

Vitamin D status and hypertension: a review

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Abstract: Vitamin D is a steroid prohormone synthesized in the skin following ultraviolet exposure and also achieved through supplemental or dietary intake. While there is strong evidence for its role in maintaining bone and muscle health, there has been recent debate regarding the role of vitamin D deficiency in hypertension based on conflicting epidemiological evidence. Thus, we conducted a scoping systematic literature review and meta-analysis of all observational studies published up to early 2014 in order to map trends in the evidence of this association. Mixed-effect meta-analysis was performed to pool risk estimates from ten prospective studies (n=58,262) (pooled risk for incident hypertension, relative risk [RR] =0.76 (0.63–0.90) for top vs bottom category of 25-hydroxyvitamin D [25OHD]) and from 19 cross-sectional studies (n=90,535) (odds ratio [OR] =0.79 (0.73–0.87)). Findings suggest that the better the assessed quality of the respective study design, the stronger the relationship between higher 25OHD levels and hypertension risk (RR =0.67 (0.51–0.88); OR =0.77 (0.72–0.89)). There was significant heterogeneity among the findings for both prospective and cross-sectional studies, but no evidence of publication bias was shown. There was no increased risk of hypertension when the participants were of older age or when they were vitamin D deficient. Younger females showed strong associations between high 25OHD levels and hypertension risk, especially in prospective studies (RR =0.36 (0.18–0.72); OR =0.62 (0.44–0.87)). Despite the accumulating evidence of a consistent link between vitamin D and blood pressure, these data are observational, so questions still remain in relation to the causality of this relationship. Further studies either combining existing raw data from available cohort studies or conducting further Mendelian analyses are needed to determine whether this represents a causal association. Large randomized controlled trials are also needed to determine whether vitamin supplementation may be beneficial in the prevention or the treatment of hypertension.

Keywords: 25OHD, high blood pressure, meta-analysis, prospective, cross-sectional, blood pressure

Introduction

Despite recent downward trends in cardiovascular disease (CVD) mortality rates,¹ CVD still represents 50% of noncommunicable disease deaths worldwide,² and there is an exponential increase in CVD incidence in lower- and middle-income countries.³ Hypertension, which is also increasing,⁴ is one of the primary modifiable risk factors for CVD, and as such, any new modifiable risk factor associated with prevention of this condition is important for public health measures. Obesity and lack of physical activity (PA) and increased salt intake are well-known and studied modifiable environmental factors associated with hypertension. In recent times, vitamin D deficiency has also been postulated to be such a factor.^{5–8}

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Vitamin D is a steroid prohormone synthesized in the skin following ultraviolet exposure. It is also achieved through supplemental or dietary intake. While there is strong evidence for its role in maintaining bone and muscle health,⁹ there has been recent debate regarding the role of vitamin D deficiency in CVD conditions^{10,11} based on conflicting epidemiological evidence.

There is a growing body of evidence from animal¹² and clinical studies¹³ that vitamin D-mediated reduction of hypertension involves increased activation of the renin–angiotensin–aldosterone system, which is the main regulator of electrolyte and volume homeostasis that contributes to the development of arterial hypertension.

Epidemiologically, cross-sectional studies have consistently shown associations of hypertension with vitamin D deficiency as measured by the level of 25-hydroxyvitamin D (25OHD) (in nanomoles per litre) in the blood,⁷ and the most recent meta-analyses of prospective studies⁸ have also found this association to be persistent over time. However, meta-analysis results from randomized controlled trials (RCTs) (the gold standard of epidemiological studies) of 25OHD blood levels and hypertension have been null.¹⁴ This discrepancy may well be due to the small size and specialized population samples of the RCTs.

Due to the continued interest and debate in this area, we conducted a scoping systematic literature review and meta-analysis of all observational studies published up to early 2014 in order to map trends in the evidence on the association between blood vitamin D levels and the risk of hypertension.

Methods

For this systematic review, studies concerned with hypertension and 25OHD were identified using a predefined protocol and in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁵ Unlike previous reviews,^{7,8} we included studies that varied by culture of respondents for broader perspective (Supplementary material).

Data source and study search

We systematically conducted independent searches of Scopus and PubMed databases for published articles from January 1, 2007 until February 22, 2014. Identical search strategies were applied for each database search with combined terms of “25OHD”, “25-hydroxyvitamin D”, “vitamin D”, “hypertension”, “vitamin D supplementation (cholecalciferol [vitamin D3], ergocalciferol [vitamin D2])”, “systolic blood pressure (SBP)”, or “diastolic blood pressure (DBP)”. Reference lists

of retrieved articles were automatically imported into Endnote X5 and manually scanned for relevant review articles. Duplicated references from two databases were detected by Endnote X5. In order to proceed further in the review process, retrieved articles’ abstracts were read by two independent reviewers (KB and LK). Only those abstracts that were related to 25OHD levels and hypertension were kept for full-text review and meta-analysis. Disagreements were resolved by a consensus or by reference with co-authors: statistician (MK) and/or vitamin D physiologist (RSM). We restricted the search to human studies and those published in English.

Study selection

As a very recent meta-analysis has been published on RCTs,¹⁴ only observational (cross-sectional and prospective) studies were included in this meta-analysis. For these observational studies, the independent risk factor was plasma or serum vitamin D levels measured as 25OHD in blood, and the outcome was hypertension or SBP and DBP. Dietary vitamin D was not included in this systematic review. Figure 1 shows a flowchart of the data extraction.

We restricted this meta-analysis (Tables 1–4 and Figures 2A and 3A) to studies which recruited healthy adult study populations (aged greater than 18 years) from the general population. Prospective studies were included if they had at least 1 year of follow-up, with 25OHD levels measured at baseline, and if the results were reported categorically as a relative risk (RR) or an odds ratio (OR) with 95% confidence intervals (CIs).

Studies were excluded if the study sample was not recruited from the general population (ie, participants who had hypertension at baseline or participants with conditions that may influence vitamin D metabolism such as obese population groups¹⁶ or autoimmune diseases¹⁷). Exclusions applied as well if there was more than one study that investigated the same data (eg, The National Health and Nutrition Examination Survey (NHANES)¹⁸ duplicates were excluded).

Table 5 contains other extracted studies that reported associations with linear 25OHD levels. These studies were included in the systematic review results and discussion but not in the formal meta-analysis mapping.

Data extraction and quality assessment

The following data were extracted from each study:

- first authors’ last name, year of publication, study name, year of study conducted, and quality score;
- country of studies’ origin and study population;

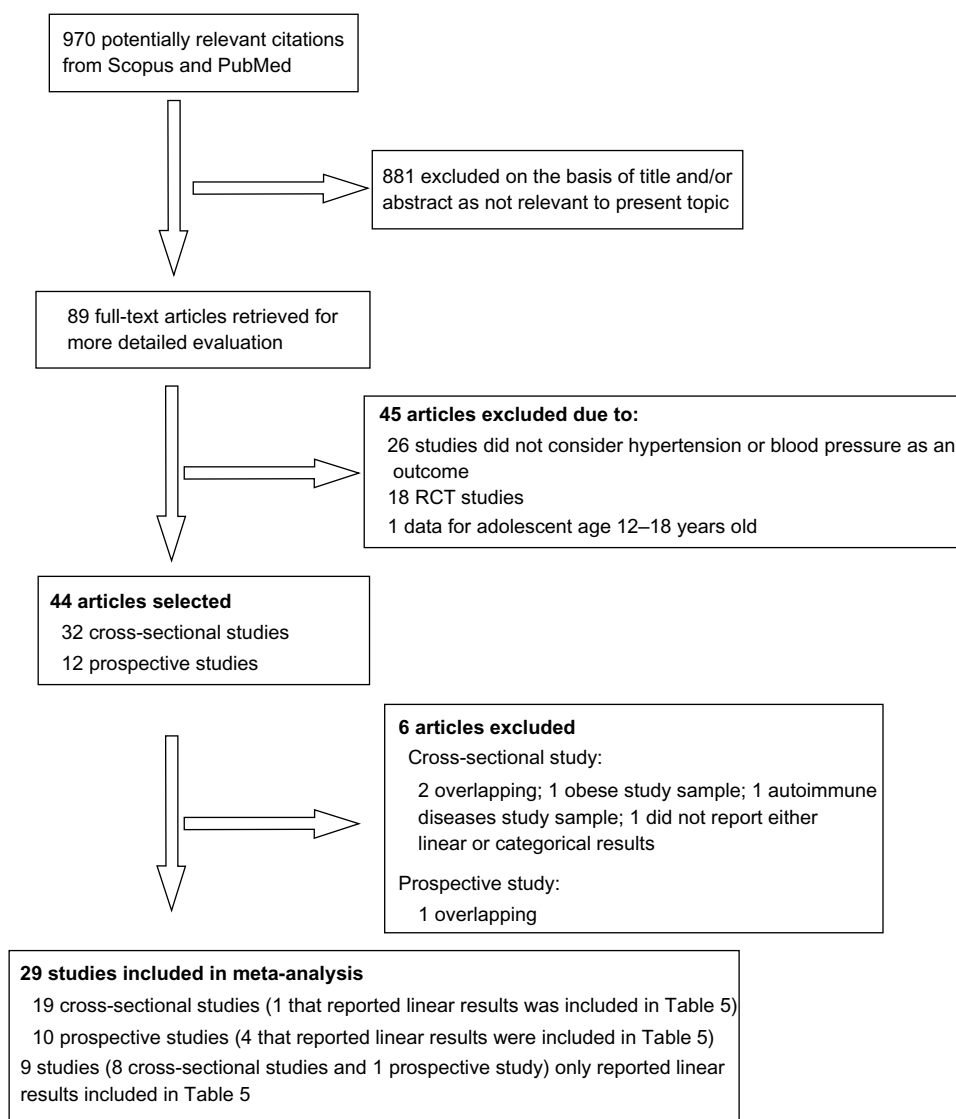


Figure 1 Flowchart of meta-analysis data extraction.

