

## RESEARCH

# The Relationship Between Vitamin D Status and Bone Mineral Density in the Elderly: A Systematic Review

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Vitamin D plays an extremely crucial role for the development, growth, and maintenance of a healthy skeleton, and vitamin D deficiency is a contribute factor for osteoporosis and relating fractures. The purpose of this study was to conduct a review that elucidated vitamin D status and bone mineral density in the elderly through reviewing the literatures. English-language searches of the electronic databases in Google Scholar, ScienceDirect and PubMed were conducted from 1960 to April 2019, using the following search terms: 'Vitamin D status', 'bone mineral density', 'osteoporosis' and 'the elderly'. This study is of eighteen papers, the majority of subjects are from Europe, with 11 studies (55%) investigating the association between the vitamin D status and BMD on them. The overall results of this study found no consistent association between the serum 25(OH)D concentration and BMD in elderly people. Several factors, such as races, countries, measuring means, and different lifestyle habits would have an impact on vitamin D status and its relationship with BMD.

**Keywords:** Bone mineral density; Osteoporosis; Vitamin D status; The elderly

## Introduction

Osteoporosis is a systemic skeletal disease characterized by microarchitectural deterioration of bone tissue and lower bone mineral density (BMD). The consequent increase in bone fragility greatly increases the risk of fractures (Genant et al., 1999). Calcium absorption decreased from digestive tract when vitamin D status are inadequate ( $<75$  nmol/L) (Heaney et al., 2003). Due to the adequate vitamin D status is essential for efficient intestinal calcium absorption, the role of hypovitaminosis D in the pathogenesis of osteoporosis or low BMD is increasingly recognized (Chailurkit et al., 2011). Severe vitamin D deficiency may lead to secondary hyperparathyroidism, high bone turnover, bone loss, mineralization defects and it predisposes to fractures.

The vitamin D status is usually assessed by measuring the serum 25-hydroxyvitamin [25(OH)D]. Vitamin D was divided to three ranks according to serum 25(OH)D levels, vitamin D adequacy ( $25(\text{OH})\text{D} \geq 75$  nmol/L), hypovitaminosis D ( $25(\text{OH})\text{D} 50\text{--}74.9$  nmol/L), vitamin D insufficiency ( $25(\text{OH})\text{D} < 50$  nmol/L) (Mithal et al., 2009). Low 25(OH)D concentrations may increase serum parathyroid hormone (PTH) concentration, cause calcium resorption from bone, and enhance the osteoporosis process (F et al., 2015). Sunlight and dietary habits are the two sources of vitamin D in human's body. Cholecalciferol is primarily generated in the skin from 7-dehydrocholesterol when exposed to the ultraviolet of sunlight (UVB 290–315 nm). It can also be obtained from fish, such as eel and salmon (Genant et al., 1999). In Japan, the 25(OH)D concentration of dwellers who consumed fish frequently ( $\geq 4$  times/week) was 10.1 nmol/L higher than that of counterparts with a moderate consumption of fish (1–3 times/week) (Nakamura et al., 2000). Restricted sunlight exposure, diet with low vitamin D and calcium intake, and advanced age may negatively affect 25(OH)D concentration (Mannion et al., 2006; Outila et al., 2000).

The relationship between 25(OH)D and BMD may differ by race and ethnicity. La-or et al. (2011) found that the mean vitamin D level in Thai elderly women is higher than some European countries where sunlight is scare during winter, 67.6 nmol/L and 21–48 nmol/L, respectively (F et al., 2015). Yan et al. (2003) also found

there was a significant difference in plasma 25OH-D concentrations between Shenyang, China (29 nmol/L) and Cambridge, UK (35.7 nmol/L). Some studies (Dawson-Hughes, 2004; Looker et al., 2002; Vasikaran et al., 2000) found African Americans have a higher prevalence of vitamin D deficiency.

Vitamin D deficiency is common in the elderly since the capacity of the skin to synthesize provitamin decreases with increasing age (Venning, 2005; Gennari C., 2001). The dramatic increase in life expectancy has significantly contributed to the rise of the elderly population. Hip fractures with a high morbidity and mortality are a very common lower limb disease, especially among the elders, and the osteoporosis is a key factor results in it (Feng et al., 2016). Bakhtiyarova et al. (2006) found that serum 25(OH)D for hip fracture subjects were significantly lower than normal people. Compared to 47% in the control group, 65% of hip fracture patients with severe hypovitaminosis D (<25 nmol/L). In 1990, about one million hip fractures occurred worldwide, and the number is expected to exceed six million by 2050 (Genant et al., 1999). Measuring vitamin D status and BMD is vital for the prevention of fractures, and saving cost for medical care.

