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THE EFFECT OF VITAMIN D SUPPLEMENTATION ON BONE HEALTH AMONG ONCOLOGY PATIENTS

Cervantes, Carlos H.

Monterey, CA; Naval Postgraduate School

NAVAL POSTGRADUATE SCHOOL

MONTEREY, CALIFORNIA

THESIS

THE EFFECT OF VITAMIN D SUPPLEMENTATION ON BONE HEALTH AMONG ONCOLOGY PATIENTS

by

Carlos H. Cervantes

September 2018

Thesis Advisor: Andrew T. Anglemyer
Second Reader: Robert A. Koyak

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We performed a meta-analysis of all published data regarding the possible benefits of vitamin D and/or calcium supplementation for increasing bone mineral density (BMD) in cancer patients. Currently, there is no medical community consensus as to whether vitamin D and/or calcium affects bone health among cancer patients enough to offset the effects of chemotherapy. The Department of Defense's drug formulary, managed by the Pharmaceuticals and Therapeutics (P&T) committee, states that insurance does not cover multivitamin/multimineral supplements. The lack of coverage and consensus leaves patients in the dark about a potential benefit to a treatable disease. Therefore, we assessed the known research to offer more clarity to the committee. The thesis weighs evidence with a "pooled" effect, or weighted average, known as meta-analysis, and assessed risk of bias and quality of evidence via GRADEpro software. Of over 700 possible studies, 14 met our inclusion criteria, including four randomized control trial (RCT) and 10 observational studies. One RCT (with an outcome on 25(OH)D levels) and three observational studies found significant evidence of supplementation's benefits, while the rest showed no significant findings. While overall we determined there was no significant benefit, we offer a solid base of understanding to the committee and recommend further research.

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THE EFFECT OF VITAMIN D SUPPLEMENTATION ON BONE HEALTH AMONG ONCOLOGY PATIENTS

Carlos H. Cervantes
Lieutenant, United States Navy
BS, Southern Illinois University at Carbondale, 2008
MBA, San Diego State University, 2010

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requirements for the degree of

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September 2018

Approved by: Andrew T. Anglemyer
Advisor

Robert A. Koyak
Second Reader

W. Matthew Carlyle
Chair, Department of Operations Research

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ABSTRACT

We performed a meta-analysis of all published data regarding the possible benefits of vitamin D and/or calcium supplementation for increasing bone mineral density (BMD) in cancer patients. Currently, there is no medical community consensus as to whether vitamin D and/or calcium affects bone health among cancer patients enough to offset the effects of chemotherapy. The Department of Defense's drug formulary, managed by the Pharmaceuticals and Therapeutics (P&T) committee, states that insurance does not cover multivitamin/multimineral supplements. The lack of coverage and consensus leaves patients in the dark about a potential benefit to a treatable disease. Therefore, we assessed the known research to offer more clarity to the committee. The thesis weighs evidence with a "pooled" effect, or weighted average, known as meta-analysis, and assessed risk of bias and quality of evidence via GRADEpro software. Of over 700 possible studies, 14 met our inclusion criteria, including four randomized control trial (RCT) and 10 observational studies. One RCT (with an outcome on 25(OH)D levels) and three observational studies found significant evidence of supplementation's benefits, while the rest showed no significant findings. While overall we determined there was no significant benefit, we offer a solid base of understanding to the committee and recommend further research.

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LIST OF ACRONYMS AND ABBREVIATIONS

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
BMD	bone mineral density
CI	confidence interval
DHA	Defense Health Agency
DoD	Department of Defense
FE	fixed effects
HR	hazard ratio
NOS	Newcastle-Ottawa scale
OR	odds ratio
PICO	population, intervention, comparison, outcome
P&T	Pharmacy and Therapeutics
P-value	probability value
RCT	randomized controlled trial
RE	random effects
RR	rate ratio
SD	standard deviation
SMD	standardized mean difference
25(OH)D	25-hydroxyvitamin D (Calcifediol)

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EXECUTIVE SUMMARY

Cancer is a devastating disease and the second most common cause of death in the United States after heart disease (Siegel, Miller, & Ahmedin, 2017), and, according to Siegel et al., "a major public health problem" (p. 7). In children, the most common malignancy among the different types of cancers is leukemia, accounting for about 29% of all pediatric cancers (Siegel et al., 2017). Without a cure, medicine has also turned to examining the disease's long-term side effects and treatments (van der Sluis, van den Heuvel-Eibrink, Hählen, Krenning, & de Muinck Keizer-Schrama, 2000). These same authors noted there are many studies that show cancer patients with reduced bone mineral density (BMD) during their therapy treatments. In their study, these authors focused on calcium and vitamin D's effect on BMD (van der Sluis et al., 2000). Many studies consider calcium supplementation in combination with vitamin D intake. According to Peterlik, Grant, and Cross (2009), both together are generally considered to significantly reduce cancer incidence levels.

The causes of low BMD are not known completely. According to a study by Díaz et al. (2008), there have been some general recommendations given to preserve normal levels of bone mass, such as physical exercise and the procurement of a balanced nutrition to contain adequate proteins, calcium and vitamin D. Additionally, in that same study, it is mentioned that sunlight exposure is usually lower for acute lymphoblastic leukemia (ALL) children as they accumulate more time indoors or without direct sunlight than healthy children do. The lack of sunlight diminishes the absorption of vitamin D, which can affect children's intake and metabolism of this vitamin (Díaz et al., 2008). Another study conducted by Simmons et al. (2011), describes some factors that have shown relation to low BMD, at least partially, are physical inactivity, prolonged glucocorticoid treatment, increased pro-inflammatory cytokines, and vitamin D deficiency/insufficiency.

Therefore, although we see that some studies do find significant benefits with supplementation for cancer patients, unfortunately, others fail to find any significant results or fail to measure a valid outcome adequately. The reasons why it is hard to demonstrate as significant outcomes vary from study to study.

We perform a meta-analysis to demonstrate whether there is any significance on taking vitamin D and/or calcium supplementation to enhance bone mineral density on oncology patients. To accomplish this, we have produced a systematic review of published studies that are looking for key clinical factors that affect the BMD of these patients. Specifically, we evaluated the effect of vitamin D and/or calcium in comparison with placebos or standard treatment control groups on bone health outcomes among cancer patients by performing a systematic review.

From the start of the search, it became critical to find a good amount of studies and as many as possible. Studies such as randomized controlled trials (RCT) were best but also any other non-randomized clinical study meeting this thesis inclusive criterion were considered, so a meta-analysis would be viable. This search identified 14 published studies for this thesis. Four of these were RCT and the rest were observational studies.

Observational studies, due to their nature of the lack of randomization, go through additional screening to measure their level of bias. This is because observational studies are mostly carrying a high risk of bias throughout their phases of development, compared to an RCT study, which mostly carries a low risk of bias. This risk of bias assessment is analyzed according to a scale commonly used in the medical field. This assessment is called the Newcastle-Ottawa scale (NOS) and according to its criteria, each observational study receives a scaled metric that helps assess the level of risk of bias according to the criteria set by the reviewer. This NOS assessment tool helped determined that, according to our criteria, four observational studies were accepted with having a low risk of bias, while the rest, six studies were considered to have a medium to high risk of bias.

A challenge found in most of the studies was that many had their own way of doing analysis, and with this came different ways in reporting measurements or a lack of them. We considered the most common metrics in use in this thesis. These metrics were measurements of the lumbar spine BMD, hip BMD, total BMD, 25(OH)D levels at various lengths of time and levels over 40 units at various lengths of time, and last but not least, proximal femur BMD. To overcome some of these differences in reporting outcomes, a standardized mean difference was used as base comparison for all the continuous unit-based analyses and odds ratio (OR) used for the dichotomous unit-based analyses.

Additional statistical analysis performed with the studies was to compare their RE, FE, heterogeneity, and their probability values for significance between studies if more than one study was involved. A significant finding was noted if the 95% confidence interval for a SMD for any outcome was entirely above or below zero, suggesting the difference between groups was significantly positive or negative.

Results obtained from this meta-analysis produced statistical evidence that these supplements in question are not significant overall for improving BMD. From the RCT studies, only one was found to have significant evidence about supplementation making an impact on bone health (study by Khan et al.[(2017]), according to its outcome on 25(OH)D levels. From the observational studies, just three out of the 10 studies showed some significant evidence on the use of supplementation making positive impact:

- Schnabel et al. (2013), in their hip BMD assessment
- Schneider et al. (2004) (boys' group), in their total BMD assessment (see Figure 6), and
- Khan et al. (2010), in their 25(OH)D levels > 40 units at 16 weeks assessment (see Figure 7)

The remainder of the observational studies demonstrated neither positive nor negative significant outcomes.

Many point estimates show increases/benefits for supplementation being effective for BMD, but not significantly. Perhaps future studies should be more driven to detect smaller differences, perhaps with larger sample sizes.

As a last step, we looked at evaluating the quality of the evidence with the assistance of an analysis software called GRADEpro GDT (GRADEpro GDT, 2015). The GRADEpro approach gave us an overview on the certainty of the evidence from the outcomes of all of our studies used in this thesis. We used this as a tool to make informed decisions regarding how each study is influenced through its certainty and its findings we obtained from them. All the RCT studies result in GRADEpro having a certainty of high, while all other studies such as the observational studies have some other level of certainty.

Overall, we determined these outcomes with estimates produced by observational studies to be rated as very low quality. The exception was for lumbar spine BMD, which we estimated as low quality per our GRADEpro quality of evidence assessment.

These findings add evidence for clinicians and healthcare policy makers for decision-making and making recommendations for cancer patients. Our findings should also be considered in the context that these supplements are relatively cheap and not harmful, but their benefits are also not evidenced. We strongly encourage further research to help make conclusions stronger; the results of this thesis hopefully can serve as a basis for additional clarity, further analysis, and consideration for the DoD P&T committee. This committee controls the formulary that all DoD beneficiaries use. Therefore, this thesis offers an effective basis from which the committee can study the effects of vitamin D and calcium supplements to increase BMD for oncology patients.

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I. INTRODUCTION

A. BACKGROUND

Cancer is a devastating disease and is the second most common cause of death in the United States after heart disease (Siegel et al., 2017), and considered, according to Siegel et al., "a major public health problem" (p. 7). The same authors state that in 2017 alone, it was projected there would be 1,688,780 new cancer cases in which 10,270 would be children (birth to 14 years), and 600,920 cancer deaths (1,190 being children) in the United States.

In children, the most common malignancy among the different types of cancers is leukemia, accounting for about 29% of all pediatric cancers (Siegel et al., 2017), with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) as the most common types (Gurney et al., 2014). Moreover, in another study by Kaste et al. (2006), researchers estimate that "[i]n the United States two-thirds of the 3,000-4,000 persons who receive a diagnosis of [ALL] each year are children" (Kaste et al., 2006, p. 77).

In adults, cancer is the second most common cause of death, trailing behind heart disease, for all men and women of all ages according to Siegel et al. (2017). According to American Cancer Society (2018), 43% of all cancer deaths in men are attributed to cancers of the prostate, lung and bronchus, and colon and rectum. For women, 47% of all cancer mortality can be attributed to cancers of the breast, lung and bronchus, and colon and rectum. Four percent of all cancer deaths are attributed to leukemia among adults (American Cancer Society, 2018).

According to Kadan-Lottick et al. (2001), the stages children with leukemia go through have the potential to be a disruptive process for their bone metabolism. The same author explains these children are at increased risk for reduced bone peak mass as well as for bone fractures. Furthermore, cancer treatment will usually lead patients to have lower levels of physical activity, thus further inhibiting bone mineral density (BMD) during and after treatment (Kadan-Lottick et al.. 2001). Cancer treatments such as chemotherapy have the main benefit such as to augment the survivability of the patients, especially for cancers

like ALL; however, these treatments tend to induce several negative effects on the body, such as alterations in vitamin D absorption. In other words, children's bone metabolism may deteriorate due to mechanisms associated with the treatment or with the illness itself. In fact, researchers have found that children after cancer treatment tend to have lower BMD when compared to healthy children (Díaz et al., 2008). According to the same author, 1,25(OH)2 vitamin D or also known as calcitriol, enhances calcium and phosphorous absorption through the intestines, as well as assists with bone mineralization. Additionally, the same author states that patients with ALL tend to have vitamin D deficits right from the beginning of treatment, and sometimes even before treatment, thus representing an ideal population to supplement with vitamin D (Díaz et al. , 2008).

Predictors of childhood cancers continue to be at the forefront of many studies by scientists. One of many possible predictors of childhood cancer is environmental exposure, perhaps even the parents' jobs or occupations, although these are mostly speculative. Exposure to environmental factors has been evaluated in some studies, such as the potential exposures among military personnel who served time in Southeast Asia. Some believe, according to Goldberg, Eisen, True, and Henderson (1992), that there were negative effects from "a dioxin-contaminated herbicide, also known as 'Agent Orange'" (Goldberg et al., 1992, p. 842). Parental occupations is another predictor for childhood cancers as studies have looked for evidence suggesting a link, however, according to Savitz & Chen (1990), there is not clear evidence of this association. The same authors also describe a parental toxicity as a potential mechanism for producing genetic effects that could later alter the susceptibility of cancer in the child. Additionally, the authors also state that transplacental toxicity could be related to exposures to lead and alcohol though the role of paternal occupational exposures is still considered to be more questionable (Savitz & Chen, 1990).