Abbreviation: RCT, randomized controlled trial.

- gender and age;
- sample size (number of cases of hypertension in the case of prospective studies);
- baseline 25OHD as either percent of vitamin D deficiency or mean of 25OHD and vitamin D assay method;
- 25OHD categories;
- mode of hypertension measurement;
- risk estimates (RRs or ORs) with corresponding CIs for blood 25OHD concentrations; and
- confounders measured and taken account for in analysis.

Study quality score was assessed based on the nine-star Newcastle–Ottawa Scale (NOS)¹⁰ using predefined criteria namely selection (population representativeness), comparability (adjustment for confounders such as age, gender, body mass index [BMI], PA, ethnicity, season, antihypertensive

treatment, and diabetes status used), and ascertainment of outcome. In this predefined scoring method, a maximum of four points were given for selection, two points for comparability, and three points for outcome. Nine points on the NOS reflect the highest study quality.¹⁹

Data synthesis and analysis

Mixed-effect meta-analysis²⁰ was performed to pool risk estimates for both observational and prospective studies. For both studies, we synthesized RR (for prospective studies) or OR (for cross-sectional studies), and 95% CI. These estimate compare the lowest vitamin D status as defined by categorical levels of 25OHD (as the reference group) to the highest vitamin D levels in order to estimate the risk of association with hypertension (primary endpoint).

Table 1 Characteristics of prospective studies

Author (year), ^{reference} study and year of conduct, quality score [†]	Country, study population	Gender, age (range or mean \pm SD) (years)	Sample size (cases)	Baseline mean \pm SD or % 25OHD, assay
Forman et al (2007), ²² NHS2 1976–1990, HPFS 1986–1994, 5	US, nurses and health professional	34% male, 43–82	1,811 (407)	62% <75, RIA
Griffin et al (2011), ²³ MBHMS 1992–1993, 6	US, general population	100% female, 22–44	413 (104)	Mean =59, 81% <75, RIA
Anderson et al (2010), ²⁴ IHS 2000–2009, 6	US, general population	25% male, 55 \pm 21	41,504 (2,490)	64% <75, CLIA
Jorde et al (2010), ²⁵ Tromsø Study 1994–2008, 7	Norway, general population	35% male, 50–74	1,268 (331)	54 \pm 16, CLIA
Kim et al (2010), ²⁶ Chungju city 2003–2007, 6	Korea, general population	38% male, 66 \pm 9	1,330 (851)	47, CLIA
Margolis et al (2012), ²⁷ WHI 1993–1998, 5	US, general population	100% female, 50–79	2,153 (891)	54% <50, CLIA
Gagnon et al (2012), ²⁸ Aus-Diab 2000–2005, 7	Australia, general population	50% male, 25–75+	4,164 (1,291)	68, RIA
Wang et al (2013), ²⁹ PHS 1982–2009, 5	US, physicians	100% male, 40–84	660 (367)	73 \pm 26, RIA
Ke et al (2013), ³⁰ ATBC 1985–1993, 4	Finland, general population	100% male (smokers), 50–69	1,957 (252)	69% <50, RIA
van Ballegooijen et al (2014), ³¹ MESA 2000–2002, 5	US, general population	47% male, 45–84	3,002 (1,229)	31% <50, HPLC

Note: [†]Quality score based on Newcastle–Ottawa Scale.

Abbreviations: NHS2, Nurses' Health Study 2; HPFS, Health Professional Follow-up Study; MBHMS, Michigan Bone Health and Metabolism Study; IHS, Intermountain Healthcare System; WHI, Women's Health Initiative; Aus-Diab, Australian Diabetes, Obesity and Lifestyle Study; PHS, Physicians' Health Study; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; MESA, Multi-Ethnic Study of Atherosclerosis; SD, standard deviation; 25OHD, 25-hydroxyvitamin D; RR, relative risk; CI, confidence interval; RIA, radioimmunoassay; US, United States; BMI, body mass index; PA, physical activity; BP, blood pressure; HTN, hypertension; CLIA, chemiluminescence immunoassay.

Risk estimate values of less than 1.00 were associated with a decreased risk for hypertension as a result of increased blood levels of 25OHD. We performed sensitivity analyses to assess the influence of each individual study by removing one study at a time and calculating a pooled estimate for the remainder of the studies. No one study influenced the overall results, suggesting balanced selection.

We tested study heterogeneity by the I^2 statistic (significance set at 95% level, ie, $P < 0.05$).²¹ Potential publication bias was assessed by the Egger's test and presented in a Begg's funnel plot²¹ of standard mean differences against their standard error (Figures 2B and 3B). The meta-analysis procedure was conducted using Comprehensive Meta-Analysis, version 2.

Results

Study selection

Our initial search identified 970 potentially relevant citations (Figure 1). After screening of titles and abstracts, 89 articles remained for further evaluation. Following detailed assessment, 51 articles were excluded. Therefore, 38 studies were included in this study, but only 29 studies (ten prospective studies and 19 cross-sectional studies)

were included in the formal meta-analysis; the other nine studies (one prospective study and eight cross-sectional studies) that reported linear results. In addition four studies which were prospective studies and one cross-sectional study, which also reported linear results, are included in Table 5.

Characteristics of included studies – prospective studies

The pooled RR (95% CI) for incident hypertension (primary endpoint) in a comparison of individuals in the top category of 25OHD levels with lowest category (as reference group) of 25OHD levels was 0.76 (0.63–0.90) (Figure 2A).

There was evidence of heterogeneity among the findings of the studies that measured blood 25OHD levels ($I^2=67.05$, $P < 0.01$). The Egger's test based on all included studies showed no evidence of publication bias for blood 25OHD concentrations and hypertension ($P=0.53$), with the funnel plot shown in Figure 2B.

Overall, we identified eleven prospective studies,^{22–32} of which ten have been included in this formal meta-analysis.^{22–31} One study by Skaaby et al³² from Denmark

25OHD (nmol/L) comparison	Follow-up (years)	Primary endpoint: hypertension (mmHg)	RR (95% CI)	Confounders
<37 vs \geq 75	4	Self-report	0.31 (0.14–0.72)	Age, BMI, PA, ethnicity, diabetes status
<80 vs \geq 80	14	BP \geq 140/90	0.33 (0.12–0.99)	Age, % body fat, season, HTN treatment
<38 vs \geq 75	1.3	BP \geq 140/90	0.62 (0.53–0.73)	Age, gender, season, HTN treatment, diabetes status
<41 vs \geq 63	14	BP \geq 140/90	0.99 (0.76–1.28)	Age, gender, BMI, PA, season, HTN treatment
<20 vs \geq 89	4	BP \geq 140/90	0.47 (0.27–0.82)	Age, gender, BMI, PA, season, HTN treatment
<34 vs \geq 65	7	BP \geq 140/90	0.86 (0.60–1.23)	Age, BMI, PA, ethnicity, season, HTN treatment, diabetes status
<45 vs \geq 85	5	BP \geq 130/85	0.71 (0.51–0.98)	Age, gender, PA, ethnicity, season, diabetes status
<50 vs \geq 100	15	Self-report	0.94 (0.69–1.27)	Age, BMI, PA, ethnicity, season, HTN treatment, diabetes status
<25 vs \geq 80	4	BP \geq 140/90	1.00 (0.60–1.50)	Age, BMI, PA, season
<50 vs \geq 75	9	BP \geq 140/90	0.81 (0.71–0.93)	Age, gender, BMI, PA, ethnicity, season, HTN treatment

only reported a linear association between 25OHD and blood pressure and as such, was not included in the formal meta-analysis but is reported in Table 5. In summary, Table 1 presents ten prospective studies with aggregate data on 58,262 nonoverlapping participants and 8,213 incident hypertension cases as potentially relevant for the present meta-analysis.

Thus, Table 1 and Figure 2A include two cohort studies^{24,25} and eight prospective studies,^{22,23,26–31} which were cohort studies in design but only reported baseline 25OHD levels and subsequent future hypertension incidence.

Of these ten studies, two studies^{25,30} also reported baseline as well as follow-up cross-sectional categorical data from the same cohort data, which were included in the cross-sectional meta-analysis (Tables 3 and 4). Four other studies reported baseline 25OHD data in linear format from these cohorts,^{23,26,27,29} and these data are reported in Table 5.

Table 1 provides details of the eligible studies that evaluated vitamin D status and the RRs of hypertension incidence. Six studies^{22–24,27,29,31} were carried out in the US, two studies were conducted in Europe,^{25,30} and two^{26,28} were conducted

in the Asia Pacific region including Australia.²⁸ Most of the study samples were from general populations.^{23–28,30,31} In two studies, populations were recruited from nurses, health professionals, or physicians^{22,29} and in one study, the population were male smokers.³⁰ The age of participants ranged from 25 years to 85 years (mean age =55 years), and more than half of the studies^{22,24–26,28,31} sampled included both male and female. Ascertainment of hypertension was mostly by measuring blood pressure,^{23–28,30,31} and the follow-up period ranged from 1.3 years to 15 years. Table 1 also provides assay characteristics of measured levels of 25OHD from studies contributing to the analyses; five studies^{22,23,28–30} used the radioimmunoassay (RIA) method, four^{24–27} used the chemiluminescence immunoassay (CLIA), and only one³¹ used the gold standard “high-pressure liquid chromatography” (HPLC) analysis.