Therefore, the present study is aimed to evaluate vitamin D status and bone mineral density in the elderly through reviewing the literatures. The gender, area, and diet on serum 25(OH)D levels was also collected and compared in this review.

## **Methods**

### ***Eligibility criteria and study selection***

#### **Inclusion criteria**

The inclusion criteria for screened articles included the choices of participants, study methods, study purposes, and outcomes analysis. (1) Subjects: only the old people was included in this review (age > 60), and gender was not an influence factor; (2) Study methods: we included both observational and experimental studies in the present review; (3) study purposes: the studies should aimed to evaluate vitamin D, or prevent and treat osteoporosis (including vitamin D supplementation and sunlight); (4) Outcomes: The results should elucidated the relationship between vitamin D [25(OH)D] and bone mineral density. Only full texts and published materials were included, and five conference papers were excluded due to insufficient data presented.

#### **Exclusion criteria**

The studies that did not meet the criterion were excluded: (1) no the elderly subjects; (2) using the indexes to evaluate BMD except vitamin D; (3) there is no quantitative 25(OH)D in articles. No minimum subject's number criteria were set.

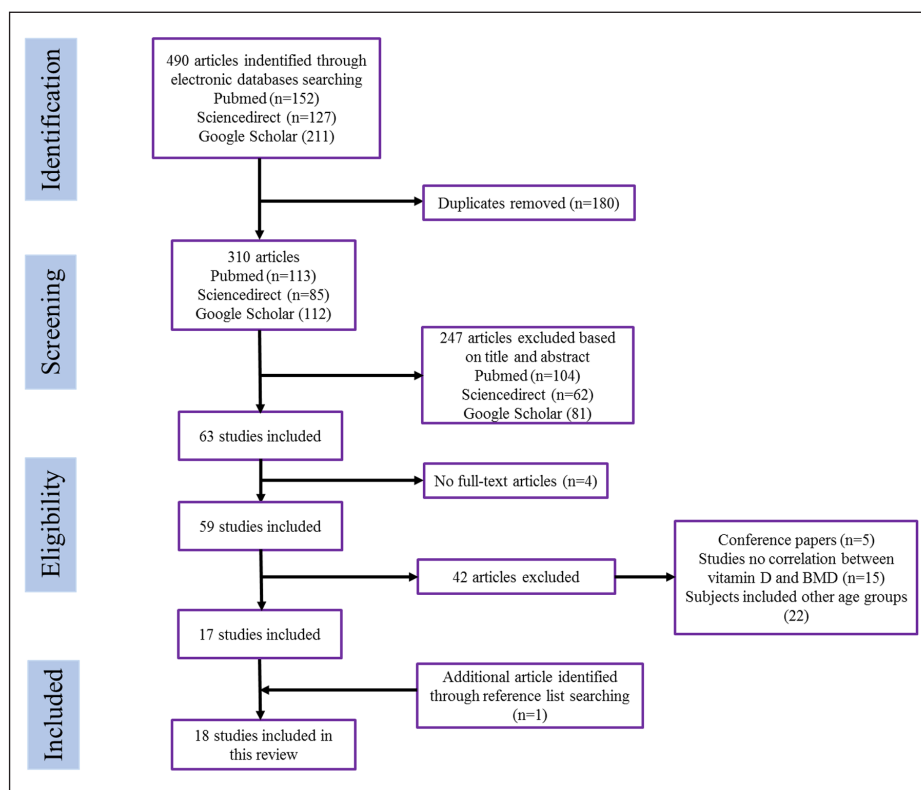
### ***Search strategy***

The search strategy was used to find the relevant published studies of Vitamin D status and bone mineral density in the elderly. English-language searches of the electronic databases in PubMed, ScienceDirect and Google Scholar were conducted for the period 1960 to April 2019, using the following search terms: 'Vitamin D status', 'bone mineral density', 'osteoporosis' and 'the elderly'. In Google Scholar, an 'advanced search' was chosen: using the option 'with all of the words', we selected 'Vitamin D status', 'bone mineral density', 'osteoporosis' and 'the elderly'; in the field of 'where my words occur', the option of 'anywhere in the article' was chosen. In the ScienceDirect database, we searched in all fields using document type 'article'. Then, we choose a document search with keywords: 'Vitamin D status', 'bone mineral density', 'osteoporosis' and 'the elderly'. In Pubmed database, we choose advanced search and search field in all field. Then, entered the keywords in turn: 'Vitamin D status', 'bone mineral density', 'osteoporosis' and 'the elderly'.

