Vitamin D and the Prevention of Hypertension and Cardiovascular Diseases: A Review of the Current Evidence

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Vitamin D plays an essential role in bone mineralization and calcium homeostasis. More recently, there has been growing evidence for a role of vitamin D in extraskeletal health, including beneficial effects in the cardiovascular system. Daylight exposure and vitamin D intake in many western populations are insufficient for maintaining an adequate vitamin D status. It is at present unclear whether vitamin D supplementation could improve cardiovascular health. This paper summarizes the evidence from observational studies and randomized–controlled trials on the relation of vitamin D with blood pressure (BP) and risk of cardiovascular diseases (CVDs). Epidemiological data suggest that optimal vitamin D status is important for CVD prevention, but results from different studies are conflicting and confounding cannot be ruled out. Randomized–controlled trials of vitamin D supplementation and BP have yielded inconsistent results, and trials that addressed the effect of vitamin D on CVDs are lacking. It is therefore premature to recommend supplemental vitamin D intake specifically for the prevention of hypertension or CVDs. Data from large, well-controlled clinical trials in this field with vitamin D supplements of sufficiently high doses are awaited to settle this issue.

Keywords: *25-hydroxyvitamin D; arterial pressure; blood pressure; calcidiol; calciferol; cardiovascular diseases; cholecalciferol; clinical trials; diet; epidemiology; hypertension; vitamin D; nutrition; prevention; prospective cohort studies; randomized–controlled trials; review; vitamin D intake; vitamin D status; vitamin D supplementation*

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Vitamin D has long been known for its central role in bone mineralization and maintenance of calcium homeostasis, *via* regulation of parathyroid hormone (PTH) secretion (**Figure 1**).[1,2] More recently, evidence has accumulated that an adequate vitamin D status is also important for many other health conditions, including cardiovascular health.[3,4] Vitamin D deficiency may predispose to hypertension *via* elevation of PTH and disturbed calcium homeostasis.[5–7] Furthermore, it has been linked to insulin resistance, systemic inflammation, and regulation of the renin–angiotensin system.[8–10] Many tissues express the vitamin D receptor,[11–13] including the myocardium, endothelium, and macrophages, and it has been proposed that vitamin D also influences cardiovascular health *via* autocrine and paracrine actions (**Figure 1**).[2] At present, however, the role of vitamin D in the prevention of hypertension and cardiovascular diseases (CVDs) in humans is not yet clear. This article aims to provide an unbiased overview of the current evidence on vitamin D intake and status in relation to blood pressure (BP), hypertension and risk of CVD. For this purpose, data are summarized from epidemiological studies and randomized–controlled trials of vitamin D supplementation.

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VITAMIN D: SOURCES AND REQUIREMENTS

Vitamin D (calciferol) is a generic name for a group of fat-soluble steroids of which the two major forms are vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Vitamin D_3 can be obtained from a limited number of animal foods (e.g. oily fish, egg yolk), fortified products (e.g. milk, margarines), and dietary supplements.[4,14,15] Vitamin D_2 (ergocalciferol) is formed in plants, fungi, and invertebrates during ultraviolet (UV) light exposure, and is also provided *via* prescribed supplements. More important to humans than dietary sources, however, is the endogenous production of vitamin D in the skin during exposure to UVB light (wavelengths of 280–315 nm).[1–4] Upon UVB exposure, 7-dehydrocholesterol in the skin is converted into precholecalciferol, after which spontaneous thermal isomerization occurs and vitamin D_3 is formed (**Figure 1**). Biologically inert vitamin D_3 then undergoes hepatic conversion into 25-hydroxyvitamin D (25(OH)D or calcidiol) and further conversion in the kidney by 1-α-hydroxylase, yielding the physiologically active 1,25-dihydroxyvitamin D (1,25(OH)2D or calcitriol).[1–4]

The amount of vitamin D produced is affected by age, time spent outdoors, degree of latitude, skin color, the amount of skin exposed, and use of sunscreen.[15,16] In the winter at