Moreover, treatment of cancers, especially leukemia, usually goes through advanced therapeutic services proven to increase the survival of these individuals with ALL. However, among the drawbacks of these treatments is that they enhance the susceptibility of certain side effects, which usually worsen, especially after prolonged periods of application. Such effects from therapy treatments can be as bad as the "illness itself, [the] therapy, poor food intake, poor physical activity, and prolonged rest" (Díaz et

al., 2008, p. 15). Other factors not mentioned that contribute to deficient BMD after treatment are according to Kaste et al. (2006), the "irradiation of endocrine organs that control bone accretion …, genetic predisposition …, and pubertal status" (Kaste et al., 2006, p. 77). Some of these factors, according to the same author, in the long term, "may predispose survivors to osteoporosis of greater severity and earlier onset" (Kaste et al., p. 77).

According to Simmons et al. (2011), children's overall cancer survival rate is now in excess of 80% (Simmons et al., 2011). Therefore, as stated by van der Sluis, van den Heuvel-Eibrink, Hählen, Krenning, & de Muinck Keizer-Schrama, (2000), the emphasis in medicine has turned to examining the long-term side effects of the disease and its treatments, rather than only focusing on curative agents. Van der Sluis et al. (2000) studied the long-term effects in cancer patients by evaluating vitamin D and its effect on BMD (van der Sluis et al., 2000). The causes of low BMD are not known completely, however. According to Simmons et al. (2011), some factors that have shown relation to low BMD, at least partially, are physical inactivity, prolonged glucocorticoid treatment, increased pro-inflammatory cytokines, and vitamin D deficiency/insufficiency (Simmons et al., 2011). Moreover, vitamin D has been found to be insufficient in about 70% children and adolescents in the United States (Simmons et al., 2011). Children with leukemia, ALL in particular, are suspected to be particularly susceptible to low BMD and this risk may "persist into adulthood" (Gurney et al., 2014, p. 2). BMD is usually affected by having this pediatric malignancy, but may also by an artifact of receiving high doses of chemotherapy treatments in the long-term. According to the same author, these treatments usually include high doses of glucocorticoids and methotrexate, both of which interfere with skeletal growth and affect BMD recovery. The degree of recovery or decline regarding BMD, among cancer survivors of childhood ALL and AML, is not well understood (Gurney et al., 2014).

According to Díaz et al. (2008), there have been some general recommendations given to preserve normal levels of bone mass, such as physical exercises, and the procurement of a balanced nutrition to contain adequate proteins, calcium and vitamin D. The same author says that these recommendations are normally emphasized for children

with ALL due to their relative attrition on physical activity they are exposed to, at least during their treatment periods. Additionally, sunlight exposure is usually lower for ALL children as they accumulate more time indoors or without direct sunlight than regular healthy children do. The lack of sunlight diminishes the absorption of vitamin D, which can affect their intake and metabolism of this vitamin (Díaz et al., 2008).

Some studies find significant benefits with supplementation for cancer patients; unfortunately, some others fail to find any significant results, or fail to measure a valid outcome adequately. The reasons why it is hard to demonstrate significant outcomes vary from study to study. Some of these reasons include the failure to measure the effect of calcitriol in children because of their age when they were in the study. As an example, in a study by Diaz et al. (2008) the participants had a mean age of 6.6 years at the end of the study. The problem here is that this age is also known as a period of steady bone growth. This makes this pubertal period hard to demonstrate measureable or clinically significant results for any bone accretion (Díaz et al., 2008).

Complicating researchers' ability to properly gauge the effects of supplementation, some studies find improved bone health during post-treatment stages. However, other factors can confound these relationships, such as how the true amount of any dietary supplements taken, and for how long. Another example could be the improvement coming naturally from the healthier quality of life after treatment and as the growing stages to adulthood of the children in which there are expected stages of bone growth.

The method for determining which bones to measure BMD among oncology patients is based on a whole body of literature regarding cancer and bone health. Lumbar spine bone density, for example, has been found to be the primary affected section in both men and women that have had various types of cancer. However, other areas are also frequently affected and are commonly found by doing a whole body scan. According to Guise (2006), screening for BMD has a standard measurement methodology in which they usually rely on a special type of equipment known as "dual-energy x-ray absorptiometry (DXA)…which has been widely used for quantifying bone loss in the spine, proximal femur, and total body" (Guise, 2006, p. 1124). These bone sections will be found with measurements in the majority of our included studies.

In this study, we will perform a systematic review and meta-analysis regarding the use of supplementation for oncology patients. Using this methodology, we will look to combine multiple studies together that pertain to our research question and weigh all the evidence available to make assertions about the relationship. Meta-analyses are commonly conducted in scientific fields such as medical scientific research, for example. Meta-analysis is used with a purpose of pooling or combining findings of multiple studies enabling production of a more powerful statistical outcome, or more credible findings thanks to the larger amounts of empirical data.

There have been multiple studies that have made use of meta-analysis techniques using military data or involving military or Department of Defense (DoD) populations. For example, Wilson's study (2016) published a meta-analysis evaluating the prevalence of military sexual trauma. The author conducted a review of 584 citations of which 69 studies were used for the meta-analysis. The main focus was on those studies that contained estimates of sexual harassment or sexual assault regarding military service members and veterans. Wilson found that the military sexual trauma rates among the women and men in their studies were most likely higher than the rates the Veterans Affairs (VA) had suggested based on their massive database (Wilson, 2016).

B. OBJECTIVE

We are looking to determine whether multiple studies on bone loss in cancer patients from taking vitamin D and calcium supplements can be combined to yield evidence that such an effect exists.

C. SCOPE, LIMITATIONS AND ASSUMPTIONS

All the studies mentioned in this thesis are based on clinical results that are often taken many years post-treatment. There is no clear evidence as to whether there is substantial benefit for patients with cancer to take these supplements. With no clear evidence going forward, health insurance companies such as Tricare for our military would probably find it hard to approve vitamin D supplementation for most patients unless it actually works. The DoD Defense Health Agency (DHA) manages the medical services program known as Tricare. Tricare has expressed support for treatments with vitamin

supplementations, but only if there is evidence of their effectiveness and provided by the approval of the pharmacy and therapeutics (P&T) committee, per the guidelines set by Tyler et al. (2008). This committee manages the drug formulary that is used by Tricare.

On the other hand, there are some studies that do suggest otherwise, such as a randomized controlled trial (RCT) conducted by Khan et al. (2017) in which 84% of patients treated with vitamin D3 achieved higher levels of 25(OH)D, compared to only 10% of the patients receiving the standard treatment group (Khan et al., 2017). Additionally, while it may be difficult to find strong evidence of effectiveness of these supplements, many doctors say the benefits outweigh the costs for oncology patients (Kadan-Lottick et al., 2001). Another key assumption in this thesis is that we are grouping studies together with disparate populations and treatments, and cancers. Our methodology attempts to address these sources of heterogeneity, however.

D. COURSE OF STUDY

The purpose of this thesis is to evaluate if there is any evidence as to whether the supplementation of calcium and vitamin D, either together or individually, produce a positive effect in BMD or other bone health outcomes. To accomplish this, we have produced a systematic review of published studies aforementioned that are looking for key clinical factors that affect BMD of oncology patients. Specifically, we evaluate the effect of vitamin D and/or calcium in comparison with placebo or standard treatment control groups on bone health outcomes among cancer patients by performing a systematic review and meta-analysis.

II. METHODOLOGY

This thesis bases its methodology on the research and analysis protocols of *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins & Green, 2011). We detail our data process and our analysis approach in the following sections.

A. TYPES OF STUDIES, PARTICIPANTS, AND INTERVENTIONS

We examined both RCTs and non-randomized clinical trial experiments that compared the effects of vitamin D or calcium supplementation in cancer patients. Our research includes studies, as defined in the handbook by Higgins and Green (2011), as RCTs and observational studies that compare clinical effects between patients given vitamin D and patients not (or given placebos) (Higgins & Green, 2011).

We included randomized trials and cluster randomized trials, and included observational studies to include case-control, cross-sectional studies, and retrospective and prospective cohort studies. We excluded studies that had no comparison arm or studies that lacked specificity as it pertains to vitamin D or calcium intake or levels.

To clearly lay out the specific inclusion criteria we are employing, we use the PICO framework (Higgins & Green, 2011):

- Population: cancer patients
- Intervention: vitamin D or calcium supplementation
- Comparison/Comparator: no vitamin D, or calcium (or placebo), or some variation of any of these supplements
- Outcome: bone health outcomes (e.g., bone mineral density)

After removing duplicate references from the search results, we excluded all studies not meeting our inclusion criteria. In addition to screening titles and abstracts, an additional researcher, by employing similar screening strategies and applying the inclusion criteria, performed the same operations. By independently performing the screening using the criteria for study inclusion and working out disagreements, if any, between both researchers, we resolved these by discussion. If needed, we allowed for adjudication by a

third subject matter expert. Next, we further eliminated studies that failed to meet the inclusion criteria upon full-text review. Also considered, were the remaining primary studies for further analysis.

After identifying the studies, we compared the effects of measures between patients receiving calcium or and/or those receiving vitamin D supplements to include the following:

- vitamin D alone
- vitamin D plus calcium
- calcium alone

B. TYPES OF OUTCOME MEASURES

We considered multiple outcomes of interest, with primary outcomes including BMD and fracture risk, and as secondary outcomes, any change in vitamin D levels. BMD included measures at the hip, lumbar spine, and proximal femur. Vitamin D changes also included vitamin D levels or 25(OH)D levels after supplementation. We also considered bone specific alkaline phosphatase (BALP) as another outcome of interest. It is important to note that studies were not excluded from this review if they did not report an outcome of interest. This was done so that there was no bias of the results toward studies selectively reporting specific outcomes. However, if a study did not state an outcome of interest, this was retained for qualitative and/or descriptive purposes.

C. SEARCH METHODS USED FOR IDENTIFYING SUITABLE STUDIES

This thesis employed a thorough search strategy in order to find appropriate and applicable studies. Studies based on publication status or type were still considered (i.e., had there been any manuscripts found still in press or unpublished, we would have considered them) or language. We searched an electronic database, PubMed, in 2018 and with no boundaries on publication dates. Also used were some MeSH terms and other relevant keywords in the search strategy. The terms used were:

- musculoskeletal abnormalities
- infant or child or adolescent or adult

- neoplasms
- vitamin D

The search performed used an iterative search strategy. For example, upon identifying a primary study for inclusion, we did a cross-reference of its references for additional references.

D. DATA EXTRACTION AND MANAGEMENT

An initial search for studies yielded data on study interventions, and we entered these data onto data collection sheets. In addition, we performed this data extraction independently and any discrepancies in data extraction were discussed. The extracted data had the following guidelines per Anglemyer et al. (2014).

