 50 years and older also participated in less different types of weight-bearing activities compared to people without epilepsy in the same age group this difference was not significant (Table 4).

4.5.5 Weight-bearing Activity – Frequency

Among those 50 years and older, PWE participated in weight-bearing activities significantly ($p<0.001$) less often in a 3 month period than those without epilepsy (Table 4). Women with epilepsy who were 50 years and older reported participating in weight-bearing activities significantly ($p<0.020$) more often than their male counterparts. Although among those without epilepsy the younger subgroup participated in weight-bearing activities significantly ($p<0.006$) more often than the older subgroup, this difference was not observed among PWE.

Table 4. Participation in weight-bearing activities, CCHS 2010

Age Group Epilepsy Status Gender	Participated In Weight-bearing Activity (%)	Number of Different Types of Activities Participated in (mean)	Number of Times Participated in Activity in Past 3 Months (mean)
18–49 year olds			
With Epilepsy	87.3*	2.13[a,b]	74.68
Without Epilepsy	88.5*	2.75[a,c]	82.71[d]
50 years and older			
With Epilepsy	82.4	1.39[b]	57.42[e]
Male	81.0	1.50	39.93[h,i]
Female	82.9	1.27	74.69[h]
Without Epilepsy	80.3	1.53[c]	76.46[d,e]
Male	78.7[f]	1.51[g]	76.69[i]
Female	81.7[f]	1.55[g]	76.26

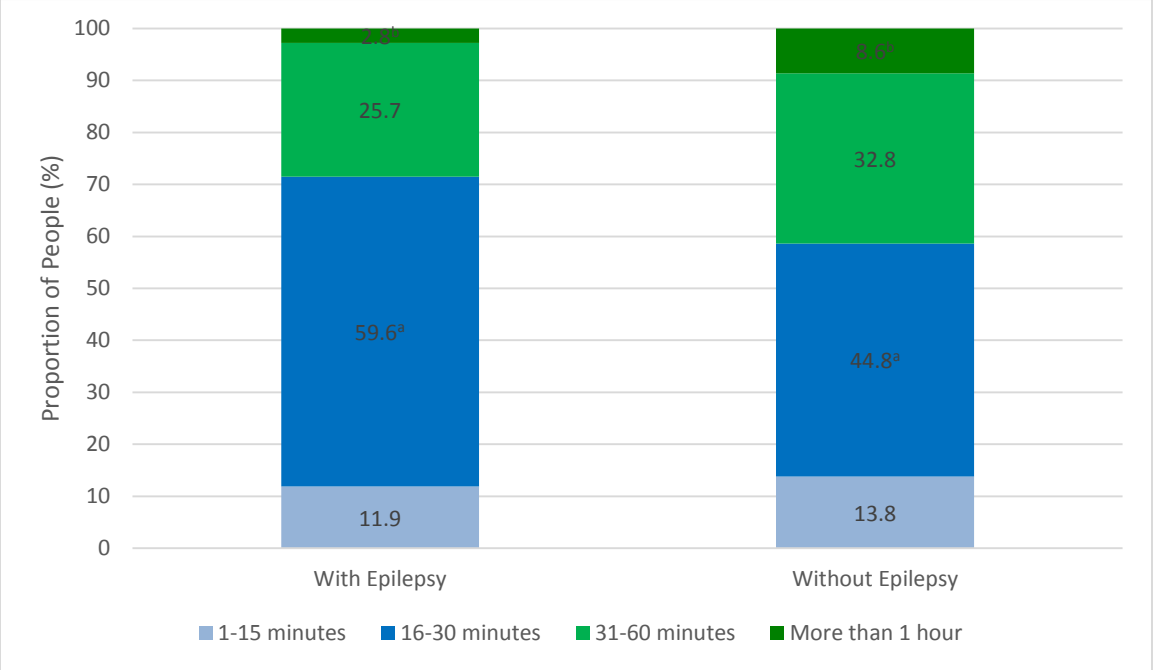
Within group percentages shown in parentheses, % = Chi square, mean = ANOVA, * = non-ambulatory people were excluded from analysis, a = $p<0.001$ between groups, b = $p<0.025$, c = $p<0.0001$, d = $p<0.001$, e = $p<0.001$, f = $p<0.0001$, g = $p<0.029$, h = $p<0.020$, i = $p<0.0001$

4.5.6 Weight-bearing Activity – Duration

Duration of activity was measured in ordinal categories and participants who engaged in more than one activity would have more than one value for duration (one per each reported activity), therefore means of these values were calculated and re-sorted into the original categories. Before investigating each category, overall means between those with and without epilepsy were compared to determine if there were any significant differences. Among those 50 and older, overall PWE were on average significantly ($p<0.011$) more likely to participate in weight-bearing activities for shorter time intervals per session than those without epilepsy, scoring 2.20 out of 4 compared to 2.40 out of 4. Upon finding this difference, further investigation was conducted to ascertain in which time interval category or categories this difference was apparent. We found that significantly ($p<0.002$) more PWE reported to 16–30 minutes of exercise than those without epilepsy while significantly ($p<0.013$) less PWE reported to more than one hour of

exercise than those without epilepsy (Figure 5). Among those without epilepsy who were 50 years and older, men reported participating in weight-bearing activities for significantly ($p<0.0001$) longer time intervals than women, scoring 2.42 out of 4 compared to 2.31 out of 4; this difference was not significant among PWE in the same age group with men 50 and older with epilepsy scoring 2.23 out of 4 and women 50 and older with epilepsy scoring 2.16 out of 4. Among those without epilepsy, the younger subgroup participated in weight-bearing activities for significantly ($p<0.0001$) longer time intervals than the older subgroup, scoring 2.46 out of 4 compared to 2.36; this difference was not significant within PWE with 18–49 year olds scoring 2.44 out of 4 compared to those 50 and older scoring 2.20.

Figure 5. Average time spent participating in weight-bearing activity per session by those 50 years and older, CCHS 2010



