Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies

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STUDY QUESTION

What is the association of circulating biomarker and supplements of vitamin D with mortality due to cardiovascular disease, cancer, or other causes?

SUMMARY ANSWER

Evidence from observational studies shows inverse associations of circulating 25-hydroxyvitamin D concentration with risks of cardiovascular, cancer, and other deaths, whereas supplementation with vitamin D_3, but not D_2, significantly reduced overall mortality among older adults.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Vitamin D may be associated with many extraskeletal disease conditions, including overall mortality outcomes. Combined data from all relevant randomised intervention studies show that, when given alone, vitamin D supplementation may not reduce overall mortality significantly among older adults; however, vitamin D_3, given singly, reduced mortality significantly by 11%.

Selection criteria for studies

We searched Medline, Embase, and the Cochrane databases up to 1 August 2013. We also searched reference lists of relevant studies and contacted authors by email. We included prospective cohort studies and randomised controlled trials in human adults, which reported associations between vitamin D (measured as circulating 25-hydroxyvitamin D concentration or vitamin D supplement given singly) and cause specific mortality outcomes.

Primary outcome(s)

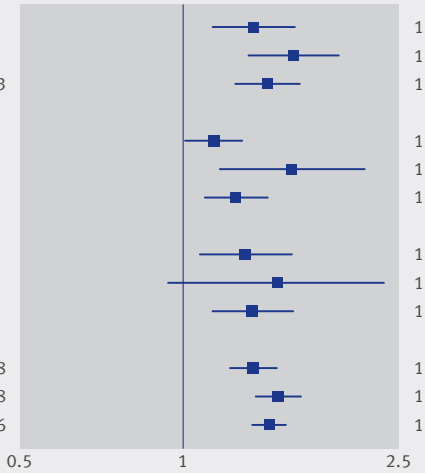
The main outcomes were total and cause specific mortality.

Main results and role of chance

Data were available from 73 cohort studies (849 412 participants) and 22 randomised controlled trials (vitamin D given alone versus placebo or no treatment; 30 716 participants). In the primary prevention observational studies, comparing the bottom versus top thirds of baseline circulating 25-hydroxyvitamin D distribution, pooled relative risks were 1.35 (95% confidence interval 1.13 to 1.61) for cardiovascular death, 1.14 (1.01 to 1.29) for cancer death, 1.30 (1.07 to 1.59) for non-vascular, non-cancer death, and 1.35 (1.22 to 1.49) for all cause mortality. Subgroup analyses in the observational studies indicated that the mortality risk was significantly higher in studies with lower baseline use of vitamin D supplements. In randomised controlled trials, relative risks for all cause mortality were 0.89 (0.80 to 0.99) for vitamin D_3 supplementation and 1.04 (0.97 to 1.11) for vitamin D_2 supplementation. The effects observed for vitamin D_3 supplementation remained unchanged when grouped by various characteristics. However, for vitamin D_2 supplementation, increased risks of mortality were observed in studies with lower intervention dose and shorter average intervention period.

Association of circulating 25-hydroxyvitamin D concentrations with cause specific mortality in observational cohort studies

	No of studies	No of participants	No of deaths	Relative risk (95% CI)* for cause specific mortality
Cardiovascular death				
Primary prevention cohorts	19	80 662	6416	1.35 (1.13 to 1.61)
Secondary prevention cohorts	10	20 987	3787	1.60 (1.32 to 1.94)
All cohorts	29	101 649	10 203	1.43 (1.25 to 1.64)
Cancer death				
Primary prevention cohorts	12	104 353	5003	1.14 (1.01 to 1.29)
Secondary prevention cohorts	5	16 382	1617	1.59 (1.17 to 2.16)
All cohorts	17	120 735	6620	1.25 (1.10 to 1.43)
Non-cardiovascular, non-cancer death				
Primary prevention cohorts	7	38 526	1444	1.30 (1.07 to 1.59)
Secondary prevention cohorts	3	13 035	1121	1.49 (0.94 to 2.35)
All cohorts	10	51 561	2565	1.34 (1.13 to 1.60)
All cause mortality				
Primary prevention cohorts	27	780 990	48 488	1.35 (1.22 to 1.49)
Secondary prevention cohorts	41	59 918	16 148	1.50 (1.36 to 1.65)
All cohorts	68	840 908	64 636	1.44 (1.34 to 1.55)



* Pooled estimates are based on random effects meta-analysis

Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials

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STUDY QUESTION

What health related outcomes have been linked to vitamin D, and are the claimed associations of vitamin D valid and free from bias?

