

Calcium, Vitamin D and Cardiovascular Disease

Idris Guessous^{a, b} Murielle Bochud^b Olivier Bonny^c Michel Burnier^c

^aUnit of Population Epidemiology, Division of Primary Care Medicine, Department of Community Medicine, Primary Care and Emergency Medicine, Geneva University Hospitals, Geneva, ^bCommunity Prevention Unit, University Institute of Social and Preventive Medicine (IUMSP), and ^cDepartment of Medicine, Service of Nephrology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

Key Words

Calcium · Cardiovascular disease · Vitamin D

Abstract

The relationship between calcium and cardiovascular diseases (CVD) has been explored for a long time. Studies exploring the effect of calcium intake or calcium supplementation on cardiovascular risk suggest that systolic blood pressure increases under low calcium intake and decreases with calcium supplementation. A lower calcium intake has been associated with an increased risk of stroke. However, the impact of calcium supplementation on stroke risk remains unclear. Calcium supplementation may increase the risk of myocardial infarction. The relationship between vitamin D and CVD has been explored more recently. Negative correlations between vitamin D levels and the risk of hypertension, myocardial infarction, and stroke have been reported in several observational studies. The effect of vitamin D supplementation on blood pressure is still unclear and no effect of vitamin D supplementation on coronary heart disease or stroke has been clearly demonstrated. There is a lack of randomized clinical trials primarily addressing the effect of these parameters on CVD. Therefore, the real impact of calcium and vitamin D on cardiovascular outcomes remains to be documented by appropriate experimental data.

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Introduction

Molecular, animal and human studies have established that both calcium and vitamin D are associated with cardiovascular diseases (CVD). Due to the high prevalence of calcium supplementation and to the high prevalence of vitamin D deficiency in the general population, determination of the cardiovascular benefits and risks associated with calcium and vitamin D plasma levels or with calcium and vitamin D supplementation is a public health concern.

In this review, the actual evidence on the role of calcium and vitamin D on CVD are reviewed. We have limited the discussion on the epidemiological studies associating calcium and vitamin D with blood pressure (BP), coronary heart disease (CHD) and stroke. Evidence from randomized controlled trials of supplements is discussed first, followed by observational data on dietary intake, and serum levels, and finally, possible action mechanisms that might explain these findings are presented.

Calcium and Cardiovascular Disease

Calcium and Blood Pressure

Calcium Supplementation and Blood Pressure

More than 60 trials have evaluated the effect of calcium supplementation on BP. These trials have been summarized in six systematic reviews (table 1) [1–6] which have been recently reviewed [7].

Table 1. Reported dietary calcium intake, or calcium supplements, and BP in prospective studies

Association	Reference (first author)	Method	Country and participants	Result ¹
Calcium supplementation and change in BP	Cappuccio, 1989 [3]	Systematic review of RCTs	NT+HT	SBP (supine): -0.13 (-0.46, +0.19) DBP (supine): +0.03 (-0.17, +0.22)
	Bucher, 1996 [2]	Systematic review of RCTs	NT	SBP: -0.27 (-1.80, +1.27) DBP: -0.33 (-1.56, +0.90)
	Allender, 1996 [1]	Systematic review of RCTs	NT	SBP: -0.53 (-1.56, +0.49) DBP: -0.28 (-0.99, +0.42)
	Griffith, 1999 [5]	Systematic review of RCTs	NT+HT	SBP: -1.44 (-2.20, -0.68) DBP: -0.84 (-1.44, -0.24)
	Van Mierlo, 2006 [6]	Systematic review of RCTs	NT+HT	SBP: -1.86 (-2.91, -0.81) DBP: -0.99 (-1.61, -0.37)
	Dickinson, 2006 [4]	Systematic review of RCTs	HT	SBP: -2.53 (-4.45, -0.60) DBP: -0.81 (-2.07, +0.44)
Calcium intake and incidence of hypertension (observational studies)	Ford, 1991 [12]	Cohort study (not available)	USA, men + women, ≥25 years	No association
	Ascherio, 1992 [10]	Cohort study, FFQ	USA, men + women, 40–75 years	No association
	Ascherio, 1996 [14]	Cohort study, FFQ	USA, women, 30–55 years	No association
	Dwyer, 1996 [11]	Cohort study, 24 h recall	USA, men + women, <40 years	Lower calcium intake → increased risk of HT
	Alonso, 2005 [9]	Cohort study, FFQ	Spain, men + women, 20–90 years	No association
	Wang, 2008 [13]	Cohort study, FFQ	USA, women, >45 years	Lower calcium intake → increased risk of HT

NT = Normotensive people; HT = hypertensive people; FFQ = food frequency questionnaire; RCT = randomized controlled trial; SBP = systolic blood pressure; DBP = diastolic blood pressure.

The systematic reviews that reported on study heterogeneity found significant heterogeneity. For calcium supplementation, only results from systematic reviews are reported.

¹ For systematic reviews of RCTs, results are expressed as mean changes (95% CI) between intervention group and control group.

Systematic reviews of trials in which analyses were performed on normotensive subjects found no effect of calcium supplementation on BP [1, 2]. On the other hand, three [1, 2, 4] out of the four systematic reviews [1–4] that analyzed the effect of calcium supplementation on BP in hypertensive patients reported significant effects. Calcium supplementation decreased systolic BP (SBP) by 2–4 mm Hg compared to placebo, but generally had no effect on diastolic BP (DBP). Only one systematic review found an effect of calcium supplementation on DBP (-1.5 mm Hg) [2].

