Special Article

Nutrition Reviews

Vitamin D and dental caries in controlled clinical trials: systematic review and meta-analysis

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Vitamin D has been used to prevent and treat dental caries. The objective of this study was to conduct a systematic review of controlled clinical trials (CCTs) assessing the impact of vitamin D on dental caries prevention. Random-effects and meta-regression models were used to evaluate overall and subgroup-specific relative-rate estimates. Twenty-four CCTs encompassing 2,827 children met the inclusion criteria. Twenty-two of the 24 CCTs predated modern clinical trial design, some of which nonetheless reported characteristics such as pseudo-randomization (n = 2), blinding (n = 4), or use of placebos (n = 8). The relative-rate estimates of the 24 CCTs exhibited significant heterogeneity ($P < 0.0001$), and there was evidence of significant publication bias ($P < 0.001$). The pooled relative-rate estimate of supplemental vitamin D was 0.53 (95% CI, 0.43–0.65). No robust differences were identified between the caries-preventive effects of vitamin D_2, vitamin D_3, and ultraviolet radiation (Prob > F = 0.22). The analysis of CCT data identified vitamin D as a promising caries-preventive agent, leading to a low-certainty conclusion that vitamin D may reduce the incidence of caries.

INTRODUCTION

The discovery of vitamin D went hand in hand with suggestions that vitamin D could arrest and prevent dental caries.[1,2] The hypothesized mechanisms by which vitamin D decreased dental caries included better tooth development, better dentinal mineralization responses to caries throughout life, a topical fluoride-like effect, changes in the amount or biochemical composition of saliva, and the prescient hypothesis – at least for the 1930s – that vitamin D modulated caries activity through immunological factors.[3,4] At least 20 prospective clinical studies evaluating the impact of vitamin D on dental caries were initiated in Europe, North America, and Asia within two decades of the discovery of vitamin D.

Professional and governmental groups interpreted this scientific body of evidence in contradictory ways. The American Medical Association and the US National Research Council concluded in the middle of the 20th century that vitamin D was beneficial in managing dental caries.[5,6] Around the same time, the American Dental Association released a statement to the contrary.[7] In the ensuing decades, these opposing perspectives became largely forgotten, along with the evidence from which they were drawn. The US National Research Council – despite positive evidence produced in the intervening years – downgraded the dental caries/vitamin D association in 1989 to "unresolved."[8] More recent reviews conducted by the Institute of Medicine, the US Department of Human Health and Services, or the American Dental Association do not report on the vitamin D evidence as it relates to dental caries.[9–11] Such conflicting approaches to a set of clinical trial data are difficult to reconcile with the concept of evidence-based medicine. The aim of this study was to provide a systematic review of the available controlled clinical trial data on supplementation with

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vitamin D for dental caries prevention when compared with no such supplementation, in any population.

METHODS

Eligibility criteria

Controlled clinical trials (CCTs) of supplemental dietary vitamin D or ultraviolet (UV) radiation were considered eligible if they satisfied the following four criteria: reporting of incident caries counts and follow-up time, inclusion of a concurrent control group, the assignment to vitamin D under control of the investigator and for the purpose of prevention, and a prospective trial design. There were no restrictions on the method of treatment assignment or the participant characteristics. Trials of salivary or microbiological surrogates of caries were excluded.

Information sources

Four databases (JSTOR, PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials) and three reference works on dental caries,[6,12,13] two of them commissioned by National Research Councils, were searched for citations on the topic of vitamin D and dental caries. There was no a priori protocol or registration of a protocol. No date restrictions were established for the searches.

Search

The full electronic search strategy for all four databases can be found in Appendix S1. Titles, abstracts, full text articles, and textbooks were screened for additional references.

Definition and selection of controlled clinical trials

Retrospective studies, cross-sectional studies, letters to the editors, and studies in which vitamin D assignment was based on medical need were excluded. The caries data abstraction was limited to the period prior to cross-over for crossover CCTs.