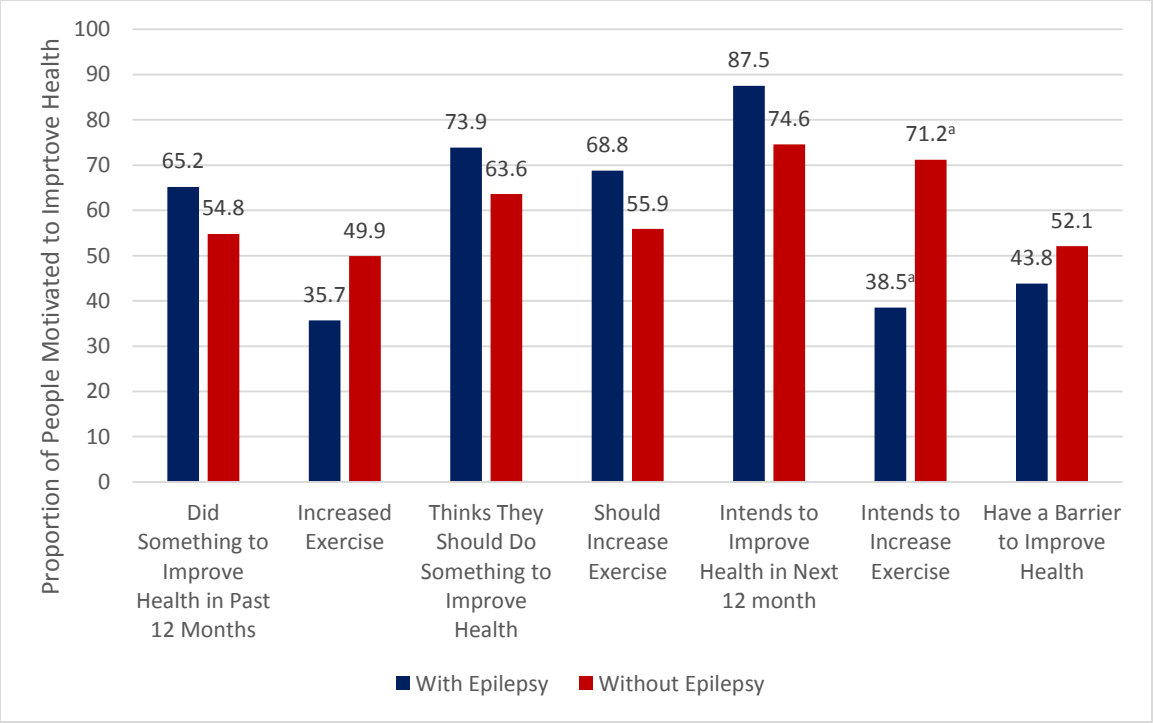
Chi square, a = p<0.001, b = p<0.013

4.5.7 Motivation

There was no significant difference in PWE 50 years and older who reported having a barrier (such as illness) that prevented them from improving their health as compared to those without epilepsy in the same age subgroup (Figure 6). There was no significant difference based on epilepsy status in the proportion of people who reported believing that they should improve their physical health (73.9% of PWE vs. 63.6% without epilepsy) or in those who reported doing something to improve their physical health in the past 12 months (65.2% vs. 54.8%) or in those who reported intending to do something to improve their physical health in the next year among those 50 years and older (87.5% vs. 74.6%). There was also no significant difference based on epilepsy status in the number of people

who reported that they thought increasing exercise is the most important thing they should do to improve their health (68.8% of PWE vs. 55.9% of those without) or who reported that exercising more was the most important thing they did to improve their health in the past 12 months among those 50 years and older (35.7% vs. 49.9%). However, among this older age group significantly ($p<0.015$) fewer PWE reported that they intended to exercise more in the next year to improve their health as compared to those without epilepsy (38.5% of PWE vs. 71.2% without epilepsy).

Figure 6. Motivation to improve health in those 50 years and older, CCHS 2010

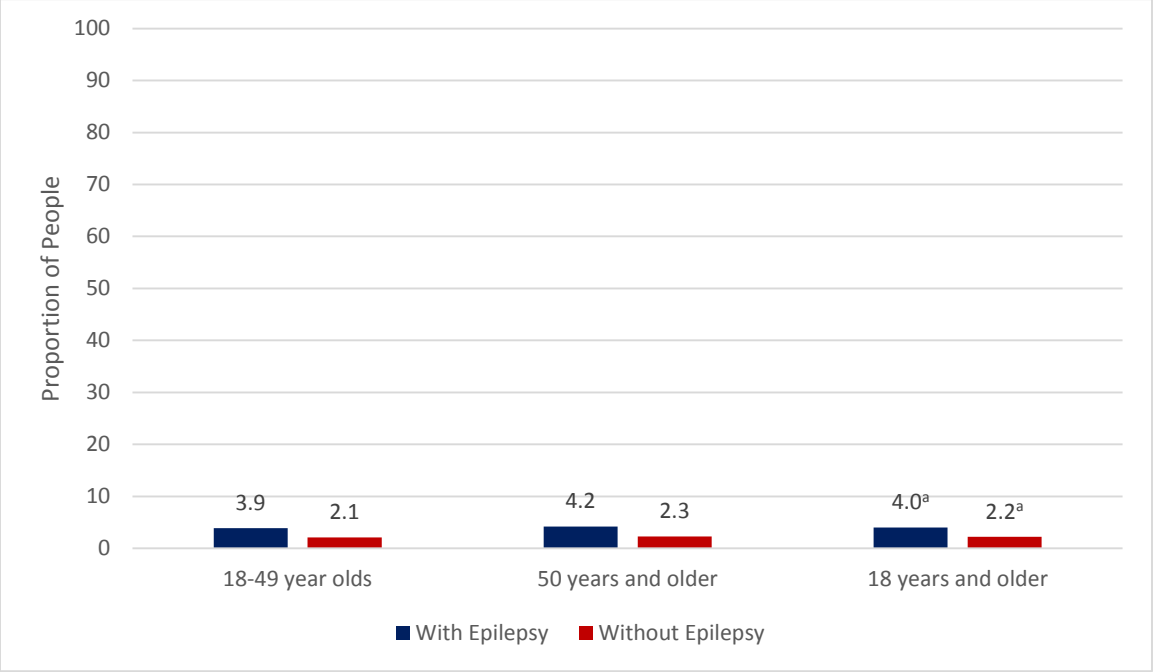


Chi square, a = $p<0.015$

4.5.8 Fracture

There was no significant difference in fracture occurrence based on epilepsy status in either age subgroup (Figure 7). However, when considering the entire adult (18 years and older) population, a significantly ($p<0.042$) higher number of PWE reported having a fracture in the past 12 months as compared to people without epilepsy.

Figure 7. Proportion that reported a fracture in the past 12 months, CCHS 2010



Chi square, a = $p<0.042$

4.6 Discussion

Consistent with the reports of higher risk of fracture among people with epilepsy, this study found that in the 2010 CCHS survey among adults (aged 18 years and older) significantly more PWE reported experiencing a fracture in the past 12 months than people without epilepsy though the higher number of fractures in PWE was not significant when looking only at those aged 50 and older. A retrospective matched cohort study conducted in

Manitoba looking specifically at osteoporotic fractures in individuals aged 50 and older with a larger sample size (79 cases of PWE with a fracture compared to 6 cases of PWE with a fracture in this study) found that individuals with an osteoporotic fracture were significantly more likely to have epilepsy and that use of the AEDs carbamazepine, clonazepam, gabapentin, phenobarbital and phenytoin, regardless of epilepsy status, were all significantly associated with osteoporotic fracture[120]. Considering the small sample size of PWE and the low number of reported fractures in our study, it is unsurprising that a significant difference is not observable when the population is broken into subgroups.

This study investigated several osteoprotective behaviours among those aged 50 and older that may impact fracture occurrence to determine if there was a difference in these behaviours between PWE and those without epilepsy in this especially vulnerable older group. Some differences became apparent from an in depth analysis of physical activity, specifically the weight-bearing type which is beneficial to bone. No significant differences in osteoprotective food choices or sun exposure were found among those aged 50 and older.