All systematic reviews that combined subjects with and without hypertension and analyzed the effect of calcium supplementation on BP [1–3, 5, 6] reported an effect of calcium supplementation on SBP (-0.9 to -1.9 mm Hg), and two out of five found an effect on DBP as well (-0.8 to -1.0 mm Hg) [5, 6].

These systematic reviews have shown that (i) calcium supplementation (1,000–1,500 mg/day) can reduce SBP, particularly among hypertensive subjects, (ii) the effect of calcium supplementation on DBP is inconsistent, and (iii) there is no evidence of a beneficial effect of calcium supplementation among normotensive subjects.

Limitations of these systematic reviews are those of the original trials. Trials were heterogeneous with respect to calcium dose (range 400–2,000 mg/day), eligibility criteria (such as age, normo/hypertensive status), and supplementation duration (range 1–10 months) [7].

Calcium Intake and Blood Pressure

International epidemiological comparisons as well as studies of migrants suggested that diet, and notably dairy product consumption, could determine BP [8]. Because calcium is one of the major nutrients of dairy products, it has been presented as a possible determinant of BP variability.

Five cohorts evaluated the association between calcium intake and the incidence of hypertension (table 1) [9–14]. Calcium intake was determined by either food frequency questionnaire (FFQ) [9, 10, 13, 14], or 24 h recall [11]. All studies included normotensive participants at baseline. Chung et al. [7] recently summarized the evidence emerging from these studies. There was no association between calcium intake and the risk of hypertension.

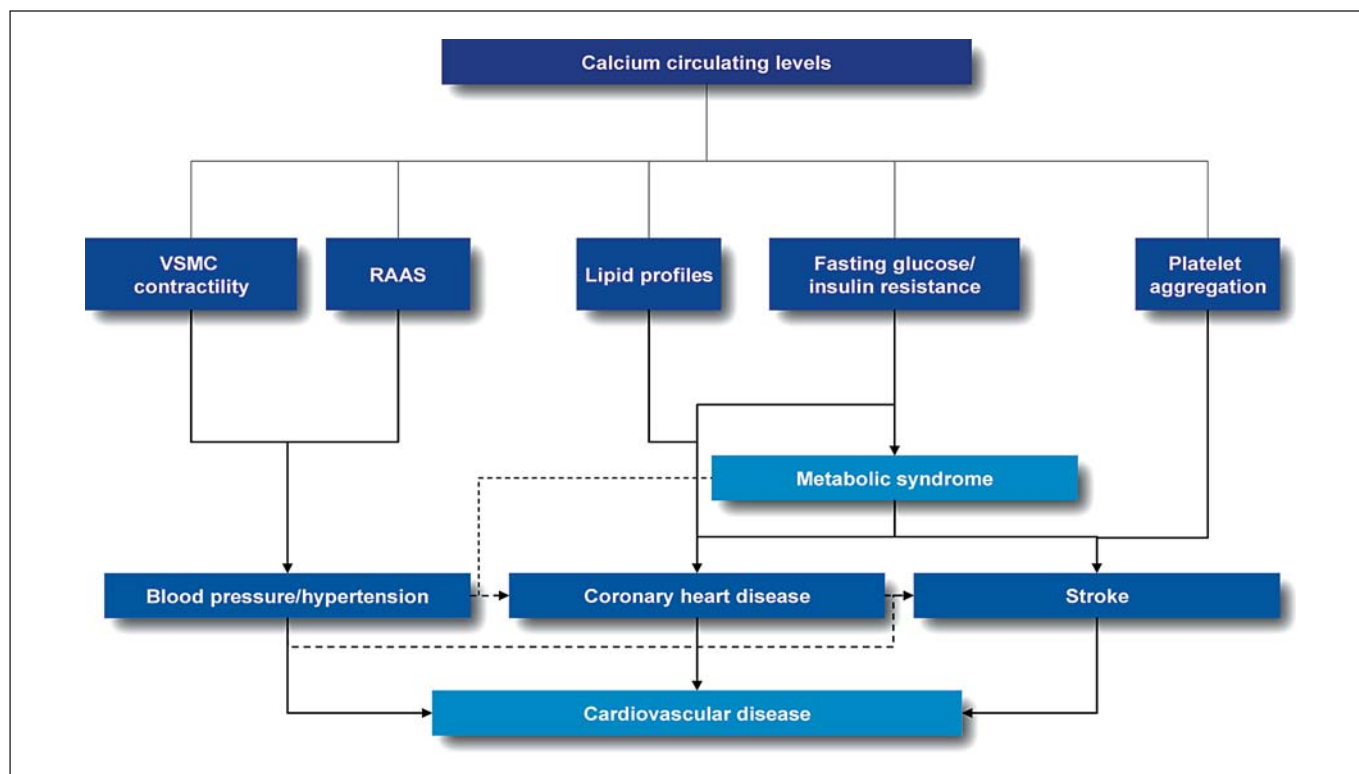


Fig. 1. Main hypothetical mechanism of actions of calcium circulating levels on cardiovascular disease (mechanisms related to parathormone and vitamin D are not displayed for the purpose of clarity, refer to the text for details). VSMC = Vascular smooth muscle cells; RAAS = renin-angiotensin-aldosterone system.

Two of the cohort studies restricted their analyses to <40-year-olds [11] and <50-year-olds [10]. Both studies found that lower calcium intake was associated with an increased risk of hypertension compared to higher calcium intake (relative risk (RR) 1.52 for <500 vs. >1,100 mg/day calcium intake, $p < 0.05$ [10]; RR 1.33 per 1-g/day increase of calcium intake, $p < 0.04$ [11]). These associations were not found in older adults. One study found higher rates of hypertension (RR 1.12, 95% CI 1.05–1.20) among women consuming lower calcium per day (<558 mg/day) compared to those with higher consumption (>679 mg/day) [13]. Two other studies found no such associations in women [12, 14].