- Study details: citation, start and end dates, location, eligibility criteria, (inclusion and exclusion), study designs compared, interventions compared
- Comparison of supplementation details: effect estimates from each study design within each publication
- Risk of bias details: all elements needed to determine the risk of bias within each primary study
- Outcome details: primary outcomes identified in each study. (Anglemyer et al., 2014, p. 6)

E. ASSESSMENT OF RISK OF BIAS IN INCLUDED STUDIES

Once more, following methodology outlined in Higgins (2011) cited by Anglemyer, Agrawal, & Rutherford, (2014), this thesis "independently assessed risk of bias for each study using the bias assessment tool described in the *Cochrane Handbook"* (emphasis added) (Anglemyer et al., 2014, p. 6). An additional researcher independently assessed these assessments, as well, and if there were any disagreement in assessment, we discussed differences and used a third researcher to break the tie. Higgins and Green (2011) describe a methodology for assessing the risk of bias that we used for our review. This methodology uses six domains for study evaluation: "sequence generation, allocation concealment, blinding, incomplete outcome data,… selective outcome reporting [and other

potential biases]" (Higgins & Green, 2011, p. 8.44). The details of the bias assessment analysis are detailed in the following list as cited by Anglemyer et al. (2014):

- Sequence generation (checking for selection bias)
- Adequate: investigators described a random component in the sequence generation process, such as the use of random number table, coin tossing, card or envelope shuffling
- Inadequate: investigators described a non-random component in the sequence generation process, such as the use of odd or even date of birth, algorithm based on the day or date of birth, hospital or clinic record number
- Unclear: insufficient information to permit judgment of the sequence generation process
- Allocation concealment (checking for selection bias)
- Adequate: participants and the investigators enrolling participants cannot foresee assignment (e.g., central allocation; [*sic*] or sequentially numbered, opaque, sealed envelopes)
- Inadequate: participants and investigators enrolling participants can foresee upcoming assignment (e.g., an open random allocation schedule, a list of random numbers), or envelopes were unsealed, non- opaque or not sequentially numbered
- Unclear: insufficient information to permit judgment of the allocation concealment or the method not described.
- Blinding (checking for performance bias and detection bias)
- Adequate: blinding of the participants, key study personnel and outcome assessor and unlikely that the blinding could have been broken. Not blinding in the situation where non-blinding is unlikely to introduce bias
- Inadequate: no blinding or incomplete blinding when the outcome is likely to be influenced by lack of blinding
- Unclear: insufficient information to permit judgment of adequacy or otherwise of the blinding
- Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

- Adequate: no missing outcome data, reasons for missing outcome data unlikely to be related to true outcome or missing outcome data balanced in number across groups
- Inadequate: reason for missing outcome data likely to be related to true outcome, with either imbalance in number across groups or reasons for missing data
- Unclear: insufficient reporting of attrition or exclusions
- Selective reporting
- Adequate: a protocol is available which clearly states the primary outcome is the same as in the final trial report
- Inadequate: the primary outcome differs between the protocol and final trial report
- Unclear: no trial protocol is available or there is insufficient reporting to determine if selective reporting is present
- Other forms of bias
- Adequate: there is no evidence of bias from other sources
- Inadequate: there is potential bias present from other sources (e.g., early stopping of trial, fraudulent activity, extreme baseline imbalance or bias related to specific study design)
- Unclear: insufficient information to permit judgment of adequacy or otherwise of other forms of bias. (Anglemyer et al., 2014, p. 6)

As an additional evaluation tool for the measurement of bias in observational studies, a method is commonly used in the medical field named the Newcastle-Ottawa Scale (NOS). This method by Wells et al. (2008) defines a quantitative assessment scale that enables us to assess each observational study according to three broad areas: selection, comparability, and exposure (Wells et al., 2008). This method is useful for this review as it evaluates the quality of observational studies and can act as a stratification tool for subgroup analysis. See the reference for Wells for details on the Newcastle-Ottawa Scale assessment tool.

F. STATISTICAL METHODS

In general, we retained the raw data extracted from the primary studies. However, if a study provided summary outcome measures including risk ratio (RR), odds ratio (OR), or hazard ratio (HR), we also extracted those results.

1. Data Synthesis

We synthesized data using meta-analytical procedures, when appropriate. Specifically, we pooled studies that had similar design (e.g., observational studies vice RCTs) and similar comparison arms (e.g., vitamin D supplementation versus placebo). We analyzed the pooled data using both a fixed-effect (FE) and a random-effects (RE) model. We used the Dersimonian and Laird method for the random-effects model (Dersimonian & Laird, 1986). The majority of the included studies were analyzed with a random-effect model, because, as expected, we found considerable heterogeneity between studies. Had we used a fixed-effect model, we would have assumed that the studies had a common estimator common between them, thus enabling a common true effect size for our analysis across their populations.

When pooling our data initially, we found that the data in various publications were reported in dissimilar units. For this reason, and to be able to compare many outcomes together so what we can perform pooled estimates, we use the standardized mean difference (SMD). The SMD allows for the researcher to pool outcomes that come from studies using different measurement scales. The SMD combines these different outcomes to a more uniform scale that can facilitate the assessment of relative intervention and variability between those observed studies. Further, the SMD equals the "difference in mean outcome between groups [directly proportional to the] standard deviation of outcome among participants" (Higgins & Green, 2011, p. 256). Specifically, Hedges and Olkin (1985), describe an effect size measurement called Hedges' (adjusted) g, which has the purpose of differentiating one group from another. They derive this method as:

$$\mathrm{g} = \frac{M_1 - M_2}{SD^*_{weighted}},$$

where the numerator is the difference in the means and the denominator has the standard deviation that is either weighted (as used by Hedges and Olkin) or pooled (used by other authors) (Hedges & Olkin, 1985).

Additionally, when pooling the data, we needed to account for individual study sizes and their variability. Therefore, whether using a RE or a FE model, we employed a weighted average for each study. In the end, the sum of all weights across all studies in a meta-analysis should sum 100%. In FE models, all studies in a meta-analysis share common estimator (a common true effect size). This model assumes that all factors affecting the effect are the same across all populations studied. Additionally, the FE assumes that random error explains the difference between studies. The RE model assumes the studies are drawn from populations that are different (in turn, affecting effect estimates). It assumes that random error and true variation explains the difference between studies. Another assumption of RE is that *k* number of studies included in the meta-analysis are a random selection from a larger population of studies. Lastly, the RE model assumes that the true effects or outcomes in the population of studies are normally distributed (τ^2 is the variance of true effect in population [the amount of heterogeneity in true effects]).

The FE model is fitted with weight as determined by $w_i = 1/v_i$, while the RE model is fitted with weight $w_i = 1/(\tau^2 + v_i)$, where τ^2 denotes the variance of the true-effects or outcomes in the population (or also interpreted as the amount of heterogeneity in true-effects). The v_i denote the variance for study *i*. In cases where discrepancies were noted between the FE and RE models, we performed a search for possible causes, including performing subgroup analyses.

To perform an assessment in the value of the review's findings, we also employed a quality assessment tool called GRADEpro (GRADEpro GDT, 2015). With this software tool, GRADEpro, an evidence table and summary of findings were produced (GRADEpro GDT). Some additional benefits of using this software tool is that it can be used as an aid for healthcare leaders to have concise and important information that can be useful for different purposes, such as for analyzing different healthcare choices, and for policy

evaluations, among other things. These assessments can be found in Appendix B. All statistical analyses were performed in R using packages including *meta* (Schwarzer, 2007) and *metafor* (Viechtbauer, 2017) and RevMan (2014).

2. Assessment of Heterogeneity

We combined data from selected studies to compare vitamin D or calcium supplementation effects on bone outcomes in cancer participants. We pooled data from the RCTs and observational studies separately. Because of various dosings, supplementations, cancer diagnoses, and even patient settings, we had an expectation of obtaining high heterogeneity between primary studies. To determine the extent of heterogeneity between studies, we used the I^2 statistic and the X^2 statistic with a significance level of 0.05. Further, we qualitatively assessed heterogeneity using the I^2 statistic as follows: between 30% and 60% is moderate heterogeneity, 50% to 90% substantial heterogeneity, and 75% to 100% as a high level of heterogeneity.

3. Subgroup Analysis and Investigation of Heterogeneity

We also explored heterogeneity by performing analysis on subgroups. The goal here was to analyze the effects of the supplementation, but also to have the effects be stratified by stratum-specific heterogeneity groups. We also aimed to examine comparisons of pooled outcomes between pediatric and adult subgroups.

III. STUDIES

The electronic search yielded 729 studies of which their abstracts were initially pulled. After sorting out a few duplicates (n = 12), we excluded a large number of studies based on their abstract clearly not meeting our inclusion criteria (n = 677). We pulled the remaining 40 studies for full text review to determine if they met our inclusion criteria. We identified a total of 11 studies with an additional three studies found from cross-referencing bibliographies of included studies, yielding 14 total primary studies. Four RCT and 10 observational studies met our inclusion criteria. A flow diagram (see Figure 1), adapted from Moher et al., (2009), illustrates the selection process.

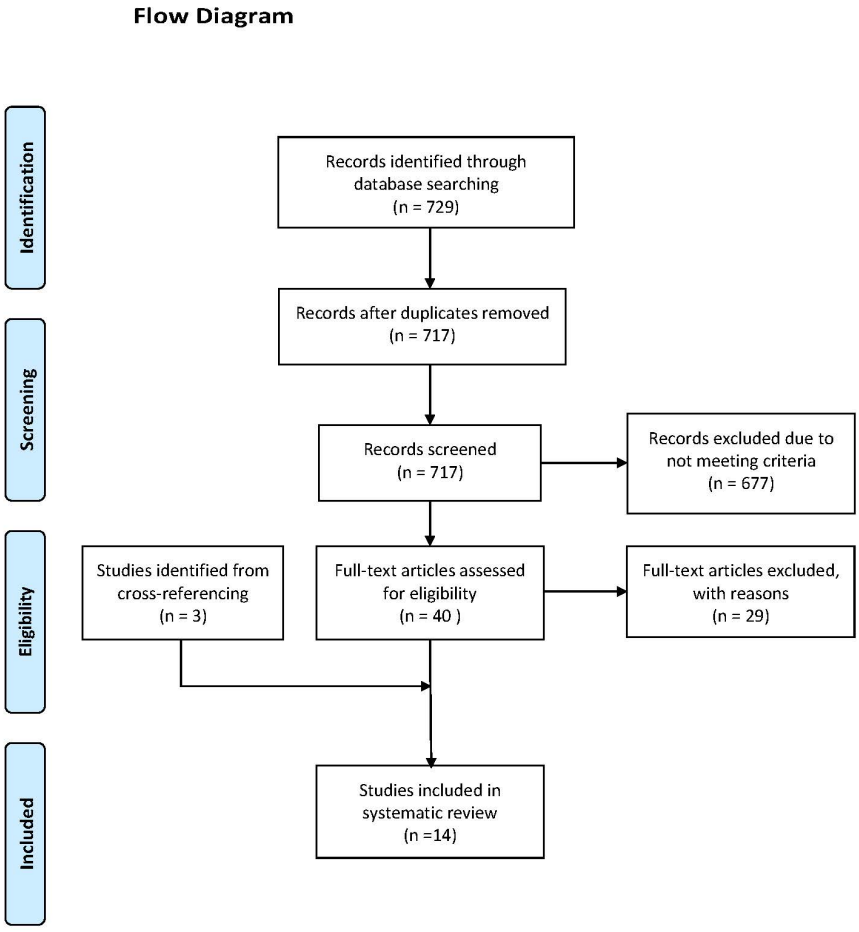


Figure 1. Study flow diagram. Adapted from Moher et al. (2009)

A. INCLUDED STUDIES

The following details the studies we included. These 14 studies were published between 1989 and 2017 and met our inclusion criteria.

Demirsoy et al. (2017) performed a study to find how the supplementation of vitamin D and calcium can be related to children with ALL. They started their study in March 2013 and lasted 20 months at the Pediatric Hematology Unit in the Kocaeli University. They had 93 participants and their ages ranged from one to 18 years of age at their time of diagnosis. There were 22 siblings nearest to some of these patients enrolled in the trial as well. Three patients dropped due to resistance, induction failure, and stem cell transplantation. Study observed that calcium and Vitamin D supplementation in these patients was not significant to halt the loss in bone mineral density during the intensive chemotherapy, however, as other studies show, as there is a gradual decrease in the first two years, there is also a gradual increase afterward.

Díaz et al. (2008) investigated in a randomized case-control trial, how effective the supplementation of calcitriol could protect the bone mass of 16 pediatric participants in a study during a period of 12 months. They made two equal groups split randomly and only one group was to receive the supplementation. These children participated starting in June 2001 for 21 months and they did this after being in remission of chemotherapy for a month. Group One received calcium and calcitriol and Group Two received only calcium. In this other study, they found that calcitriol was well tolerated and that it enhanced lumbar bone growth in participants that initially had reduced lumbar bone mineral density.

Iniesta et al. (2016) investigated 25(OH)D plasma concentrations and factors that contributed to inadequate vitamin D levels within the study participants. 82 consecutive patients and 35 healthy controls were recruited who were part of the prospective cohort of Scottish children treated for cancer. The study began in August 2010 and ended 41 months later at Edinburgh, or Ninewells Hospital in Dundee. Measurements obtained at baseline and at 3, 6, 9, and 12 months, and every 6 months thereafter. The results of this study were similar with pediatric oncology participants with matched age of healthy control group on

the inadequacy of 25(OH)D. However, the pediatric cancer patient cohort showed no seasonal variations.

Jain et al. (2017) did a cross-sectional observational study of childhood ALL survivors, diagnosed and treated between 1996 and 2008, and who have been in therapy cessation for at least 2 years. A total of 65 pediatric ALL survivors and 50 siblings enrolled for evaluation. These participants did the study in India. Their bone mineral density was evaluated and then transformed into z-scores. Findings showed these score values were not that different among participants and siblings. Therefore, as Jain et al. (2017) concluded, "there was no significant adverse impact of the disease or its treatment, including cranial irradiation on BMD in ALL survivors" (Jain et al., 2017, p. 6).

Kaste et al. (2014) performed a RCT for 275 participants having a median age of 17 years. These participants were survivors from having leukemia during treatments ranging in the years of 1984 to 1997, and they have been cleared for five years or more. Blinded to supplementation, the treatment group received daily calcium and cholecalciferol. Similar looking supplement tablets filled with inactive ingredients were given to the placebo group. This is the second RCT study so far after Diaz et al., however, in this one it was found that neither the nutritional counseling nor the supplementation given for two years were significant at increasing their bone mineral density.