The reference list of all eligible studies was also reviewed to identify other potentially eligible studies. Subsequently, these studies were searched in other databases to get the full texts, using the specific authors and article reference titles. The search procedure was shown in the flowchart (**Figure 1**).

### ***Data extraction and quality assessment***

The search flowchart is shown in **Figure 1**. 490 articles were searched from three databases and 180 repeated papers were removed. 247 studies were excluded via checking the title and abstract, and 4 papers were removed because no full-text could be found. In 59 remain studies, 42 articles were excluded: 5 conference papers, 22 studies only related to younger people, and 15 articles study no correlation between 25[OH]D and BMD. 1 paper were found through the searching of the reference list. Thus, 18 articles were included in this review.



**Figure 1:** The search flowchart.

## Results

**Table 1** summarize the study characteristics for all full-text articles included in the review. Of the 18 included studies, 11 studies included only women, 4 studies included both men and women, 1 study included only men, and 2 studies without specifying the gender of subjects. The mean age of the subjects in most of the studies ranged from 60 to 80 years. Most of subjects are health elderly people, while the study performed by Sato et al. investigated the association between the vitamin D status and BMD in elderly women with AD in Japan. **Figure 2** presents the regional distribution of subjects in the literature included in this review. The vast majority of subjects are from Europe, with 10 studies (55%) investigating the association between the vitamin D status and BMD on them. Subjects in 5 studies (28%) are from Asia while subjects in 3 studies (17%) are from America.

Of all the studies included in this review, 13 studies reported an association between the serum 25(OH)D concentration and BMD while 5 studies did not observe an association. However, various sites have been used for BMD measurement. Most studies measured the BMD at the lumbar spine, femoral neck, and hip. Some studies measured the BMD at one or two of these three sites. Moreover, one study used bone mineral content (BMC) rather than BMD because the comparison in bone health was made between Chinese people and Caucasian people living in the UK. Some of the included studies also reported serum parathyroid hormone (PTH). A few found a negative association between PTH and serum 25(OH)D or between PTH and BMD. Of these studies that did not observe an association between vitamin D status and BMD, subjects in 4 studies are from Britain, Sweden, Netherland, and Iceland, which are all in Europe.

In addition, one study investigated the relationships among parathyroid hormone, vitamin D, and bone mineral status of Older people in China and the United Kingdom. They found that a weak positive association between bone mineral content at the femoral neck and 25OH-D concentration were found in Cambridge but not in Shenyang.

## Discussion

The main purpose of this systematic review was to evaluate vitamin D status and bone mineral density in the elderly through reviewing the literatures. The overall results of this study found no consistent association between the serum 25(OH)D concentration and BMD in elderly people. Of the 18 studies included in this review, 13 reported a positive association while 5 did not.

**Table 1:** Description of studies investigating the association between the vitamin D status and BMD in the elderly population.