Overall, (i) the association of calcium intake with the risk of hypertension seems to be limited to young subjects and (ii) a gender modification effect is not consistently observed.

Limitations of these studies include reliance on self-reported hypertension (BP was measured by investigators in only one study [13]), as well as limitations associated with the use of FFQ or 24 h recall [15].

Calcium Serum Levels and Blood Pressure

In 1976, Bulpitt et al. [16] first reported an association between serum calcium levels and SBP in a general population. Since then, several studies have explored this relation and results are conflicting [17–27]. Overall, it appears that association, if any, of serum calcium levels with BP is limited to SBP. It also seems that the association is absent in subjects with normal renin activity [19]. Few of these studies measured ionized calcium, or used values corrected for blood pH and/or albumin levels, or adjusted for potential confounders such as PTH and vitamin D (see section Vitamin D and Blood Pressure).

Possible Action Mechanisms (fig. 1)

The relationship of calcium metabolism with BP is supported by biological observations [28]. Calcium controls vascular smooth muscle cell (VSMC) contractility and thus modulates peripheral vascular resistances [29–32]. Calcium ATPase (PMCA1 or ATP2B1), sodium/calcium exchanger and TRPC6, three proteins related to calcium transport, have been involved in the control of

Table 2. Reported dietary calcium intake and CHD in prospective studies

Association	Reference (first author)	Method	Country and participants	Result ¹
Ca supplementation and CHD (RCTs) ²	Prince, 2006 [42]	RCT, calcium carbonate 600 mg twice daily or placebo, 5 years	Australia, women >70 years	Risk ratio: 1.12 (0.77–11.64)
	Hsia, 2007 [41]	RCT, calcium carbonate 500 mg with vitamin D 200 IU twice daily or placebo, 7 years	USA, women, 50–79 years	Risk ratio: 1.08 (0.99–1.19)
	Bolland, 2008 [39]	RCT, 1,000 mg of citrate calcium or placebo daily, 5 years	New Zealand, postmenopausal women, ≥55 years	Risk ratio: 2.12 (1.01–14.47)
	Bolland, 2010 [43]	Systematic review of RCTs	Includes unpublished data provided by authors	Risk ratio: 1.31 (1.02–1.67)
Calcium intake and incidence of CHD (observational studies)	Van der Vijver, 1992 [49]	Cohort study, FFQ	The Netherlands, men + women 40–65 years	No association
	Bostick, 1999 [45]	Cohort study, FFQ	USA, women, 55–69 years	Higher calcium intake → lower ischemic heart disease mortality
	Al-Delaimy, 2003 [44]	Cohort study, FFQ	USA, men, 40–75 years	No association
	Marniemi, 2005 [46]	Cohort study, dietary history interviews	Finland, men + women, 65–99 years	No association
	Umesawa, 2006 [47]	Cohort study, FFQ	Japan, men, 40–79 years	No association
	Umesawa, 2008 [48]	Cohort study, FFQ	Japan, men + women, 40–59 years	No association

RCT = Randomized controlled trial; FFQ = food frequency questionnaire; CHD = coronary heart disease.

¹ For RCTs, results are expressed as risk ratio (95% CI) of CHD comparing the intervention group to the control group.

² None of these studies have been primarily designed to assess the relationship between calcium supplementation and CHD.

VSMC contractility [33, 34]. PMCA1 has been associated with hypertension in one genome-wide association study [35]. Extracellular ionized calcium inhibits renin secretion by interacting with the calcium-sensing receptor expressed in the juxtaglomerulus apparatus [36–38].

Calcium and Coronary Heart Disease

Calcium Supplementation and Coronary Heart Disease

No randomized control trial (RCT) has yet been primarily designed to assess the effect of calcium supplementation on CHD. Four trials [39–42] are secondary analyses of RCTs primarily designed to assess the effect of calcium supplementation on bone density and fracture in postmenopausal women (table 2).

The most recent RCT of calcium supplementation reported an increased risk of myocardial infarction (MI). Compared to the placebo group, postmenopausal women randomized to receive 1,000 mg/day of calcium for 5 years had a twofold increased risk of MI (RR 2.12, 95% CI 1.01–4.47) [39].

While this result contrasts with the findings reported in two previously published RCTs (Women Health Initiative [41] and Prince et al. [42]), increased risks, though not significant, were actually also reported in these two

RCTs (hazard ratio (HR) 1.08, 95% CI 0.99–1.19 [41] and HR 1.12, 95% CI 0.77–1.64 [42]). A recent meta-analysis of trials reported an increased risk of MI associated with calcium supplements (without vitamin D supplement) (HR 1.31, 95% CI 1.02–1.67) [43].

Taken together, no definitive conclusion can be drawn from these secondary analyses, but at least two questions can be raised: (1) Did the supplementation of vitamin D together with calcium in RCTs blunt a significant increase in CHD events associated with calcium supplementation? A small increase in CHD events has been reported in the group supplemented with calcium *and* vitamin D versus the group receiving only placebo (and no calcium) in the Women Health Initiative study. (2) By which mechanism, if any, would calcium supplementation increase the risk of CHD? In the two RCTs that assessed the impact of supplementations on the lipid profile, calcium alone and calcium plus vitamin D were associated with beneficial trends in levels of HDL cholesterol and LDL cholesterol; unfavorable changes in lipids are unlikely to explain the increased risk. The effects of supplementation on BP (SBP and DBP) might have played a role. After a 5-year follow-up, Bolland et al. [43] reported no difference in SBP or DBP between groups, while Hsia et al. [41] reported, after a 2-year fol-

low-up, a significant increase in both SBP (+0.4%) and DBP (+0.4%) in the calcium/vitamin D group compared to the placebo group. Whether such small changes in BP may have contributed to the increased risk is questionable. Therefore, these questions remain to be answered.