Despite there being no significant difference in the proportion of people who participated in any weight-bearing activity regardless of epilepsy status, there were differences in the number of different types of activities people participated in, how often they participated in these activities over 3 months and how long they spent on these activities per session. Older adults (50 years and older) with epilepsy typically engaged in weight-bearing activities less often and for shorter duration than older adults without epilepsy. Older men with epilepsy reported participating in weight-bearing activities less

often, not only than men without epilepsy, but also than women with epilepsy. Younger adults (aged 18 to 49 years old) reported more variety in the weight-bearing activities they participated in compared to their older counterparts, but those with epilepsy showed significantly less variety than those without. On the other hand, while in the general population younger adults unsurprisingly participated in weight-bearing activities significantly more often and for significantly longer duration than their older counterparts this was not observed among PWE. Overall, older adults with epilepsy appeared to be less active than older adults without epilepsy and this overall pattern was not observed in younger adults (excluding a tendency for less variety in the weight-bearing activity choice of younger PWE).

A previous study examining Canadians aged 12 years and older found that those with epilepsy were less active than the general population while a study examining those aged 12–39 years old did not: our findings may explain this disagreement, suggesting that this difference in physical activity may be more pronounced in the older age range. Women with epilepsy who are at increased risk of fracture not only due to epilepsy status but due to their biological sex do appear to participate in higher amounts of physical activity than men with epilepsy. This could be indicative of a gender bias in the education on bone health awareness; an intervention study conducted on 2,438 people found that women scored higher than men on an osteoporosis knowledge test both before and after an educational intervention[121,122]. However, the same pattern is not observed in those aged 50 and older without epilepsy and, in fact, women with and without epilepsy participate in a similar amount of physical activity as men without epilepsy. This suggests that rather than women with epilepsy being more active it is a case of men with epilepsy being less active.

Other studies have found patients with epilepsy to be less active and less physically fit than the general population[123–125]. One study investigating patients with epilepsy between 5–17 years of age and their non-epileptic siblings found that the patients with epilepsy to be less active, significantly so in those 13–17 years old when comparing number of hours spent in group sports and total sports[125]. In the 13–17 age group, significantly more parents of patients with epilepsy reported their children as being "less active than they would like" as compared to sibling controls; parents of 61% of the patients with epilepsy cited "laziness or lack of interest in exercising" as a reason for their child's perceived lack of activity as compared to 31% for controls[125]. A non-significant association between increased seizure frequency and less sports activity was found in all patients[125]. The lower sports activity observed in patients with epilepsy in the more autonomous age group of 13–17 years as compared to 5–12 years may demonstrate teenagers with epilepsy forming their own personal exercise habits that could persist into adulthood. A cohort-matched control study of 100 adults with a mean age of 36.5 years and with recurrent, unprovoked seizures since childhood without associated initial neurological impairment or disability did not find a significant difference in frequency of exercise in those with epilepsy compared to controls however they did find that those with epilepsy were significantly less physically fit as measured by several muscle-power tests[126]. Though frequency of exercise was investigated, duration of exercise was not which may explain discrepancies between exercise frequency and physical fitness.

In the past, people with epilepsy were cautioned against physical activity which may in part explain the trend of less exercise and lower physical fitness than their non-epileptic counterparts. The American Medical Association Committee on Medical Aspects of Sports

encouraged avoidance of both collision sports and non-contact sports in people with epilepsy in 1968[123,127]. However by 1997 the International League Against Epilepsy was recommending that only skydiving and scuba diving should be avoided by people with epilepsy[123,128]. There is little evidence that exercise induces seizures in PWE or that the repetitive minor head trauma that may occur during contact sports worsen seizure frequency or severity[123]. There is evidence that exercise can improve mental and social functioning in PWE[124,129–132] and that restricting participation in sports can be emotionally distressing[129,133].

In our study the lower level of physical activity seen in older PWE did not appear to be associated with self-perceived barriers among PWE because self-report of having a barrier to improving health was similar between PWE and those without epilepsy. It is possible that this item in the CCHS does not have the nuance to examine the relationship between epilepsy and exercise habits but ours is not the only study to find this. A previous study investigating physical activity in 176 adults with epilepsy found that of the 22% of patients with epilepsy who reported reducing physical activity in the previous year due to illness (as compared to 24% of matched controls), only 2% cited epilepsy as the reason[126]. There was also no observed association between continuation of seizures, AED use or self-perceived health with physical activity in patients with epilepsy[126].

In this study, the proportion of older PWE who reported increasing their exercise to improve their physical health in the past 12 months and believing that they should increase their exercise to improve their physical health was not significantly different compared to the general population, however significantly less PWE had the intention of increasing their

exercise in the next 12 months. This suggests a lack of motivation to exercise not caused by perceived inability to exercise nor by the belief that more exercise is unnecessary. A study in children with epilepsy did find a non-significant association between higher seizure frequency and less sports activity[125]. Epilepsy concern influencing exercise behaviours in childhood that persist in adulthood, though epilepsy concern during physical activity may be less salient, is a possible theory. Our study observed less physical activity in younger PWE aged 18–49 than their non-epileptic counterparts though the difference was only significant between PWE aged 50 and older and their non-epileptic counterparts. Further investigation into motivation to exercise in individuals with epilepsy is necessary to understand the lower physical activity seen in people with epilepsy and to examine the gender difference found in this study. The motivation findings in this study suggest that lower exercise is not due to a lack of knowledge on the benefits of exercise and thus may not be improved by increased education as PWE were similar to those without epilepsy in thinking that they should exercise more to improve their physical health. Gender analysis on motivation could not be completed due to low sample size of PWE.

Though older PWE are at an increased risk of fracture, their dietary choices based on calcium content and osteoporosis concern were similar to older adults without epilepsy. Sun exposure, the main source of vitamin D, was also similar between older PWE and those without epilepsy. A study administering the Osteoporosis Knowledge Test in 94 patients with epilepsy with a mean age of 45 found that knowledge scores on calcium and exercise were lower than that found in previous studies on the general population[134]. This lower osteoprotective knowledge may explain our findings and, overall, this may be indicative of a lack of knowledge on the increased risk of bone disease associated with epilepsy.

There were limitations in this study due to the use of the CCHS which is a survey on general health and not focused specifically on bone disease or epilepsy. Data were not collected for the use of vitamin D or calcium supplements and calcium dietary intake was not investigated therefore the measurement of these osteoprotective behaviours in this analysis was indirect. The small sample size of adults with epilepsy also limited our analysis, particularly low fracture occurrence within the past 12 months as well as the low response rates on questions regarding sun exposure and dietary choices. Future research investigating vitamin D and calcium intake in older adults with epilepsy is necessary.

Despite these limitations, this study did find that, though they face an increased risk of bone disease, the application of osteoprotective behaviours in older adults with epilepsy is similar or lower than older adults without epilepsy. Motivation to exercise in adults with epilepsy merits further investigation, especially considering the psychosocial benefits of physical activity in PWE as well as the osteoprotective benefits.