Study	Title	Study population	Age of subjects (mean ± SD)	s-25(OH)D (mean ± SD)	Association between vitamin D status and BMD
Bakhtiyarova et al. (Bakhtiyarova et al., 2006) (2006)	Vitamin D status among patients with hip fracture and elderly control subjects in Yekaterinburg, Russia.	Elderly inhabitants of Yekaterinburg (63 elderly people with hip fracture and 97 independently living elderly people).	Elderly people with hip fracture: 68.8 ± 9.5 years; Independently living elderly people: 70.2 ± 8.3 years.	Elderly people with hip fracture: 22.4 ± 11.4 nmol/L; Independently living elderly people: 28.1 ± 10.1 nmol/L.	Serum 25(OH)D in the hip fracture group was significantly lower than in independently living group.
Chailurkit et al. (Chailurkit et al., 2011) (2011)	Vitamin D status and bone health in healthy Thai elderly women.	446 healthy elderly women in Thailand.	67.5 ± 6.0 years.	67.6 ± 15.7 nmol/L.	A positive relationship was observed between serum 25(OH)D level and femoral neck BMD but not lumbar spine L <sub>2</sub> -L <sub>4</sub> BMD.
Deplas et al. (Deplas et al., 2004) (2004)	Bone density, parathyroid hormone, calcium and vitamin D nutritional status of institutionalized elderly subjects.	64 white Caucasian subjects, 44 of whom were women.	80.6 ± 7.1 years.	8.56 ± 5.2 µg/l.	Vitamin D deficiency and low calcium intake were observed in a large number of elderly subjects who had osteoporosis.
Gerdhem et al. (Gerdhem et al., 2005) (2005)	Association between 25-hydroxy vitamin D levels, physical activity, muscle strength and fractures in the prospective population-based PRA Study of Elderly Women.	986 elderly women in Sweden.	75.0–75.9 years.	40% below 20 ng/ml (50 nmol/l), and 26% below 30 ng/ml (75 nmol/l).	There is no association between baseline 25OHD and bone quality (as measured by aBMD).
Kärkkäinen et al. (Kärkkäinen et al., 2010) (2010)	Effect of calcium and vitamin D supplementation on bone mineral density in women aged 65–71 years: a 3-year randomized population-based trial (OSTPRE-FPS).	593 elderly women in Finland.	66–71 years.	The baseline serum 25(OH)D levels were 50.1 ± 18.8 nmol/l and 49.2 ± 17.7 nmol/l in the intervention and control groups.	Daily vitamin D and calcium supplementation have a positive effect on the skeleton in ambulatory postmenopausal women with adequate nutritional calcium intake.
Kruavit et al. (Kruavit et al., 2012) (2012)	Prevalence of Vitamin D insufficiency and low bone mineral density in elderly Thai nursing home residents.	93 elderly Thai women.	75.2 ± 6.0 years.	64.3 ± 14.9 nmol/L.	More than one-third of Thai elderly women residing in nursing homes had vitamin D insufficiency. Almost all nursing home residents had osteoporosis and/or osteopenia.