Notwithstanding the limitations of both observational and experimental studies, one could reasonably conclude that there is no strong evidence of a benefit of calcium supplementation with respect to CHD. Evidence of increased risk of MI associated with calcium supplementation has recently been reported [43] and deserves to be further investigated.

Calcium Intake and Coronary Heart Disease

The association between calcium intake and CHD (fatal and nonfatal MI) has been reported in six observational studies (table 2) [44–49].

With the exception of the Iowa Women Health Study, no observational studies reported an association between calcium intake and CHD. In the Iowa Women Health Study, the investigators reported a higher risk of CHD death (RR 1.58, 95% CI 1.02–2.50) in white women aged 55–69 years with low calcium intake (<696 mg/day) compared to those with high calcium intake (>1,425 mg/day) [45].

Calcium Levels and Coronary Heart Disease

Elevated serum calcium levels have been associated with increased risk of CVD. In 1987, Palmer et al. [50] reported a lower survival rate among persons with hypercalcemia (defined as an albumin-corrected serum calcium >2.60 mmol/l) compared to normocalcemic age- and sex-matched controls. In a large population-based study, increased serum calcium was associated with increased mortality in men aged less than 50 years, which was mainly attributable to CVD [51]. In another study, serum calcium was associated with the incidence of acute MI in Swedish men (HR 2.33, 95% CI 1.21–4.51) [52]. Total serum calcium levels were measured in 27,158 men and women (25–97 years) in the Tromsø Study (Norway) during 1994 and 1995. In all age groups, serum calcium levels were a predictor of MI in men (OR 1.2 per 0.1 mmol/l increase in serum calcium). In women, no significant trend was seen [20].

Possible Action Mechanisms (fig. 1)

Putative mechanisms of actions encompass effects of calcium on lipid profile, on fasting glucose levels, on platelet aggregation and on phosphate levels. Most studies, however, pointed to the beneficial effect of calcium

intake on BP as the main putative mechanism of action for its protective effect on CHD [53].

Calcium may bind bile acids in the lumen of the intestine and increase their excretion. This may lower blood cholesterol levels and hence reduce the risk of CHD [45]. A reduction of serum total cholesterol has been reported in hypercholesterolemic subjects given 1 g of calcium for 8 weeks [54, 55]. More recently, it has been shown that calcium supplementation with 1 g/day of calcium for 1 year increased HDL cholesterol and decreased LDL cholesterol levels compared to placebo [56, 57]. Serum calcium concentrations have been associated with impaired glucose tolerance [58] and with markers of insulin resistance [52, 58, 59].

Overall, calcium has been associated with deleterious effects on lipid profile and glucose tolerance, suggesting a possible link with the metabolic syndrome.

At last, platelet aggregation has been shown to be inversely related to calcium intake [60, 61]. The precise mechanism is, however, not known. Calcium also binds to phosphate in the intestinal lumen and thus contributes to lower plasma phosphate levels. Low phosphate levels may be protective for CVD [62, 63].

Another emerging mechanism linking calcium to CHD is the presence of calcium in atherosclerotic lesions, and the reported value of coronary artery calcium (CAC) to predict CHD events [64]. While the clinical utility of CAC scoring, usually calculated using computed tomography, remains controversial [64, 65], a legitimate question is whether calcium supplementation can raise the level of CAC, and thus the risk of CVD events. A recent analysis of the Women's Health Initiative-Coronary Artery Calcium Study suggested that moderate (~1,000 mg/day) calcium supplementation does not raise CAC levels, at least when combined with 400 IU of vitamin D₃ [66]. It remains, however, uncertain whether higher or lower doses of calcium, or different ratios of calcium and vitamin D, would modify the level of CAC [66].

Calcium and Stroke

Calcium Supplementation and Stroke

A recent meta-analysis, which included unpublished data provided by authors, reported no association between calcium supplements and the risk of stroke (table 3) [43]. A well-designed RCT could confirm or refute a beneficial effect of calcium supplementation on stroke prevention. However, the trial, if any, should monitor very closely the effect of calcium supplementation on CHD. Given the recent debate regarding the safety of cal-

Table 3. Reported dietary calcium intake and stroke in prospective studies

Association	Reference (first author)	Method	Country and participants	Result
Calcium supplementation and stroke (RCTs)	Bolland, 2010 [43]	Systematic review of RCTs	Includes unpublished data provided by authors	Risk ratio: 1.20 (0.96–1.50)
Calcium intake and incidence of stroke (observational studies)	Ross, 1997 [70]	Cohort study, FFQ	China, men, 45–64 years	No association
	Ascherio, 1998 [68]	Cohort study, FFQ	USA, men, 40–75 years	No association
	Iso, 1999 [69]	Cohort study, FFQ	USA, women, 32–57 years	No association
	Marniemi, 2005 [46]	Cohort study, dietary history interviews	Finland, men + women, 65–99 years	No association
	Umesawa, 2006 [47]	Cohort study, FFQ	Japan, men + women, 40–79 years	No association
	Larsson, 2008 [53]	Cohort study, FFQ	Finland, men, 50–69 years	No association
	Umesawa, 2008 [48]	Cohort study, FFQ	Japan, men + women, 40–59 years	Higher calcium intake → decreased risk of stroke
	Weng, 2008 [71]	Cohort study, FFQ	Taiwan, men + women, >40 years	Higher calcium intake → decreased risk of stroke

RCT = Randomized controlled trial; FFQ = food frequency questionnaire.

cium supplementation [67], it is not clear how acceptable such a trial would be from an ethical point of view.