SUMMARY ANSWER

Vitamin D supplementation is probably linked to a decrease in dental caries in children and parathyroid hormone concentrations in patients with chronic kidney disease requiring dialysis and to an increase in maternal vitamin D concentrations at term and in birth weight.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The vitamin D literature is often confusing and has led to heated debates about its role, optimal concentrations, and related guidelines for supplementation. This umbrella review provides a synopsis of the compound literature on circulating vitamin D concentrations and randomised clinical trials of vitamin D supplementation.

Selection criteria for studies

We searched Medline and Embase to October 2013 for systematic reviews or meta-analyses of observational studies of circulating vitamin D concentrations and meta-analyses of randomised trials assessing supplementation of vitamin D in relation to any clinical outcome.

Primary outcome(s)

We evaluated the breadth, validity, and presence of bias of the associations of vitamin D with diverse outcomes.

Evidence of relation between high vitamin D concentrations or vitamin D supplementation and clinical outcomes

Evidence category	Health benefits/risks
Convincing*	None
Probable†	Decreases risk of dental caries in children
	Increases levels of birth weight and maternal vitamin D concentrations at term
	Decreases levels of parathyroid hormone concentrations in CKD RD
Suggestive‡	Decreases risk of colorectal cancer, non-vertebral fractures, CVD, CVD prevalence, hypertension, ischaemic stroke, stroke, cognition, depression (cohort studies), body mass index, metabolic syndrome prevalence, type 2 diabetes, small for gestational age birth, gestational diabetes mellitus
	Decreases levels of balance sway, alkaline phosphatase concentrations in CKD RD, parathyroid hormone concentrations in CKD NRD
	Increases levels of head circumference at birth, low density lipoprotein, bone mineral density in femoral neck, muscle strength
	Increases rate of falls (community) and risk of hypercalcaemia in CKD NRD

CKD=chronic kidney disease; CVD=cardiovascular disease; NRD=not requiring dialysis; RD=requiring dialysis.
*Evidence from both observational studies and randomised controlled trials, association/effect in same direction, statistically significant at P≤0.001, free from bias.
†As for "convincing," but excess significance could not be tested; or evidence existed from randomised trials, effect was statistically significant at P≤0.001, and no contrary results from observational data.
‡Evidence from randomised trials with an effect at 0.001≤P≤0.05 and with no contrary results from observational data; or evidence from meta-analyses of observational studies showing association at P≤0.001, with no contrary results from randomised data, I^2≤75%, no evidence for excess significance, based on cumulative evidence of >500 events or >5000 total participants if type of metric was continuous.

Main results and role of chance

We identified 107 systematic literature reviews and 74 meta-analyses of observational studies of plasma vitamin D concentrations and 87 meta-analyses of randomised trials of vitamin D supplementation. The relation between vitamin D and 137 outcomes has been explored, covering a wide range of skeletal, malignant, cardiovascular, autoimmune, infectious, metabolic, and other diseases. Ten outcomes were examined by both meta-analyses of observational studies and meta-analyses of randomised trials, but the direction of the effect and level of statistical significance was concordant only for birth weight. Despite a few hundred systematic reviews and meta-analyses, highly convincing evidence of a clear role of vitamin D does not exist for any outcome, but associations with a selection of outcomes are probable. In contrast to previous reports, evidence does not support the notion that vitamin D only supplementation increases bone mineral density or reduces the risk of fractures or falls in older people. The lack of convincing associations and the relative dearth of probable associations suggest that evidence for benefits that may be reaped from population-wide vitamin D supplementation is weak at least for supplementation levels considered by studies included in this review. Probable associations, for which highly significant effects appear in randomised trials, hold the most promise for clinical translation, but they pertain to specific populations.