Data collection process

Characteristics of CCTs were abstracted using both content-specific data abstraction forms and a quality assessment form.[14]

Data items

For each CCT, information was collected on the vitamin D source, the reported caries statistics, the nutritional interventions that accompanied the vitamin D supplementation, and design and analysis characteristics. The following information was used to calculate vitamin D doses: one international unit (USPX or IU) equals 0.37 Steenbock units. One gram (0.92 cc), one mL (or 1 cc), one drachm (3.6 cc), one teaspoon (5 cc), and one tablespoon (14 cc) of cod liver oil was estimated to contain 69, 75, 266, 375, and 1,050 IU of vitamin D.[15] When a massive vitamin D dose was provided in a short time span (less than a week), the total dose given was reported.[16] Vi-delta Liquid emulsion® was classified as a vitamin D_3.[16] When commercial preparations were changed during the period of the CCT, the most recent preparation listed was used.[17] An Ostelin® tablet between 1924 and 1929 had the vitamin D content of one drachm of cod liver oil[18] and was prepared using the Zucker process, leading to a vitamin D_3 product. From 1929, Ostelin contained a vitamin D_2-ergosterol mixture prepared using the Steenbock process, and from 1932, pure vitamin D_2 became the basis of Ostelin® production.[19] Calciferol in one study was classified as a vitamin D_2 preparation.[20] One drop of 250 D (vitamin D potency was expressed in D units) was equivalent to 250 IU.[21,22] When a range of dietary doses was supplemented, the average of the lowest and highest doses was calculated. The control intervention most closely approximating a placebo was selected for estimating vitamin D efficacy. For instance, "milk" or "olive oil" was selected for estimating the efficacy of "milk-vitamin D mixtures" or "cod-liver oil," and not a "no-milk" or "treacle" control group.

Measures of caries incidence were ranked in order of preferred criteria as defined by the American Dental Association.[11,23] The diets that complemented the vitamin D supplementation were classified as either an unspecified diet or a mineralizing diet. The latter was described by investigators using terms such as "a well planned diet" that included mineralizing components such as "an ample supply of milk and other protective foods." An unspecified diet could be explicitly described as being deficient in mineralizing components or remain nondiscussed in the article. The age of children enrolled in a CCT was determined on the basis of reported mean age, the median of the minimum and maximum ages at time of enrollment, school grade (first-grade children were assumed to be 6–7 years old) or weight-by-age charts when only weights were reported.[24] The CCT setting was classified as school based, institution based, hospital based, or dental practice based.

Risk of bias in individual controlled clinical trials

The CCT quality was quantified using a 21-item questionnaire[14] and content-specific measures such as method of treatment assignment, setting, clinician blinding, use of placebo, commercial funding source, loss to follow-up, and study duration (Table 1). Biased assignment was defined as present when CCT investigators purposefully made the comparison groups different on at least one characteristic, such as baseline caries severity or health awareness. Baseline comparability was assessed on the basis of reported caries prevalence at baseline. A CCT was labeled as partially commercially funded if it received vitamin D preparations or UV equipment free, or if investigators were employed by commercial companies. These risk of bias measures were related to treatment effectiveness using the methods described in the Cochrane handbook (Section 9.6.4).[25]

Measures of treatment effectiveness

Relative incidence rates and their naive standard errors were estimated using Poisson regression methods (SAS PROC GENMOD procedures).[26] The numerator of the incidence rate was the sum of the incident caries events. The denominator of the incidence rate was the sum of the time at risk. The time at risk for each surface or tooth was calculated as follows for a CCT of t years duration: t years when the surface or tooth remained caries free during the CCT, $t/2$ years when the tooth or surface erupted during the CCT and remained caries free, $t/2$ years when the tooth or surface developed a cavity during the CCT, and $t/4$ years when the surface or tooth erupted during the CCT and developed a cavity before the end of the CCT. When no information was provided on whether caries onsets occurred on erupting or erupted teeth, the caries onsets were assumed to have occurred on erupted teeth. The number of caries-free surfaces or teeth at baseline was calculated as the difference between the number of erupted and carious surfaces or teeth. For studies in which the number of sound surfaces or teeth at baseline was not reported, it was imputed based on eruption patterns, tooth counts, or caries status at baseline (see Appendix S2).