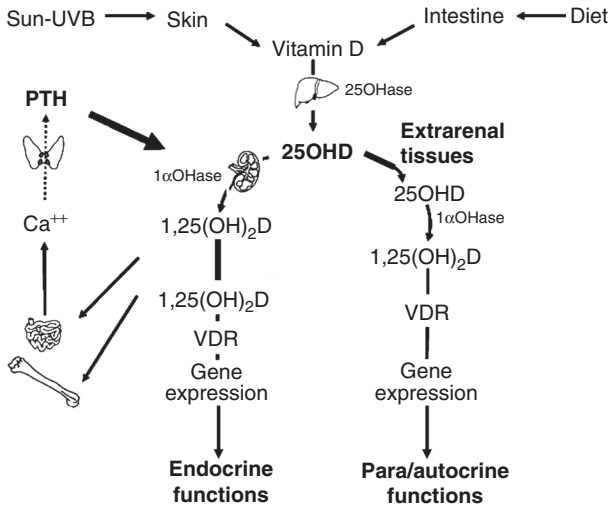


Figure 1 | Vitamin D supply and function in the human body. (Modified and reproduced from ref. 2). 1αOHase, 1α –hydroxylase; 25OHase, vitamin D (cholecalciferol) 25-hydroxylase; 25OHD, 25-hydroxy vitamin D; 1,25(OH)2D, 1,25 dihydroxy vitamin D; PTH, parathyroid hormone; UVB, ultraviolet B light; VDR, vitamin D receptor.

northern latitudes, there is insufficient UV radiation at the right wavelength for the skin to produce significant levels of vitamin D. Therefore, maintenance of a good vitamin D status depends for part of the year on vitamin D reserves in the body and on dietary intake.

Serum 25(OH)D, the transport and storage form, has a half-life of 2–3 weeks and is a good indicator of the body's vitamin D status.[1,17,18] Most experts now classify 25(OH)D concentrations as follows: ≥30 ng/ml (or 75 nmol/l), optimal; 21–29 ng/ml, insufficient; and ≤20 ng/ml, deficient.[14,15,19,20] An exploratory dose–response analysis by Cranney *et al.* based on 16 pooled studies suggested that serum 25(OH)D increases by 2.5–5 ng/ml for every 100 international units (IU) (2.5 µg) of supplemental vitamin D_3.[21] In case of deficiency, supplemental intake of 800–1,000 IU/day (20–25 µg/day) of vitamin D_3 would be needed to restore serum 25(OH)D, based on these estimates.[3] Others propose intakes as high as 2,000 IU/day to achieve serum levels of 30–40 ng/ml, which is considered to have no adverse health effects like hypercalcemia.[22]

CROSS-SECTIONAL STUDIES OF VITAMIN D AND BP OR HYPERTENSION

Already in the 1980s, reports were published that showed higher BP in individuals with low circulating 25(OH)D or vitamin D intake.[23,24] More recently, the inverse relationship between serum 25(OH)D levels and BP was confirmed in the third National Health and Nutrition Examination Survey.[25–27] In contrast, 25(OH)D levels were not associated with BP in Dutch men and women aged >65 years.[6] In the Tromsø Study in over 15,000 Norwegian men and women,[28] no association of dietary vitamin D intake with BP was found after adjustment of major confounding variables, such as body mass index, smoking, and physical activity. Vitamin D intake, however, was only 240–360 IU/day, which may have been too low to detect an association.[28] Schmitz *et al.* examined circulating vitamin D in relation to BP in 1,334 Hispanics and African Americans and found nonsignificant associations of 25(OH)D with BP after adjustment for body mass index and other potential confounders (−0.94 mm Hg systolic and −0.64 mm Hg/10 ng/ml).[29] Richart *et al.* hypothesized that an increased PTH/25(OH)D ratio promotes an inward calcium flux in target cells that are involved in glucose metabolism and arterial calcification, and that these effects are more pronounced when habitual calcium intake is low. In 542 US men and women (mean age: 50 years), they found that BP and other components of the metabolic syndrome increased significantly across quartiles of the PTH/25(OH)D ratio, whereas serum and 24-h urinary calcium decreased.[30]

In total, around 30 cross-sectional analyses mainly in Caucasians have been published of which many reported a beneficial relation between vitamin D status and BP or hypertension, although this was not consistent across all studies.[7] A disadvantage of cross-sectional analyses, however, is that no temporal relationship can be established as the exposure and outcome are measured at the same time. Therefore, one cannot conclude whether low vitamin D intake or status caused elevated BP or whether it was a consequence (e.g. less outdoor activities due to suboptimal health). Also, confounding could play a major role in observational studies. For example in the cross-sectional study by Schmitz *et al.*,[29] both vitamin D deficiency and BP were strongly associated with body mass index and the metabolic syndrome and statistical techniques could not disentangle which situation aggravated the other.[31]

PROSPECTIVE COHORT STUDIES OF VITAMIN D AND HYPERTENSION

Temporal relationships between vitamin D and risk of hypertension have been assessed in prospective epidemiological studies,[32] which are summarized in **Table 1**. Vitamin D intake was assessed by means of a food frequency questionnaire in the Nurses Health Study (NHS) I and II and the Health Professionals Follow-up Study (HPFS) in >200,000 men and women who were free of hypertension at baseline.[33] In these subjects, high vitamin D intake (roughly >500 IU/day) was not associated with the risk of hypertension during 8 years of follow-up. Blood samples were then analyzed for plasma 25(OH)D in >1,800 participants in NHS I and HPFS.[34] During 4 years of follow-up, women with a poor vitamin D status (25(OH)D <15 ng/ml) had a significant three times higher