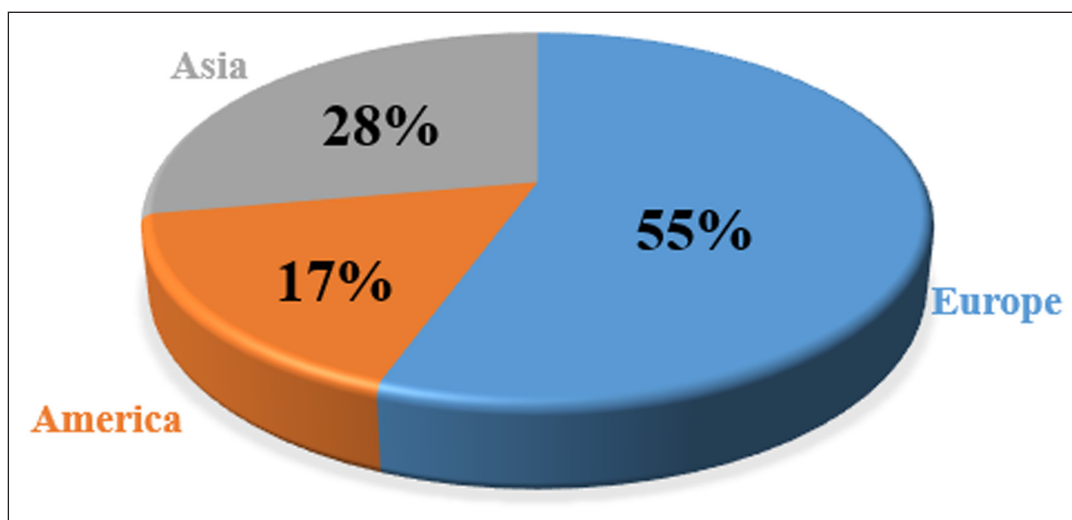
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Study	Title	Study population	Age of subjects (mean ± SD)	s-25(OH)D (mean ± SD)	Association between vitamin D status and BMD
Lee et al. (Lee et al., 2013) (2013)	Additive association of vitamin D insufficiency and sarcopenia with low femoral bone mineral density in noninstitutionalized elderly population: the Korea National Health and Nutrition Examination Surveys 2009–2010.	1,596 men and 1,886 women participated in the Fourth and Fifth Korea National Health and Nutrition Examination Surveys conducted in 2009 and 2010.	Men Normal: 68.7 ± 6.1 years; Vitamin D insufficiency: 67.6 ± 5.8 years; Women Normal: 69.4 ± 6.1 years; Vitamin D insufficiency: 69.0 ± 6.5 years. a mean age of 71.1 years old.	Men Normal: 27.2 ± 5.8 ng/ml; Vitamin D insufficiency: 15.3 ± 3.2 ng/ml; Women Normal: 26.3 ± 5.7 ng/ml; Vitamin D insufficiency: 14.4 ± 3.6 ng/ml. 28 ± 10.5 ng/mL.	These data showed that an association between vitamin D insufficiency and low BMD was more prominent in elderly subjects with sarcopenia.
Labronici et al. (Labronici et al., 2013) (2013)	Vitamin D and its Relation to Bone Mineral Density in Postmenopausal Women.	250 women in Petrópolis.	80 ± 6 years.	23 nmol/L in the placebo group and 60 nmol/L in the vitamin D group.	Any significant correlation between vitamin D levels and bone mineral density after adjusting for age.
Lips et al. (Lips, 2013) (1996)	Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial.	2578 persons (1916 women, 662 men) in Amsterdam and surrounding area.	69.5 ± 3.1 years.	26.8 ± 13.8 ng/mL.	Results do not show a decrease in the incidence of hip fractures and other peripheral fractures in Dutch elderly persons after vitamin D supplementation.
Murphy et al. (Murphy et al., 1993) (1993)	Relationships between Parathyroid Hormone, 25-Hydroxyvitamin D, and Bone Mineral Density in Elderly Men.	133 health elderly men in Cambridge.			Bone mineral density at most sites was consistently positively related to 25-hydroxyvitamin D levels but this relationship was not statistically significant.
Melin et al. (Melin et al., 2018) (1999)	Vitamin D status, parathyroid function and femoral bone density in an elderly Swedish population living at home.	104 elderly, independent Scandinavians (81 women, 23 men).	Men: 84 ± 4 years; Women: 85 ± 4 years.	Men: 28 ± 9 ng/mL; Women: 26 ± 12 ng/mL.	Femoral neck BMD to be significantly and positively associated with higher body mass index, male gender, no history of fragility fracture and 25-hydroxyvitamin D.
Ooms et al. (Ooms et al., 1995b) (1995)	Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trial.	348 elderly women in Amsterdam.	Vitamin D group: 80.1 ± 5.6 years; Placebo group: 80.6 ± 5.5 years.	Vitamin D group: 27 nmol/L; Placebo group: 25 nmol/L.	supplementation with 400 IU vitamin Ds daily in elderly women improved the vitamin D status so as to increased BMD but only at the femoral neck.

(Contd.)

Study	Title	Study population	Age of subjects (mean ± SD)	s-25(OH)D (mean ± SD)	Association between vitamin D status and BMD
Ooms et al. (Ooms et al., 1995a) (1995)	Vitamin D status and sex hormone binding globulin determinants of bone turnover and bone mineral density in elderly women.	330 elderly women in Amsterdam.	80.3 ± 5.6 years.	28.1 ± 13 nmol/L.	Vitamin D deficiency especially influences BMD of the femoral neck of elderly women in Amsterdam.
Sato et al. (Sato et al., 1998) (1998)	High prevalence of vitamin D deficiency and reduced bone mass in elderly women with Alzheimer's disease.	46 ambulatory elderly women with AD in Japan.	Control: 80.0 ± 4.7 years; Patient: 81.3 ± 5.4 years.	Control: 21.6 ± 3.1 ng/mL; Patient: 7.1 ± 3.9 ng/mL.	Vitamin D deficiency due to sunlight deprivation and malnutrition, together with compensatory hyperparathyroidism, contributes significantly to reduced BMD in AD patients.
Sigurðsson et al. (Sigurðsson et al., 2000) (2000)	The association between parathyroid hormone, vitamin D and bone mineral density in 70-year-old Icelandic women.	418 women in the registry of Reykjavik.	70 years.	53.1 ± 20 nmol/L.	No association was found between 25(OH)D levels and BMD at any site in univariate or multivariate analysis.
Von Mühlen et al. (Von Mühlen et al., 2005) (2005)	Vitamin D, parathyroid hormone levels and bone mineral density in community-dwelling older women: the Rancho Bernardo study.	615 community-dwelling elderly women in California.	74.6 ± 10 years.	102.0 ± 35.0 nmol/L.	Hip BMD was positively and independently associated with 25(OH)D levels.
Wilkins et al. (Wilkins et al., 2009) (2009)	Vitamin D deficiency is associated with worse cognitive performance and lower bone density in older African Americans.	60 older adults (30 African Americans and 30 European Americans).	74.99 ± 8.2 years.	21.59 ± 7.8 ng/mL.	Vitamin D deficiency in older African Americans was associated with worse cognitive performance and lower BMD of the hip.
Yan et al. (Yan et al., 2003) (2003)	Older people in China and the United Kingdom differ in the relationships among parathyroid hormone, vitamin D, and bone mineral status.	352 healthy volunteers (Chinese: 108 men, 110 women; British: 67 men, 67 women).	Chinese Men: 67.9 ± 3.6 years Women: 65.2 ± 3.7 years British Men: 69.1 ± 6.1 years Women: 68.2 ± 6.5 years	Chinese Men: 27.1 ± 11.5 nmol/L Women: 30.9 ± 13.5 nmol/L British Men: 36.6 ± 12.1 nmol/L Women: 34.7 ± 13.7 nmol/L	A weak positive association between BMC at the femoral neck and 25OH-D concentration were found in Cambridge but not in Shenyang.