To take into account the within-patient correlation of caries onsets, robust standard errors were estimated using one of three methods. For one CCT reporting data on individual patients, the robust standard error was estimated using Poisson regression models for correlated data.[27] For CCTs reporting the necessary data to calculate a mean difference in caries counts (Δ) and a standard error of the mean difference (SE), the robust standard error of the relative rate (RR) was estimated as RR/(Δ/SE). When the P value associated with Δ/SE was less than or equal to 0.0001, Δ/SE was set equal to 4.01 to improve the robustness of the findings.[3,16,28] For CCTs in which only caries counts and no measures of variability were reported, the robust standard error was estimated as the naive standard error multiplied by a scale factor of 2.1. This scale factor is a number reflecting the magnitude of the within-patient correlation of caries events.[29] The estimate of 2.1 was derived from two large clinical trials in which the typical scale factor for primary teeth and permanent teeth was 1.9 (range, 1.7–2.3) and 2.2 (range, 1.9–3.2), respectively.[30,31] Differences in baseline caries severity across the compared groups were evaluated using logistic regression models.

Methods of analysis

Due to the significant heterogeneity in the vitamin D effect sizes, random effect models were used to estimate summary RRs.[25] The heterogeneity of the studies was evaluated using the Q statistic and the I^2 statistic. The CCT characteristics specified in the risk of bias section were related to the magnitude of the treatment effect by means of meta-regression models.[32] Following PRISMA guidelines, specific sensitivity and subgroup analyses were performed to assess the robustness of the conclusions.[33] Publication bias was assessed using the Egger's statistics and a funnel plot, and the impact of single studies on overall conclusions was evaluated by means of influence analyses. All analyses were completed using SAS 9.2 (including the forest and the metaanal macros) and STATA 11.2 meta-analysis software.

RESULTS

Selection of controlled clinical trials

A total of 714 unique citations from six sources were identified: 406 from JSTOR, 70 from PubMed, 168 from Web of Science, 3 from the Cochrane Central Register of Controlled Trials, 43 from a survey commissioned by the National Research Council Canada,[12] and 42 from two surveys commissioned by the National Research Council (Figure 1).[6,13] Fifty-three references were evaluated in detail, 24 of which were excluded because of the absence of incident caries outcome statistics, the lack of assignment to vitamin D by the investigator for the purpose of caries control, or the lack of controls.[34–57] Twenty-nine references remained, which included articles, abstracts, and excerpts of grant reports.[3,15–17,20,28,58–80] In one reference that reported on three CCTs,[20] one CCT without reported follow-up time was eliminated.

Characteristics of controlled clinical trials

Eleven independent investigator teams conducted 24 CCTs in 2,827 children (Figure 2). They reported a total of 38 vitamin D efficacy estimates: 17 vitamin D_3 efficacy estimates (median dose 800 IU), 15 vitamin D_2 estimates

Table 1 **Risk-of-bias table providing a summary of quality measures of controlled clinical trials (CCTs) on vitamin D supplementation and ultraviolet therapy.**

Controlled clinical trial ID	Reference(s)	Study setting	Dentition on which results were based	Experimental unit	Treatment assignment	Baseline differences	Blinding	Placebo	Industry funding	Loss to follow-up	Quality score	Mineralizing diet
1	Mellanby et al.[69]	Hospital	Mixed[a]	Patient	–[b]		*[c]			84%	15	✓
2	Mellanby and Pattison[78]	Hospital	Mixed	Patient	Biased[d]	✓	*[c]			57%	14	✓
3	MRC[15]	Institution	Adult[e]	Cluster	–[b]		*[c]	✓		75%	20	✓
4	MRC[15]	Institution	Adult	Cluster	pseudo-random		*[c]	✓	✓	75%	20	✓
5	MRC[15]	Institution	Primary[f]	Cluster	–[b]		*[c]	✓	✓	75%	20	✓
6	McKeag[75]	Institution	–[g]	Patient	–[b]		✓		✓	19%	13	
7	Schoenthal[73] Schoenthal and Brodsky[74]	PBR	Adult	Patient	Biased	✓[h]		✓[i]	✓	47%	12	✓
8	Schoenthal[73] Schoenthal and Brodsky[74]	PBR	Adult	Patient	Biased	✓[h]			✓	47%	12	
9	Hubbell and Bunting[17]	School	–[g]	Patient	–[b]			✓	✓		8	
10	McBeath[66,67] SDOSC[68] Hollander[77] McBeath and Zucker[80]	Institution	Mixed	Cluster	–[b]						15	✓
11	McBeath[66,67] SDOSC[68] Hollander[77] McBeath and Zucker[80]	Institution	Mixed	Cluster	–[b]				✓		16	
12	McBeath[66,67] SDOSC[68] Hollander[77] McBeath and Zucker[80]	Institution	Mixed	Cluster	–[b]	✓			✓		15	
13	McBeath[66,67] SDOSC[68] Hollander[77] McBeath and Zucker[80]	Institution	Mixed	Cluster	–[b]			✓	✓		16	
14	Anderson et al.[58] Agnew et al.[59,61] Tisdall[60]	Institution	Adult	Cluster	–[b]		✓	✓	✓		20	✓
15	Jameson and Cox[76]	Institution	–[g]	Patient	Biased	✓			✓		6	✓
16	Day[62,63]	School	Adult	Patient	Biased		✓		✓	26%	12	
17	Jundell et al.[65]	Hospital	Adult	Patient	Random					36%	14	
18	Goll[64]	School	Primary	Patient	–[b]					45%	15	
19	Brodsky et al.[16,79]	Hospital	Mixed	Patient	–[b]		✓		✓	49%	18	✓
20	McBeath and Verlin[3]	Institution	Mixed	Cluster	–[b]			✓		20%	17	✓
21	Strean and Beaudet[20]	Institution	Adult	Patient	–[b]						10	
22	Strean and Beaudet[20]	Institution	Adult	Patient	–[b]						10	
23	Mayron et al.[71,72]	School	Adult	Cluster	Random			✓		23%	17	
24	Hargreaves and Thompson[28]	School	Adult	Cluster	–[b]		✓	✓		19%	21	