Vitamin D status and risk of hypertension – prospective studies subgroup analysis

When studies were stratified by quality score, the RRs were significant for studies rated higher than 5 (RR =0.67 (0.51–0.88)) but were not significant for studies rated \leq 5

Table 2 Prospective studies: mixed-effect meta-analysis 25OHD and hypertension stratification

Stratification	Sample size	Risk of hypertension associated with high 25OHD	Heterogeneity (I^2)
Total	58,262	0.76 (0.63–0.90)*	67.05*
Journal quality			
High (score =6 or 7)	48,679	0.67 (0.51–0.88)*	37.62
Low (score <6 points)	9,583	0.86 (0.71–1.05)	68.67*
Demographic			
Age			
Older (≥ 55 years old)	51,874	0.81 (0.67–0.98)*	70.04*
Younger (<55 years old)	6,388	0.48 (0.26–0.89)*	55.64
Gender			
Both (female and male)	51,268	0.74 (0.59–0.94)*	71.78*
Female	3,764	0.55 (0.28–1.08)	58.31
Male	3,230	0.88 (0.57–1.36)	44.20
Country region			
Asia Pacific	5,494	0.62 (0.42–0.90)*	36.50
Europe	3,225	0.99 (0.79–1.25)	0.00
US	49,543	0.73 (0.57–0.93)*	73.95*
Ethnicity			
Asian	1,330	0.47 (0.27–0.82)*	0.00
Caucasian	53,930	0.76 (0.61–0.94)*	65.99*
Multi-ethnic groups (US)	3,002	0.89 (0.76–1.05)	0.00
Vitamin D			
Vitamin D levels			
High (≥ 50 nmol/L)	53,707	0.73 (0.59–0.90)*	68.90*
Low (<50 nmol/L)	4,555	0.81 (0.53–1.24)	66.24
High age, low 25OHD			
No	53,707	0.73 (0.59–0.90)*	68.90*
Yes	4,555	0.81 (0.53–1.24)	66.24
Season			
No season	1,811	0.31 (0.14–0.72)*	0.00
Seasons	56,451	0.78 (0.66–0.93)*	64.88*
Assay method			
CLIA	46,255	0.73 (0.54–0.99)*	75.78*
HPLC	3,002	0.89 (0.76–1.05)	0.00
RIA	9,005	0.71 (0.50–1.00)	59.06*
Hypertension			
Hypertension self-report			
No	55,791	0.76 (0.63–0.92)*	66.90*
Yes	2,471	0.58 (0.20–1.69)	83.11*
Antihypertensive treatment			
No	49,436	0.66 (0.51–0.87)*	54.57
Yes	8,826	0.85 (0.70–1.01)	44.52
Confounders			
BMI			
No	48,670	0.63 (0.55–0.73)*	0.00
Yes	9,592	0.81 (0.66–0.98)*	53.78*
PA			
No	41,917	0.58 (0.39–0.84)*	19.00
Yes	16,345	0.82 (0.69–0.97)*	48.15
Diabetes			
No	7,970	0.82 (0.63–1.05)	55.94
Yes	50,292	0.71 (0.56–0.90)*	63.02*

Note: *Significance $P < 0.05$.

Abbreviations: 25OHD, 25-hydroxyvitamin D; US, United States; CLIA, chemiluminescence immunoassay; HPLC, high-pressure liquid chromatography; RIA, radioimmunoassay; BMI, body mass index; PA, physical activity.

(RR =0.86 (0.71–1.05)). There was no statistically significant heterogeneity among studies rated higher than 5 ($I^2=37.62$, $P > 0.05$), but significant heterogeneity was found among studies rated ≤ 5 ($I^2=68.67$, $P < 0.05$). Detailed results when studies were stratified by demographic factors

(age, gender, country region, and ethnicity), vitamin D factors (vitamin D levels, season, assay methods), hypertension (measured or self-report, history of anti-hypertensive use), and confounders (BMI, PA, and diabetes status) are given in Table 2 and Figure 2A–D.

Characteristics of included studies – cross-sectional studies

The pooled OR-estimated risk of hypertension (primary endpoint) for the highest vs the lowest category of blood 25OHD concentrations was 0.79 (0.73–0.87) (Figure 3A). There was statistically significant heterogeneity among all cross-sectional studies ($I^2=45.37$, $P<0.05$). The Egger's test based on all included studies showed no evidence of publication bias for blood 25OHD concentrations and hypertension ($P=0.62$), together with the funnel plot shown in Figure 3B.

Twenty-seven cross-sectional studies were identified, of which 19^{25,30,33–49} were included in this formal meta-analysis (Tables 3 and 4 and Figure 3A). Of these 19 cross-sectional studies, one study⁴⁸ also reported linear results that are reported in Table 5. The remaining extracted cross-sectional studies only reported 25OHD estimates in linear fashion and thus were not included in the formal meta-analysis but are reported in Table 5.^{29,48,50–57}

In summary, Tables 3 and 4 represent 19 cross-sectional studies with aggregate data on 90,535 nonoverlapping participants. Tables 3 and 4 provide details of the eligible studies that evaluated vitamin D status and the ORs of hypertension. Six studies were carried out in the US,^{33,34,36,41,43,44} five studies in Europe,^{25,30,35,37,40} five studies in the Asia Pacific^{38,39,46–48} (including one in Australia³⁹), one in Middle-East,⁴² one in Puerto Rico,⁴⁵ and one in South Africa.⁴⁹ Sixteen studies were recruited from the general population,^{37–44,46,48,49} and two studies were sampled from either clinic attendees⁴⁵ or factory employees.⁴⁷ The age of participants ranged from 18 years to 92 years, and only five studies were of one gender,^{30,36,39,40,49} and the majority were mixed. Ascertainment of hypertension was mostly by measuring blood pressure and in only two studies,^{36,44} it was from self-report.

Tables 3 and 4 also provides assay characteristics of measured levels of 25OHD from studies contributing to the analyses. Nine cross-sectional studies^{30,33,38,39,41,42,44,47,48} used the RIA method, six cross-sectional studies used CLIA or electro-chemiluminescence immunoassay,^{25,34–36,45,46} one used enzyme-linked immunosorbent assay,³⁷ one used Nichols Advantage,⁴³ one used Roche Elecsys,⁴⁹ and one used HPLC⁴⁰ for blood 25OHD analyses.

Vitamin D status and risk of hypertension – cross-sectional studies subgroup analysis

When studies were stratified by quality score, the ORs were significant for studies rated 5 (OR =0.71 (0.61–0.83))

and 6 (OR =0.79 (0.73–0.87)) but were not significant for studies rated ≤ 4 (OR =0.87 (0.75–1.01)). There was no statistically significant heterogeneity among studies rated at 4 ($I^2=46.13$, $P>0.05$), 5 ($I^2=39.34$, $P>0.05$), or 6 ($I^2=0.00$, $P>0.05$). Detailed results when studies were stratified by demographic factors (age, gender, country region, and ethnicity), vitamin D factors (vitamin D levels, seasons, and assay methods), hypertension (measured or self-report, history of anti-hypertensive use), and confounders (BMI, PA, and diabetes status) are given in Table 4 and Figure 3A–D.

Discussion

Physiology of vitamin D

In humans, vitamin D is normally obtained from skin through the action of ultraviolet B irradiation on 7-dehydrocholesterol.⁵⁸ It is further metabolized to 25OHD, the major circulating vitamin D compound, and then to 1,25-dihydroxyvitamin D (1,25D), the hormonal form.^{4–6,9} The major function of vitamin D compounds is to enhance active absorption of ingested calcium (and phosphate). This assists in building bone at younger ages and ensures that bone does not need to be resorbed to maintain blood calcium concentrations. As there are vitamin D receptors in most nucleated cells, including vascular smooth muscle cells, as well as in macula densa and juxtaglomerular cells,^{59,60} vitamin D compounds appear to have direct effects to improve bone and muscle function, and there is good, though not entirely consistent, evidence that supplemental vitamin D and calcium together reduce falls and fractures in older individuals.⁶¹ Based on calcium control and musculoskeletal function, target levels of 25OHD in blood are at least 50–60 nmol/L, and there may be a case for higher targets of 75–80 nmol/L.^{10,11}

Summary and comparison with other meta-analyses

The overall results from this recent meta-analysis and systematic review are that from a total of 148,797 healthy participants (58,262 prospective; 90,535 cross-sectional) from general population samples across the world (published between 2007 and early 2014), lower 25OHD levels appear to be associated with increased hypertension levels (prospective analyses: RR =0.76 (0.63–0.90); cross-sectional analyses: OR =0.79 (0.73–0.87)). These updated results report similar findings published by Kunutsor et al for prospective studies in 2013 (RR =0.70 (0.58–0.86))⁸ and for cross-sectional studies by Burgaz et al in 2011 (OR =0.73 (0.63–0.84)).⁷

Table 3 Characteristics of cross-sectional studies

Author (year), ^{reference} study and year of conduct, quality score [†]	Country, study sample	Gender, age range or mean \pm SD (years)	Sample size, assay
Martins et al (2007), ³³ NHANES 1988–1994, 6	US, general population	48% male, 20–80	15,088, RIA
Reis et al (2007), ³⁴ RBS 1997–1999, 5	US, general population	38% male, 44–96	1,070, CLIA
Snijder et al (2007), ³⁵ LASA 1996, 6	The Netherlands, general population	50% male, 55–85	1,205, CLIA
Forman et al (2008), ³⁶ NHS2 1997–1999, 4	US, nurses	100% female, 32–52	1,484, CLIA
Hypponen et al (2008), ³⁷ 1958 BBC 2002–2004, 5	UK, general population	48% male, 45–47	6,293, ELISA
Lu et al (2009), ³⁸ NHAPC, 2005, 5	People's Republic of China, general population	44% male, 50–70	3,262, RIA
Pasco et al (2009), ³⁹ GOS 1994–1997, 5	Australia, general population	100% female, 20–92	861, RIA
Burgaz et al (2010), ⁴⁰ ULSAM 1991–1995, 6	Sweden, general population	100% male, 71 \pm 0.6	830, HPLC/MS
Jorde et al (2010), ²⁵ Tromsø Study 2008, 4	Norway, general population	37% male, 25–84	4,125, ECLIA
Zhao et al (2010), ⁴¹ NHANES 2003–2006, 6	US, general population	49% male, \geq 20	7,228, RIA
Steinvil et al (2011), ⁴² Maccabi Healthcare Services 2001–2008, 4	Israel, general population	23% male, 55 \pm 17 77% female, 55 \pm 15	34,874, RIA
Bhandari et al (2011), ⁴³ KPSCHP 2004–2006, 5	US, general population	31% male, >59	2,722, Nichols Advantage
Brock et al (2011), ⁴⁴ PLCO 1993–2001, 4	US, general population	53% male, 55–74	2,465, RIA
Caro et al (2012), ⁴⁵ no name and year, 4	Puerto Rico, clinic subjects	15% male, 21–50	219, CLIA
Dorjgochoo et al (2012), ⁴⁶ SWHS 1997–2000, SMHS 2002–2006, 4	People's Republic of China, general population	28% male, 40–75	1,460, CLIA
Sumriddetchkajorn et al (2012), ⁴⁷ no name 1997, 4	Thailand, factory employees	14% male, 35–54	274, RIA
Kim et al (2013), ⁴⁸ KNHANES 2009–2010, 5	Korea, general population	45% male, 50–90	4,513, RIA
Kruger et al (2013), ⁴⁹ PURE 2005, 4	South Africa, general population	100% female, 58 \pm 9	291, Roche Elecsys
Ke et al (2013), ³⁰ ATBC 1985–1993, 4	Finland, general population	100% male (smoker), 50–69	2,271, RIA

Note: [†]Quality score based on Newcastle–Ottawa Scale.