Table 1 | Epidemiological studies of vitamin D and risk of hypertension

Author, year	Study design and subjects	Follow-up time	Exposure	Outcome	Result[a]	Confounders in the model
Vitamin D intake						
Forman *et al.*, 2005 (ref. 33)	Prospective cohort study in US men and women (NHS I & II and HPFS); Subjects: —NHS I: *n* = 77,436 women, mean age 50 years; —NHS II: *n* = 93,803 women, mean age 36 years; —HPFS: *n* = 38,074 men, mean age 53 years; mainly whites; no self-reported hypertension at baseline.	>8 years	Vitamin D intake assessed by SFFQ	Self-reported incident hypertension	—NHS I: RR = 0.98 (0.93–1.04) for >494 vs. <117 IU/day[b]; *P* trend = 0.84 —NHS II: RR = 1.13 (0.99–1.29) for >592 vs. <175 IU/day; *P* trend = 0.11 —HPFS: RR = 1.03 (0.93–1.15) for >560 vs. <139 IU/day; *P* trend = 0.48	Age, BMI, smoking, alcohol use, intake of caffeine, protein, fiber, B-vitamins, sodium (from foods), potassium, calcium, magnesium, total energy, family history of hypertension, physical activity, use of oral contraceptives (only in NHS II), and baseline BP (only in NHS II and HPFS)
Wang *et al.*, 2008 (ref. 36)	Prospective cohort study in US women (WHS); Subjects: *n* = 28,886; mean age 54 years; mainly whites; no self-reported CVD or hypertension at baseline.	10 years	Vitamin D intake assessed by SFFQ and vitamin D from supplements	Self-reported incident hypertension	RR = 0.95 (0.88–1.02) for dietary vitamin D intake >317 vs. <141 IU/day; *P* trend = 0.02 Similar association for >243 vs. <141 IU/day RR = 1.09 (0.93–1.27) for supplemental vitamin D intake >400 vs. 0 IU/day; *P* trend = 0.27	Age, race, BMI, WHS treatment arm[d], smoking, alcohol use, physical activity, multivitamin use, diabetes, menopausal status, hypercholesterolemia, and intake of total energy, sodium (from foods), fiber, saturated fat and cholesterol.
Vitamin D status						
Forman *et al.*, 2007 (ref. 34)	Prospective cohort study in US men and women (NHS and HPFS); Subjects: —NHS I: *n* = 1,198 women, mean age 65 years; —HPFS: *n* = 613 men, mean age 57 years; mainly whites; no self-reported hypertension at the time of blood sampling.	4–8 years	Plasma 25(OH)D	Self-reported incident hypertension	4-year follow-up: —NHS: RR = 2.98 (1.24–7.20) —HPFS: RR = 5.68 (1.01–32.3) for 25(OH)D <15 vs. ≥15 ng/ml[c] 8-year follow-up: —NHS: RR = 1.42 (0.79–2.56) —HPFS: RR = 3.03 (0.94–9.76) for 25(OH)D <15 vs. ≥15 ng/ml No linear trend across tertiles 25(OH)D Similar associations for ≥30 vs. <15 ng/ml	Age, BMI, race, menopausal status (only in women), and physical activity
Forman *et al.*, 2008 (ref. 35)	Nested case–control study in US women (NHS II); Subjects: *n* = 1,484; mean age 43 years; mainly whites; no self-reported hypertension at the time of blood sampling.	7 years	Plasma 25(OH)D	Self-reported incident hypertension	OR = 1.66 (1.11–2.48) for 25(OH)D <21.0 vs. ≥32.3 ng/ml; *P* trend = 0.01	Matched for age, race, month/hour of blood sampling, and day of menstrual cycle; additionally adjusted for BMI, physical activity, oral contraceptive use, family history of hypertension and serum creatinine, PTH, calcium, phosphorous, and uric acid.
Jorde *et al.*, 2010 (ref. 37)	Prospective cohort study in Norwegian men and women (Tromsø Study); *n* = 1,268, mean age 56 years, normotensive at baseline.	14 years	Serum 25(OH)D	Incident hypertension: BP ≥140/90 mm Hg measured with automatic device or use of antihypertensive drugs	RR = 1.10 (0.77–1.57) for 25(OH)D <16.6 vs. >25.1 ng/ml	Age, sex, BMI, and physical activity.