[a] Mixed dentition.
[b] Neither random nor purposely biased.
[c] Repeated examinations were performed to check accuracy, but the term "blinding" was not reported.
[d] The treatment assignment was defined as "biased" when vitamin D assignment was based on factors such as caries experience or health awareness.
[e] Adult refers to permanent dentition.
[f] Primary refers to primary dentition.
[g] The "–" indicates that no information was provided about whether caries was diagnosed on primary or permanent dentition.[73]
[h] Significant baseline inequality may have been due to a typographical error in Table 1, p. 96 of the Schoenthal[73] publication.
[i] One publication reported that "one tablet of calcium lactate was given twice weekly merely for psychologic purposes." Another group "had their diets augmented with three 1.5 g. tablets of calcium gluconate daily." Calcium lactate and calcium gluconate, used to treat hypocalcemia, were both listed in the American Dental Association's *Accepted Dental Remedies* (1935) manual as accepted therapies for caries, making their description as a placebo in one group and as an active intervention in another group puzzling.[79] The use of these medications was not described in a parallel publication.
Abbreviations: ID, identification; PBR, practice-based research.

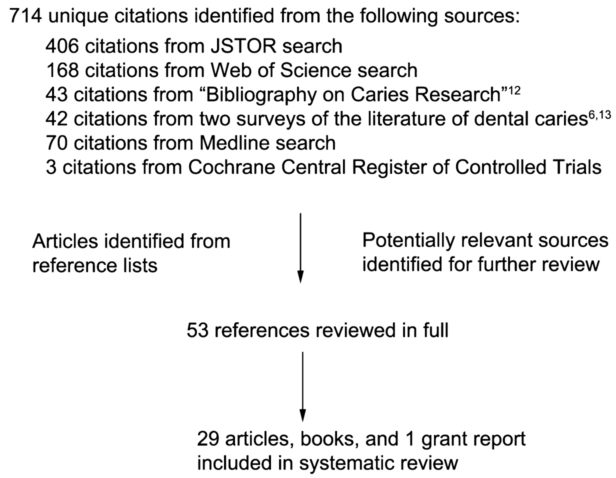

Figure 1 **Article selection.**

(median dose 3,750 IU), and 6 UV radiation estimates (4 delivering erythemal doses, 2 using full-spectrum fluorescent lighting). The CCTs were conducted in the United States (11 of 24), the United Kingdom (6 of 24), Canada (4 of 24), Austria (1 of 24), New Zealand (1 of 24) and Sweden (1 of 24). CCTs were conducted in institutional settings (13 of 24), school-based settings (5 of 24), practice-based settings (2 of 24), or hospital-based settings (4 of 24). The enrolled subjects were children or young adults between the ages of 2 years and 16 years, with a weighted mean age of 10 years. Most CCTs enrolled both genders (15 of 24), four CCTs enrolled either exclusively females or males, and five CCTs did not specify the gender enrolled. The median duration of follow-up was 12 months, and the median sample size was 101 children. Caries counts were reported at a patient level (1 of 24), a tooth level (10 of 24), and a surface level (13 of 24). The caries data were based on permanent teeth (11 of 24), primary teeth (2 of 24), permanent and primary teeth combined (8 of 24), or unspecified teeth (3 of 24).