4.7 Disclosures

This research was supported by funds to the Canadian Research Data Centre Network (CRDCN) from the Social Sciences and Humanities Research Council (SSHRC), the Canadian Institute for Health Research (CIHR), the Canadian Foundation for Innovation (CFI) and Statistics Canada.

Mandatory, as stated in the Microdata Research Contract: “Although the research and analysis are based on data from Statistics Canada, the opinions expressed do not represent the views of Statistics Canada.”

5 Survey: Vitamin D intake among older adults with epilepsy

5.1 Rationale

AEDs are thought to compromise bone health in people with epilepsy and so the application of osteoprotective behaviours such as physical activity and calcium and vitamin D intake in this population is of interest, especially in those aged 50 and older who are even more vulnerable to metabolic bone disease[74,75]. There is research investigating physical activity in people with epilepsy and nationwide data on physical activity in Canadians with epilepsy is available[71,72]. However, vitamin D and calcium intake information in people with epilepsy is not as prevalent. The association between enzyme-inducing AEDs and decreased bone health is thought to function via a decrease in serum vitamin D; a systematic review on the effect of vitamin D treatment on bone health in adults with epilepsy found some evidence for beneficial effects but was lacking in conclusions on optimal dosing and so information on vitamin D intake in adults with epilepsy is particularly important. Other studies have gauged vitamin D and calcium supplementation in adults with epilepsy to be from as high as 25.4% in adults with a mean age of 41.9 years to as low as 4.9% in a veteran population with a mean age of 55.7 years[66,67]. The prevalence of vitamin D supplementation in Canadian adults aged 50 and older with epilepsy is not known. Differences in vitamin D supplementation based on AED type (enzyme-inducing vs. non-inducing) in older Canadian adults is not known. Finally, a survey in Norway on women aged 16–42 years being treated for epilepsy found that 88% of those who were

taking AEDs known to interact with bone metabolism were not aware of this adverse effect[65]. This study did not consider adults aged 50 and older and excluded men.

Our study will aim to fill in these gaps in information regarding supplementation in older Canadian adults with epilepsy as well as the awareness of the association between AEDs and decreased bone health.

5.2 Objectives

Primary Objective:

1. To determine the prevalence of vitamin D supplementation in Canadian adults aged 50 and older with epilepsy and to investigate if there is a difference based on type of AED(s) being used or based on gender.

Secondary Objectives:

2. To determine the total vitamin D intake via diet and supplements in Canadian adults aged 50 and older with epilepsy
    a. Is there a difference based on type of AED(s) being used?
    b. Is there a difference based on gender?
3. To conduct an exploratory analysis of the awareness of the association between AEDs and decreased bone health in Canadian adults aged 50 and older with epilepsy
    a. Is there a difference based on type of AED(s) being used?
    b. Is there a difference based on gender?

5.3 Hypothesis

The prevalence of vitamin D supplementation in older adults with epilepsy will be comparable to the 4.9% found in a previous study[66].

5.4 Methodology

5.4.1 Study Design

An epidemiological cross-sectional survey was designed to investigate several aspects of bone health in older adults with epilepsy, including: vitamin D supplement use, calcium supplement use, dietary vitamin D intake and osteoporosis/osteopenia diagnosis. Due to the involvement of human participants, this research has been approved by the University of Waterloo Research Ethics Board.

3.3.2 Questionnaire

With permission, a survey by Fedorenko and colleagues was used as a foundation for the survey design[67]. Details on epilepsy treatment will be collected: current and past AED use, type of AED(s), dose and duration. Questions probing the awareness of bone health and the increased risk of bone disease associated with AEDs are included. The type of data being collected is observational and are largely prevalence values and so do not necessitate intervention study designs or longitudinal designs. A survey is ideal as the ease of study design and data collection is optimized.

The survey used by Fedorenko and colleagues was designed by adopting items from validated surveys (National Health and Nutrition Examination Survey (NHANES), Behavioral Risk Factor Surveillance System (BRFSS) questionnaire) and previously published articles. In this project the survey has been modified by modeling questions on supplementation and dietary intake more closely to those from the validated source (NHANES)[135,136]. Additional questions to be investigated that were not addressed by Fedorenko, Wagner & Wu to probe the awareness of the association between AEDs and bone loss and if this association has been brought to attention by the participants' doctor(s) were created. The questionnaire consists of 15 items, with 4 additional questions included in the online version (see Appendix B, Figure 8).

3.3.3 Survey Validation

The survey largely consists of adopted items from previously validated surveys. Co-investigators provided feedback on clarity, comprehensibility and precision of items which were incorporated in the final design.

5.4.2 Sample Size

Using the 4.9% prevalence of vitamin D and calcium supplement use in people with epilepsy found by Espinosa and colleagues[66], a 95% confidence interval and a standard error of 0.05, in order to accurately determine the proportion of older adults (≥50 years old) with epilepsy who take vitamin D supplements, a sample of at minimum 72 participants must be recruited (see Figure 9). Sample size was calculated using a formula for estimating the proportion of a binary outcome in a descriptive study[137].

Formula 1. Sample size calculation

$$n = \frac{z^2 \frac{a}{2} p(1-p)}{d^2}$$

Where: a 95% confidence interval results in $a = 0.05$ and therefore $z^2 \frac{a}{2} = 1.96$

Vitamin d prevalence is $p = 0.049$ and therefore $1 - p = 0.951$

Absolute standard error is $d = 0.05$

$$n = \frac{1.96^2 \times 0.049 \times 0.951}{0.05^2}$$

$$n \cong 72$$

5.4.3 Participant Recruitment

Inclusion Criteria

This study is investigating both male and female older adults (aged 50 years and above) with self-identified epilepsy or seizure disorder. Participants should have past or present AED use.

Exclusion Criteria

Individuals who are unable to provide informed consent will be excluded from this study. Ability to consent may be impaired in non-English speakers without translators and in individuals with cognitive impairment. Exclusion of non-English speakers without translators and of individuals with cognitive impairment is also to improve reliability of answers by limiting the possibility of a lack of comprehension of survey questions.

Potential participants have been invited to participate in the survey through epilepsy support organizations: Epilepsy South Central Ontario and the Canadian Epilepsy

Alliance. Recruitment flyers have been posted in public spaces such as libraries and grocery stores as well as independent living facilities and on social media. Individuals with epilepsy from previous studies have been contacted for participation. See Appendix B, Figure 10 for recruitment protocol.

5.4.4 Survey Administration

The survey has been made available via several routes: internet, mail and telephone. The primary route of administration is online hosted by SuveyMonkey. This is because targeted recruitment via epilepsy organizations is mainly facilitated by the internet (e.g. recruitment emails, social media). Potential participants have been invited to contact the researchers to arrange to complete the survey using an alternate method (telephone, mail). Online consent is obtained by participants choosing to open the survey link; phone surveys require verbal consent and mailed surveys had signed consent. Information and feedback letters with study details, confidentiality and ethical statements are included as part of the survey package in online and mailed administration and for phone surveys is both verbally conveyed and sent to participants via email, fax or mail. ID numbers have been assigned to participants; separate ID number classifications are used for each route of administration. ID numbers are linked to completed surveys.