25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; HPFS, Health Professionals Follow-up Study; IU, international units; NHS, Nurses Health Study; OR, odds ratio; PTH, parathyroid hormone; RR, relative risk; SFFQ, semiquantitative food frequency questionnaire; WHS, Women's Health Study.

[a]RR and OR are presented with 95% CIs in parentheses. [b]The biological activity of 40 IU vitamin D is equal to 1 μg; [c]To convert 25(OH)D in ng/ml to nmol/l, multiply by 2.496. [d]This prospective cohort analysis was embedded in the WHS 2 × 2 factorial trial of low-dose aspirin and vitamin E supplementation for CVD and cancer prevention.

Table 2 | Epidemiological studies of vitamin D and risk of cardiovascular diseases

Author, year	Study design and subjects	Follow-up time	Exposure	Outcome	Result[a]	Confounders in the model
Bostick *et al.*, 1999 (ref. 38)	Prospective cohort study in postmenopausal US women (IWHS); Subjects: *n* = 34,486; mean age 62 years; mainly whites; no self-reported history of CHD at baseline; 36% used vitamin D supplements at baseline	8 years	Vitamin D intake assessed by SFFQ and vitamin D from supplements	CHD mortality based on death certificates.	RR = 0.99 (0.70–1.41) for dietary vitamin D intake >345 vs. <114 IU/day; *P* trend = 0.13 RR = 0.85 (0.54–1.34) for supplemental vitamin D intake >400 vs. 0 IU/day; *P* trend = 0.50	Age, total energy intake, BMI, waist/hip ratio, diabetes, smoking, alcohol use, education, marital status, postmenopausal estrogen use, and dietary intake of calcium, vitamin E, and saturated fat
Giovannucci *et al.*, 2008 (ref. 39)	Nested case–control study in US men (HPFS); Subjects: *n* = 1,354; mean age 64 y; mainly whites; no self-reported CVD at the time of blood sampling.	10 years	Plasma 25(OH)D	Self-reported incident nonfatal MI (~70% verified) or CHD mortality.	RR = 2.09 (1.24–3.54) for 25(OH)D ≤15 vs. ≥30 ng/ml; *P* trend = 0.02. Significantly elevated risk at all levels of 25(OH)D <30 ng/ml	Matched for age, month and year of blood collection, and smoking; additionally adjusted for race, region, BMI, alcohol use, family history of MI <60 years, history of diabetes, history of hypertension, fasting status, multivitamin use, n-3 fatty acid intake, LDL- and HDL-cholesterol, triglycerides, and physical activity.
Wang *et al.*, 2008 (ref. 40)	Prospective cohort study in US men and women (Framingham Offspring Study); Subjects: *n* = 1,739; mean age 59 years; all whites; no self-reported CVD at baseline.	5 years	Serum 25(OH)D, standardized for season	Incident CVD (including MI, angina, stroke, TIA, heart failure, claudication, coronary insufficiency), based on hospital records.	RR = 1.81 (1.03–3.18) for 25(OH)D <10 vs. ≥15 ng/ml[b]; *P* trend = 0.01. Significantly elevated risk at all levels of 25(OH)D <15 ng/ml Stronger association in hypertensives (RR = 2.43) than normotensives (RR = 1.08)	Age, sex, BMI, smoking, systolic BP, antihypertensive treatment, diabetes, serum creatinine, total/HDL cholesterol ratio. Similar results after additional adjustment for physical activity, vitamin D supplementation, education, and season.
Dobnig *et al.*, 2008 (ref. 41)	Prospective cohort study in German men and women (LURIC study) who were routinely referred to coronary angiography; Subjects: *n* = 3,258; mean age 62 years; all whites; two-thirds had significant CHD (≥ 50% stenosis).	8 years	Serum 25(OH)D	CVD mortality based on death certificates.	RR = 2.22 (1.57–3.13) for low 25(OH)D (median: 7.6 ng/ml) vs. high 25(OH)D (median: 28.4 ng/ml).	Age, sex, BMI, physical activity, smoking, diabetes, serum albumin, cystatin C, triglycerides, N-terminal pro-BNP, systolic and diastolic BP, LDL- and HDL-cholesterol, and use of statins, aspirin, β-blockers, bronchodilators, and ACE-inhibitors