Bias, confounding, and other reasons for caution

We did not identify prominent bias in the observational plasma vitamin D literature, with respect to either the excess significance test or the small study effects test. However, other types of confounding or biases, such as reverse causality, might operate in this field. Furthermore, the quality of our review is directly relevant to the quality of the included studies. We decided to exclude observational meta-analyses of vitamin D supplementation, as they are unlikely to be more reliable than the meta-analyses of observational studies of associations with vitamin D concentrations.

Study funding/potential competing interests

This study had no specific funding.

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- Research: Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies (*BMJ* 2013;346:f1169)
- Minerva: Vitamin D deficiency and other stories . . . (*BMJ* 2013;347:f686)
- Research news: Vitamin D supplementation to prevent osteoporosis is not warranted, study concludes (*BMJ* 2013;347:f615)

Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis

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STUDY QUESTION

Is use of selective digestive decontamination or selective oropharyngeal decontamination associated with improvements in mortality compared with topical oropharyngeal chlorhexidine in adult patients in general intensive care units?

SUMMARY ANSWER

In adults in general intensive care units, selective digestive decontamination is associated with reduced mortality; both selective digestive decontamination and selective oropharyngeal decontamination are superior to oropharyngeal chlorhexidine; chlorhexidine use might be associated with an increase in mortality.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Numerous studies and meta-analyses have shown a mortality benefit of selective digestive decontamination and meta-analyses have shown that oropharyngeal chlorhexidine reduces the incidence of ventilator associated pneumonia without an effect on mortality. Using a network meta-analysis, we suggest that selective digestive decontamination and selective oropharyngeal decontamination confer a mortality benefit compared with chlorhexidine. We also suggest that oropharyngeal chlorhexidine might be associated with an increase in mortality.

Selection criteria for studies

We searched Medline, Embase, and CENTRAL until December 2012 as well as previous meta-analyses, conference abstracts, and key journals. We sought prospective randomised controlled trials that recruited adult patients in general intensive care units and investigated selective digestive decontamination, selective oropharyngeal decontamination, or oropharyngeal chlorhexidine compared with standard care. We did not stipulate placebo control or blinding. We excluded studies of children and specialised populations such as cardiac surgery and liver transplantation. We defined "selective digestive decontamination" as the application of a combination of poorly absorbable antibiotics to both the oropharynx and the stomach combined with empirical intravenous antibiotics. We defined "selective oropharyngeal decontamination" as the application of a combination of poorly absorbable antibiotics to the oropharynx only and "chlorhexidine" as the application of any concentration of chlorhexidine by any formulation to the oropharynx.

Results of meta-analyses of effect of selective digestive decontamination (SDD), selective oropharyngeal decontamination (SOD), and topical oropharyngeal chlorhexidine for prevention of death in adults in intensive care

	OR (95% CI/CrI)	
Comparison	Direct evidence	Mixed (direct and indirect) evidence
Chlorhexidine *v* control	1.25 (1.05 to 1.50)	1.23 (0.99 to 1.49)
SDD *v* control	0.73 (0.64 to 0.84)	0.74 (0.63 to 0.86)
SOD *v* control	0.85 (0.74 to 0.97)	0.82 (0.62 to 1.02)
SDD *v* chlorhexidine	—	0.61 (0.47 to 0.78)
SOD *v* chlorhexidine	—	0.67 (0.48 to 0.91)
SDD *v* SOD	0.97 (0.79 to 1.18)	0.91 (0.70 to 1.19)

Primary outcome

The primary outcome was mortality. We did not study the incidence of ventilator associated pneumonia.