Khan et al. (2010) in this prospective study they performed an effects analysis on how vitamin D levels affect 25(OH)D serum levels as well as how it affects for pain in the joints and for fatigue in women that start the treatment with letrozole for breast cancer. Women were given 50000 IU weekly of oral vitamin D3 for a 16 week time with weekly follow-ups. However, this high dose was only given to women that had low levels of 25(OH)D in their serum that was less than or equal to 40 ng/ml which accounted for a total of 47 women, while 13 women had higher levels so these were given standard dosage. Going back to observational studies, the results of this study showed a significant improvement between other things, on joint pain experienced by women that were starting treatments with letrozole.

Khan et al. (2017) conducted a randomized trial of vitamin D in 160 women with breast cancer that were being treated with letrozole. Medication or supplementation of vitamin D3 was randomized with a placebo-controlled trial to analyze if vitamin D3 supplementation given weekly for 24 weeks can prevent worsening symptoms of their musculoskeletal system. Participants were asked to enroll if they had stage I-III hormone receptor positive breast cancer and which were about to start a letrozole treatment as well as having a low level of 25(OH)D less than or equal to 40 ng.ml. This study is the third RCT so far and it concluded that the intake of vitamin D3 at 30000 IU per week dose was found to be safe for women that were starting the abovementioned treatment. Their serum levels of 25(OH)D increased as their results showed.

Leonova et al. (2015) did a cross-sectional study to look at the effects of vitamin D3 and calcium supplementation along with TSH therapy on bone mineral density. A total of 124 participants were invited to the study as a follow up for possible radiation exposure after a 14-year timeframe since the Chernobyl accident. Conclusions for this study showed beneficial effects on bone mineral density from the intake of vitamin D3 and calcium as well as evidence that there is no effect on bone mineral density from having TSH-suppressive therapy treatment.

Modan-Moses et al. (2012) performed a study to assess vitamin D levels in children with cancer and to try to find reasons to explain any deficiency. A total of 142 patients gave blood specimen to get these measurements and were taken between July 2010 and February 2011. The study took place in Israel. Participants with initial low 25(OH)D levels were offered supplementation. Patients were also offered glucocorticoids if needed as well as calcium intake, besides the maintenance, if any, given of 25(OH)D. This study showed they were unable to obtain a healthy control group, however it was not considered critical as they considered the medical history of all of their patients as a sort of baseline. Results showed that 24.6% of participants were vitamin D deficient, while 23.2% were insufficient. Additionally, participants that had a history of a malignant disease were high in both of the vitamin D problems.

Peppone et al. (2011) performed a retrospective study that analyzed women diagnosed with stage 0-III breast cancer to study various effects of vitamin D

supplementation to include bone mineral densities. All 224 women in the study were prescribed supplementation of vitamin D, either a low dose or a high dose depending on baseline total of 25(OH)D levels. These doses were administered once weekly. In the results, only 126 women completed the follow up and those that had 25(OH)D levels <32 ng/ml had significantly lower mean BMD than those with levels over 32 ng/ml.

Rai et al. (2008) performed a RCT in two phases. Study one involved estimating the prevalence of diminished bone mineral density in children with leukemia. Study two is the RCT phase. Participants were at St. Jude Children's Research Hospital. Phase one had 424 participants 279 of which were selected due to their BMD deficit to participate in the second phase as the RCT study. Participants for study two had continuous clinical nutrition services occurring at three-month intervals for a two-year study intervention. The placebo tablets were also masked of texture and flavor to aid in concealment by the research staff. Outcome from this RCT study, which is the fourth and final RCT of our thesis, describes among other things, that BMD is deficit among most participants, with only 34% of the study cohort falling at the mean or greater.

Schnabel et al. (2013) performed a retrospective clinical study that analyzed 36 subjects composed of 13 males and 23 females of which their ages ranged from 32–63 years. Ten of these participants did not complete the treatment, as it is not specified in the study. In addition, one other male participant mentioned as well, is unknown of his status throughout the study. This brought the analysis down to 25 complete results. The work in this study was to analyze the effects of vitamin D3 on mineral bone density in patients that have NF1. Study results for this study describe that the treatment with cholecalciferol proves to be effective for increasing bone mineral density in adults having NF1.

Schneider et al. (2004) performed an observational study analysis involving 208 children that underwent total thyroidectomy due to thyroid carcinoma. Of this 208, 119 were girls. These patients were referred to the study authors' institution for radioiodine treatment after having their thyroidectomy treatment due to their thyroid carcinoma disease. Intervention divided them into two groups, one placebo and one receiving AT-10/ CA supplementation. In this study from Schneider et al., final observations showed measureable disturbances in the growth-related rate of bone mass accrual. This was seen

only in the boys and the effects from this were neutralized apparently by the supplementation they received.

Watsky et al. (2014) conducted a sub study from a RCT to investigate how supplementation of vitamin D and/or calcium affects bone mineral density in children with leukemia. A total of 424 patients from ages 9 to 36 years of age when enrolled completed the study. All patients were treated at a single institution between 1984 and 1997. Their treatment consisted of blood serum samples obtained at baseline visit beside other information obtained from medical charts, and their nutritional intakes from validated questionnaires that were used to estimate the supplementation intakes. Their findings from this study, contrary to the previous from Schneider et al. (2004) where there was at least some partial positive disturbance from supplementation, this one showed the supplementation intake did not have a relation to bone outcome in these children who survived leukemia.

B. EXCLUDED STUDIES

We excluded 29 studies following full-text review for various reasons. The exclusions were mainly because the study lacked the comparison of a treatment and a placebo group (n = 29). In addition, some of these studies studied only the benefits and nutritional behavior outcomes of vitamin D (n = 6) with no comparison. Others did not involve cancer patients (n = 10). For detailed descriptions of these excluded studies, see Appendix A.

C. BIAS ASSESSMENTS

We appraised the studies and evaluated whether their explanations or definitions of various common sources of bias were satisfactory. Four RCTs, Diaz et al. (2008), Kaste et al. (2014), Khan et al. (2017), and Rai et al. (2008), were generally found to be free of obvious bias though Diaz, Khan, and Kaste had an unclear risk of selective reporting bias. See Figures 2 and 3. We also rated observational studies using this same scale, as per the Cochrane guidelines (Higgins & Green, 2011) even though by design they will be high risk using these risk of bias criteria.

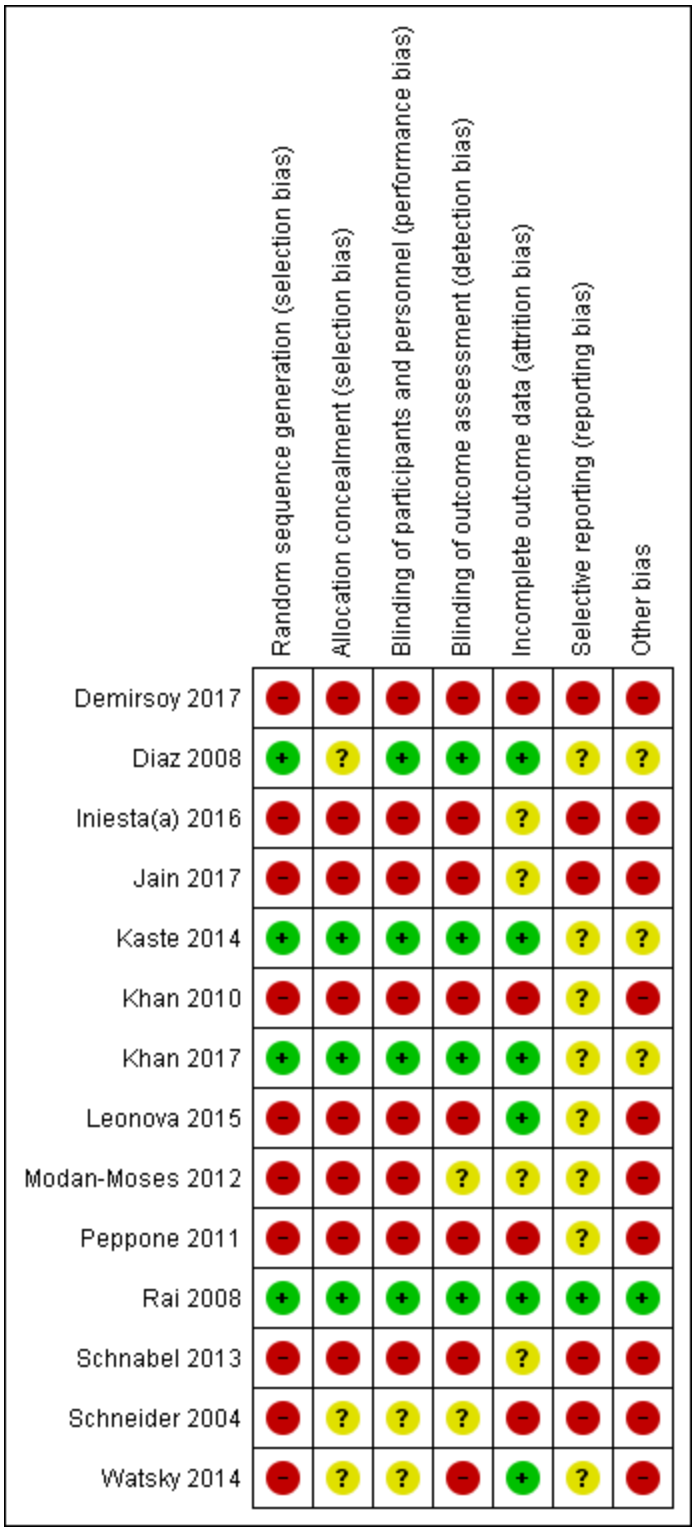


Figure 2. Risk of bias summary: The authors' judgments for all risk of bias items for each of our 14 studies. Adapted from Higgins and Green (2011).

The rating process essentially allows the researcher to assign one of three choices: “yes,” “no,” or “unclear” to each criterion. Also with choices, the overall risk of bias has “low,” “unclear,” or “high” because of these assessments. In Figure 3, we see that 45% of studies had either low risk or unclear risk due to participant selection. Additionally, 45% of studies also had either a low risk or unclear risk for blind control of patients as a degree of performance. In addition, about 45% of studies had either a low risk or an unclear risk of bias for blinding of outcome assessment as a detection measure. About 75% of studies had either a low or an unclear risk due to attrition. Of the RCTs, all were found to be the lowest in risk mainly due to their design employing randomization. However, only three of the four RCTs were found to have their measure of risk of bias to be low for their selection protocol (Kaste et al., 2014; Khan et al., 2017; Rai et al., 2008), while one had an unclear risk (Díaz et al., 2008). Figure 3 is adapted from the RevMan study analysis software made by the Cochrane Collaboration (Higgins and Green 2011).

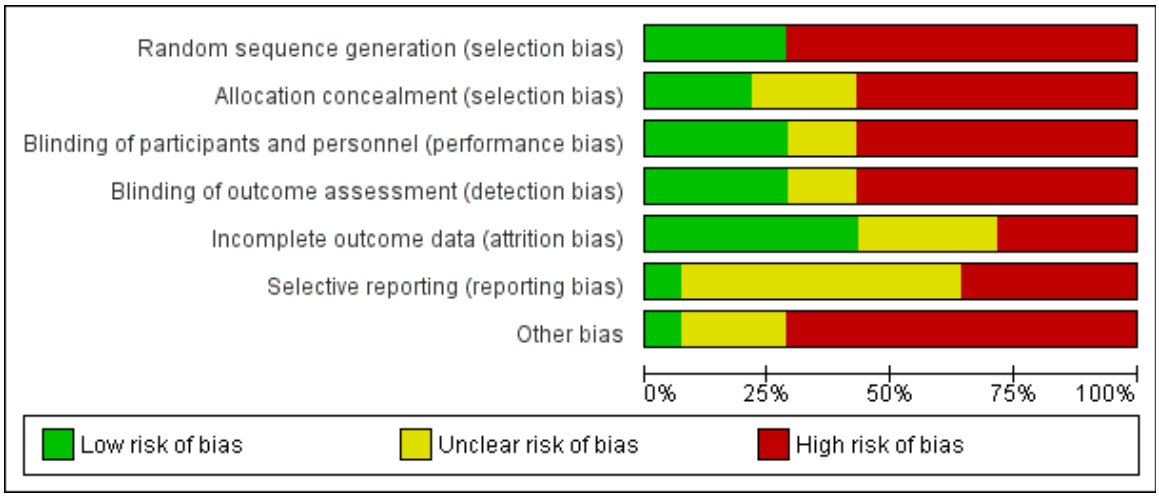


Figure 3. Risk of bias summary: displays pooled studies and how the overall risk of bias affects each control. Adapted from Higgins and Green (2011).