Table 2 | Continued on next page

Table 2 | Continued

Author, year	Study design and subjects	Follow-up time	Exposure	Outcome	Result[a]	Confounders in the model
Pilz *et al.*, 2008 (ref. 42)	Prospective cohort study in German men and women (LURIC study) who were routinely referred to coronary angiography; Subjects: *n* = 3,299; mean age 62 years; all whites; two-thirds had significant CHD (≥50% stenosis).	8 years	Serum 25(OH)D	Mortality from heart failure and sudden cardiac death, based on death certificates.	Mortality from heart failure: RR = 2.63 (1.07–6.44) for 25(OH)D <10 vs. ≥30 ng/ml[b] Sudden cardiac death: RR = 5.35 (2.09–13.67) for 25(OH)D <10 vs. ≥30 ng/ml. Significantly elevated risk at all levels of 25(OH)D <30 ng/ml Strongest associations in subjects without CHD	Age, sex, month of blood sampling, smoking, BMI, smoking, physical activity, diabetes, arterial hypertension, glomerular filtration rate, LDL- and HDL-cholesterol, triglycerides, C-reactive protein, CHD, and use of diuretics, β-blockers, and ACE-inhibitors. Additional adjustment for serum calcium and PTH yielded similar results.
Pilz *et al.*, 2008 (ref. 43)	Prospective cohort study in German men and women (LURIC study) who were routinely referred to coronary angiography; Subjects: *n* = 3,299; mean age 62 years; all whites; two-thirds had significant CHD (≥ 50% stenosis).	8 years	Serum 25(OH)D	Fatal ischemic and hemorrhagic stroke, based on death certificates.	OR = 0.67 (0.47–0.94) per *Z* value increase in 25(OH)D; *P* trend = 0.03.	Age, sex, month of blood sampling, smoking, BMI, smoking, physical activity, diabetes, arterial hypertension, glomerular filtration rate, LDL- and HDL-cholesterol, triglycerides, C-reactive protein, CHD, and use of diuretics, β-blockers, and ACE-inhibitors. Additional adjustment for serum calcium and PTH yielded similar results.
Bolland *et al.*, 2010 (ref. 44)	Prospective cohort study embedded in a calcium supplementation trial in healthy community-dwelling US women; Subjects: *n* = 1,471; mean age 74 years	5 years	Seasonally adjusted serum 25(OH)D	Fatal CVD and self-reported nonfatal CVD events verified in medical records	RR for 25(OH)D <20 vs. ≥20 ng/ml: MI: 1.2 (0.7–2.2) Stroke: 1.4 (0.8–2.5) MI, stroke or sudden death: 1.2 (0.8–1.8) TIA: 1.1 (0.6–2.0) Congestive heart failure: 1.0 (0.4–2.4)	Treatment allocation (calcium vs. placebo), age, BMI, smoking, systolic BP, history of CHD, stroke or TIA, dyslipidemia, and diabetes.

25(OH)D, 25-hydroxyvitamin D; ACE, angiotensin-converting enzyme; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular diseases; HDL, high-density lipoprotein; HPFS, Health Professionals Follow-up Study; IU, international units; IWHS, Iowa Women's Health Study; LDL, low-density lipoprotein; LURIC, Ludwigshafen Risk and Cardiovascular Health; MI, myocardial infarction; OR, odds ratio; PTH, parathyroid hormone; RR, relative risk; SFFQ, semiquantitative food frequency questionnaire; TIA, transient ischemic attack.
[a]RR and OR are presented with 95% confidence intervals in parentheses. [b]To convert 25(OH)D in ng/ml to nmol/l, multiply by 2.496.

risk of incident hypertension compared to women with levels ≥15 ng/ml. In men with low 25(OH)D, the risk was even more strongly increased. It should be noted, however, that only 33 subjects were deficient in 25(OH)D, which creates large uncertainty about the observed associations. Moreover, after 8 years of follow-up, relative risks (RRs) for incident hypertension were attenuated and no longer statistically significant (**Table 1**).

Table 3 | Long-term randomized, double-blind trials of vitamin D_3 supplementation, and BP[a]

Author, year	Subjects	Mean age	Duration	Intervention	Outcome[b]
Schleithoff *et al.*, 2006 (ref. 49)	123 German patients (83% male) with congestive heart failure	55 years	9 months	Vitamin D_3 (2,000 IU/day) or placebo; both groups received additional calcium (500 mg/day)	Systolic BP: + 1 mm Hg ($P = 0.87$) Diastolic BP: −1 mm Hg ($P = 0.38$)
Margolis *et al.*, 2008 (ref. 50)	36,282 postmenopausal US women (WHI); 9% blacks; >25% used cardiovascular drugs	62 years	7 years	Vitamin D_3 (400 IU/day) plus calcium (1,000 mg/day) or placebo	Systolic BP: +0.22 mm Hg (95% CI: −0.05 to 0.49; $P = 0.11$) Diastolic BP: + 0.11 mm Hg (−0.04 to 0.27; $P = 0.14$) RR for incident hypertension: 1.01 (0.96–1.06; $P = 0.69$)
Zittermann *et al.*, 2009 (ref. 51)	165 overweight German subjects (33% male)	48 years	1 years	Vitamin D_3 (3,332 IU/day) or placebo; both groups participated in a weight reduction program	Systolic BP: −1 mm Hg ($P = 0.35$) Diastolic BP: 0 mm Hg ($P = 0.53$)
Jorde and Figenschau, 2009 (ref. 52)	32 Norwegian diabetic patients (50% male) on antidiabetic drug treatment	56 years	6 months	Vitamin D_3 (5,714 IU/day) or placebo	Systolic BP: −4.9 mm Hg ($P = 0.15$) Diastolic BP: −1.6 mm Hg ($P = 0.25$)
Jorde *et al.*, 2010 (ref. 53)	330 Norwegian overweight and obese subjects (38% male)	49 years	1 years	Vitamin D_3 (2,857 IU/day or 5,714 IU/day) or placebo; all groups received additional calcium (500 mg/day)	Dose 2,857 IU/day: Systolic BP: +4.6 mm Hg ($P < 0.05$) Diastolic BP: +0.8 mm Hg (NS)
					Dose 5,714 IU/day: Systolic BP: +3.3 mm Hg (NS) Diastolic BP: +0.8 mm Hg (NS)