Calcium Intake and Stroke

Eight observational studies compared the risk of stroke or stroke death based on calcium intake in humans [46–48, 53, 68–71]; half of them were performed in Asian populations [47, 48, 70, 71] (table 3). Two studies, both performed in Asia, reported an association between calcium intake and risk of stroke, a higher calcium intake decreasing the risk of stroke. For example, compared to subjects with a median calcium intake of 233 mg/day, subjects with median calcium intake of 439, 603, and 753 mg/day had a 21, 22, and 29%, respectively reduced risk of stroke [48]. None of the studies performed in North American/European populations and none of the studies that used stroke death as an outcome actually found any association with calcium intake. A possible explanation for the different results observed between populations is the lower (almost 50%) average calcium intake reported in Asian populations compared to North American/European populations.

Calcium Levels and Stroke

While the role of serum calcium levels has been investigated as a prognostic factor after ischemic stroke [72, 73], we found no large population-based information on the association of calcium levels with stroke.

Possible Action Mechanisms (fig. 1)

Some animal experiments have suggested a protective effect of a high calcium intake on stroke [74]. Action

mechanisms are generally thought to be related to the hypotensive and antiplatelet aggregation properties of calcium.

Vitamin D and Cardiovascular Disease

Vitamin D and Blood Pressure

Vitamin D Supplementation and Blood Pressure

Three RCTs assessed the efficacy of vitamin D supplementation on BP [75–77] (table 4). Compared with calcium alone (1,200 mg/day), vitamin D (800 IU/day) and calcium (1,200 mg/day) supplements resulted in 9.3% decreased SBP ($p = 0.02$) in a 8-week trial including 148 women (mean age 74 years) with a 25(OH)D level <50 nmol/l [75]. One study investigated the impact of three times weekly full-body UVB irradiation, and thus indirectly vitamin D production, on ambulatory BP and reported a 162% rise in plasma concentrations of 25(OH)D and a significant effect of UVB to lower systemic BP [78].

Overall, there are several studies but not enough robust evidence to conclude whether vitamin D supplementation is beneficial for, or detrimental to, BP. In the context of large food fortification of vitamin D, the possible increased risk of arterial stiffness and hypertension related to vitamin D needs to be further investigated.

Vitamin D Intake and Blood Pressure

In 2008, Wang et al. [13] investigated the associations of vitamin D intake with the incidence of hypertension in a 10-year prospective cohort of 28,886 US women aged

Table 4. Vitamin D levels, or vitamin D supplements, and BP in prospective studies

Association	Reference (first author)	Method	Country and participants	Result ¹
Vitamin D supplementation and BP (RCTs)	Pfeifer, 2001 [75]	RCT, 1,200 mg calcium + 800 IU vitamin D ₃ daily or 1,200 mg calcium daily, 8 weeks	Germany, women with 25(OH)D <50 ng/ml, 70–86 years, NT+HT	SBP: -7.4 (-13.2, -1.2) DBP: -0.3 (-0.7, -0.1)
	Scragg, 1995 [77]	RCT, 100,000 IU vitamin D ₃ or placebo, once	UK, men + women, 63–76 years, NT+HT	SBP: 0 (-4.0, +4.0) DBP: 0 (-3.0, +3.0)
	Nagpal, 2009 [76]	RCT, 120,000 IU vitamin D ₃ or placebo, every 2 weeks during 6 weeks	India, men, ≥35 years	SBP: +3.95 (-0.02, +8.00) DBP: +1.69 (-1.5, +4.9)
Vitamin D levels and incidence of hypertension (observational studies)	Forman, 2007 [98]	Cohort study, 25(OH) ₂ D radioimmunoassay	USA, men + women, 40–75 years	Lower vitamin D levels → increased risk of HT
	Forman, 2008 [97]	Cohort study, 25(OH) ₂ D enzyme immunoassay	USA, women, 40–46 years	Lower vitamin D levels → increased risk of HT
	Forouhi, 2008 [95]	Cohort study, 25(OH) ₂ D radioimmunoassay	UK, men + women, 40–69 years	No association with change in SBP or DBP
	Jorde, 2010 [98]	Cohort study, 25(OH) ₂ D radioimmunoassay	Norway, men + women, 50–74 years	No association with change in SBP or DBP. No association with risk of HT

NT = Normotensive people; HT = hypertensive people; FFQ = food frequency questionnaire; RCT = randomized controlled trial.

¹ For RCTs, results are expressed as mean changes (95% CI) between intervention group and control group.

≥45 years. Vitamin D intake was assessed from FFQ. The risk of hypertension decreased in the higher quintiles of dietary vitamin D, even after adjustment for dietary calcium intake. This observation was reported for vitamin D intake from diet, not from supplements. Associations of vitamin D intake with BP were also suggested in two previous smaller studies [79, 80].

25(OH)D Levels and Blood Pressure

Association between 25(OH)D levels and BP has been assessed in several cross-sectional studies. Large cross-sectional studies show a significant inverse association between 25(OH)D levels and BP. In one of the largest studies, the NHANES III (12,644 participants aged >20 years), SBP was lower in the highest 25(OH)D quintile compared to the lowest quintile (-3.0 mm Hg, standard error 0.7) [81]. Associations were also reported in two large European studies [82, 83]. Nine studies reported no significant associations [84–90] and four reported a positive correlation (higher level of 25(OH)D associated with higher prevalence of hypertension [91–94]).