Main results and the role of chance

We included 29 studies: 11 included chlorhexidine, 14 included selective digestive decontamination alone, three included selective oropharyngeal decontamination alone, and one included selective digestive decontamination and selective oropharyngeal decontamination—a large cluster crossover study. We used pairwise meta-analysis to combine intervention-control studies and derive a pooled odds ratio with 95% confidence intervals. We found a reduction in mortality with selective digestive decontamination and selective oropharyngeal decontamination and an increase in mortality with oropharyngeal chlorhexidine. We also performed a network meta-analysis within a Bayesian framework to derive direct and indirect evidence, presented as odds ratios and 95% central credible intervals. This shows that both selective digestive decontamination and selective oropharyngeal decontamination are superior to chlorhexidine. Any difference between the two decontamination treatments is uncertain. We calculated the probability of death for each intervention as 0.213 for selective digestive decontamination, 0.228 for selective oropharyngeal decontamination, 0.266 for control, and 0.305 for chlorhexidine. The probability of each intervention being best is 0.740 for selective digestive decontamination, 0.260 for selective oropharyngeal decontamination, and <0.001 for both control and oropharyngeal chlorhexidine.

Bias, confounding, and other reasons for caution

The results pertain only to adult patients in general intensive care units. Despite our inclusion criteria, some areas of clinical heterogeneity remain, including variability in recruitment criteria and in the exact decontamination regimens applied. The included studies span a wide time period, and there is wide geographical representation; accordingly, control groups might have been treated differently, a limiting factor in a network meta-analysis. Mortality was not the primary outcome in any of the chlorhexidine studies, and a significant increase in mortality was seen in only one of the 11 contributory studies.

Treating infant colic with the probiotic *Lactobacillus reuteri*: double blind, placebo controlled randomised trial

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- Clinical review: Management of infantile colic (*BMJ* 2013;347:f4102)
- Research news: Migraine in childhood linked to colic in infancy (*BMJ* 2013;346:f2419)
- Editorial: Probiotic supplements (*BMJ* 2013;347:f713)

STUDY QUESTION

Does the probiotic *Lactobacillus reuteri* DSM 17938 reduce crying or fussing in a broad community based sample of both breastfed infants and formula fed infants aged less than 3 months with colic?

SUMMARY ANSWER

L reuteri DSM 17938 did not benefit a community sample of breastfed infants and formula fed infants with colic.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous small trials suggested that *L reuteri* effectively treats colic in breastfed infants; however these studies had limitations, and the effect of the probiotic on formula fed infants with colic were unknown. *L reuteri* treatment did not reduce crying or fussing in infants with colic, nor was it effective in improving infant sleep, maternal mental health, family or infant functioning, or quality of life.

Design

This was a double blind, placebo controlled randomised trial of *L reuteri* DSM 17938 compared with placebo, at an oral dose of five drops (1×10^8 colony forming units *v* none) daily for one month. Randomisation was stratified by method of feeding and age, using block randomisation and computer generated allocation.

Participants and setting

The trial included 167 breastfed infants and formula fed infants aged less than 3 months and meeting Wessel's criteria for crying or fussing, recruited from a community based sample (primary and secondary care centres) in Melbourne, Australia. 85 were randomised to receive probiotic and 82 to receive placebo.

Primary outcome

Daily duration of infant cry or fuss at age 1 month.

Main results and the role of chance

Of 167 infants randomised from August 2011 to August 2012, 127 (76%) were retained to primary outcome. Adherence was high. Mean daily duration of cry or fuss fell steadily in both groups. At one month, the probiotic group cried or fussed 49 minutes more a day than the placebo group (95% confidence interval 8 to 90, P=0.02); this mainly reflected more fussing, especially for formula fed infants. The groups were similar on all secondary outcomes.

Harms

No study related adverse events occurred.

Bias, confounding, and other reasons for caution

The rigorous methods of the trial, including adequate randomisation, blinding, allocation concealment, and use of validated measures of primary and secondary outcomes, ensured minimal bias. We adjusted analyses for confounding factors.

Generalisability to other populations

The results are generalisable to almost all infants with colic. Most infants in the trial presented to emergency or urgent care settings. We excluded infants with a possible diagnosis of allergy to cow's milk protein.

Study funding/potential competing interests

This trial was funded by the Equitee Trustees Georgina Menzies Maconachie Charitable Trust. BioGaia Sweden supplied the investigational product and placebo at no cost.

Trial registration number

Current Controlled Trials ISRCTN95287767.

Daily duration of cry or fuss during study and at 6 month follow-up