BP, blood pressure; CI, confidence interval; IU, international units; NS, not statistically significant ($P > 0.05$); RR, relative risk; WHI, Women's Health Initiative.
[a]The table includes trials with an intervention period of ≥6 months. [b]Net effect of vitamin D_3 supplementation compared to placebo.

Forman *et al.* subsequently performed a nested case–control study in NHS II and assessed plasma 25(OH)D in women who developed hypertension during follow-up, and in a matched sample of normotensive controls.[35] Plasma 25(OH)D was inversely associated with risk of hypertension, with an odds ratio of 1.66 (95% CI, 1.11–2.48) for levels <21 ng/ml compared to >32 ng/ml. No dose-response was observed, and the risk of hypertension was already increased for levels 21–32 ng/ml. In a prospective cohort analysis by Wang *et al.* of almost 30,000 participants in the Women's Health Study,[36] the risk of hypertension was ~5% lower for higher dietary vitamin D intakes (>243 IU/day), whereas it was not related to >400 IU/day intake from supplements (**Table 1**).

In the Tromsø study, serum 25(OH)D assessed in 1994 was examined in relation to change in BP and incident hypertension during 14 years of follow-up.[37] There was no significant difference in risk of hypertension (i.e. BP >140/90 mm Hg and/or initiation of antihypertensive treatment) when comparing extreme quartiles of serum 25(OH)D in 1,268 subjects who were normotensive at baseline. In 1,605 subjects not treated with antihypertensive drugs during follow-up, systolic blood pressure increased by 6.4 mm Hg and diastolic blood pressure by 1.1 mm Hg in subjects with serum 25(OH)D >25.1 ng/ml compared to those with levels <16.6 ng/ml, although this was not statistically significant. The risk of hypertension did not differ between these groups (**Table 1**).

PROSPECTIVE COHORT STUDIES OF VITAMIN D AND CVD

Bostick *et al.* examined dietary vitamin D intake, assessed by questionnaire, and use of vitamin D supplements in relation to coronary heart disease (CHD) mortality in Iowa women who were followed for 8 years.[38] No association was found with dietary intake of vitamin D with RR close to 1 (**Table 2**). For supplemental vitamin D intake, inverse but nonsignificant associations were found (RR = 0.85 for >400 IU/day and RR = 0.86 for 1–400 IU/day, compared to nonuse; $P = 0.50$).

In more recent years, there has been increasing interest in the relation between vitamin D status and cardiovascular events (**Table 2**). Giovannucci *et al.* performed a nested case–control study in 1,354 US Health Professionals who were followed for 10 years, and examined 25(OH)D in baseline plasma samples in relation to incident nonfatal myocardial infarction.[39] The risk of myocardial infarction was significantly doubled in men with initial 25(OH)D levels ≤15 ng/ml compared to men with levels ≥30 ng/ml, after adjustment for

relevant confounders. For levels between 15 and 30 ng/ml, the risk was increased by ~50%.

Wang *et al.* examined 1,739 men and women from the Framingham Offspring Study and found a 60–80% higher risk for incident CVD in subjects with 25(OH)D levels below 15 ng/ml compared to subjects with higher levels.[40] After stratification for prevalent hypertension at baseline, this elevated risk appeared to be only significant for hypertensives (RR = 2.43 (95% CI, 1.23–4.80) for 25(OH)D <10 vs. ≥15 ng/ml).