As part of our planned analyses exploring the source of heterogeneity between studies, we performed subgroup analyses by risk of bias groups. For our identified non-randomized studies, we consider the following as criteria for risk of bias subgroups:

- High or medium risk of bias = 7 or fewer stars
- Low risk of bias = 8 or 9 stars

Using these criteria, Schnabel et al. (2013), Iniesta(a) et al. (2016), Khan et al. (2010), Peppone et al. (2011), Schneider et al. (2004), and Watsky et al. (2014) all had a high/medium risk of bias. For a good example of why we concluded high or medium risk of bias for these studies, we can point to the cohort study by Watsky et al. Using the NOS scale, we note that the study had two stars in the selection category as it failed to show the use of a comparison control group as well as the demonstration of the outcome not being present prior to the start. For the comparability category, we assigned the maximum of two stars for controlling two different outcomes of interest. However, in the last category of outcome assessment, the study authors made no statement adequate to explain the loss to follow-up of participants. The rest of the studies, Demirsoy et al. (2017), Leonova et al. (2015), Modan-Moses et al. (2012), and Jain et al. (2017), had low risk of bias, as seen in Table 1 (adapted from Anglemyer, Horvath, & Rutherford 2014). We partitioned the studies with lower risk (or highest amount of stars) and those studies that had a higher risk (or fewest amount of stars).

Table 1. Evaluation summary of included studies via the use of the NOS assessment for observational studies. Adapted from Anglemyer et al. (2014)

Study, Year (Reference)	Stars, *n*		
	Selection†	**Comparability‡**	**Exposure§**
Cohort studies			
Demirsoy 2017	4	2	3
Iniesta (a) 2016	2	1	3
Khan 2010	2	1	3
Leonova 2015	3	2	3
Modan-Moses 2012	3	2	3
Peppone 2011	3	1	2
Schnabel 2013	2	1	2
Schneider 2004	2	1	3
Watsky 2014	2	2	2
Case Control studies			
Jain 2017	4	1	3

† Maximum 4 stars
‡ Maximum 2 stars
§ Maximum 3 stars

Please see the Newcastle-Ottawa scale reference by Wells et al. (2008) for information summarizing the risk of bias assessments for the observational studies.

IV. META-ANALYSIS RESULTS AND GRADEpro QUALITY OF EVIDENCE

In this chapter, we provide results for each outcome using evidence from both randomized and observational studies. First, we look at all RCT studies, followed by the observational studies, and lastly some additional subgroup analyses that could include both of these types of designs.

A. BONE MINERAL DENSITY

The studies in this thesis that contained a quantitative assessment of BMD are described in this section. There was significant evidence in BMD differences related to the intake of supplementation of vitamin D3 and calcium in certain studies. However, we only made a note of this evidence in singular studies and not as a pooled effect. Jain (2017) noted studies that found differences included a subgroup of boy cancer patients in Schneider (2004) and Schnabel (2013), but also a slight positive difference for the study in both of its subgroups. Overall, there was no significant evidence evaluating the pooled effects from BMD outcomes. There were also some single studies slightly negative effects of supplementation such as the subgroup of girl cancer patients in Schneider (2004), Diaz (2008), and Kaste (2014), though none were significant. More details can be found in the following subsections.

1. Lumbar Spine BMD

This section contains the studies that evaluated whether supplementation affected BMD measured specifically at the lumbar spine. This is one of the most common approaches to measuring BMD and was the most commonly reported outcome from all the studies.

a. Number of Studies that Estimated This Outcome

We pooled together five studies, two RCT and three observational, which performed lumbar spine BMD measurements to evaluate the pooled effect. The two RCT

were Diaz et al. (2008) and Kaste et al. (2014), and the three observational studies included Jain et al. (2008), Leonova et al. (2015), and Schnabel et al. (2013).

b. Studies that Found a Positive or Negative Effect

Neither of the RCTs found a significant effect of calcium and vitamin D supplementation for improving BMD in the lumbar spine. In fact, both studies have negative point estimates, suggesting a slight decrease overall, though these results are highly variable. We derived four point-estimates from three observational studies. One study (Jain 2008) had two different exposure groups compared to a placebo and both were included in our analysis. Of the four point-estimates from observational studies, three showed an improvement in lumbar spine BMD. However, none was significant.

c. Pooled Effects

The pooled effect of supplementation from the two RCTs (see Figure 4) shows no significant effect of supplementation on lumbar BMD (SMD=-0.06; 95% CI= -0.29, 0.17). In all, there were 149 participants who received supplementation and 142 participants from a control group. The RE p-value was not significant (p=0.59), and the test for heterogeneity indicated no evidence (p=0.57).

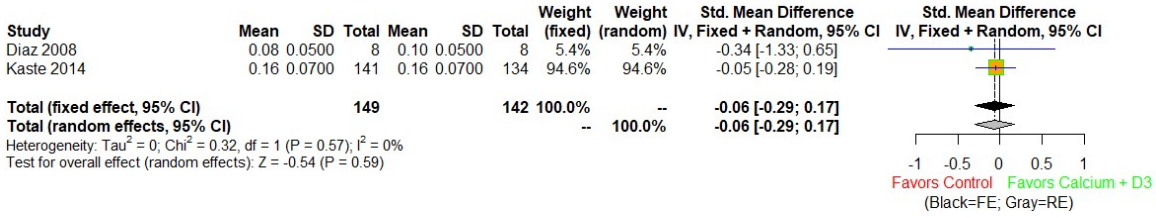
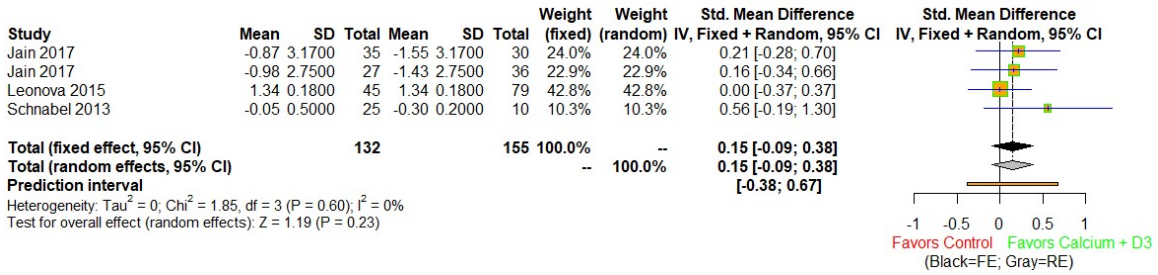


Figure 4. Lumbar spine BMD measurements analysis from RCT studies. Adapted from Higgins and Green (2011).

Further, we pooled the four point-estimates from the observational studies (see Figure 5) and found no significant effect from supplementation on lumbar BMD (SMD=0.15; 95% CI -0.09, 0.38) from the RE model. In total, 132 participants received supplementation, and 155 participants made up the control treatment group. The

heterogeneity test between the groups was not significant, indicating no important differences between studies and that a FE model may be an appropriate assumption.



Footnotes: (in order of appearance) Jain 2017(1): calcium vs. low calcium supplements comparison. Jain 2017(2): vitD vs. low vitD supplements comparison.

Figure 5. Lumbar spine BMD measurements analysis from observational studies. Adapted from Higgins and Green (2011).

2. Total BMD

a. Number of Studies that Estimated This Outcome

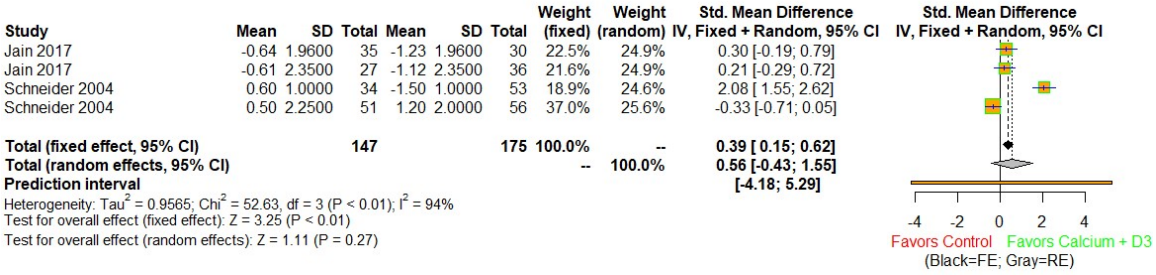
Only one RCT (Diaz 2008) and two observational studies (Jain [2017], and Schneider [2004] with two sub studies) evaluated the effects of supplementation on total BMD.

b. Studies that Found a Positive or Negative Effect

In the RCT, there was a non-significant negative effect of calcium and vitamin D supplementation for improving total BMD (SMD=-0.89; 95% CI -2.01, 0.24). In the observational studies, the overall effect for RE provided no significant results, however, FE did provide significant results, and their heterogeneity was significant at 94%. Neither of the two point-estimates obtained from Jain et al. (2017) were significant. We note that Schneider et al. (2004) found that the point estimate for the boys' group was highly significant with a p-value of less than 0.01, while the same effect was less significant among the girls with a p-value of 0.09.

c. Pooled Effects

We did not pool effects from RCTs because we only had one RCT that evaluated total BMD. The RCT included only five participants with supplementation and six participants from a control group. The pooled effect from the two point-estimates from Jain et al. (2017), though positive, remained non-significant. Together with the results from Jain et al., we note that Schneider et al. (2004) also stratified their results by gender. We found that, if we assumed a FE model, the pooled effects would actually be significant, indicating a positive effect of supplementation on total BMD (SMD=0.39; 95% CI 0.15, 0.62), however the RE model may be more appropriate in the presence of high heterogeneity. One of the four estimates found a significant positive effect of calcium and vitamin D supplementation for improving total BMD (SMD=2.08; 95% CI 1.55-2.62), which was specifically among boys (Schneider et al.). However, an opposite effect was found among girls (SMD=-0.33; 95% CI -0.71, 0.05) (Schneider et al.). The authors note that these differences may be due to basically their gender-related differences such as in muscle bone proportions and the estrogen-induced enhancement responding differently within their bone cells due to this induced stimulation (Schneider et al., 2004). The total number of participants who received supplementation was 147 and they were compared to 175 who were in the control group. Heterogeneity between the four studies was significant (p=0.01) and substantial heterogeneity was noted (I^2 = 94%) (See Figure 6).



Footnotes: (in order of appearance) Jain 2017(1): calcium vs. low calcium supplements comparison. Jain 2017(2): vitD vs. low vitD supplements comparison. Schneider 2004(1): boys. Schneider 2004(2): girls.

Figure 6. Total BMD measurement analysis from observational studies. Adapted from Higgins and Green (2011).

3. Hip BMD

a. Number of Studies that Estimated This Outcome

Only two studies evaluated BMD measured at the hip, one RCT (Diaz 2008) and one observational study (Schnabel 2013).

b. Studies that Found a Positive or Negative Effect

In the one RCT, there was a non-significant reduction in hip BMD among the supplemented group in comparison to the control group (SMD=-0.91; 95% CI -2.19, 0.36).

In the one observational study, there was a significant positive effect of calcium and vitamin D supplementation for improving BMD in the hip (SMD=1.17; 95% CI 0.38, 1.96).

c. Pooled Effects

We did not pool the data for this outcome because we only had single studies. The findings from the RCT came from a study of five participants with supplementation and six participants from a control treatment group. The observational study evaluated a total of 25 participants with supplementation and 10 participants from a control group.

4. Proximal Femur BMD

a. Number of Studies that Estimated This Outcome

Only one observational study (Leonova 2015) performed proximal femur BMD measurements.

b. Studies that Found a Positive or Negative Effect

In this single study, there was no effect of calcium and vitamin D supplementation for improving BMD in the proximal femur (SMD=0.00; 95% CI -0.37, 0.37).

c. Pooled Effects

In the one study, a total of 45 participants received supplementation and 79 participants were in the control treatment group.

B. 25(OH)D LEVELS

This section contains all the study analyses that pertain to the measurement results of vitamin D levels provided the results and a baseline were given in each study. Since vitamin D is critically important for the proper development of mineral bone density, a study would be significant if it shows evidence of this relationship with supplementation. Single study effects that demonstrate positive evidence of given supplementation are from Khan (2017), and studies with a slight positive effect are from Demirsoy (2017) and Peppone (2011) for both of its subgroups. Studies with a slight effect towards controls are from Modan-Moses (2012), and Iniesta(a) (2016). The meta-analysis had one study with significant findings towards supplementation and another study slightly towards control, which gave an overall non-significant finding regarding supplementation effects. More details on these studies are found in the following subsections.

1. At Four Weeks

The 25(OH)D levels at four weeks measurements taken from studies that provided this information is described here.

a. Number of Studies that Estimated This Outcome

Only one study (Demirsoy 2017) evaluated 25(OH)D levels at four weeks measurements after supplementation. .

b. Studies that Found a Positive or Negative Effect

In this single study, there was a slight positive effect of supplementation for improving 25(OH)D levels at four weeks, though this was not significant (SMD=0.05; 95% CI -0.5, 0.59).

c. Pooled Effects

We did not pool these effects because we identified only one study. The study included a total of 34 participants with supplementation and 21 participants from a control treatment group.