Risk of bias within controlled clinical trials

Thirteen of the 24 CCTs assigned patients to treatments (Table 1). Five of these 13 CCTs assigned patients to vitamin D on the basis of health awareness or caries experience.[63,73,76,81] Eleven of the 24 CCTs assigned clusters of patient to treatment, with the clusters being institutions ($n = 2$),[15] cottages ($n = 6$),[3,15,80] classrooms ($n = 1$),[72] schools ($n = 1$),[28] or unspecified groupings ($n = 1$)[58] None of the 11 cluster CCTs reported assigning vitamin D on the basis of health awareness or caries experience. One cluster CCT reported blinded vitamin D assignment towards disease status.[28] Random assignment was performed for three CCTs.[15,65,72]

Comparability in baseline caries score between intervention and control groups could be evaluated for 23 of 38 treatment comparisons, and significant baseline inequality in caries experience was present for 4 vitamin D estimates (Appendix S3).[73,76,78,80] The quality score ranged from 6 to 21, with a mean of 14.8 (standard deviation, 4.0). Common potential sources of bias included the lack of examiner blinding (19 of 24), the lack of placebos (14 of 24), and partial funding by commercial companies (13 of 24). Dropout rates were not reported in 9 CCTs, and the median dropout rate among the remaining 15 CCTs was 47%. Twelve CCTs reported evaluating the effect of dietary vitamin D supplements against a background of a mineralizing diet.

Results of individual controlled clinical trials

The 38 vitamin D efficacy estimates are displayed in Figure 2. Details on the number of caries onsets are provided in Appendix S4.

Synthesis of results

The pooled RR for supplemental dietary vitamin D and UV radiation was 0.53 (95% confidence interval [CI], 0.43–0.65). Supplemental UV radiation, vitamin D_3, and vitamin D_2 were associated with a relative caries risk rate of 0.36 (RR = 0.36; 95% CI, 0.17–0.78), 0.51 (RR = 0.51; 95% CI, 0.40–0.65), and 0.64 (RR = 0.64; 95% CI, 0.48–0.86), respectively. No significant differences were identified between vitamin D_2, D_3, and UV therapy (F-statistic$_{2,\ 35}$ degrees of freedom = 1.58; Prob > F = 0.22) (Figure. 2). RRs exhibited significant overall heterogeneity (Q = 134.4 on 37 degrees of freedom, $P < 0.0001$). Retrospective exploration suggested that biased treatment assignment was a significant determinant of the heterogeneity. The I-squared statistic decreased from 72% to 49% when CCTs with biased treatment assignment were eliminated from analysis.

Risk of bias across controlled clinical trials

Three observations suggest the presence of publication bias: a statistical measure assessing publication bias was highly significant (Egger's statistic: P value < 0.001), the funnel plot was asymmetrical (Appendix S5), and reports in the literature were suggestive of negative publication bias (see Appendix S6).

Sensitivity analyses

The vitamin D effect was highly significant for the range of scale factors that is typical in caries studies ($P < 0.0001$). Influence analysis indicated no single study