The study is ongoing; data is currently being collected.

5.4.5 Statistical Analysis

Descriptive statistics on prevalence of vitamin D supplement use and vitamin D dietary intake will be reported. Regression modeling for vitamin D supplement use as a response incorporating the explanatory factors age, gender, epilepsy medication and seizure frequency will be completed if sample size and response rates allow. Self-reported osteoporosis will be controlled for. See Appendix J for full statistical analysis plan.

6 Conclusion

6.1 Management of bone health in people with epilepsy

It is well established in the literature that many AEDs have been linked to decreased bone health[15,22,138]. A management plan for this adverse effect associated with AEDs has not established. Management of age-related bone loss in the general population can be used as a basis for management of AED-related bone loss; weight-bearing exercise as well as calcium and vitamin D intake are recommended non-pharmacological osteoprotective behaviours[42–45]. Typically age-related bone loss becomes a salient issue at ages of 50 years and older[74,75], therefore adults with epilepsy 50 years and older have an accumulation of risk for bone loss that is of particular concern.

6.2 Exercise as an osteoprotective measure in people with epilepsy

An analysis of the 2010 CCHS data found that adults with epilepsy participate in weight-bearing physical activity less often than adults without epilepsy and that this difference is significant in those 50 and older. PWE 50 and older also participate in weight-

bearing activities for significantly shorter duration than those 50 years and older without epilepsy. This is in agreement with previous research that has found people with epilepsy to be less active and less physically fit[72,124–126].

It is worth noting that there older adults were less active as compared to younger adults, regardless of epilepsy status in the CCHS 2010 data. This phenomenon is also evident in the literature[139–142]. A review on 38 intervention studies on physical activity in adults with a minimum age of 40 years and an average age of 50 years and older found little evidence on long-term effectiveness[143].

In the 2010 CCHS data, a significantly larger proportion of people with epilepsy 50 years and older reported having no intention to increase their exercise to improve their physical health as compared to those 50 years and older without epilepsy. Due to AED use, people with epilepsy have an additional risk of decreased bone health. Their participation in the osteoprotective behaviour of exercise, however, does not correspond to this increased risk and, in fact, is lower than the general population.

Considering the previous, now defunct, warnings against exercise in people with epilepsy, while the 2010 CCHS data show that people with epilepsy 50 years and older do not report significantly more self-perceived barriers to improving their health than those without epilepsy, the reasoning behind lower levels of exercise in people with epilepsy is unclear. Moreover, as the 2010 CCHS data shows that people with epilepsy 50 years and older are similar in their belief that they should increase their exercise to improve their health to those without epilepsy, it appears that any programs to education and/or engage people with epilepsy with the goal of increasing exercise in this population would require

nuance and a thorough understanding of the underlying relationship between exercise and epilepsy status. More research is necessary to delineate this relationship.

6.3 Calcium and Vitamin D as an osteoprotective measure in people with epilepsy

According to the NHANES survey of 2003–2006, 8–22% of 4061 adults 51 years and older were reaching adequate intake of calcium via their diet and 1–7% of 1924 adults 51 years and older were reaching adequate intake of vitamin D via their diet[69]. There was a clear trend in both calcium and vitamin D dietary intake showing that with increasing age, the amount of people reaching adequate intake levels decreased[69].

Supplementation is a convenient, feasible method of improving intake levels of these vital nutrients; data from the 2007–2009 Canadian Health Measures Survey in 5306 Canadians aged 6–79 years old found that vitamin D supplement users had significantly higher serum vitamin D concentrations than non-users[68]. In the general population, the prevalence of regular (5 years or more) calcium supplementation was found to be approximately 33% in a survey of 100,196 people aged 45–75 years old[144]. In the NHANES survey of 2003–2006, of 20,470 Americans aged 1 year and older, 43% reported using calcium supplements and this number increased to 51%–67% when considering only those aged 51 years and older; use of vitamin D supplements was 37% in those aged 1 year and older and this number increased to 40%–49% when considering only those aged 51 years and older[69].

In comparison, there are very little data on calcium and vitamin D intake, via diet or supplementation, in people with epilepsy. Two studies that investigated both calcium and

vitamin D found that prevalence of supplementation in adults with epilepsy was 4.9% and 25.5% in samples with mean ages of 55.7 and 41.9 years respectively. Though these prevalence percentages are very different, they are both lower than those found in the general population. The CCHS 2010 cycle received low response rates for questions on dietary choices related to osteoporosis concern or calcium content and for sun exposure; using these indirect measures of calcium and vitamin D intake it was found that there was no significant difference between older adults with and without epilepsy.

6.4 Challenges with managing bone health in people with epilepsy

Along with the previously mentioned decline in physical activity with increasing age seen in all adults, regardless of epilepsy status, the relationship between epilepsy and motivation to exercise is not yet understood. It is possible then that the programs that exist to encourage physical activity in older adults may not be as effective in older adults who have epilepsy. Moreover, interventions in older adults without epilepsy have not shown strong evidence for adherence in the long-term. Targeting this osteoprotective behaviour to manage bone health in people with epilepsy, particular older adults, may require additional nuance.

In comparison, calcium and vitamin D supplementation may be a more convenient and feasible route. Of the AEDs that have been linked to detrimental effects on bone, the majority are enzyme-inducing and have been associated with decreased biologically active vitamin D. As vitamin D intake is already considered to be osteoprotective, this evidence-based connection to AEDs that are commonly used by people with epilepsy makes it

particularly appealing for managing the adverse effect of decreased bone health in people with epilepsy.

A systematic review on the effect of vitamin D supplementation on bone health in adults with epilepsy had overall positive findings in the studies reviewed, though there was a lack of standardized procedures. Previous research in the general population has found that recommended doses of vitamin D are too low to see an effect on fracture outcome; the systematic review did not provide any clarity on the issue of optimal vitamin D dosing regimen. This serves as an obstacle towards developing a standardized management plan for bone health in adults with epilepsy.

A ubiquitous challenge when facing the management of any adverse effect is awareness. Regardless of choice of osteoprotective measure, one needs to be aware that the potential for bone loss exists in order to confront it. The negative effect on bone associated with many AEDs has been researched as early as the 1960s[15]. However few epilepsy treatment guidelines make note of this adverse effect[10,56,57] and a study conducted in an area that did have local recommendations of vitamin D and calcium supplementation for women taking enzyme-inducing AEDs found that less than 5% of the women taking enzyme-inducing AEDs were informed of this[65].

A currently ongoing cross-sectional study of original design will aim to fill in the challenges caused by gaps of knowledge stated here. Prevalence of vitamin D supplementation specifically, rather than in combination with calcium, will be determined in older adults with epilepsy. Dosing of vitamin D in this population will be investigated. Prevalence of calcium supplementation as well as dietary intake of vitamin D will also be

investigated. Finally, an exploratory analysis of awareness of the adverse bone health effect associated with some AEDs in older adults with epilepsy will be conducted; this will consider both the awareness of the adverse effect as well as the source of the awareness (such as family doctor, friends, family, their own research).