2. At 12 Weeks

The 25(OH)D levels at 12 weeks measurements taken from studies that provided this information is described here.

a. Number of Studies that Estimated This Outcome

Only one RCT (Khan 2017) and one observational study (Modan-Moses 2012) performed 25(OH)D levels at 12 weeks measurements.

b. Studies that Found a Positive or Negative Effect

In the RCT, there was significant, positive effect of vitamin D supplementation for improving 25(OH)D levels at 12 weeks (SMD=1.96; 95% CI 1.57, 2.36). However, in the observational study, there was no similar effect (SMD=-0.05; 95% CI -0.64, 0.54).

c. Pooled Effects

Due to different designs, we did not pool the two studies together. The RCT evaluated 70 participants with supplementation and 77 participants in the control group. The observational study included very few participants, 12 with supplementation and 130 in the control group.

3. At 16 Weeks

The 25(OH)D levels at 16 weeks measurements taken from studies that provided this information is described here.

a. Number of Studies that Estimated This Outcome

Only one observational study (Peppone 2011) was identified that evaluated 25(OH)D levels at 16 weeks. The authors had two exposure groups: low dose and high dose supplementation.

b. Studies that Found a Positive or Negative Effect

Both the low dose and the high dose supplementation groups showed a slight improvement in 25(OH)D levels at 16 weeks, though neither was significant.

c. Pooled Effects

The pooled effects from Peppone 2011 indicated no significant effect of supplementation (low dose or high dose) on 25(OH)D levels at 16 weeks (SMD=0.31; 95% CI -0.19, 0.81). The authors included 64 participants with high dose supplementation, 53 participants with low dose, and 9 participants from a control group. The test for heterogeneity was no significant (p=0.93).

4. Greater than 40 Units at 10 Weeks

The 25(OH)D levels greater than 40 units at 10 weeks measurements taken from studies that provided this information are described here.

a. Number of Studies that Estimated This Outcome

Only one study (Khan 2017) evaluated 25(OH)D levels > 40 units at 10 weeks.

b. Studies that Found a Positive or Negative Effect

In this single study, the patients who received supplementation were 40 times more likely to have 25(OH)D levels > 40 units at 10 weeks than control patients (OR=40.53; 95% CI 15.71-104.52).

c. Pooled Effects

We did not pool these effects due to only one study being identified. However, this study identified 59 individuals reaching optimal 25(OH)D levels out of 70 participants with supplementation, and only 9 reaching optimal levels out of 77 control participants.

5. Greater than 40 Units at 16 Weeks

The 25(OH)D levels greater than 40 units at 16 weeks measurements taken from studies that provided this information are described here.

a. Number of Studies that Estimated This Outcome

We identified two studies which evaluated 25(OH)D levels > 40 units at 16 weeks. These two studies are Iniesta(a) et al. (2016), and Khan et al. (2010).

b. Studies that Found a Positive or Negative Effect

For this outcome, we found opposing effects. We found a positive effect on calcium and vitamin D supplementation for improving 25(OH)D levels > 40 units at 16 weeks in Khan et al. (2010) (OR=43.62; 95% CI 2.01-945.91), however a non-significant reduced effect in Iniesta(a) et al. (2016) (OR=0.29; 95% CI 0.01-6.39).

c. Pooled Effects

We pooled these two studies as seen in Figure 7, and the RE model yielded a non-significant pooled OR of 3.58 (95% CI 0.03- 490.21). However, the FE model yielded a non-significant pooled OR as well of 2.91 (95% CI 0.73-11.58). A total of 54 participants achieved the desirable outcome among the 58 participants with supplementation. Moreover, 11 control participants achieved the outcome out of the 14 control patients. Heterogeneity between the two studies was significant (p=0.02) and substantial heterogeneity was noted (I^2 = 80%).

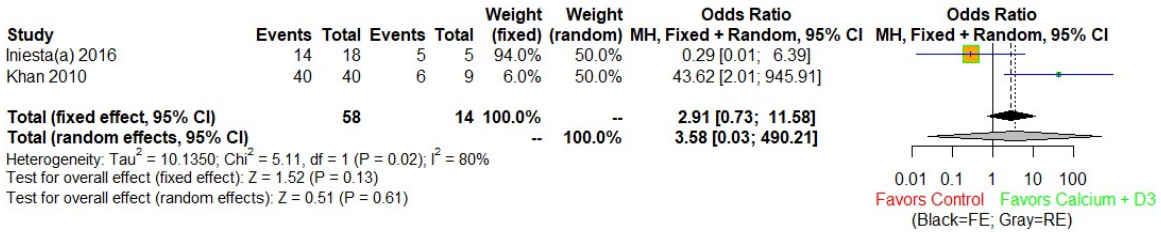


Figure 7. 25(OH)D levels > 40 units at 16 weeks analysis from observational studies. Adapted from Higgins and Green (2011).

6. Greater than 40 Units at 24 Weeks

The 25(OH)D levels greater than 40 units at 24 weeks measurements taken from studies that provided this information are described here.

a. Number of Studies that Estimated This Outcome

Only one study (Khan 2017) evaluated 25(OH)D levels > 40 units at 24 weeks.

b. Studies that Found a Positive or Negative Effect

In this single study, there was positive effect on calcium and vitamin D supplementation for improving 25(OH)D levels > 40 units at 24 weeks in participants from this study.

c. Pooled Effects

This study identified 59 individuals reaching optimal 25(OH)D levels at 24 weeks out of 70 participants with supplementation, and only 8 reaching optimal levels out of 77 control participants.

C. SUBGROUP ANALYSES SECTION

In the final section of this chapter, we find some different comparisons among some or all the studies, according to the criteria in question.

1. Lumbar Spine BMD: Observational Studies (High/Medium vs. low Risk of Bias)

This subgroup of observational studies comparing according to their level of risk of bias per NOS, was the only subgroup possible out of all of our studies. This is because there was no other measurements section to have at least two different studies that are purely observational.

a. Number of Studies that Estimated This Outcome

Four studies in this subgroup performed lumbar spine BMD measurements and were pooled together according to their risk of bias per NOS outcomes from Table 1. The objective is to analyze for any significant outcomes between the two groups.

(1) High/medium risk of bias studies

- Schnabel et al. (2013)

(2) Low risk of bias studies

- calcium vs. low calcium supplementation groups from Jain et al. (2017)

- vitamin D vs. low vitamin D supplementation groups from Jain et al. (2017)
- Leonova et al. (2015)

b. Studies that Found a Positive or Negative Effect

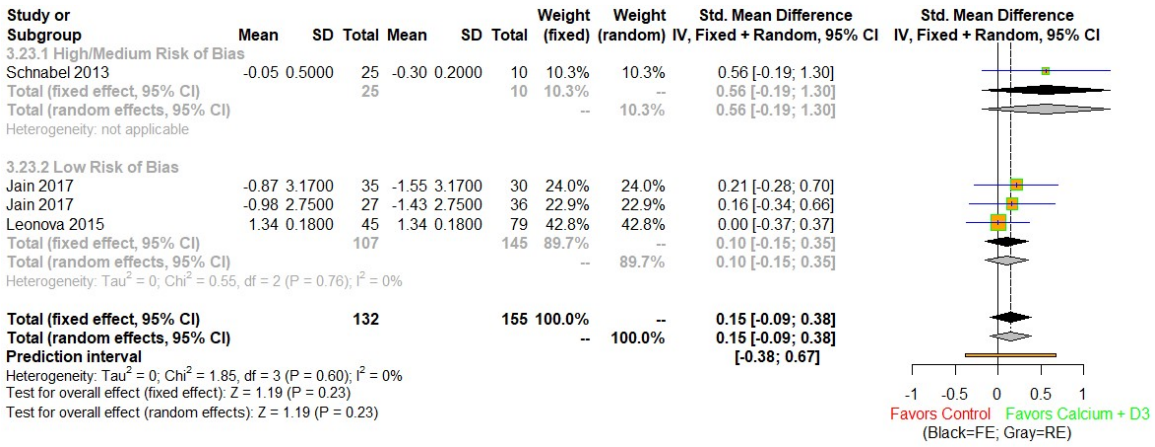
In this case, there were no studies that found a positive effect on calcium and vitamin D supplementation for improving bone mineral density in the lumbar spine BMD measurements.

c. Pooled effect. SMD or OR, p-value, and I^2 est. (heterogeneity)?

Only one study is part of the high/medium risk level of bias subgroup, as displayed in Figure 8, show a SMD of 0.56 with a CI of [-0.19, 1.30] that come from having a total of 25 participants with supplementation, and 10 participants from a control treatment group such as a placebo.

The three studies pooled together to form the low risk level of bias, as displayed in Figure 8, show a SMD of 0.10 with a CI of [-0.15, 0.35] that come from having a total of 107 participants with supplementation, and 145 participants from a control treatment group such as a placebo.

Their pooled FE has a SMD of 0.15, and their RE has the same values. Their test for overall FE and RE had a p-value of 0.23, which is not significant. However, their I^2 for heterogeneity was 0%, which is not significant.



Footnotes: (in order of appearance) Jain 2017(1): calcium vs. low calcium supplements comparison. Jain 2017(2): vitamin D vs. low vitamin D supplements comparison.

Figure 8. Lumbar spine BMD analysis from subgroup made of observational studies between high/medium risk vs. low risk of bias. Adapted from Higgins and Green (2011).

2. Total BMD: Observational Studies (High/Medium vs. Low Risk of Bias)

This subgroup of observational studies comparing

a. Number of Studies that Estimated This Outcome

We pooled six studies in this subgroup and performed total BMD measurements according to their risk of bias per Newcastle-Ottawa outcomes from Table 1. The objective is to analyze for any significant outcomes between the two groups (see Figure 9).

(1) High/medium risk of bias studies

- Schneider et al. (2004) boys subgroup
- Schneider et al. (2004) girls subgroup

(2) Low risk of bias studies

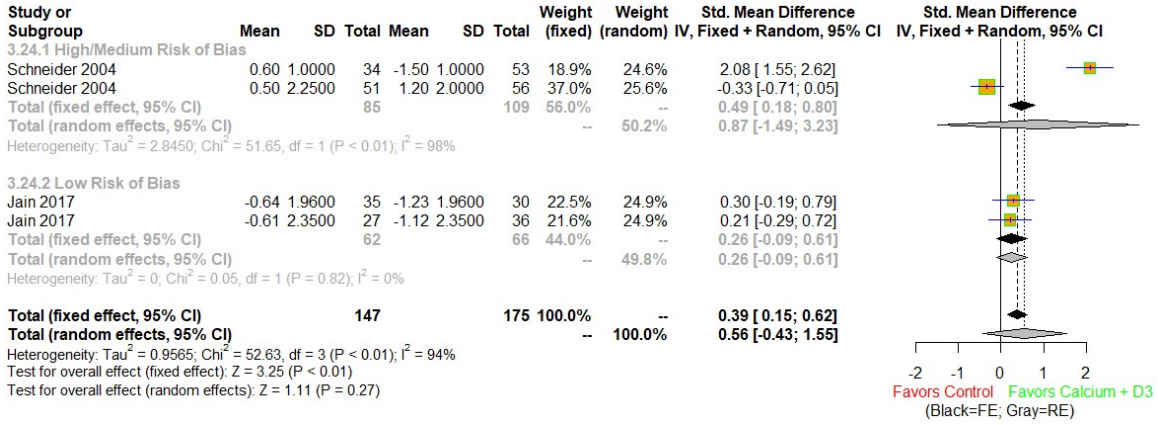
- calcium vs. low calcium supplementation groups from Jain et al. (2017)
- vitamin D vs. low vitamin D supplementation groups from Jain et al. (2017)

b. Studies that Found a Positive or Negative Effect

In this case, there was only one study out of the high/medium risk of bias subgroup that found a significant effect, which was to favor calcium and vitamin D supplementation for improving bone mineral density in the total BMD measurements. Not all other studies were significant although one had a slight negative effect; however, the overall is also not significant.

c. Pooled Effect. SMD or OR, p-value, and I^2 est. (Heterogeneity)?

The pooled FE model yielded a significant pooled OR with a SMD of 0.39 with a CI of [0.15, 0.62], however their RE model yielded a non-significant pooled OR and has a SMD of 0.56 with a CI of [-0.43, 1.55]. Their I^2 came out as 94%, which is highly significant for heterogeneity and with a p-value of less than 0.01.



Footnotes: (in order of appearance) Schneider 2004(1): boys. Schneider 2004(2): girls. Jain 2017(1): calcium vs. low calcium supplements comparison. Jain 2017(2): vitamin D vs. low vitamin D supplements comparison.

Figure 9. Total BMD analysis from subgroup made of observational studies between high/medium risk vs. low risk of bias. Adapted from Higgins and Green (2011).

3. Pediatric vs. Adult Studies

This subgroup analysis is made of studies and sub studies that contain the lumbar spine BMD measurements, which we then pooled together according to their patient

classification of either pediatric or adult. The objective is to analyze for any significant outcomes between the two classification groups.

a. Number of Studies that Estimated This Outcome

We pooled four studies in this subgroup and performed lumbar spine BMD measurements to analyze for any significant outcome (see Figure 10).