Author[a]	Year (19xx)	Vit D (x100 IU)	Country	# of exp. patients	Gender	Mean age	Study length(months)	RR(95% CI)	Controlled Clinical Trial(CCT) ID	Reference(s)
Vitamin D3 versus no supplement										
McBeath	38	3	USA	30	F	12	6	0.98 (0.40, 2.42)	13	66-68,77,80
McBeath	42	4	USA	40	.	12	8	0.54 (0.40, 0.73)	20	3
McBeath	38	4	USA	26	M	12	6	0.52 (0.22, 1.18)	12	66-68,77,80
MRC	36	5	GBR	35	M,F	4	30	0.61 (0.13, 2.85)	5	15
McKeag	30	5	GBR	16	M	10	12	0.64 (0.08, 5.50)	6	75
McKeag	30	5	GBR	19	M	10	12	0.33 (0.03, 4.23)	6	75
Mellanby	24	6	GBR	13	.	8	8	0.46 (0.07, 2.86)	1	69
Mellanby	26	7	GBR	24	.	10	8	0.29 (0.05, 1.78)	2	78
McBeath	38	8	USA	28	F	12	6	0.24 (0.05, 1.06)	13	66-68,77,80
McBeath	42	8	USA	40	.	12	8	0.36 (0.22, 0.59)	20	3
McBeath	38	10	USA	75	M,F	12	6	0.17 (0.03, 0.83)	10	66-68,77,80
Goll	39	11	AUT	56	.	4	6	0.87 (0.22, 3.35)	18	64
Mellanby	24	11	GBR	9	.	8	8	0.23 (0.01, 3.94)	1	69
Jundell	38	11	SWE	118	M,F	12	16	0.90 (0.52, 1.57)	17	65
MRC	36	13	GBR	75	M,F	10	36	0.70 (0.36, 1.38)	3	15
Mellanby	26	14	GBR	23	.	8	8	0.22 (0.03, 1.70)	2	78
Brodsky	41	3050	USA	33	M,F	10	12	0.33 (0.15, 0.75)	19	16,79
Subtotal D3 estimate								0.51 (0.40, 0.65)		
Test for subtotal effect:P < 0.0001										
Test for heterogeneity: P < 0.0240										
Vitamin D2 versus no supplement										
Strean	45	4	CAN	30	M,F	10	8	0.12 (0.02, 0.91)	22	20
Strean	45	4	CAN	57	M,F	10	6	0.83 (0.16, 4.39)	21	20
McBeath	42	8	USA	40	.	12	8	0.54 (0.40, 0.73)	20	3
Hubbell	32	20	USA	19	.	12	16	1.55 (0.51, 4.73)	9	17
Anderson	34	20	CAN	87	M,F	10	12	0.50 (0.16, 1.56)	14	58-61
McBeath	38	30	USA	21	M	12	6	0.81 (0.29, 2.24)	11	66-68,77,80
McBeath	42	32	USA	40	.	12	8	0.50 (0.36, 0.70)	20	3
Schoenthal	33	38	USA	34	M,F	10	12	0.89 (0.43, 1.86)	8	73,74
Schoenthal	33	38	USA	88	M,F	10	14	1.08 (0.53, 2.20)	7	73,74
Day	34	40	USA	147	M,F	14	14	1.13 (0.86, 1.46)	16	62,63
MRC	36	50	GBR	31	M,F	4	30	0.48 (0.09, 2.65)	5	15
Jameson	33	100	NZL	5	M,F	.	16	2.04 (0.31, 13.25)	15	76
McBeath	38	101	USA	21	M	12	6	0.48 (0.19, 1.20)	12	66-68,77,80
MRC	36	109	GBR	60	M,F	10	30	0.52 (0.24, 1.15)	4	15
Brodsky	41	6000	USA	35	M,F	10	12	0.14 (0.06, 0.36)	19	16,79
Subtotal D2 estimate								0.64 (0.48, 0.86)		
Test for subtotal effect:P < 0.0031										
Test for heterogeneity: P < 0.0001										
UV therapy versus no UV therapy										
Schoenthal	33	.	USA	11	M,F	10	14	1.04 (0.34, 3.16)	8	73,74
Schoenthal	33	.	USA	12	M,F	10	14	1.26 (0.33, 4.87)	7	73,74
Mayron	75	.	USA	38	M,F	8	10	0.17 (0.07, 0.43)	23	71,72
Hargreaves	89	.	CAN	31	M,F	10	22	0.26 (0.11, 0.61)	24	28
McBeath	38	.	USA	19	M	12	6	0.14 (0.02, 1.09)	11	66-68,77,80
McBeath	38	.	USA	27	M	12	6	0.23 (0.08, 0.68)	12	66-68,77,80
Subtotal UV estimate								0.36 (0.17, 0.78)		
Test for subtotal effect:P < 0.0088										
Test for heterogeneity: P < 0.0005										
Any vitamin D supplementation										
Overall D2,D3 & UV estimate								0.53 (0.43, 0.65)		
Test for overall effect: P < 0.0001										
Test for heterogeneity: P < 0.0001										
Egger's test (publication bias):P <0.001										