7 Implications

This research has explored several aspects of bone health in people with epilepsy and the findings have both provided information to guide research and highlighted gaps in knowledge. The finding that the lower physical activity seen in people with epilepsy does not appear to be related to self-perceived barriers suggests that further research is needed to explore the reasoning behind lower physical activity in people with epilepsy. Findings from the systematic review suggested that there is some beneficial effect of supplementation on bone health outcomes in adults with epilepsy but that optimal dosing regimen is unknown and that methodology was heterogeneous, motivating further research into this area. Findings from the upcoming original survey will provide information on the prevalence of vitamin D supplementation in older adults with epilepsy as well as what doses are typically being used. Comparing these findings to prevalence of supplementation in the general population as well as recommended doses in the general population will allow a deeper understanding of the degree of participation in this osteoprotective behaviour by people with epilepsy. Information on if people with epilepsy are aware of the adverse bone health effect associated with many AEDs along with where they are getting this information from will help to guide any future efforts to improve education and awareness on this topic.

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Appendices

Appendix A – Database keywords and search terms

Database	Keywords	Search terms	Limitations
Clinical Trial.gov	Epilepsy (condition); Vitamin D (intervention)	osteoporosis; osteomalacia; osteopenia	Adults
Cochrane Trials		epilepsy; vitamin D	
Embase	Bone Density; Bone Strength; Osteoporosis; Osteopenia; Osteomalacia; Bone Disease; Epilepsy; Anticonvulsive Agent; Vitamin D; Ergocalciferol; Colecalciferol	bone adj2 health*; epilep*; calciferol	Human; Adult; Exclude Medline results
EU Clinical Trials Register		epilepsy; vitamin D	Adult and Elderly
Health Canada Clinical Trial Database	Epilepsy (medical condition)		
International Pharmaceutical	Epilepsy	epilep*; anticonvulsant; anti epileptic drug; vitamin D; ergocalciferol; cholecalciferol; colecalciferol; calciferol	
Medline	Bone Density; Osteoporosis; Bone Diseases, Metabolic; Epilepsy; Anticonvulsants; Vitamin D; Ergocalciferols; Cholecalciferols;	bone adj2 health*; osteopenia; epilep*; calciferol	Humans; All adults
PubMed		epilepsy; vitamin D	Human; Clinical Trials or Case Report or Comparative Studies or Controlled Clinical Trials
Scopus		epilepsy; vitamin D	Articles; Adult; exclude book source

Appendix B – Search phrases for a systematic search using Google

Search #	Search phrase
1	epilep AND “vitamin d” AND ~trial AND ~supplement AND -children
2	epilepsy AND ergocalciferol AND ~trial AND -children
3	epileptic AND “vitamin d” AND -children AND bmd
4	~epilepsy AND ~bone AND ergocalciferol AND intervention
5	epilep AND ~osteoporosis AND calcitriol AND ~intervention
6	~epileptic AND osteoporosis AND ergocalciferol
7	epilepsy AND bmd AND ~trial AND ~ergocalciferol
8	“epilepsy” AND “vitamin d” AND ~bone AND -children
9	aed AND “vitamin d” AND bmd
10	~aed AND ~ergocalciferol AND ~bone AND -children

Appendix C – Summary of included studies

Study	Location	Study design	Sample size	Study length	AED(s) used	Vitamin D intervention (IU/day)	Bone outcomes measured
Christiansen *et al.*, 1973*	Europe	RCT	226	3 months	PB PR PH	2,000 D2	ALP, BMC, calcium
Hahn & Halstead, 1979	USA	QE	6	4 months	PB PH	4,000 D3 (2,000 twice daily)	25-OHD, ALP, calcium, forearm bone mass, inorganic phosphate, PTH
Hoikka *et al.*, 1982	Europe	QE	9	6 months	PH PR PH	2,000 D2	25-OHD[#], biopsy, BMD, calcium, inorganic phosphate
Krishnamoorthy *et al.*, 2010*	India	RCT	66	3 months	VPA PH	400 25-OHD	25-OHD, ALP, calcium
Mikati *et al.*, 2005	Asia	RCT		12 months	CBZ VPA PB PH PR LTG TP GB CLN	400/4,000 25-OHD	25-OHD, BMD
Mosekilde *et al.*, 1977	Europe	QE	20	9 months	PH	9,000 D3	25-OHD, ALP, biopsy, phosphorous, PTH
Offermann *et al.*, 1979	Europe	RCT	95	9 months	PB PH PR	214/714/1429 D3	25-OHD, ALP, calcium, PTH
Pedrera *et al.*, 2000	Europe	QE	30	1 month	CBZ PH VPA	120,000 D3 (once)	25-OHD, ALP, hand Ad-SOS, PTH
Sherk & Snape, 1977	USA	QE	27	8 months	PB PH	7,143 D3 (50,000 weekly)	25-OHD, ALP, calcium, phosphorous

*studies with a calcium control for both the placebo and treatment arms, [#] measured after 3 months instead of full 6 months, Ad-SOS = Amplitude-dependent speed of sound ultrasound, ALP = alkaline phosphatase, BMC = bone mineral content, BMD = bone mineral density, CBZ = carbamazepine, CLN = clonazepam, GB = gabapentin, LTG = lamotrigine, PB = phenobarbital, PH = phenytoin, PR = primidone, PTH = parathyroid hormone, QE = quasi-experimental study, RCT = randomized controlled trial, TP = topiramate, VPA = valproate[84–92]

Appendix D – Modified Newcastle-Ottawa Scale for non-randomized studies

Biases	**Hahn & Halstead, 1979**	**Mosekilde *et al.*, 1977**	**Pedrera *et al.*, 2000**	**Sherk & Snape., 1977**	**Hoikka *et al.*, 1982**
Representativeness	2	2	2	2	2
Sample size power	1	2	2	2	1
Confounder adjustment	1	2	3	2	3
Appropriate statistics use	3	3	3	3	3
Treatment of missing data	2	2	3	2	0 Not verified
Methods/outcome measurements stated and appropriate	3	3	3	3	2
Objective assessment of outcomes	2	2	2	2	2
Total (out of possible 21)	14	16	18	16	13

0=definitely no, 1=mostly no, 2=mostly yes, 3=definitely yes, Not verified=not explicitly stated in study [85,86,89,91,92]

Appendix E – Cochrane Collaboration Tool – Risk of bias assessment for randomized studies

Biases	**Christiansen *et al.*, 1973**	**Krishnamoorthy *et al.*, 2010**	**Mikati *et al.*, 2005**	**Offermann *et al.*, 1977**
Adequate generation of allocation sequence	1	1	1	1
Adequate concealment of allocation	1	0 Not verified	1	0 Not verified
Adequate prevention of knowledge of intervention	0 Not verified	0 Not verified	0	0 Not verified
Incomplete data adequately addressed	1	1	1	1
No selective outcome reporting	1	1	1	1
No other problems that would lead to high risk of bias	1	1	1	1
Total (out of possible 6)	5	4	5	4