Abbreviations: NHANES, National Health and Nutrition Examination Survey; RBS, Rancho Bernardo Study; LASA, Longitudinal Aging Study Amsterdam; NHS2, Nurses' Health Study 2; BBC, British Birth Cohort; NHAPC, Nutrition and Health of Aging Population in China; GOS, Geelong Osteoporosis Study; ULSAM, Uppsala Longitudinal Study of Adult Men; KPSCHP, Kaiser Permanente Southern California Health Plan; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SWHS, Shanghai Women's Health Study; SMHS, Shanghai Men's Health Study; KNHANES, Korea National Health and Nutrition Examination Survey; PURE, Prospective Urban Rural Epidemiology Study; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; SD, standard deviation; 25OHD, 25-hydroxyvitamin D; OR, odds ratio; CI, confidence interval; RIA, radioimmunoassay; US, United States; UK, United Kingdom; BP, blood pressure; BMI, body mass index; HTN, hypertension; CLIA, chemiluminescence immunoassay; PA, physical activity; WC, waist circumference; ELISA, enzyme-linked immunosorbent assay; HPLC, high-pressure liquid chromatography; MS, mass spectrometry; ECLIA, electro-chemiluminescence immunoassay; SBP, systolic blood pressure.

In addition, our systematic review of 172,259 participants and 38 studies concurs with observations from the above meta-analyses in that 60% of studies reported a significant inverse association between blood 25OHD and hypertension. Of these, 40% were reported from prospective studies (Table 1), 56% from cross-sectional studies (Table 3), and 64% from those studies that reported linear associations of 25OHD with hypertension (Table 5).

It should be noted that mostly these effects were of a small magnitude and have not been confirmed in results from RCTs.¹⁴ Probably, because of these facts and other

even less-convincing data from mortality studies^{62,63} and other CVD outcomes,^{4–6,9} critics have hypothesized that observational associations may be due to an association between low vitamin D and general “ill health”,⁶⁴ a conclusion observational studies cannot fully address due to their study design. Thus, the major criticism of observational studies is that results may be due to reverse causality (such as already unwell participants) and/or unmeasured bias or confounding (such as obesity and lack of PA), which RCTs attempt to take into account by randomization. This review has attempted to address

Mean or % 25OHD (nmol/L)	25OHD (nmol/L) comparison	Primary endpoint: hypertension (mmHg)	OR (95% CI)	Confounders
75, 60% <75	<53 vs ≥93	BP ≥ 140/90	0.78 (0.67–0.88)	Age, gender, BMI, ethnicity, season, HTN treatment
Male: 109	<78 vs ≥120	BP ≥ 130/85	1.28 (0.58–2.82)	Age, abdominal obesity, PA, season, HTN treatment, diabetes status
Female: 102	<88 vs ≥126		1.01 (0.53–1.93)	
37% <50	<25 vs ≥75	BP ≥ 140/90	1.12 (0.59–2.13)	Age, gender, BMI, WC, PA, season, HTN treatment
68, 66% <75	<42 vs ≥95	Self-reported	0.60 (0.40–0.90)	Age, BMI, PA, ethnicity, season
Male: 54,	<27 vs ≥150	BP ≥ 140/90	0.72 (0.61–0.85)	Age, gender, BMI, PA, season, HTN treatment
Female: 52				
40, 70% <50	<29 vs ≥58	BP ≥ 130/85	0.66 (0.51–0.85)	Age, gender, BMI, PA, season, HTN treatment, diabetes status
33% <50	<53 vs ≥74	BP ≥ 140/90	0.40 (0.22–0.70)	Age, weight, season, HTN treatment
70	<38 vs ≥50–75	BP ≥ 140/90	0.31 (0.09–1.11)	Age, BMI, PA, season, HTN treatment
54	<41 vs ≥63	BP ≥ 160/95	0.87 (0.60–1.27)	Age, gender, BMI, PA, HTN treatment
80	<38 vs ≥75	BP ≥ 140/90	0.80 (0.72–0.89)	Age, gender, BMI, PA, ethnicity, HTN treatment, diabetes status
79% male <75	<38 vs ≥75	BP ≥ 160/95	0.90 (0.77–1.05)	Age, HTN treatment
78% female <75			0.84 (0.76–0.92)	
15% <75	<37 vs ≥100	BP ≥ 160/95	0.37 (0.19–0.88)	Age, gender, ethnicity, HTN treatment
29% <50	<37 vs ≥80	Self-report	1.00 (0.70–1.40)	Age, gender, BMI, PA, season
60% <75	<75 vs ≥75	BP ≥ 140/90	0.90 (0.29–2.86)	Age, gender, BMI, HTN treatment
96% <75	<24 vs ≥51	BP ≥ 140/90	0.86 (0.38–1.95)	Age, gender, BMI, PA, season, HTN treatment
36% <70	<70 vs ≥70	BP ≥ 140/90	1.82 (1.06–3.03)	Age, gender, BMI
49, 53% <50	<25 vs ≥50	BP ≥ 140/90	0.80 (0.61–1.05)	Age, BMI, PA, HTN treatment,
			0.76 (0.59–0.98)	
63% <75	<75 vs ≥75	SBP ≥ 146	0.54 (0.31–0.95)	Age, BMI
69% <50	<25 vs ≥80	BP ≥ 140/90	0.90 (0.60–1.40)	Age, BMI, season

some of these issues by stratification and sensitivity analyses.

Quality of included studies

When prospective studies were stratified by the journal quality ratings score (≥ 6 vs lower),¹⁹ the association between low 25OHD and increased hypertension was both significant and not heterogeneous in the better-quality studies^{23–26,28} (score ≥ 6 , RR = 0.67 (0.51–0.88); score < 6, RR = 0.86 (0.71–1.05)) (Figure 2C). A similar pattern occurred in cross-sectional studies, although the effect was not quite as marked in that all the studies remained significant in their category and also had no heterogeneity, but the “higher

quality”^{33,35,40,41} studies showed a stronger association between lower 25OHD levels and hypertension vs “moderate quality”^{34,37–39,43,48} (score = 6, OR = 0.79 (0.73–0.87); score = 5, OR = 0.72 (0.65–0.80); score = 4, OR = 0.86 (0.80–0.93)) (Figure 3C).

Heterogeneity and publication bias

As with the previous meta-analyses, there was no publication bias reported, probably due to the strict criteria used for selecting the studies to be used. However, in contrast to the two previous meta-analysis,^{7,8} which reported no heterogeneity in their results, this present meta-analysis reported heterogeneity among studies of blood 25OHD concentrations and

Table 4 Cross-sectional studies: mixed-effect meta-analysis 25OHD and hypertension stratification

Stratification	Sample size	Risk of hypertension associated with high 25OHD	Heterogeneity (I^2)
Total	90,535	0.79 (0.73–0.87)*	45.37*
Journal quality			
High (score =6)	23,521	0.79 (0.73–0.87)*	0.00
Middle (score =5)	23,676	0.71 (0.61–0.83)*	39.43
Low (score =4)	43,338	0.87 (0.75–1.01)	46.13
Demographic			
Age			
Older (≥ 55 years old)	18,736	0.79 (0.70–0.89)*	0.00
Younger (<55 years old)	71,799	0.79 (0.70–0.88)*	63.83*
Gender			
Both (female and male)	42,881	0.81 (0.71–0.93)*	57.76*
Female	33,540	0.72 (0.59–0.87)*	45.96
Male	14,114	0.86 (0.75–0.99)*	6.68
Country region			
Asia Pacific	10,370	0.78 (0.59–1.04)	70.21*
Europe	14,724	0.79 (0.65–0.95)*	17.93
US	35,384	0.79 (0.68–0.91)*	3.39
Others	30,057	0.85 (0.78–0.93)*	44.10
Ethnicity			
Asian	9,509	0.85 (0.65–1.12)	66.10*
Caucasian	20,604	0.79 (0.55–0.95)*	42.63
Multi-ethnic groups (US)	17,810	0.58 (0.28–1.18)	78.86*
Others	42,612	0.83 (0.78–0.89)*	0.00
Vitamin D			
Vitamin D level			
High (≥ 50 nmol/L)	76,408	0.78 (0.71–0.86)*	46.98*
Low (<50 nmol/L)	14,127	0.85 (0.70, 1.05)	49.38
High age, low 25OHD			
No	78,166	0.79 (0.71–0.88)*	57.63*
Yes	12,369	0.81 (0.70–0.94)*	0.00
Season			
No season	55,107	0.80 (0.71–0.91)*	56.60*
Season	35,428	0.77 (0.69–0.86)*	23.45
Assay method			
CLIA	9,563	0.84 (0.68–1.05)	0.00
ELISA	6,293	0.72 (0.61–0.85)*	0.00
HPLC	830	0.31 (0.09–1.09)	0.00
Nichols Advantage	2,722	0.37 (0.19–0.71)*	0.00
RIA	70,836	0.82 (0.78–0.87)*	53.90*
Roche	291	0.54 (0.31–0.95)*	0.00
Hypertension			
Hypertension self-report			
No	86,586	0.79 (0.73–0.87)*	45.61*
Yes	3,949	0.78 (0.48–1.29)	71.50*
Antihypertensive treatment			
No	6,785	0.88 (0.61–1.28)	71.95*
Yes	83,750	0.79 (0.73–0.85)*	31.37
Confounders			
BMI			
No	37,596	0.81 (0.66–0.99)*	70.32*
Yes	52,939	0.79 (0.71–0.87)*	39.00*
PA			
No	56,600	0.79 (0.67–0.94)*	67.71*
Yes	33,935	0.78 (0.72–0.84)*	1.63
Diabetes status			
No	74,462	0.80 (0.70–0.90)*	55.87*
Yes	16,073	0.79 (0.72–0.86)*	0.00