In the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, over 3,000 German men and women who had been referred to coronary angiography were followed for 7.7 years for CVD mortality.[41–43] In this study, the risk of fatal CVD was doubled for subjects with low baseline 25(OH)D levels, i.e. RR of 2.22 (95% CI, 1.57–3.13) for bottom quartile (median, 7.6 ng/ml) and 1.82 (1.29–2.58) for second quartile (median, 13.3 ng/ml) compared to top quartiles (median, 28.4 ng/ml).[41] Further analyses showed that 25(OH)D levels <10 ng/ml were related to heart failure mortality, and levels <30 ng/ml to sudden cardiac death.[42] For fatal stroke, no thresholds for vitamin D status were examined but a significantly lower risk was reported per standard unit increase in 25(OH)D.[43]

Finally, Bolland *et al.* examined the risk of cardiovascular events in relation to vitamin D status in US women.[44] This observational analysis was conducted within the framework of a 5-year trial of calcium supplementation and fracture incidence in which baseline 25(OH)D was assessed in 1,471 participating women. The risk of myocardial infarction, stroke, or other cardiovascular events did not differ between women with seasonally adjusted serum 25(OH)D levels <20 ng/ml and ≥20 ng/ml. It should be noted, however, that part of the women were treated with vitamin D supplements at some time during follow-up (30% in the low 25(OH)D group and 20% in the high 25(OH)D group).

OBSERVATIONAL DATA: A NEED FOR CAUTION

It should be noted that associations of vitamin D with BP in cross-sectional and prospective cohort studies need not be causal, due to selection bias, information bias, or confounding. Vitamin D intake and status in free-living populations are strongly related to other dietary and lifestyle factors. For dietary intake data, there is a need to properly adjust for other food components that may influence the risk of CVD, e.g. n-3 fatty acids from fish that are ingested along with vitamin D. Furthermore, vitamin D supplement users could be more highly educated and health conscious. Despite extensive adjustment for varying potential confounders in multivariable models (**Tables 1** and **2**), residual confounding resulting from inaccurate measurement of these factors, unknown confounders, or factors not included in the model cannot be ruled out.

Levels of 25(OH)D in the blood are mainly influenced by UVB exposure, which is turn is strongly determined by being outdoors. In epidemiological studies, it is not possible to disentangle the cardiovascular benefits from outdoor physical activities from benefits related to UVB exposure, which also hampers statistical adjustment for confounding by physical activity. Furthermore, being outdoors and daylight exposure are also determined by behavioral and socioeconomic factors (e.g. type of job). In addition, daylight influences circadian rhythm, sleeping patterns, and the regulation of hormones like serotonin and melatonin, which may be important in BP regulation and possibly also exert other effects in the cardiovascular system.[45–47] Causality between 25(OH)D and BP or CVD can therefore not be established on basis of observational data.

RANDOMIZED–CONTROLLED TRIALS OF VITAMIN D AND BP

Problems of confounding that exist in observational epidemiological studies can be overcome by well-conducted randomized–controlled trials. A disadvantage of trials, however, is that only specific doses of vitamin D (mostly *via* supplements) can be studied and that optimal compliance to treatment is hard to achieve. Trials are of relatively short duration, and if health effects only occur after long-term (or maybe even life-long) exposure, this will likely be missed in randomized–controlled trials. Furthermore, long-term well-controlled trials of endogenously produced 25(OH)D after UVB exposure or vitamin D in its natural food matrix are not feasible.

In a recent meta-analysis, Pittas *et al.* pooled 10 trials of vitamin D supplementation and BP and found no significant effect on systolic BP (weighted mean difference: −1.9 mm Hg, 95% CI −4.2 to 0.4) or diastolic BP (−0.1 mm Hg, −0.7 to 0.5).[32] Doses of vitamin D varied largely from 400 to >5,000 IU/day. Higher doses of vitamin D had a larger effect on diastolic BP (−1.5 vs. +0.1 mm Hg for ≥1,000 vs. <1,000 IU/day, $P = 0.04$), but not on systolic BP. BP effects were similar for vitamin D alone and for vitamin D in combination with calcium. In most trials, vitamin D_3 (cholecalciferol) was provided. In a trial by Krause *et al.*, however, the effect of endogenously produced vitamin D on BP was examined.[48] A total of 18 German subjects were randomized to whole-body UVA (wavelengths of 315–400 nm) or UVB radiation (3 times/week) for 6 weeks at the end of the winter season. Plasma 25(OH)D increased by 162% and PTH decreased by 15% during UVB therapy, and UVB had a significant beneficial effect on systolic and diastolic BP (−6 and −8 mm Hg, respectively, $P < 0.001$).