0=high risk of bias, 1=low risk of bias, Not verified=not explicitly stated in study[84,87,88,90]

Appendix F – Description of outcomes measured in included studies

Outcomes measured	**Description**
Alkaline phosphatase (ALP)	A bone turnover marker, ALP is a marker of bone formation. The normal range of ALP varies by age and gender; bone diseases may cause elevations in ALP[101]
Amplitude-dependent speed of sound (Ad-SOS) ultrasound	Bone health was approximated by ultrasound of the non-dominant hand in one study[91]. Larger speed of sound measurements indicate higher bone density.
Biopsy	Two studies used quantitative morphometric analyses of biopsies to study bone quality in subjects[86,89]. Examining a participant's bone sample under microscope can allow insight into the microarchitecture of bone, such as level of calcification.
Bone mineral content (BMC)	A measure of bone density using bone mass per area measured. The study that measured BMC used single photon absorptiometry (SPA)[84].
Bone mineral density (BMD)	A measure of bone density using BMC divided by weight. The studies that measured BMD used dual x-ray absorptiometry (DXA)[88]and the Am-241 gamma ray attenuation method[86].
Forearm bone mass	One study approximated bone health by measuring bone mass of the forearm[85].
Inorganic phosphate/phosphorous	A bone turnover marker; high inorganic phosphate levels can decrease bone resorption[145].
Parathyroid hormone (PTH)	A bone turnover marker; elevated PTH is associated with vitamin D insufficiency and osteomalacia[103].

Appendix G – Items to be extracted from CCHS 2010 questionnaires[117]

Concept	CCHS Variable(s)	Variable Codes
Epilepsy	Neurological Conditions	NEU_Q030 – Q033
Lifestyle behaviours beneficial to bone health	Physical Activities Sun Safety Behaviours Food Choices Changes Made to Improve Health	PAC_Q1–Q7; SSB_Q06, FDC_Q1D; FDC_Q2C; CIH_Q1–Q8
Lifestyle behaviours detrimental to bone health	Smoking Alcohol Use Alcohol Use during the Past Week Chronic Conditions Mammography Illicit Drug Use	CCC_Q036; CCC_Q051; CCC_Q091; CCC_Q101; CCC_Q105; CCC_Q171; CCC_Q280; SMK_Q201; SMK_Q202; SMK_Q204; SMK_Q205; SMK_Q208; ALW_Q5; DRG_Q24, NEU_Q100, NEU_Q101
Fractures, broken bones	Injuries	INJ_Q01; INJ_Q02; INJ_Q05; INJ_Q06
Ambulatory status	Health Utility Index	HUI_Q14–HUI_Q18; HUI_20
Demographics	Height and Weight Age of Respondent Proxy Interview Socio-demographic Characteristics	ANDB_Q01; ANDB_Q01; ANC_Q03; HWT_Q1; SDC_Q1; SDC_Q4; SDC_Q4_1; SDC_Q4_3

Appendix H – Examples of questions from the CCHS[117]

Variable Code	Question
ANDB_Q01	What is [respondent name]'s age?
SEX_Q01	Is [respondent name] male or female?
ANC_Q03	What is your age?
CIH_Q1	In the past 12 months, did you do anything to improve your health? (For example, lost weight, quit smoking, increased exercise
CIH_Q2	What is the single most important change you have made?
CIH_Q3	Do you think there is anything you should do to improve your physical health?
HUI_Q14	Are you usually able to walk around the neighbourhood without difficulty and without mechanical support such as braces, a cane or crutches?
HUI_Q15	Are you able to walk at all?
HUI_Q16	Do you require mechanical support such as braces, a cane or crutches to be able to walk around the neighbourhood?
HUI_Q17	Do you require the help of another person to be able to walk?
HUI_Q18	Do you require a wheelchair to get around?
HUI_Q20	Do you need the help of another person to get around in the wheelchair?
FDC_Q1D	(Do you choose certain foods or avoid others:) ...because you are concerned about osteoporosis (brittle bones)?
FDC_Q2C	(Do you choose certain foods because of:) ...the calcium content?
PAC_Q1	Have you done any of the following in the past 3 months, that is, from [date three months ago] to yesterday?
PAC_S1V	What was this activity?
PAC_Q2N	In the past 3 months, how many times did you [participate in identified activity]?
PAC_Q3N	About how much time did you spend on each occasion?
PAC_Q7	Other than the times you already reported walking for exercise, was there any time in the past 3 months when you walked to and from work or school?
PAC_Q7A	How many times?
PAC_Q7B	About how much time did you spend on each occasion?
SSB_Q01	In the past 12 months, has any part of your body been sunburnt?
SSB_Q06	About how much time each day do you spend in the sun between 11 am and 4 pm?
INJ_Q01	Not counting food poisoning, in the past 12 months, that is, from [date one year ago] to yesterday, were you injured?
INJ_Q05	What type of injury did you have? For example, a broken bone or burn.
NEU_Q030	Do you have epilepsy?

Appendix I – Statistical analyses outline for CCHS data

Question	Statistical Analysis	Population	Independent Variable	Dependent Variable(s)
What percent of our sample has epilepsy?	Frequency	50+ 18–49	Epilepsy status Age	
What is the gender distribution of epilepsy in our sample?	Frequency Chi square	50+ 18–49	Sex Age	Epilepsy status
What is the age distribution of epilepsy in our sample?	Means T-test	50+ 18–49	Age	Epilepsy status
What percent of the PWE are ambulatory?	Frequency Chi square	50+ 18–49	Epilepsy status	Ambulatory status (made up of 6 variables)
Is there a difference in the number of people who have or have not participated in a physical activity at all between PWE and those without? And is there a difference between adults under 50 and those over 50?	Frequency Chi square	PWE 50+ PWE 18–49 50+ 18–49	Epilepsy status	Have or have not participated in a physical activity
Is the amount of physical activity that PWE or without epilepsy participate in similar? And is there a difference between adults under 50 and 50 and over?	Means ANOVA & Sheffe	PWE 50+ PWE 18–49 50+ 18–49	Epilepsy status	Amount of physical activity (interval/ratio) participated in for the past 3 months
Is the amount of physical activity that PWE or without epilepsy participate in similar? And is there a difference between men and women?	Means ANOVA & Sheffe	MWE 50+ WWE 50+ Men 50+ Women 50+	Epilepsy status	Amount of physical activity (interval/ratio) participated in for the past 3 months
Is the duration of physical activity that PWE or without epilepsy participate in similar? And is there a difference between adults under 50 and those over 50?	Kruskal-Wallis & Pairwise	PWE 50+ PWE 18–49 50+ 18–49	Epilepsy status Age	Amount of time interval (ordinal) spent on physical activity.
Is the amount of physical activity that PWE or without epilepsy participate in similar? And is there a difference	Kruskal-Wallis & Pairwise	MWE 50+ WWE 50+ Men 50+ Women 50+	Epilepsy status Gender Age	Amount of time interval (ordinal) spent on physical activity.

between men and women?				
Is the rate of dietary choices based on osteoporosis concern similar between PWE and those without?	Chi square	PWE 50+ 50+	Epilepsy status Age	Chooses/avoids foods due to osteoporosis concerns
Is the rate of dietary choices based on calcium content similar between PWE and those without?	Chi square	PWE 50+ 50+	Epilepsy status Age	Chooses/avoids foods due to calcium content
Is the motivation to improve health similar between PWE and those without?	Chi square	PWE 50+ 50+	Epilepsy status Age	Intends to/does not intend to improve health
Is the amount of fractures similar between PWE and those without?	Chi square	PWE 50+ 50+ PWE 18+ 18+	Epilepsy status Age	Had a fracture in the past 12 months.