The number of prospective studies examining 25(OH)D levels and the incidence of hypertension or change in BP are limited and results are inconsistent [95–98] (table 4). Most studies were small, had suboptimal BP measurement (e.g., single measure of BP), or did not control for potential confounders such as PTH [99].

Possible Action Mechanisms (fig. 2)

Molecular evidence revealed actions of 1,25(OH)₂D on mechanisms related to kidney function and BP. These mechanisms include a direct inhibition of 1,25(OH)₂D on the renin-angiotensin system and nuclear factor-κB (NF-κB) pathway. The vitamin D receptor (VDR) is expressed in the juxtaglomerular apparatus and modulates renin synthesis. Mice in which VDR was abolished are hyperreninemic and present high BP and cardiac hypertrophy [100]. By contrast, when VDR was overexpressed in the mouse juxtaglomerular apparatus, hyporeninemia was noted [101].

NF-κB is a family of transcription factors that functions as a master regulator of immune response [102]. It regulates a wide range of genes involved in inflammation, proliferation and fibrogenesis and is known to have a key role in kidney disease [103]. Both the renin-angiotensin system and the NF-κB promote the production of pro-fibrotic and pro-inflammatory factors, increase oxidative stress, and damage podocytes.

In addition, vitamin D can regulate BP through the prevention of secondary hyperparathyroidism [104]. Vitamin D seems to have a direct effect on vascular cells and endothelial function as well [105, 106]. Vitamin D could potentially contribute to arterial stiffening and hypertension. Richart et al. [107] proposed mechanisms of renal versus extrarenal activation of vitamin D in relation to atherosclerosis, arterial stiffening, and hypertension.

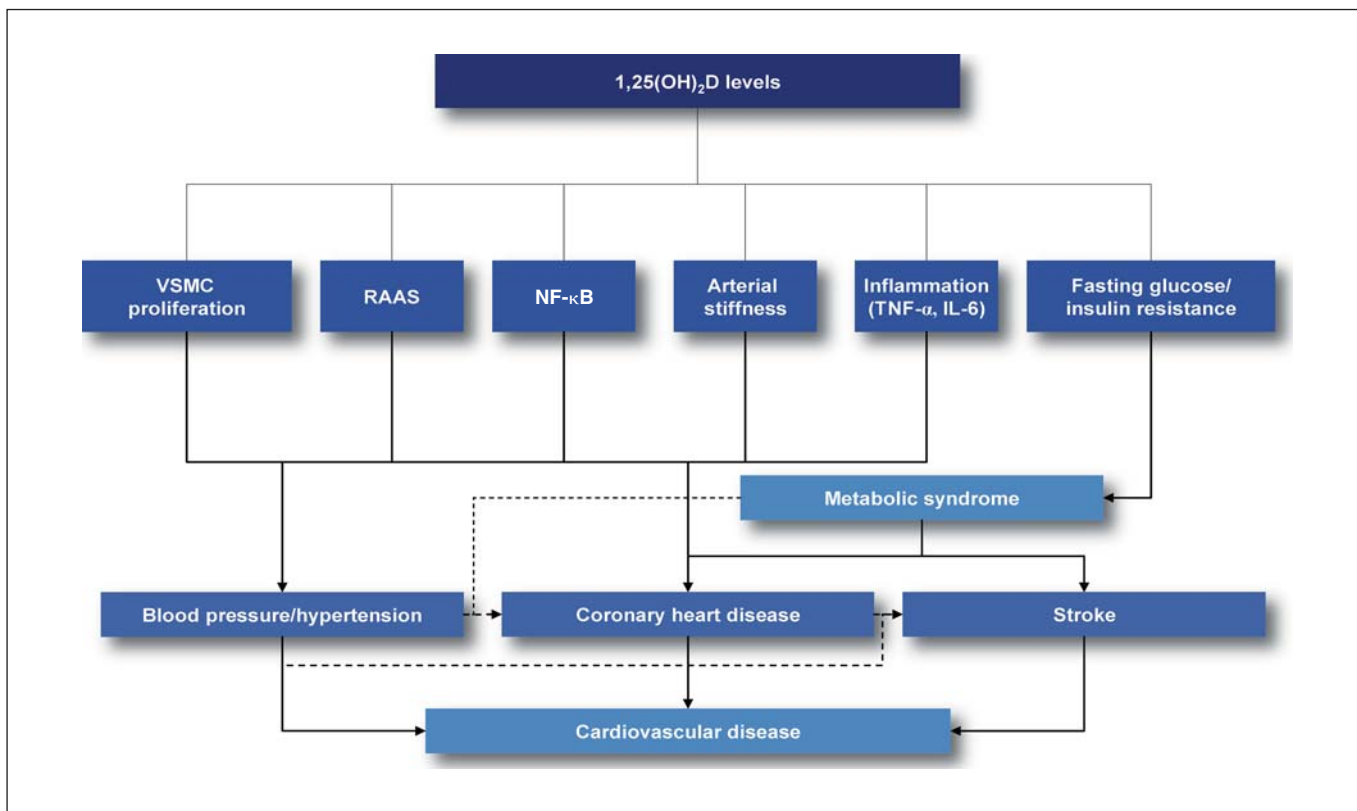


Fig. 2. Main hypothetical mechanism of actions of vitamin D on cardiovascular disease (mechanisms related to parathormone and calcium are not displayed for the purpose of clarity, refer to the text for details). VSMC = Vascular smooth muscle cells; RAAS = renin-angiotensin-aldosterone system; NF-κB = nuclear factor-κB; TNF-α = tumor necrosis factor-α; IL-6 = interleukin-6.