Table 3 provides an overview of trials with a duration of at least 6 months, 4 of which[49–52] had also been included in the meta-analysis by Pittas *et al.*[32] Only in a 6-month trial by Jorde and Figenschau in diabetic patients,[52] there was some evidence for a BP-lowering effect of a high dose of vitamin D_3 (two capsules of 20,000 IU/week), but this finding was not statisti-

cally significant, which may be due to the small sample size. A recently published 1-year trial by the same group showed an elevation rather than decrease in BP with relatively high doses of vitamin D in overweight and obese subjects.[53] BP was assessed as an ancillary end point in the Women's Health Initiative (WHI) study in which 36,282 postmenopausal US women were randomly allocated to 400 IU of vitamin D_3 plus 1 g of calcium per day, or placebo.[50] No significant effects of this relatively low dose of vitamin D on BP were found after 7 years of follow-up.

RANDOMIZED–CONTROLLED TRIALS OF VITAMIN D AND CVD

Studies on vitamin D and calcium supplementation in the prevention of cardiovascular events have recently been reviewed by Wang *et al.*[54] No trials primarily addressed the effect of vitamin D on CVD. Two randomized, placebo-controlled trials of vitamin D supplementation and fractures or falls also provided data on CVD events during follow-up. Trivedi *et al.* randomly assigned 2,686 UK men and women aged 65–85 years to a high dose of oral vitamin D (100,000 IU) or placebo every 4 months, for a period of 5 years, and found that risks of total CVD, fatal CVD, and nonfatal CHD were nonsignificantly decreased in the vitamin D group by 10, 16, and 6%, respectively.[55] In a small trial in 302 Australian women aged 70–90 years with serum 25(OH)D levels ≤24 ng/ml, the rate of CHD after 1 year of follow-up was lower in subjects who received 1,000 IU/day of supplemental vitamin D, added to calcium supplements, compared to subjects who received calcium supplements only (1.3 and 2.0%, respectively).[56] However, there was no difference in the occurrence of stroke (2.0% in both groups).

In the aforementioned WHI study, the effect of calcium and vitamin D treatment on incident CHD, stroke, and other CVD was assessed.[57] After vitamin D supplementation (400 IU/day) compared to placebo, RRs were 1.04 (95% CI, 0.92–1.18) for incident CHD and 0.95 (0.82–1.10) for incident stroke. Also for other CVD outcomes no association was found.

Sanders *et al.* randomly assigned 2,256 community-dwelling US women aged ≥70 years to study to a single annual dose of 500,000 IU of oral vitamin D_3 each autumn to winter, or placebo, for 3–5 years.[58] The primary outcome was risk of fractures and falls. Incident CVD was monitored as an adverse event, which did not differ significantly between the vitamin D and placebo groups (1.5% vs. 1.2%).

CONCLUSION

Prospective epidemiological studies provide little evidence for a link between dietary intake of vitamin D and BP or CVD.[33,36,38] Apart from no causal relationship being present, this could be due to residual confounding or the relatively narrow range of vitamin D intake within populations. Alternatively, it could indicate that vitamin D intake *via* foods, which is generally below 400 IU/day, is too low to exert a biologically meaningful effect. In a number of short-term trials, BP was reduced by relatively large doses of vitamin D,[32] but long-term trials have not confirmed this antihypertensive effect.[49–51,53]

Observational studies in US populations support the hypothesis that a suboptimal vitamin D status (25(OH)D below 15–20 ng/ml) increases the risk of hypertension.[34,35] It is too early, however, to draw conclusions because the number of prospective studies of vitamin D status and BP is limited and negative findings have also been reported.[37] Concerning CVD, however, there is a larger number observational studies showing a significant relation of low 25(OH)D with an increased risk of fatal and nonfatal cardiovascular events.[39–43]

Because observational data are prone to bias and confounding, evidence for a causal relationship should come from well-controlled trials. However, one should be aware that these may not capture the right time window of exposure for answering questions on vitamin D status and health. Furthermore, it is possible that endogenously produced vitamin D *via* UVB irradiation acts differently on health than vitamin D supplements. Repeating the trial by Krause *et al.*[48] of UVB vs. UVA exposure in a larger number of subjects with a low vitamin D status is therefore warranted. Also, there is a need for trials with higher doses of supplemental vitamin D in different populations (especially blacks) to establish its potential for the prevention of hypertension and CVD.

More clarity will hopefully come from the recently initiated Vitamin D and Omega-3 Trial (VITAL), a 2 × 2 factorial study of vitamin D and fish oil that is funded by the National Institutes of Health (www.vitalstudy.org; accessed on 1 May 2010). In this study, 20,000 older US men and women will be randomized to daily dietary supplements of vitamin D (about 2,000 IU) or placebo and followed for the occurrence of CVD and other diseases.

At present, it is premature to recommend vitamin D supplements for the prevention of hypertension or CVD. However, frequent outdoor physical activity can be advised to all to improve vitamin D status and cardiovascular health.

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