Appendix J – Statistical analysis plan for Vitamin D intake among older adults with epilepsy survey

Question	**Variables**	**Analysis**
Demographics/Descriptives of sample		
What is the average age?	Age	Mean
What is the gender distribution?	Gender	Chi square
What is the average age of first seizure?	Age of first seizure	Mean
What is the average frequency of seizure?	Seizure frequency (monthly)	Mean
What is the average number of years on AED medication?	AED history	Mean
Research questions		
Is there a difference in AED type (inducer vs. non-inducer) used based on age?	Age AED history	T-test
Is there a difference in AED type (inducer vs. non-inducer) based on gender?	Gender AED history	Chi square
Is there a difference in AED type (inducer vs. non-inducer) based on seizure frequency?	Seizure frequency (monthly) AED history	T-test
Vitamin D		
What is the prevalence of vitamin D supplementation?	Vitamin D supplement use	Frequency
What is the average number of times vitamin D supplementation was taken for past 30 days?	Vitamin D supplement use	Mean
What is the average number of servings of vitamin D rich food consumed (for past 30 days)?	Vitamin D rich diet	Mean

Appendix K – Vitamin D intake among older adults with epilepsy survey

1. With full knowledge of all foregoing, I agree, of my own free will, to participate in this study.
   ☐Yes, I consent
   ☐No, I do not consent
2. Do you have epilepsy/seizure disorder?
   ☐Yes
   ☐No
3. Are you aged 50 years or older?
   ☐Yes
   ☐No
4. Have you ever been diagnosed with any type of cognitive impairment?
   ☐Yes
   ☐No
5. Please state your age in years. (Move bar to the right to select age)
   >Options: 0–150
   _____
6. What is your ethnic background? Please mark all that apply:
   ☐White
   ☐Black (e.g., African, Caribbean, North American)
   ☐First Nation/Aboriginal/ Métis/Inuit
   ☐East Asian (e.g., Chinese, Korean, Japanese, Filipino)
   ☐South Asian (e.g., East Indian, Pakistani, Sri Lankan)
   ☐Latin American/Central American/South American (e.g., Mexican, Brazilian, Chilean, Guatemalan)
   Other (please specify): [text box] _____
7. What is your biological sex?
   ☐Male
   ☐Female
8. Are you post-menopausal?
   ☐Yes
   ☐No

The next questions are about your personal experience with seizures/epilepsy:

9. At what age did you experience your first seizure? (Move bar to the right to select age)
   >Options: 0–100
   _____
10. How many seizures do you have per month, on average? (Move bar to the right to select number)
    >Options: 0–100
    _____
11. Which of the following seizure medications are you currently taking or have taken in the past? For how long? Please leave duration unanswered for medications that you have never taken.

☐ Acetazolamide (Acetazolam)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No

☐ Carbamazepine (Tegretol, Mazepine)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No

☐ Clobazam (Frisium)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No
☐ Clonazepam (Rivotril, Clonpam)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No
☐ Diazepam (Valium, Diastat, Diazemuls, Dipam)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No
☐ Ethosuximide (Zarontin)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No
☐ Fosphenytoin (Cerebyx)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No
☐ Gabapentin (Neurontin)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No
☐ Lacosamide (Vimpat)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No
☐ Lamotrigine (Lamictal)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No
☐ Levetiracetam (Keppra)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No
☐ Lorazepam (Ativan, Loraz)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No
☐ Nitrazepam (Mogadon, Nitrazedon)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No
☐ Oxcarbazepine (Trileptal)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No
☐ Phenobarbital (Phenobarb)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No
☐ Phenytoin (Dilatin, Tremytoin)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No
☐ Pregabalin (Lyrica)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No
☐ Primidone

How long (in years or months)?_____
Currently taking? ☐Yes ☐No

☐ Rufinamide (Banzel)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No

☐ Stiripentol (Diacomit)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No

☐ Topiramate (Topamax)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No

☐ Valproic Acid (Epival, Depakene, Depakote, Valproate)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No

☐ Vigabatrin (Sabril)
How long (in years or months)?_____
Currently taking? ☐Yes ☐No

Other, please specify medication name, number of years taken and if you are still currently taking it: _____

We are interested in your typical eating habits:

12. In the past 30 days, how often did you have a serving of food rich in vitamin D? For example a serving would be 1 cup of milk to drink or on cereal, 75g (2 ½ oz) of fish or pork, 2 egg yolks, or 1 teaspoon of margarine or cod liver oil. (Move bar to the right to select number)
    >Options: 0–100
    _____

The next questions are about any dietary supplements you take, both prescription and non-prescription:

13. In the past 30 days, have you taken supplements?
    ☐Yes
    ☐No, I do not take supplements
14. In the space provided beside each supplement, please indicate how many times in the past 30 days you took the supplement (i.e. 0, 1, 2, 3 …100). Leave the space blank if you do not take that specific supplement. If you take a combination product, please also list the ingredients. If you take a Multivitamin, please also state the brand.
    Calcium: [text box] _____
    Vitamin D [text box] _____
    Combination product (e.g. Calcium + Vitamin D, Magnesium + Vitamin D), please list the ingredients: [text box] _____
    Multivitamin, please state the brand: [text box] _____
15. In the space provided beside each supplement, please indicate what is the dose per one (1) pill/tablet/serving (for example, 200 mg, 800 IU, etc.). Leave the space blank if you do not take that specific supplement.
    Calcium [text box] _____
    Vitamin D [text box] _____
    Combination product (e.g. Calcium + Vitamin D, Magnesium + Vitamin D): [text box]_____
    Multivitamin [text box]_____
16. For what reason do you take these supplements? (Please mark all that apply)
    ☐ For my general health

☐ Specifically for my bones/bone health
☐ For my seizures/epilepsy
☐ It was recommended by my doctor
☐ Other (please specify): [text box] _____

Next, we will ask you some questions about your bone heath:

17. Has your doctor told you that you have osteopenia/osteoporosis?
    ☐Yes
    ☐No
18. Are you aware that some medications used to treat seizures are thought to affect bones (for example linked to osteoporosis and fractures)?
    ☐Yes
    ☐No
19. Where did you learn this information? (Please mark all that apply)
    ☐Family doctor
    ☐Neurologist
    ☐Pharmacist
    ☐My own research
    ☐Family/Friends
    Other (please specify): [text box] _____

Questions 1–4 are available only online and answers are mandatory to move forward

Appendix L – Recruitment protocol