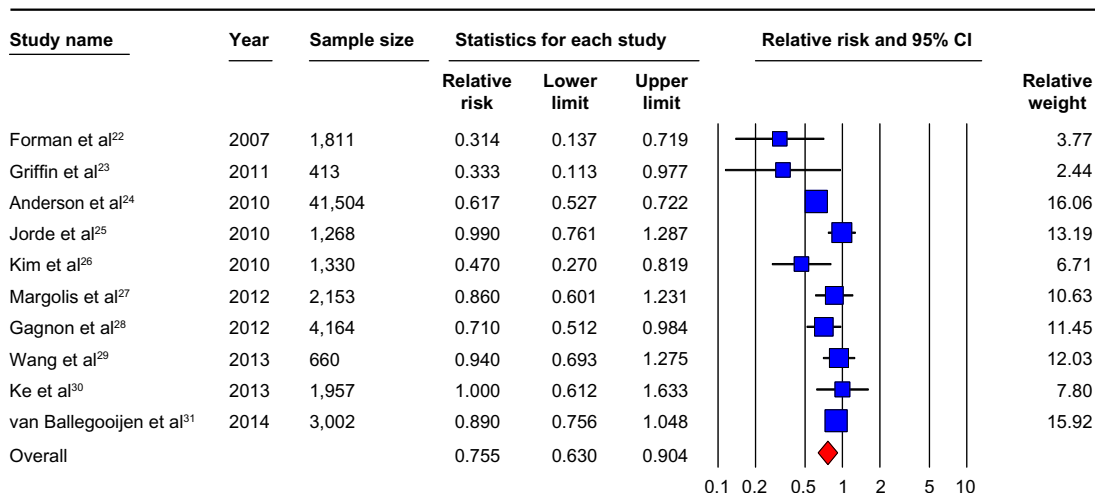
Note: *Significance $P < 0.05$.

Abbreviations: 25OHD, 25-hydroxyvitamin D; US, United States; CLIA, chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; HPLC, high-pressure liquid chromatography; RIA, radioimmunoassay; BMI, body mass index; PA, physical activity.

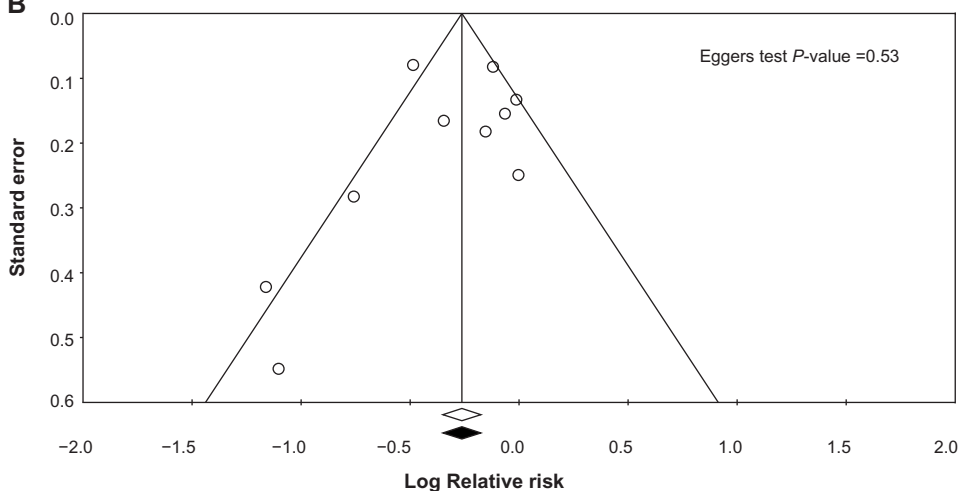
hypertension (in both prospective and cross-sectional studies) (Tables 2 and 4). The previous meta-analyses restricted their study selection to defined populations (eg, primarily Caucasian from either Europe or the US). The heterogeneity reported

in the present meta-analysis is probably due to the wide scope of the literature search in demographic range (age, gender, country location, and ethnicity) of the studies assessed and also the different 25OHD assay technologies used.

A



B



C

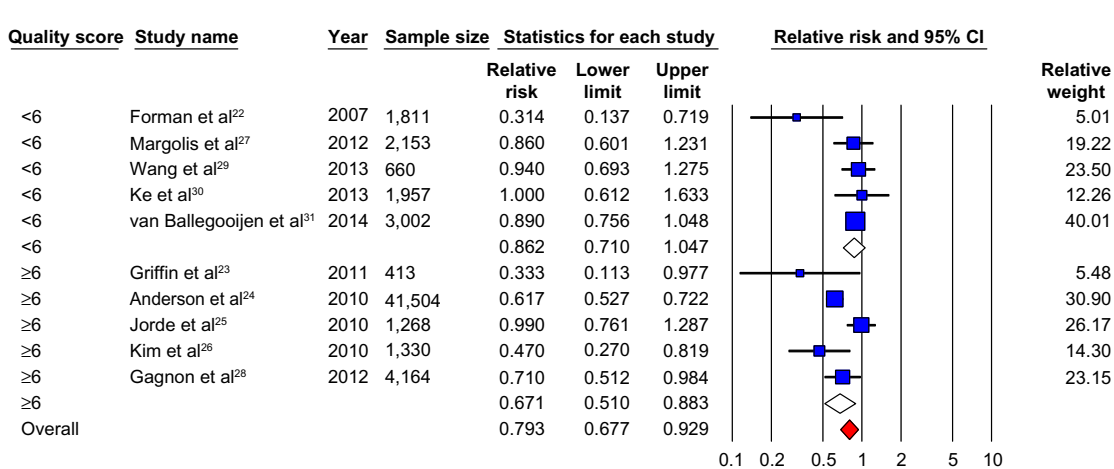


Figure 2 (Continued)

D

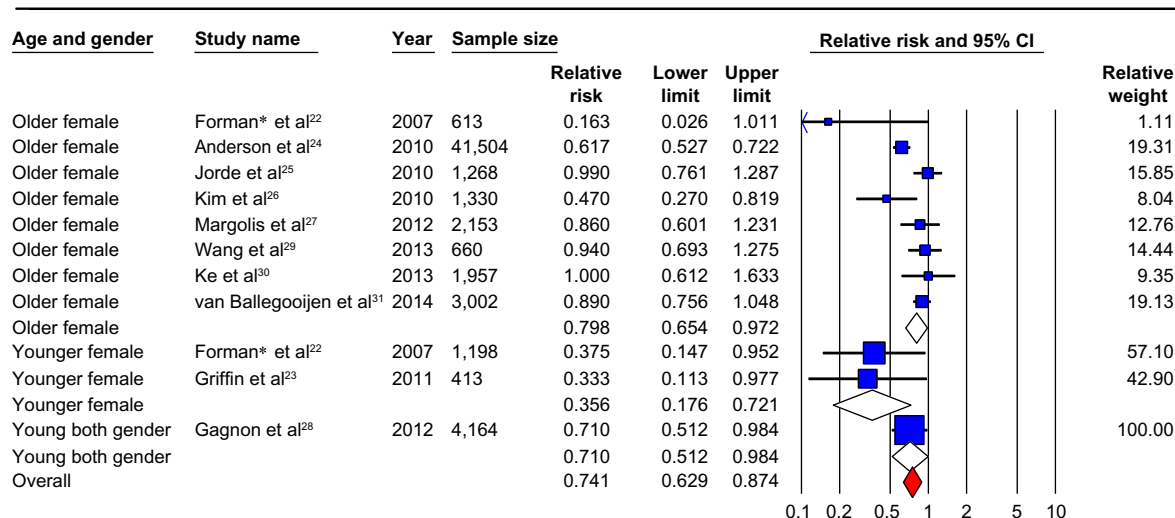


Figure 2 Prospective studies.

Notes: (A) Prospective studies of vitamin D and hypertension risk: the effect of higher vitamin D (measured as quartiles of 25OHD) on hypertension risk expressed as relative risk (RR) for individual studies (blue) and the calculated overall RR (red). (B) Funnel plot showing standard error by log RR for the prospective studies. (C) Prospective studies of vitamin D and hypertension risk sub-groups: the effect of higher vitamin D (measured as quartiles of 25OHD) on hypertension risk stratified by quality score expressed as RR for individual studies (blue), sub-groups total (white) and the calculated overall RR (red). (D) Prospective studies of vitamin D and hypertension risk sub-groups: the effect of higher vitamin D (measured as quartiles of 25OHD) on hypertension risk stratified by age and gender expressed as RR for individual studies (blue), sub-group total (white) and the calculated overall RR (red). *Studies published in one paper.