Macrophages in atherosclerotic lesions can locally activate 25(OH)D to calcitriol, which could act as a vasoactive and pro-oxidative substance on VSMCs.

Vitamin D and Coronary Heart Disease

There is an increasing body of literature linking vitamin D to CHD. Ecological studies have reported an inverse relationship between ischemic heart disease and the amount of hours of sunlight [108], as well as the strong seasonal pattern of CHD mortality consistent with the vitamin D blood level seasonal pattern [109].

Vitamin D Supplementation and Coronary Heart Disease

No RCT has been conducted to evaluate the effect of vitamin D supplementation (with or without calcium) on CHD as primary outcome. One RCT, primarily designed to determine the effect of vitamin D supplementation on the risk of fractures, reported data on CHD. The investi-

gators randomized 1,686 elderly men and women to vitamin D 100,000 IU three times a year or placebo for 5 years. They reported no effect of vitamin D supplementation on ischemic heart disease. There was a tendency for fewer events among the interventions group (16.7 vs. 17.4%) [110] (table 5). Another RCT, which randomized postmenopausal women to vitamin D (400 IU/day) and calcium (1,000 mg/day) or placebo for an average of 7 years, reported no difference in cardiovascular mortality [111].

Specifically designed RCT(s) will be needed to determine whether vitamin D supplementation can reduce CHD events and mortality.

Vitamin D Intake and Coronary Heart Disease

Only one study has assessed associations of vitamin D intake with CHD. In 1999, Bostick et al. [45] investigated whether vitamin D intake protected against ischemic heart disease mortality. In this prospective study of more

Table 5. Vitamin D levels, or vitamin D supplements, and CHD in prospective studies

Association	Reference (first author)	Method	Country and participants	Result ¹
Vitamin D supplementation and CHD (RCTs) ²	Trivedi, 2003 [110]	RCT, 100,000 IU oral vitamin D ₃ or placebo every 4 months over 5 years	UK, men + women, 65–85 years	Risk ratio: 0.94 (0.77–1.15)
Vitamin D levels and incidence of CHD (observational studies)	Marniemi, 2005 [46]	Cohort study, 25(OH)D and 1,25(OH) ₂ D radioimmunoassay	Finland, men and women, 66–99 years	No association
	Giovanucci, 2008 [119]	Cohort study, 25(OH)D radioimmunoassay	USA, men, 40–75 years	Lower vitamin D levels → increased risk of MI

¹ For RCTs, results are expressed as risk ratio (95% CI) of CHD comparing the intervention group to the control group.
² None of these studies have been primarily designed to assess the relationship between vitamin supplementation and CHD.

than 30,000 postmenopausal women in the USA, the authors found no association between baseline vitamin D and ischemic heart disease mortality.

25(OH)D Levels and Coronary Heart Disease

At least eleven observational studies on vitamin D and CHD have been published (table 5). 25(OH)D was estimated using FFQ or measured in blood, generally by radioimmunoassay. Outcomes included angina or MI (nonfatal or fatal).

In four studies, no specific association of vitamin D with CHD, on the one hand, and stroke, on the other, could be assessed separately, as they used composite outcome. Wang et al. [112] reported an increased risk of CVD (CHD and stroke combined) in individuals with 25(OH)D <15 ng/ml compared to those with higher 25(OH)D levels (HR 2.13, 95% CI 1.30–3.48). This was evident in participants with hypertension only. Risk of CVD was also increased (about twofold) among subjects with lower 25(OH)D levels compared to higher levels in a German prospective study, even after adjustment for hypertension [113]. Using NHANES III (1988–1994) data, Kendrick et al. [114] indicated an association of 25(OH)D deficiency with prevalent CVD, but Melamed et al. [115] previously analyzed these data and found no association between 25(OH)D levels and risk of CVD mortality.

At least five studies reported CHD outcome specifically (table 5). One study tested the association of low 25(OH)D levels with prevalent CHD using more recent NHANES (2001–2004) data. After full adjustment, no association was found [116]. No association between vitamin D intake or vitamin D and the risk of MI were found in a Finnish population-based study of elderly subjects [46]. A case-control study in South India reported an increased odds of ischemic heart disease among patients with 25(OH)D levels >89 ng/ml compared to those with

lower levels (odds ratio 3.18, 95% CI 1.31–7.73) [117]. This result contrasts with a previous case-control study performed in the USA [118]. While the authors acknowledged that even strong and prolonged UVB light cannot be toxic, they suggested that the high intake of foods rich in vitamin D, such as the one observed in India, could be deleterious. Opposite findings were reported in a nested case-control study of the Health Professional Follow-Up Study (HPFS). Compared to men with vitamin D ≥30 ng/ml, men with vitamin D deficiency (≤15 ng/ml) were at increased risk of MI (RR 2.09, 95% CI 1.24–3.54) [119].

Overall, independent association between vitamin D and prevalence or risk of CHD is not evident from observational studies conducted so far. A case-control study in India found a deleterious effect of vitamin D on ischemic heart disease. While most other studies suggested that vitamin D had no effect or a tendency to protect from CHD or CVD, definitive conclusion based on robust evidence is currently impossible to draw.

Possible Action Mechanisms (fig. 2)

Different mechanisms have been proposed on how vitamin D could be associated with CHD [120]. Some mechanisms are indirect. Vitamin D could be related to CAD via its effect on BP, on glycemic control or on PTH. Because an excess of PTH levels can by itself promote atherosclerosis [121], it is not clear how much of the effect of vitamin D on atherosclerosis is attributable to vitamin D deficiency or to PTH excess caused by vitamin D deficiency.