(1) Pediatric studies

- calcium vs. low calcium supplementation groups from Jain et al. (2017)
- vitamin D vs. low vitamin D supplementation groups from Jain et al. (2017)

(2) Adult studies

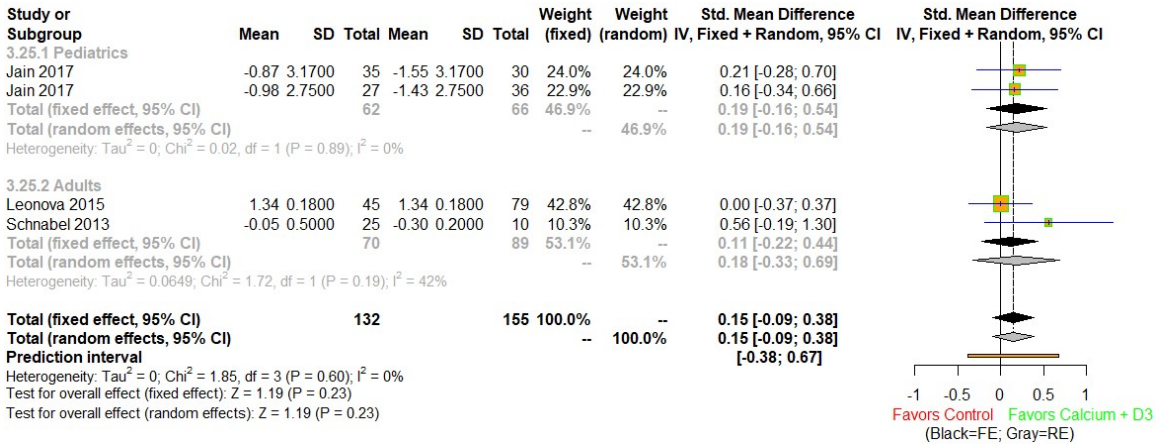
- Leonova et al. (2015)
- Schnabel et al. (2013)

b. Studies that Found a Positive or Negative Effect

In this case, there was no study that found a positive or even negative effect on calcium and vitamin D supplementation for improving bone mineral density in the lumbar spine BMD measurements. Although no studies were significant, most had a slight positive effect toward supplementation; however, the overall is not significant.

c. Pooled Effect. SMD or OR, p-value, and I^2 est. (Heterogeneity)?

Their pooled FE model yielded a non-significant pooled OR with a SMD of 0.15, and their RE model also yielded a non-significant pooled OR with the same SMD. Furthermore, their I^2 for heterogeneity came out as 0%, which is not significant and shows its p-value of 0.60.



Footnotes: (numbered in order of appearance) Jain 2017(1): calcium vs. low calcium supplements comparison. Jain 2017(2): vitD vs. low vitD supplements comparison.

Figure 10. Lumbar spine BMD analysis from subgroup made of observational studies between pediatric and adult study groups. Adapted from Higgins and Green (2011).

D. PUBLICATION BIAS ASSESSMENT

Due to a small number of identified publications evaluating the effect of supplementation on various bone outcomes, we were unable to adequately assess publication bias. For added clarity, we created a funnel plot to evaluate graphically with some validity, the studies' publication bias. An example of this is noted in Figure 11. In the figure, we can see there are four visible studies outside the contour lines of the funnel, which form a shape as of a triangle. These four studies are significantly different from the rest due to their smaller standard error and smaller SMD or plainly a larger SMD overall.

We found useful data for our study in three of the four RCT studies and so only those three are shown here. Two of these are outside the funnel delineated by red squares. Kaste et al. (2014) is one of these two and it stands outside the intervals of the funnel mainly due to its sample size large enough and having an outcome favorable to controls, which leaned its SMD into the left, and having a small spread of SE as well, made it be outside the overall SMD for the group. Khan et al. (2017) is the other RCT study outside the funnel located on the right. This study found significant findings on its outcomes favoring supplementation, however, the reason this RCT stands out to the far right is that it was the only RCT that contained vitamin D outcomes. Hence, there was no true effect

comparison with this RCT so the reason of the effect that it shows a different outcome value.

The other two studies outside the funnel are actually two sub studies from the same study by Schneider et al. (2004). This study did analysis on a boys' group and analysis on a girls group. Their findings were that the boys' group had significant evidence on positive effects on supplementation, while the opposite was found for the girls, as previously explained. Schneider et al. was the only observational study we found containing significant findings, hence the reason it stands outside the SMD interval of the rest of the group. However, our NOS scale to contain high-risk level of bias assessed Schneider et al. study.

Although it is important to note that there is bias in this assessment as many of these studies contain different types of measurements as seen previously that for BMD as well as for the levels of 25(OH)D, there are different scales. More importantly, we are showing in this graph both RCT and observational studies. Therefore, the figure in this section is for illustration purposes only and not to make a decision based on its output.

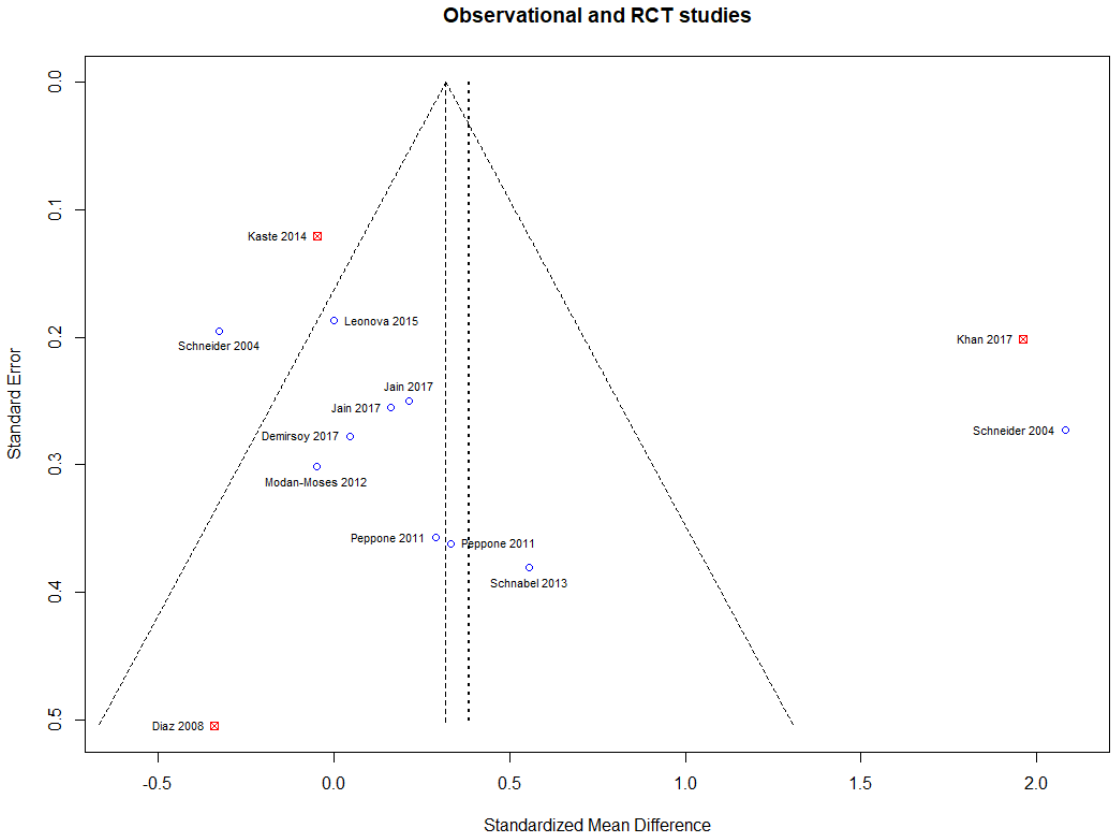


Figure 11. Funnel displaying observational and RCT studies. Red squares are RCT and blue circles are observational studies.

E. QUALITY OF EVIDENCE EVALUATION

We also evaluated the quality of evidence provided by the analysis made via the GRADEpro GDT application (GRADEpro GDT, 2015). For each of the 14 studies, we evaluated each outcome and its pooled effect for assessing quality of evidence. The GRADEpro approach offers reviewers an overview on the certainty of the evidence from the outcomes. It is a tool to make informed decisions regarding how each study is influenced through its certainty and its findings. GRADEpro outcomes have four levels of certainty ranging from very low confidence to high.

All the RCT studies result in a high certainty score from GRADEpro while the observational studies range from very low to low certainty mostly due to study design deficits. Therefore, all these outcomes with estimates produced by observational studies

were determined to be very low quality, except for lumbar spine, which was the only outcome we determined to have low quality via GRADEpro. Usually upon submitting an assessment in GRADEpro for an observation study or any study that will not have high level of certainty, the system will ask for submitting a note or comment so others can see a description of why a certain study had lower certainty level. In our studies, some of the comments submitted for the observational studies were:

1. Performed with voluntary participants
2. Ten of the participants did not complete the treatment, as it was not specified in the study. In addition, one other male participant mentioned is unknown of his status throughout the study assessments.
3. Among eligible ALL survivors identified for the study, these patients consented to receive treatment, therefore not randomized.
4. Recruitment of participants from the Chernobyl accident between 15 January 2007 and 23 December 2010 lacked randomization.

These comments mentioned are also found in the GRADEpro Appendix B.

V. CONCLUSIONS

We performed a meta-analysis to determine whether taking vitamin D and/or calcium supplementation enhances BMD for oncology patients. As of today, there is no consensus among medical researchers on whether this supplementation at all affects bone health outcomes in cancer patients. Currently, Tricare does not cover multivitamins or multiminerals, and its online drug formulary only lists one type of vitamin D out of 44 different vitamin D formulas as eligible for coverage although they have a disclaimer for coverage of medically necessary and proven medical services. This lack of coverage along with the uncertainty of significant improvement for BMD in cancer patients inspired us to perform a systematic review of all relevant studies to find a better predictor.

We first needed to find as many studies as possible. Randomized controlled trials were best, but we also considered any non-randomized clinical study that met thesis inclusive criterion, so a meta-analysis would be viable. The search started with over 700 study abstracts of which, by using the PICO framework analysis, we found 40 potentially viable studies, and, finally, after performing a full study analysis, chose 14. Those disqualified were mostly non-randomized studies, and/or lacked some or most of the thesis's inclusion criteria. The 14 studies include four RCTs and ten observational studies. This selection flow can be seen in Figure 1.

Observational studies, due to their nature of the lack of randomization, went through additional screening to measure their level of risk of bias. Observational studies carry a high risk of bias throughout all phases of development, compared to RCT studies, inherently less biased due to randomization. We assessed this risk of bias level according to the NOS assessment. This risk of bias assessment helped analyze each observational study by looking at key elements where risk of bias could be inherent, and thus converting this qualitative analysis into a numeric score or scaled metric (as seen in Table 1), which helps assess the level of risk of bias according to the criteria set by the reviewer. This criteria was set as a scale in which we classified each observational study into a high/ medium risk of bias, which transferred from those studies that had the lowest numeric score starting from six and below, and into a low risk of bias analysis for those studies that had

the topmost numeric scores starting from seven up to the nine total points possible. This NOS assessment tool helped determine that, according to our criteria, four observational studies had a low risk of bias while the other six studies had a medium to high risk of bias. A good comparison analysis of the difference of effectiveness within these two groups can be seen in two different analyses illustrated in Figure 8 and Figure 9.

We met challenges including a core challenge that most of the studies had their own distinctive way of doing analysis while others described somewhat different outcome measurements and thus different reporting measurements, or, even worse, a lack of reporting on some of the important measurements for our study. We met this challenge both by carefully selecting only 14 studies of the 700, looking for common quantitative, rather than qualitative factors. We included studies that shared some common metrics: measurements of the lumbar spine BMD, hip BMD, proximal femur BMD, total BMD, 25(OH)D levels at various lengths of time, and 25(OH)D levels over 40 units at various lengths of time. To overcome some differences in reporting outcomes, we used a SMD as a base comparison for the entire continuous unit-based analyses and an OR effect measure as a baseline for the dichotomous unit-based analyses.

Additional statistical analyses performed with the studies included examining their pooled effect and the variation across the studies. We also compared intervention effect estimates by looking at their RE and FE, as well as looking at their heterogeneity effect overall with probability values for significance between studies if more than one study was involved. In FE models, all studies in a meta-analysis share common estimator (a common true effect size). The RE model assumes the studies are drawn from populations that are different (in turn, affecting effect estimates). The effect of heterogeneity was qualitatively assessed using the I^2 statistic as follows: between 30% and 60% considered moderate heterogeneity, 50% to 90% considered substantial heterogeneity, and 75% to 100% considered the effect as a high level of heterogeneity.