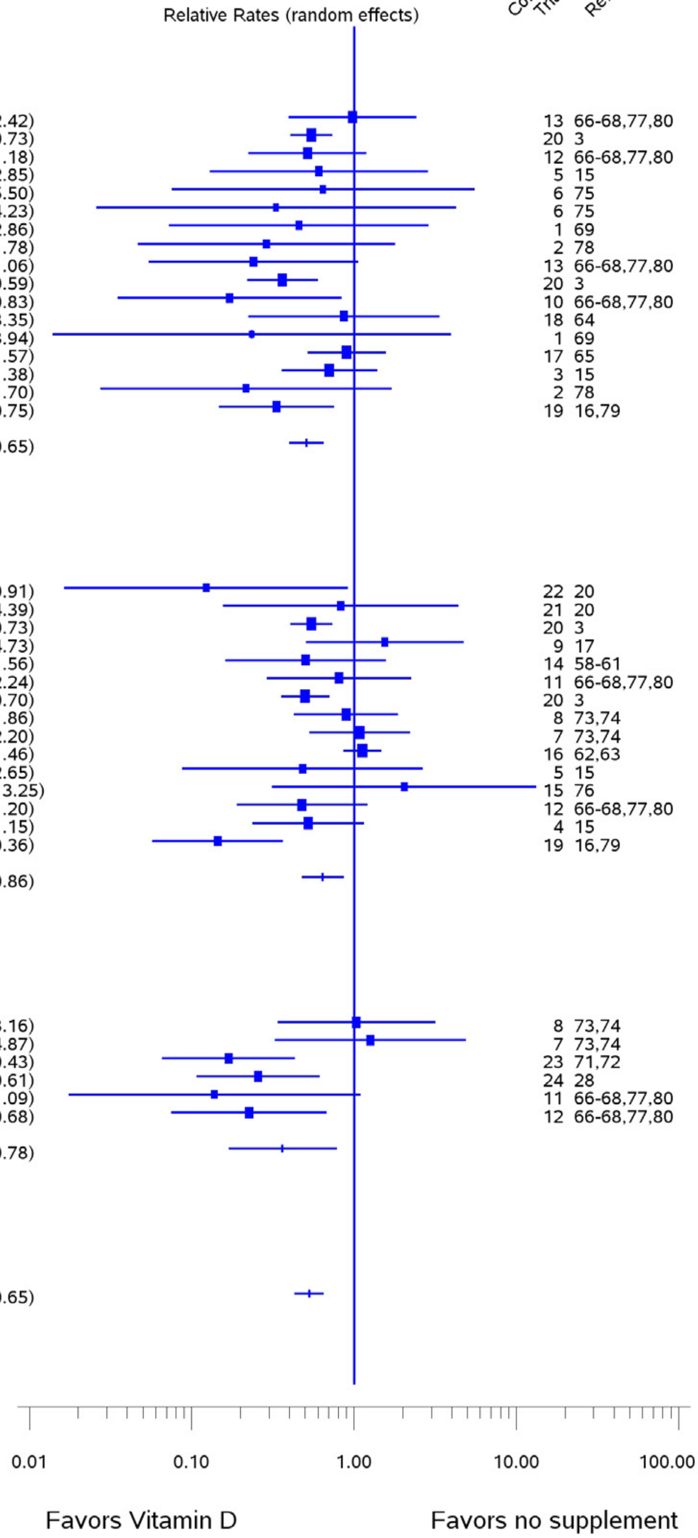

Figure 2 **Relative rate of dental caries associated with vitamin D supplementation.**
[a]The author name corresponds with the clinical trial but does not correspond in all cases with the first author in the cited references.

had a large impact on the reported summary estimate (Appendix S7). The identified lack of significance between dietary vitamin D_2, vitamin D_3, and UV therapy was not robust. Deletion of the Schoenthal CCTs[73] from analysis led to significant differences favoring UV therapy and vitamin D_3 over vitamin D_2 (P value < 0.05) for all imputations described.

Meta-regression results

Study characteristics that significantly decreased vitamin D effectiveness included low study quality ($P < 0.005$), conduct of CCT in a school ($P < 0.017$), biased assignment of vitamin D ($P < 0.003$), assignment of vitamin D to patients rather than to a cluster of patients ($P < 0.041$), a mean age over 12.5 years (P value < 0.050), and CCTs conducted before 1950 ($P < 0.050$). Study characteristics that had no impact on vitamin D effectiveness included the use of placebo ($P < 0.646$), blinding of examiners ($P < 0.450$), partial commercial funding ($P < 0.630$), patient dropout ($P < 0.811$), CCT duration ($P < 0.200$), country of conduct ($P < 0.204$), dose of daily vitamin D supplementation ($P < 0.816$), and the delivery of vitamin D with a mineralizing diet ($P < 0.565$). Exclusion of CCTS with variation in carbohydrate intakes in one of the experimental arms did not impact the overall conclusions of this report.