**Figure 2:** The regional distribution of subjects in the literature included in this review.

The majority of studies included in this review were performed on European populations (Bakhtiyarova et al., 2006; Gerdhem et al., 2005; Kärkkäinen et al., 2010; Lips, 2013; Murphy et al., 1993; Melin et al., 2018; Ooms et al., 1995b; Ooms et al., 1995a; Sigurdsson et al., 2000). However, it is interesting to note that the relationship between vitamin D status and bone mineral density in the elderly is different in these studies. 6 studies reported a positive association while 4 did not. Moreover, studies in the same country in Europe have also come to different conclusions (Lips, 2013; Ooms et al., 1995b; Ooms et al., 1995a). For example, Lips et al. (2013) investigated the relationship between Vitamin D supplementation and fracture incidence in elderly persons living in Amsterdam and surrounding area and they found that there is no decrease in the incidence of hip fractures and other peripheral fractures in these people after vitamin D supplementation. However, Ooms et al. (1995b) investigated the prevention of bone loss by vitamin D supplementation in elderly women living in Amsterdam and they found that supplementation with 400 IU vitamin Ds daily significantly increased BMD of the femoral neck. By contrast, studies in other continents have not shown this controversial conclusion, which may be because the number of studies in other continents is small.

A consistent conclusion regarding the association between the serum 25(OH)D concentration and BMD in elderly people would be hampered by several parameters. For example, inclusion and exclusion criteria of participants, races and countries of participants, site of BMD measurement, and devices used to measure baseline serum 25(OH)D concentration (Man et al., 2016).

One study included in this review investigated the relationships among parathyroid hormone, vitamin D, and bone mineral status of Older people in China and the United Kingdom and they found that the positive association was only in the subjects of the United Kingdom (Yan et al., 2003). In addition, several studies included in this review have demonstrated that the serum 25(OH)D concentration only have positive relationship with BMD at certain sites (Chailurkit et al., 2011; Ooms et al., 1995b). Chailurkit et al. (2011) investigated Vitamin D status and bone health in healthy Thai elderly women and they found a positive relationship was observed between serum 25(OH)D level and femoral neck BMD but not lumbar spine L<sub>2</sub>–L<sub>4</sub> BMD. Ooms et al. (1995b) investigated the prevention of bone loss by vitamin D supplementation in elderly women and found that supplementation with 400 IU vitamin Ds daily in elderly women increased BMD but only at the femoral neck.

The present study has several limitations. Firstly, studies involved in this review used various bone sites to estimate BMD and the devices used to measure BMD are also different between studies. Moreover, the serum 25(OH)D measurement would vary between laboratories, which may hamper the comparison of vitamin D status (Holick, 2006; Lips, 2007; Lips et al., 1999; Prentice, 2008).

In conclusion, the evidence for a positive association between vitamin D status and bone mineral density in the elderly seems to be inconsistent. Several factors, such as races, countries, measuring means, and different lifestyle habits would have an impact on vitamin D status and its relationship with BMD. Therefore, more intervention studies are needed in order to find out whether there is a certain relationship between vitamin D status and bone mineral density in the elderly.

### Competing Interests

The authors have no competing interests to declare.

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


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