A significant finding in each analysis was noted if an SMD's 95% confidence interval was entirely above or below zero. Anything outside this CI is reported as not being a significant finding or as not having enough evidence for a specific parameter being statistically significant at a 95% confidence level. In our analysis, there was no significant

heterogeneity found in the lumbar spine BMD analyses (RCTs and observational), also in the lumbar spine BMD with subgroups of high/medium risk of bias vs. low risk of bias analysis, and lastly in the lumbar spine BMD analysis from the subgroup analysis made of observational studies between pediatric and adult study groups. However, significant heterogeneity was found in the total BMD analysis made of observational studies (high level heterogeneity), also in the 25(OH)D levels > 40 units at 24 weeks analysis (high level), and, lastly, in the total BMD analysis from subgroup made of observational studies between high/medium risk vs. low risk of bias (high level).

Results obtained from this meta-analysis produced no significant statistical evidence that the supplements in question improve BMD. From the RCT studies, only one was found to have significant evidence about supplementation making an impact on bone health (Khan et al. (2017)), according to its outcome on 25(OH)D levels. From the observational studies, just three out of the ten studies had some significant evidence on the use of supplementation making positive impact:

- Schnabel et al. (2013), in their hip BMD assessment
- Schneider et al. (2004) (boys' group), in their total BMD assessment (as seen in Figure 6), and
- Khan et al. (2010), in their 25(OH)D levels > 40 units at 16 weeks assessment (as seen in Figure 7)

The remainder of the observational studies demonstrated neither positive nor negative significant outcomes.

Our results found in this this thesis come with a few caveats. One limitation was such that there is not much published evidence for pediatrics, especially RCTs. The lack of RCTs in our research likely diminishes the power of evidence or the statistical significance, which is what this thesis is trying to demonstrate. The particularly narrowed search criteria considering our specific interventions and bone health as outcome, produced lower than expected studies to choose from as seen in Figure 1. Further research will most likely strengthen this meta-analysis and its power of predictability of findings, if any.

One of our findings does show a slight incline towards favoring supplementation for adults as well as for children, especially by looking at the subgroup analyses section in this thesis and looking at Figures 8–10. Although, again, no subgroup analysis in this thesis found any significant findings at a 95% confidence level regarding supplementation effects on bone health. An example of the included studies can be seen in Figure 11. Although it is not best to mix RCTs with observational studies, Figure 11 can be helpful as an overall comparison for possible effects. Keeping in mind, many of these studies are in different areas of the scale because they contain different areas of measurements according to their specific study.

As a last step, we looked at evaluating the quality of the evidence with the assistance of an analysis software called GRADEpro GDT (GRADEpro GDT, 2015). The GRADEpro approach gave us an overview on the certainty of the evidence from the outcomes of all of our studies used in this thesis. We used this as a tool to make informed decisions regarding how each study is influenced through its certainty and its findings we obtained from them. GRADEpro outcomes have four levels of certainty. These levels go from very low certainty (i.e., very low confidence) to high certainty, which means we have confidence in that estimate of the effect.

All the RCT studies result in GRADEpro having a high level of certainty, while all other studies such as the observational studies have some other level of certainty. Therefore, all these outcomes with estimates produced by observational studies were determined to be very low quality, except for lumbar spine, which we assessed as simply low quality per our GRADEpro quality of evidence assessment. This is a great tool that policymakers can use to look at how all the studies ranked in terms of certainty of the evidence and its importance overall in the study.

In conclusion, many estimates show increases/benefits for supplementation being effective for BMD changes, but few were statistically significant. Perhaps future studies should be better driven to detect differences, and/or also larger sample sizes could prove to be a great benefit.

These findings could help as support for additional evidence for clinicians and healthcare policy makers for decision-making and making recommendations for cancer patients. These findings should also be considered in the context that these supplements are relatively cheap and not harmful. However, their benefits are also not evidenced. We strongly encourage further research to help make conclusions stronger; the results of this thesis hopefully can serve as a basis for additional clarity, further analysis, and consideration for the DoD P&T committee. This committee controls the formulary that all DoD beneficiaries use. Therefore, this thesis offers an effective basis from which the committee can study the effects of vitamin D and calcium supplements to increase BMD for oncology patients.

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APPENDIX A. CHARACTERISTICS - EXCLUDED STUDIES

The following studies were excluded for the reasons noted. Following full-text screening, we excluded 29 studies from our analysis for not meeting satisfactory criteria.

Atkinson et al. (1989) children picked consecutively. No RCTs done.

Bacchetta, Ranchin, Dubourg, and Cochat (2010) study does not have RCT. Vitamin D perspectives on health effects with pediatric suggested recommendations.

Beebe et al. (2017) analyzed outcomes in HSCT subjects. No RCT, vitD/calcium treatment, placebo groups.

Bilariki et al. (2010) did an exploratory study that examined 52 consecutive cancer survivor patients for BMD and vitamin D deficiency. No RCT as it was consecutive selection.

Bryant, Worthington, and Parsons (2009) performed a qualitative review in a group of children with leukemia during their treatment of osteoporosis/osteopenia.

Cashman (2007) demonstrates classical effects of vitamin D. No mention of leukemia, etc.

Cohen, Wakefield, and Cohn (2016) performed a review of nutritional interventions

Cox, McLaughlin, Rai, Steen, and Hudson (2005) has no RCTs. Only measures health behaviors.

El-Ziny et al. (2007) study with no RCTs done. Conducted a study on consecutively recruited children to compare with healthy controls for low bone mass comparisons after chemotherapy treatment.

Esbenshade et al. (2015) did a retrospective medical records abstraction. No RCTs.

Garland et al. (1990) study does not have children nor placebos involved.

Hellstrom et al. (1988) does not have children nor placebos involved, etc.

Helou et al. (2014) comparison of 25-OH D levels to different healthy group populations.

Henderson, Madsen, Davis, and Gold (1998) no RCTs. Selection method absent other than being pediatric cancer patients undergoing chemotherapy treatments.

Revuelta Iniesta et al. (2016) is a review.

Krishnamoorthy, Freeman, Bernstein, Lawrence, and Rodd (2004) no RCTs. Retrospective and prospective data collection from medical records for selection of participants.

Mays et al. (2011) is only assessing dietary intake of calcium.

Mimouni and Shamir (2009) conducted a qualitative review in vitamin D supplementation.

Moreno, Valtueña, Pérez-López, and González-Gross (2011) conducted a vitamin D meta-analysis of observational studies regarding its health effects by having low dosage concentrations.

Reisi, Iravani, Raeissi, and Kelishadi (2015) case-control study to analyze the status of vitamin D and BMD in long-term survivors of pediatric ALL. Data was collected via questionnaire and medical charts as well as questions from parents. Blood samples were taken from participants to provide biochemical analysis. No intervention, RCTs

J de Schepper, Hachimi-Idrissi, Louis, Maurus, and Otten (1994) study has no RCTs, control or placebo groups nor nutritional intervention.

Schulte and Beelen (2004) study does not include pediatric subjects, placebos, etc.

Sinha, Avery, Turner, Bailey, and Cheetham (2011) cross-sectional observational study. A total of 121 children were then enrolled in the study and serum concentrations of 25-OH D were taken and analyzed for all cases and control groups. No intervention done.

De Smedt et al. (2017) study contains no pediatric subjects, ALL, or BMD.

Swiatkiewicz et al. (2003) evaluated for BMD and bone mineral metabolism with examinations performed twice. Prospective study. No RCTs.

Wacker and Holiack (2013) performed a vitamin D observational study on its effects on maintaining a healthy skeletal and extraskeletal (Wacker and Holiack, 2013).

Wasilewski-Masker et al. (2008) conducted a review of the literature regarding BMD deficits in survivors of childhood cancer, which is not a RCT.

Zeeb and Greinert (2010) developed a review article regarding vitamin D within cancer prevention. Not a RCT analysis.

Zittermann and Gummert (2010) developed a well extensive review article on the broad range of actions in the human body from effect coming from vitamin D.

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APPENDIX B. GRADEpro QUALITY OF EVIDENCE OUTCOMES

This appendix data was obtained by analyzing this thesis studies with GRADEpro GDT (2015).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Calcium + D3	control	Relative (95% CI)	Absolute (95% CI)		
Lumbar Spine BMD: RCT												
2	randomised trials	not serious	not serious [a]	not serious	not serious	none	149	142	-	SMD **0.06 lower** (0.29 lower to 0.17 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
Hip BMD: RCT												
1	randomised trials	not serious	not serious	not serious	not serious	none	5	6	-	SMD **0.91 lower** (2.19 lower to 0.36 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
Total BMD: RCT												
1	randomised trials	not serious	not serious	not serious	not serious	none	6	8	-	SMD **0.89 lower** (2.01 lower to 0.24 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
25OHD levels at 12 weeks: RCT												
1	randomised trials	not serious	not serious	not serious	not serious	none	70	77	-	SMD **1.96 higher** (1.57 higher to 2.36 higher)	⨁⨁⨁⨁ HIGH	CRITICAL
25OHD levels > 40 at 10 weeks: RCT												
1	randomised trials	not serious	not serious	not serious	not serious	none	59/70 (84.3%)	9/77 (11.7%)	**OR 40.53** (15.71 to 104.52)	**726 more per 1,000** (from 558 more to 816 more)	⨁⨁⨁⨁ HIGH	CRITICAL
25OHD levels > 40 at 24 weeks: RCT												
1	randomised trials	not serious	not serious	not serious	not serious	none	59/70 (84.3%)	8/77 (10.4%)	**OR 46.26** (17.45 to 122.62)	**739 more per 1,000** (from 565 more to 830 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Lumbar Spine BMD: Observational												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Calcium + D3	control	Relative (95% CI)	Absolute (95% CI)		
4	observational studies	not serious	not serious	not serious	not serious	none	217	264	-	SMD **0.43 higher** (0.22 lower to 1.09 higher)	⨁⨁ ? ? LOW	CRITICAL
Hip BMD: Observational												
1	observational studies	very serious [b]	serious [b]	serious [b]	serious [b]	publication bias strongly suspected [b]	25	10	-	SMD **1.17 higher** (0.38 higher to 1.96 higher)	⨁? ? ? VERY LOW	CRITICAL
Total BMD: Observational												
1	observational studies	serious [c]	not serious	not serious	serious [c]	publication bias strongly suspected [c]	62	66	-	SMD **0.26 higher** (0.09 lower to 0.61 higher)	⨁? ? ? VERY LOW	CRITICAL
Proximal Femur BMD: Observational												
1	observational studies	serious [d]	not serious	serious [d]	serious [d]	all plausible residual confounding would reduce the demonstrated effect	45	-	-	-	⨁? ? ? VERY LOW	CRITICAL
250HD levels at 4 weeks: Observational												
1	observational studies	serious	not serious	not serious	not serious	none	34	21	-	SMD **0.05 higher** (0.5 lower to 0.59 higher)	⨁? ? ? VERY LOW	CRITICAL
250HD levels at 12 weeks: Observational												
1	observational studies	serious [a]	not serious	not serious	not serious	none	12	130	-	SMD **0.05 lower** (0.64 lower to 0.54 higher)	⨁? ? ? VERY LOW	CRITICAL
25OHD levels > 40 at 16 weeks: Observational												
2	observational studies	serious [a]	not serious	not serious	not serious	none	54/58 (93.1%)	11/14 (78.6%)	**OR 3.58** (0.03 to 490.21)	**143 more per 1,000** (from 214 more to 687 fewer)	⨁? ? ? VERY LOW	CRITICAL
Lumbar Spine BMD: Observational (High/Medium vs. Low Risk of Bias) - High/Medium Risk of Bias												
2	observational studies	serious [a]	not serious	not serious	not serious	none	110	119	-	SMD **0.77 higher** (0.81 lower to 2.34 higher)	⨁? ? ? VERY LOW	CRITICAL
Lumbar Spine BMD: Observational (High/Medium vs. Low Risk of Bias) - Low Risk of Bias												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Calcium + D3	control	Relative (95% CI)	Absolute (95% CI)		
2	observational studies	serious	not serious	not serious	not serious	none	107	145	-	SMD **0.1 higher** (0.15 lower to 0.35 higher)	⨁◻ ◻ ◻ VERY LOW	CRITICAL
Lumbar spine BMD: Pediatric vs. adult studies - Pediatrics												
5	observational studies	serious [a]	not serious	not serious	not serious	none	255	359	-	SMD **0** (0.17 lower to 0.17 higher)	⨁◻ ◻ ◻ VERY LOW	CRITICAL
Lumbar spine BMD: Pediatric vs. adult studies - Adults												
5	observational studies	serious [a]	not serious	not serious	not serious	none	342	293	-	SMD **0.7 higher** (0.1 lower to 1.51 higher)	⨁◻ ◻ ◻ VERY LOW	CRITICAL

Explanations:

a. Performed with voluntary participants.

b. Ten of these participants did not complete the treatment, as it is not specified in the study. In addition, one other male participant mentioned as well, is unknown of his status throughout the study.

c. Among eligible ALL survivors identified for the study, these patients consented for participation. Not randomized.

d. Recruitment of participants from the Chernobyl accident between 15 January 2007 and 23 December 2010. Not randomized. Adapted from “GRADEpro GDT” (2015).

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