Abbreviation: CI, confidence interval.

Demography and ethnicity

The age range in this review was 18–96, and the effect of low 25OHD on hypertension remained significant in both younger and older strata and somewhat surprisingly, was markedly stronger in those aged <55, and in females in prospective and cross-sectional data (Figures 2D and 3D).

When it was possible to investigate gender separately, heterogeneity disappeared in both prospective and cross-sectional studies, but the associations became nonsignificant in the prospective studies, probably due to lower sample sizes. Females did seem to have a greater degree of association of hypertension risk with low vitamin D, especially at a younger age. This is puzzling as one would not expect younger females to have increased risk of hypertension, but increasingly younger females are being reported to be at risk for vitamin D deficiency, particularly in Asian populations.⁶⁵ These findings need to be further investigated; our recent data from Macau also confirm this risk in younger women.^{66,67}

When investigated by region or country of the study population, countries from Europe and the US were more similar (ie, less heterogeneity) than those from other regions of the world; previous meta-analyses have concentrated on these countries. In this meta-analysis, the effect of vitamin D deficiency on hypertension was

attenuated in the European studies compared to the total risk estimate and was, in fact, non-significant from prospective data. When ethnicity was investigated, those of “multi-ethnic group” ethnicities did not show an effect compared with others; as Burgaz et al⁷ noted, there is evidence that vitamin D synthesis is less efficient among individuals with greater skin pigmentation,^{68,69} but variations in culturally preferred covering of skin by clothing could also be an explanation for these findings.⁷⁰ More studies in different cultures are needed to disentangle these findings.

Measurement of blood pressure variables

Only three studies included in the present meta-analysis have used self-reported hypertension as outcomes (two in prospective^{22,27} and one in cross-sectional⁴⁴), which can only give a crude estimate of average blood pressure. In our stratified analysis, the effect was attenuated when studies took account of measured blood pressure, but the negative association between decreased 25OHD and hypertension remained significant. In addition, taking into account the use of antihypertensive treatments is an important confounder; two prospective studies^{22,30} and five cross-sectional studies^{30,36,44,47,49} did not have this variable; in our stratified analysis, the effect was attenuated when studies took account of antihypertensive medication, but

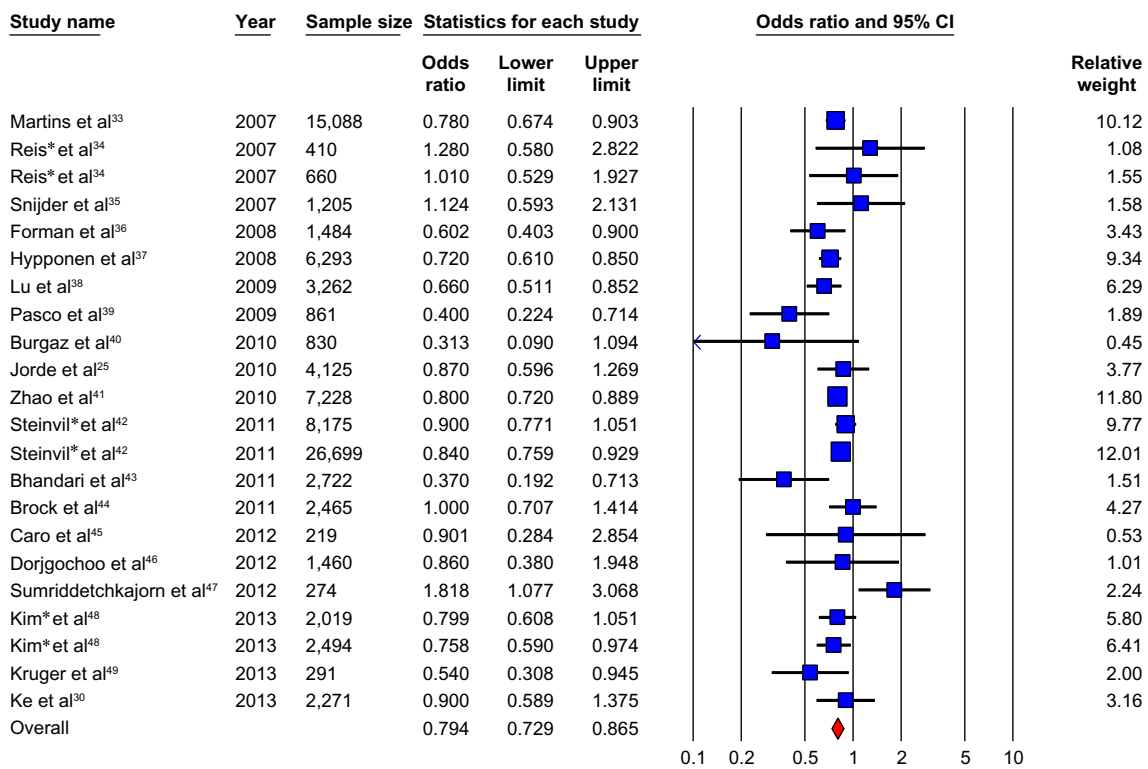
the negative association between decreased 25OHD and hypertension remained significant, and in addition, studies which took account of blood pressure medications did not have heterogeneity.

Measurement of 25OHD levels

There has been debate over the measurement of 25OHD in blood samples and its variability.⁵⁸ HPLC has been

considered the “gold standard” but as can be seen in the present stratifications, RIA was by far the most commonly used method. There were differences between these methods, which could well explain some of the heterogeneity detected in our meta-analyses. A recent paper has reported good similarity between these various methods,⁷¹ and with the exception of HPLC, all assay methods produced significant associations.

A



B

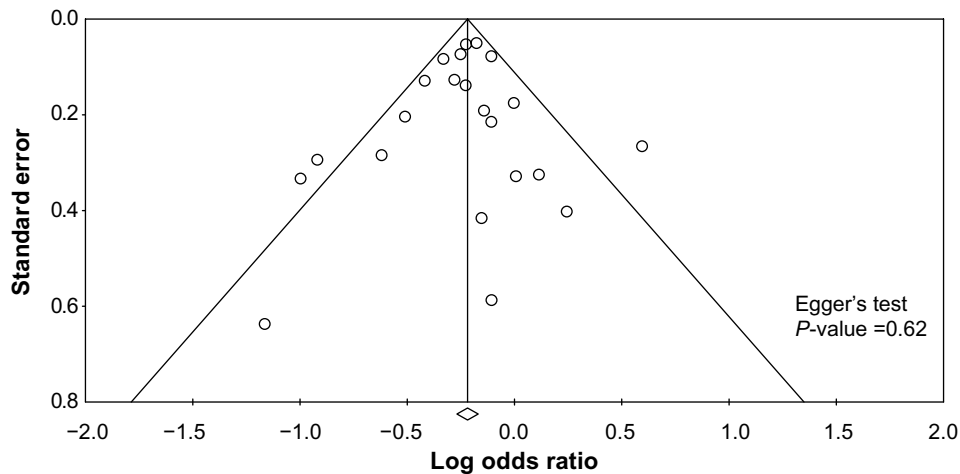
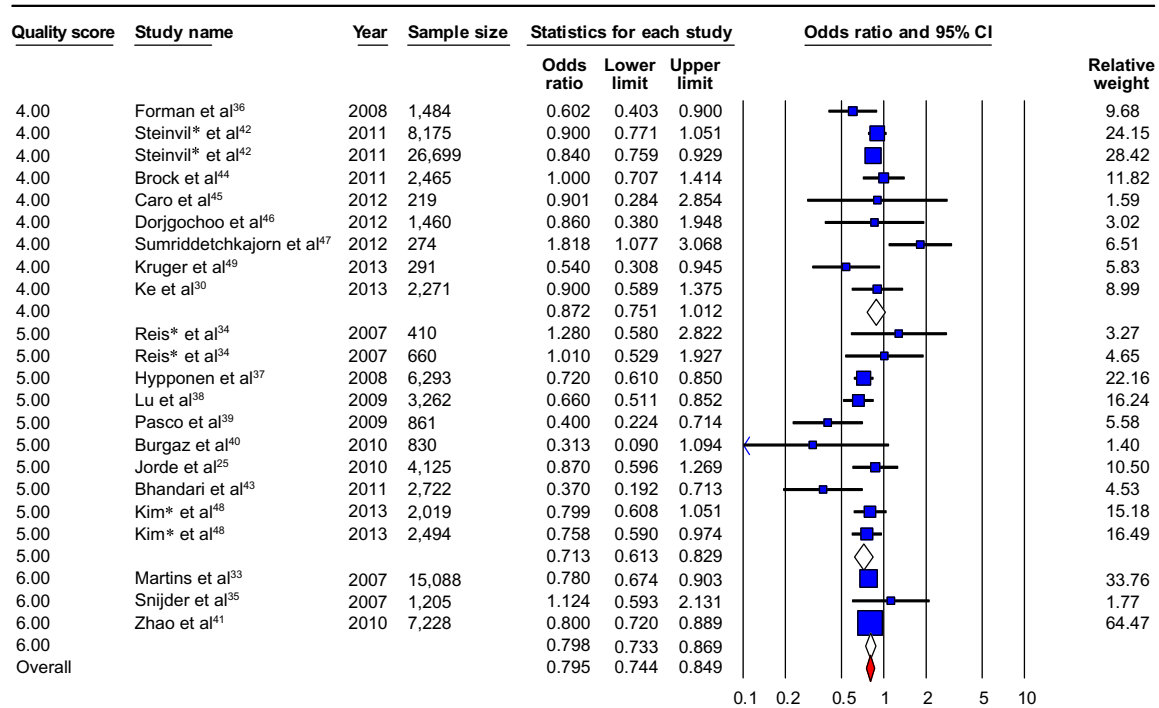


Figure 3 (Continued)