Other mechanisms are more directly related to atherosclerosis, cardiac tissues and vasculature. Animal studies highlighted the role of vitamin D on cardiomyocyte remodeling in response to injury and atherosclerosis, as well as on cardiac relaxation and contractility [122, 123]. We previously discussed that the presence of

Table 6. Vitamin D levels, or vitamin D supplementation, and stroke in prospective studies

Association	Reference (first author)	Method	Country and participants	Result ¹
Vitamin D supplementation and stroke (RCTs) ²	Trivedi, 2003 [110]	RCT, 100,000 IU oral vitamin D ₃ or placebo every 4 months over 5 years	UK, men + women, 65–85 years	Risk ratio: 1.02 (0.77–1.36)
Vitamin D levels and incidence of stroke (observational studies)	Marniemi, 2005 [46]	Cohort study, 25(OH)D and 1,25(OH) ₂ D radioimmunoassay	Finland, men + women, 66–99 years	Higher levels of 1,25(OH) ₂ D → decreased risk of stroke

¹ For RCTs, results are expressed as risk ratio (95% CI) of stroke death comparing the intervention group to the control group.

² None of these studies have been primarily designed to assess the relationship between vitamin supplementation and stroke.

calcium within coronary vasculature is associated with an increased risk of MI. Serum levels of vitamin D seem to be inversely associated with the extent of vascular calcifications in individuals at risk of ischemic heart disease [120, 124]. Vitamin D could protect from atherosclerosis and vascular calcification by its direct effect on VSMCs; vitamin D creates an acute influx of calcium in VSMCs that might inhibit their proliferation [120, 125]. Vitamin D could also be associated with CHD by down-regulating proinflammatory cytokines (e.g., TNF- α , IL-6) and upregulating an anti-inflammatory cytokine (IL-10) [120].

Finally, there is great interest in the role of vitamin D on the susceptibility for type 2 diabetes and metabolic syndrome [125]. The effects of vitamin D on type 2 diabetes could be mediated by its role on pancreatic β -cell function, insulin resistance, or inflammation [126].

Vitamin D and Stroke

So far, few studies have explored whether vitamin D levels could be predictive for stroke. Possible action mechanisms include the protective role of vitamin D on hypertension and diabetes mellitus.

Vitamin D Supplementation and Stroke

Only one study assessed the impact of vitamin D on the incidence of stroke. In this study, Trivedi et al. [110] found no significant effects of vitamin D on the incidence of cerebrovascular events (table 6).

Vitamin D Intake and Stroke

In a health survey including around 760 elderly subjects, low intake of vitamin D as well as low 1,25(OH)₂D levels were predictive of stroke [46] (table 6). Tertile cut-offs of vitamin D intake and 1,25(OH)₂D levels were not provided, but compared to the lowest tertile, the risks of stroke were more than halved for elderly people in the

middle and in the higher tertiles, for both vitamin D intake and 1,25(OH)₂D levels [46].

25(OH)D Levels and Stroke

In a case-control study, hemiplegic patients with acute stroke showed reduced 25(OH)D levels compared to controls [127]. In a cohort of patients (>3,000) referred to coronary angiography, low levels of 25(OH)D predicted fatal stroke (mean follow-up 7.7 years) [128].

Conclusions

This article reviews the associations between calcium and vitamin D with BP, CHD and stroke. Associations with other factors that also determine the risk of CVD have not been discussed. For example, chronic kidney failure (CKD) is a CVD risk factor, and vitamin D therapy and/or deficiency have been associated with CKD [129–137]. Similar associations have been made for heart failure [138], peripheral artery disease [138], and diabetes [95]. Although this review tried to present all relevant studies related to BP, CHD, and stroke, some studies may have been overlooked.

With these limitations in mind, current evidence suggests that calcium intake/levels seem (1) to decrease SBP, (2) not to be associated with CHD, and (3) to decrease the risk of stroke. Calcium supplementation seems (1) to reduce SBP among hypertensive patients, but not among normotensive people, and to have an inconsistent effect on DBP, and (2) to increase the risk of MI. Vitamin D intake/levels seem (1) to have inconsistent effects on BP and CHD, and (2) to predict the risk of stroke. Vitamin D supplementation seems to decrease SBP and to have no effect on CHD or stroke.

CVD is a major cause of morbidity and mortality in the USA and worldwide [139], and BP, type 2 diabetes,

dyslipidemia, and the metabolic syndrome are major CVD risk factors. Several mechanisms can support hypothetical associations between calcium or vitamin D and CVD and cardiovascular risk factors. The studies conducted so far have several limitations. In observational studies, causal relations cannot be established because of possible bias, confounding and reverse causation. In secondary analyses of RCTs, sample sizes are generally too small and dosage and follow-up inappropriate to study CVD outcomes.

Because there are still unexplained variations and several paradoxes in the pathogenesis of CVD [120], the quest to identify new predictors of CVD is ongoing. More than 160 studies have assessed the associations of calcium or vitamin D with CVD, but no RCT was primarily designed and conducted to investigate whether calcium or

vitamin D supplementation is able to reduce cardiovascular risk factors and CVD mortality. Thus, new RCTs are clearly needed. Performing such a RCT will raise ethical (could one not supplement a patient with vitamin D deficiency and randomize to the placebo group?) as well as logistical and economic (e.g., will require a large sample and need to be conducted for a long time) issues, but 'if complexity is the price of being relevant and addressing the major public health problems, then so be it' [140].

Acknowledgements

I. Guessous is supported by a Swiss National Science Foundation grant (SNF 33CM30-124087/1). M. Bochud is supported by the Swiss School of Public Health Plus (SSPH+).

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