C



D

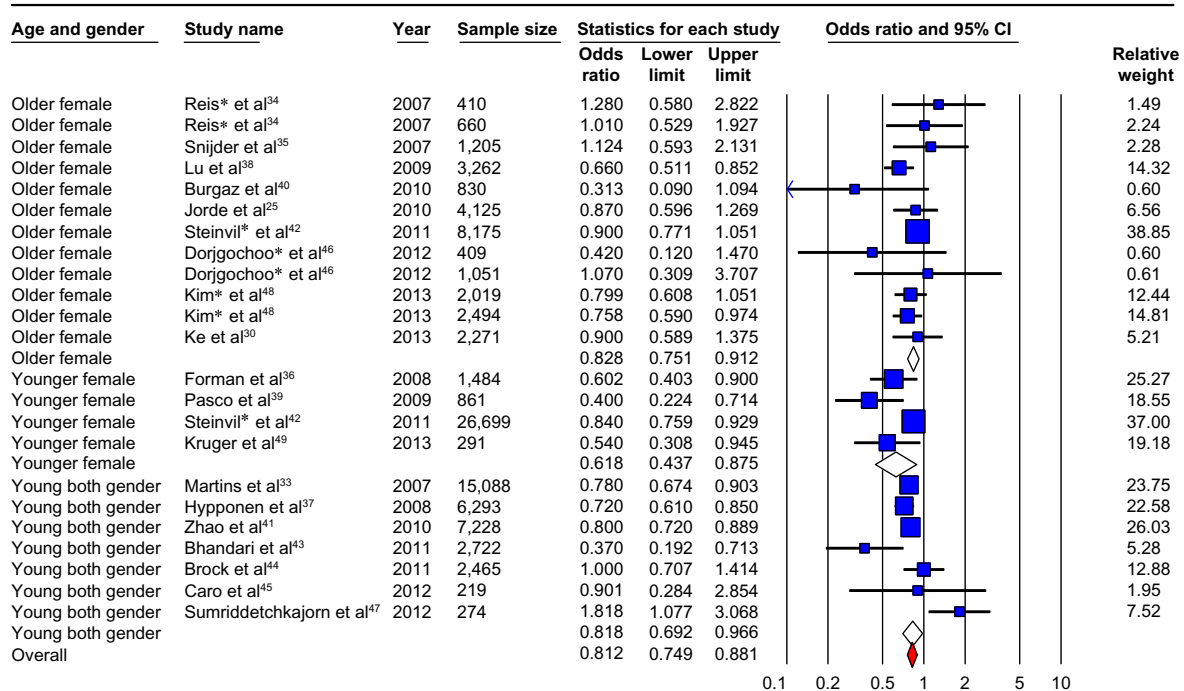


Figure 3 Cross-sectional studies.

Notes: (A) Cross-sectional studies of vitamin D and hypertension risk: the effect of higher vitamin D (measured as quartiles of 25OHD) on hypertension risk expressed as odds ratio (OR) for individual studies (blue) and the calculated overall OR (red). (B) Funnel plot showing standard error by log OR for the cross-sectional studies. (C) Cross-sectional studies of vitamin D and hypertension risk sub-groups: the effect of higher vitamin D (measured as quartiles of 25OHD) on hypertension risk stratified by quality score expressed as OR for individual studies (blue), sub-group total (white) and the calculated overall OR (red). (D) Cross-sectional studies of vitamin D and hypertension risk sub-groups: the effect of higher vitamin D (measured as quartiles of 25OHD) on hypertension risk stratified by age and gender expressed as OR for individual studies (blue), sub-groups total (white) and the calculated overall OR (red). *Studies published in one paper.

Abbreviation: CI, confidence interval.

Season of blood draw and measurement of 25OHD

It is well established that 25OHD concentrations and hypertension are associated with season.^{72,73} When studies that adjusted for season were compared with studies that did not take seasonality into account (usually by date of draw of the blood samples), the association between low 25OHD and hypertension risk remained significant. Only one prospective study²² did not adjust for season, and in cross-sectional studies, most studies appear to have taken season into account^{30,33–40,44,46} but not others. In our stratification analysis, taking season into account did reduce the effect size but not significance.

Deficiency vs sufficiency of vitamin D status

There has been some discussion that the effect of 25OHD on hypertension risk may be more potent in those who are originally vitamin D deficient vs sufficient.^{7,8,27} The opposite effect was seen in these data in that a significant effect was only seen in those who had sufficiency, not deficiency, although it should be pointed out that the deficiency studies were fewer in number and in size. In addition, when those who were older and had deficiency were investigated in prospective studies, the effect became nonsignificant and attenuated in cross-sectional studies (87% of total data).

Confounding by healthy lifestyle variables

It has been suggested that confounding by health lifestyle variables may account for the associations seen between higher 25OHD and less hypertension.⁶⁴ In particular, BMI, as a marker of obesity, is an independent risk factor for both vitamin D deficiency^{74–77} and hypertension.^{78–83} In fact, earlier investigators did not adjust for BMI in their hypertension and 25OHD analyses as they considered it to be a mediating factor and part of the causal chain.⁵⁰ More recently, Mendelian analysis has confirmed that obesity is a “cause” of vitamin D deficiency, not the other way around,⁸⁴ and recent studies have inferred that the effect of BMI may be due to a body dilution effect.⁸⁵ In this analysis, only 15% of studies (five) did not adjust for BMI, and adjustment did make the associations smaller in effect; they nevertheless remained significant. Thus, two recent Mendelian randomization studies investigating the relationship between adiposity and vitamin D concentrations have confirmed this important mediating effect of obesity and vitamin D.^{84,86}

Potential mechanisms of action to explain a protective effect of vitamin D in hypertension

As we have summarized above, there are a number of confounding mechanisms, which could explain an association between low 25OHD concentrations and high blood pressure. In particular, being overweight or obese is known to be linked to low vitamin D concentrations and to higher readings for blood pressure using a normal sphygmomanometer cuff.^{87,88}

There are also a number of plausible physiological mechanisms to explain why low vitamin D status might lead to elevated blood pressure. The active hormone of vitamin D, 1,25D, has been shown to decrease the expression of the renin gene through a vitamin D receptor-dependent mechanism, thus decreasing both renin and angiotensin II concentrations.^{89,90} This mechanism results in hypertension in mice, in which the capacity to produce 1,25D is knocked out,⁹⁰ or in mice that lack the vitamin D receptor.⁸⁹ A negative association between 25OHD, 1,25D concentrations, and plasma renin activity in patients with hypertension has been reported⁹¹ and in patients with chronic heart failure, a short course of vitamin D treatment resulted in a significant decrease in plasma renin activity and concentration.⁹² Vitamin D deficiency also results in higher than normal concentrations of PTH. High levels of PTH have long been associated with elevated blood pressure, reversed by parathyroid gland removal in mice,⁹³ while treatment of older female normotensive women with vitamin D and calcium reduced blood pressure and parathyroid hormone, more effectively than calcium alone.⁹⁴ There is also considerable evidence from both animal and human studies that the vitamin D system affects vascular endothelial function in several ways, including affecting vascular stiffness, oxidative stress, and through upregulation of endothelial nitric oxide syntheses.^{95–99}

Limitations

Our study also has several strengths and limitations as do all meta-analyses of observational studies.

Inadequate control for confounders may bias the results in either direction, toward exaggeration or underestimation of the estimates, as such residual or unknown confounding cannot be excluded as a potential explanation for the observed findings. In this analysis, stratification has attempted to answer some of these concerns (Tables 2 and 4).

As was the case with Kunutsor et al,⁸ it was not possible to correct the estimates for within-individual variation in

Table 5 Characteristics of studies reporting linear relationship between blood pressure and 25OHD

Author (year), ^{reference} study and year of conduct, quality score [†]	Country, study sample	Gender, age (range or mean \pm SD) (years)	Sample size, assay
Scragg et al (2007), ⁵⁰ NHANES III: 1988–1994, 6	US, general population	48% male, 20–80+	12,644, RIA
Hintzpetter et al (2008), ⁵¹ GNHIES 1998, 6	Germany, general population	44% male, 18–79	4,030, CLIA
Almirall et al (2010), ⁵² D'AVIS study 2006, 5	Spain, general population	47% male, 64–93	237, RIA
Fraser et al (2010), ⁵³ NHANES 2001–2002, 2003–2004, 2005–2006, 7	US, general population	48% male, 20–80+	3,958, RIA
Griffin (2011), ²³ MBHMS 1992–1993, 6	US, general population	100% female, 22–44	413, RIA
Kim et al (2010), ²⁶ Chungju city 2003–2007, 5	Korea, general population	38% male, 66 \pm 9	1,330, CLIA
Li et al (2012), ⁵⁴ Dali city 2010, 5	People's Republic of China, factory employees	60% male, 20–83	1,206, RIA
Jungert et al (2012), ⁵⁵ GISELA 2008, 5	Germany, general population	32% male, 66–96	132, ECLIA
Skaaby et al (2012), ³² Inter99 1999–2004, 6	Denmark, general population	50% male, 30–60	4,330, HPLC
Margolis et al (2012), ²⁷ WHI 1993–1998, 5	US, general population	100% male, 50–79	2,153, CLIA
Kim et al (2013), ⁴⁸ KNHANES 2009–2010, 5	Korea, general population	45% male, 50–90	4,513, RIA
Sakamoto et al (2013), ⁵⁶ AHS2 2003–2007, 5	US, general population	48% male, 30–95	568, RIA
Wang et al (2013), ²⁹ PHS 1982–2009, 5	US, physicians	100% male, 40–84	660, RIA
Sulistyoningrum et al (2013), ⁵⁷ M-CHAT 2006, 5	Canada, general population	48% male, 30–65	687, RIA

Note: [†]Quality score based on Newcastle–Ottawa Scale. * $P < 0.05$

Abbreviations: NHANES, National Health and Nutrition Examination Survey; GNHIES, German National Health Interview and Examination Survey; D'AVIS, designed to analyze the prevalence of hypovitaminosis D; MBHMS, Michigan Bone Health and Metabolism; GISELA, Giessener Senioren Langzeitstudie; WHI, Women's Health Initiative; KNHANES, Korea National Health and Nutrition Examination Survey; AHS2, Adventist Health Study-2; PHS, Physicians' Health Study; M-CHAT, Multi-cultural Community Health Assessment Trial; 25OHD, 25-hydroxyvitamin D; SD, standard deviation; US, United States; BP, blood pressure; RIA, radioimmunoassay; SBP, systolic blood pressure; DBP, diastolic blood pressure; PA, physical activity; CLIA, chemiluminescence immunoassay; HTN, hypertension; BMI, body mass index; ECLIA, electro-chemiluminescence immunoassay; TBF, total body fat; WHR, waist–hip ratio; HPLC, high-pressure liquid chromatography; WC, waist circumference; NA, not available.

vitamin D levels over time or across seasons, because data involving repeat measurements were not reported. Although there are reports that 25OHD exhibits low within-individual variability ($r^2=0.87$ between measured 25OHD levels after several years),^{100,101} studies are still needed with serial measurements of vitamin D.

Another limitation is that 19 of the studies included had a cross-sectional design, which cannot exclude the possibility of reverse causality.

Despite the general nature of these cohorts, it must be noted that our and any other study investigating 25OHD levels are only reporting on those who gave blood, not the entire cohort (average response rate =65%).

Though the meta-analysis was very comprehensive, it was, as are all meta-analyses based on data from published reports, preventing the undertaking of adjustment for confounding and assessment of potential interactions. As has recently been discussed, meta-analyses are only as accurate as the veracity of included data.¹⁰² Thus, collaborative pooling of individual participant data from cohort studies should be conducted for more detailed analyses under a broader range of circumstances as has been done in recent Mendelian analyses.^{84,103}

Strengths

In this analysis, ten prospective studies, which are better at being able to determine the role of blood 25OHD concentrations in

Mean or % 25OHD (nmol/L)	25OHD (nmol/L) comparison	Effects of 25OHD		Confounders
		Primary endpoint: BP	Linear or logistic regression	
Male: 78; female: 73	Continuous	↓ SBP, ↓ DBP	SBP: $\beta=-0.023^*$, DBP: $\beta=-0.027^*$	Age, gender, PA, ethnicity, season
45, 57% <50	Per 10 nmol/L ↑ vitamin D	↓ BP	Male: 0.97 (0.94–0.99), Female: 0.96 (0.93–0.99)	Age, season, HTN treatment
86% <75	Continuous	↓ SBP, ↓ DBP	SBP: $\beta=-0.29^*$, DBP: $\beta=-0.15^*$	Age, gender, BMI, HTN treatment, diabetes
57	Continuous	↓ SBP, ↔ DBP	SBP: $\beta=-0.032^*$, DBP: $\beta=-0.002$	Age, gender, BMI, ethnicity, season, HTN treatment, diabetes status
59, 81% <75	Continuous	↔ SBP, ↔ DBP	SBP: $\beta=-0.650$, DBP: $P>0.05$	Age, % body fat, season, HTN treatment
43	Continuous	↓ SBP, ↓ DBP	SBP: $\beta=-0.150^*$, DBP: $\beta=-0.120^*$	Age, gender, BMI, season
75% <70	Per 10 nmol/L ↑ vitamin D	↔ BP	1.00 (0.98–1.02)	Age, gender, BMI, HTN treatment
21% male <50, 23% female <50	Continuous	↑ SBP (male), ↔ DBP (male), ↔ SBP (female), ↔ DBP (female)	SBP: $\beta=-0.356^*$ male, DBP: $\beta=-0.198$ male, SBP: $\beta=-0.046$ female, DBP: $\beta=-0.104$ female	Age, TBF, WHR, HTN treatment
47, female =50	Per 10 nmol/L ↑ vitamin D	↔ BP	1.01 (0.97, 1.05)	Age, gender, BMI, PA, season
54% <50	Continuous	↑ BP	HTN% vs 25OHD quartile, Chi-square $P<0.01$	NA
49, 53% <50	Continuous	↓ SBP, ↓ DBP	SBP: $\beta=-0.128$ male, DBP: $\beta=-0.087^*$ male, SBP: $\beta=-0.156^*$ female, DBP: $\beta=-0.099^*$ female	Age, weight, WC, PA, HTN treatment, diabetes status
Whites 15% <50, Black 55% <50	Continuous	↑ SBP, ↔ DBP	SBP: $\beta=-0.250^*$ (Whites), $\beta=0.080$ (Black), DBP: $\beta=-0.110$ (total)	Age, gender, BMI, HTN treatment
Summer: 77, Winter: 56	Continuous	↔ SBP, ↔ DBP	No significant mean 25OHD difference	Age, BMI, PA, ethnicity, season, diabetes status
39, 71% <50	Continuous	↓ SBP, ↓ DBP	SBP: $\beta=-0.098^*$, DBP: $\beta=-0.104^*$	Age, gender, BMI, PA, ethnicity

the cause of hypertension, were included. Most of the studies in this meta-analysis were designed to specifically investigate the effect of blood 25OHD concentrations on the risk of hypertension in a general population. Twenty-two studies had as the main focus hypertension and the other seven had metabolic syndrome or heart diseases. More cohort studies specifically designed to investigate this question are needed with long follow-up time as the study by Jorde et al²⁵ has presented.

This is the largest meta-analysis of both prospective and cross-sectional associations conducted to date (excluding data from dietary studies and nested case-control studies) and provides precise estimates of the magnitude of the association of hypertension risk with vitamin D levels.

This present meta-analysis included studies that had recruited participants from mainly general populations, therefore reducing any effects of clinically evident preexisting disease on vitamin D levels.

In this meta-analysis, the eligible studies were carried out in many study sites and countries, which enhances generalization of our findings. Despite the general nature of these cohorts, it must be noted that our and any other study investigating 25OHD levels are only reporting on those who gave blood, not the entire cohort (average response rate = 65%, ranging from 10% to 100%).

As with any meta-analysis of published studies,^{7,8} publication bias is of concern as small studies with null results tend not to be published; however, in both prospective and

cross-sectional studies, there was no evidence of publication bias.

Sensitivity and stratification analysis conducted with these data attempted to examine the impact of known hypertension risk factors and 25OHD confounders.

Findings from our review suggest the possibility of a causal relationship, but establishing this requires robust evidence from other study designs such as clinical trials and Mendelian analyses. Mendelian analysis may shed light on whether vitamin D could be directly causal in hypertension risk. A large percentage of the variability in 25OHD levels is explained by genetic factors. Heritability of 25OHD levels has been estimated to be as high as 80%. The reason for the advantages of Mendelian randomization is that individual genotypes are assigned randomly at meiosis; thus, the effect of genetics on diseases is generally unaffected by confounding or reverse causality. Two genotypes CYP2R1 and CHCR7 have been found to function upstream of 25OHD production and affect the vitamin D metabolic system and subsequent substrate availability.¹⁰³ These genotypes affect vitamin D metabolism as proxy markers for lifelong differences in vitamin D status. Thus Vimalleswaran et al¹⁰³ in a Mendelian analysis of 108,173 individuals from 35 studies used these genetic variables to test for a causal association with blood pressure and hypertension, which showed that each 10% increase in genetically instrumented plasma 25OHD concentration was associated with a significant 8% reduced odds of hypertension (OR = 0.92 (0.87–0.97)) as well as reduced SBP ($P=0.003$) and DBP ($P=0.01$).

However, there is still a need to see what dosages of 25OHD affect hypertension risk via RCTs, and as mentioned previously, the most recent meta-analysis of vitamin D supplementation and hypertension has observed no evidence to support an effect of vitamin D supplementation on hypertension risk. Many of the RCTs are small studies on specialized subjects (often from clinics), and there are large differences in duration and doses of 25OHD.¹⁴ As many commentators have urged,^{9–12,62,63,104} there is a need for carefully designed large RCTs with long-term treatment with optimum vitamin D dosages on blood pressure. The recent and continuing Vitamin D and Omega-3 Trial (VITAL), an RCT of 20,000 US men and women >50 years, is investigating whether taking daily supplements of vitamin D3 reduces the risk of CVDs in people without prior history of these diseases, which may help disentangle and clarify this situation.¹⁰⁵

Conclusion

Despite the evidence of a consistent link between vitamin D and blood pressure, questions still remain in relation to the

causality of this relationship. Findings from this systematic literature review suggest the possibility of a causal relationship, but several RCTs have attempted to address these questions but with inconsistent results. Further studies either combining and re-analyzing existing data from available cohort studies or conducting further Mendelian analysis are needed to determine whether this represents a causal association. In addition, large RCTs are needed to determine whether vitamin supplementation or therapy may be beneficial in the prevention or the treatment of hypertension.

Disclosure

RSM receives speaker fees from Amgen Pty Ltd and AbbVie Australia. The other authors report no conflict of interest in this work.

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Supplementary material

PRISMA 2009 checklist

Section/topic	Item number	Checklist item
Title	1	Identify the report as a systematic review, meta-analysis, or both
Abstract		
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number
Introduction		
Rationale	3	Describe the rationale for the review in the context of what is already known
Objectives	4	Provide an explicit statement of questions being addressed with reference to Participants, Interventions, Comparisons and Outcomes, Studies (PICOS) design
Methods		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and if available, provide registration information including registration number
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and if applicable, included in the meta-analysis)
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means)
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified
Results		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations
Risk of bias within studies	19	Present data on risk of bias of each study and if available, any outcome-level assessment (see item 12)

(Continued)

(Continued)

Section/topic	Item number	Checklist item
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)
Discussion		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research
Funding		
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review

Abbreviation: PICOS, participants, interventions, comparisons, outcomes, and study.

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