CONCLUSION

This systematic review of CCTs suggests that supplemental vitamin D was associated with a 47% reduced risk of caries. No robust differences could be identified between the effects of UV therapy and nutritional supplementation with either vitamin D_2 or vitamin D_3. Retrospective analyses suggested that vitamin D supplementation was ineffective after the age of 13 years, particularly for girls,[58,62,65] suggesting that growth and variations in body fat may influence the effectiveness of the fat-soluble vitamin D in caries prevention. It can be concluded with low certainty (using the criteria for certainty established by the US Physician Services Task Force) that vitamin D in childhood may reduce the incidence of dental caries.[82]

The findings do not support the hypothesis that professional or governmental organizations started ignoring vitamin D because of its demonstrated ineffectiveness in controlled clinical trials. Regardless of whether trial quality was defined by an overall quality score, by individual study design characteristics, by the pivotal nature of a study, or by the time era in which the studies were conducted, higher study quality translated into higher vitamin D effectiveness. Some examples illustrate this trend. First, investigators who avoided bias in treatment assignment showed a significantly larger vitamin D benefit than investigators who assigned vitamin D on the basis of health awareness or caries experience. Second, two pivotal trials in terms of funding, scope, and sample size reported beneficial effects.[15,80] One of these trials appears modern, even from today's perspective, with sophisticated statistical methods such as last-observation carry forward and detailed physical exams complementing dental exams.[15] And lastly, two studies published in 1975 and 1989 with more current design and analysis methods, modern caries scoring methods, and study settings more reflective of current lifestyles showed larger effectiveness than the 22 CCTs conducted between the two World Wars.[28,72] Consequently, limiting the systematic review to high-quality studies leads to findings of higher vitamin D effectiveness and less heterogeneity between studies. For instance, restricting the analysis to studies with nonbiased treatment assignment increased the percent reduction in caries rate from 47% to 54%.

This systematic review explored whether the caries reduction associated with vitamin D was due to vehicle effects. Some trials used cod liver oil, raising the possibility that the observed effects were due to vitamin A, iodine, or marine fats[83–88] instead of vitamin D_3. Other trials used UV therapy, making it unclear whether the observed effects might have been due to pineal gland activation and subsequent increased salivation[89,90] and not necessarily to the skin-bound generation of vitamin D precursors. While such alternative explanations may be reasonable for individual trials, they fail to provide a simple explanation for why the reviewed trials produced consistent caries-preventive effects regardless of the vehicle or method of administration. Specifically, the results of the meta-regression show that nutritional supplementation provided a caries benefit similar to that of UV therapy, and nutritional supplementation with vitamin D_2 provided a caries benefit similar to that of nutritional supplementation with vitamin D_3.

The findings of this systematic review are consistent with more recent evidence regarding the role of vitamin D in oral health.[45,91] A 1973 randomized trial published in *The Lancet* demonstrated that vitamin D deficiency during pregnancy is associated with enamel hypoplasias in the offspring.[92,93] In turn, enamel hypoplasias have been related to caries risk[94,95] in cohort studies as recently as 2009.[94] Such studies substantiate *one* of the original mechanistic explanations of how vitamin D lowers caries risk. A 1984 cohort study suggested that postpubertal boys, but not girls, benefit from vitamin D dietary intake for caries prevention,[45] essentially confirming experimental evidence published in 1934.[58] As a final example, a 1990s double-blind randomized controlled trial published in the *New England Journal of Medicine*[96] suggested in an ancillary report that vitamin D supplements combined with calcium reduced tooth loss rates.[97] While these studies do not provide direct experimental evidence on vitamin D and dental caries, they provide a coherent and consistent picture regarding the potential role of vitamin D in caries prevention.

Perhaps the most important weakness of this systematic review was the inability to assess how the clinical-trial methodology of more than 60 years ago for 22 of the 24 trials might have biased outcomes. The issue of conflicts of interest is a particular concern, as the marketing for vitamin D was intense[98] and the lucrative patents were in the hands of academia.[98,99] A pathologist involved with patenting vitamin D_3 extraction was described as cooperating "heartily"[68] with caries trials[80] and coauthored a report suggesting that vitamin D_3 was superior to vitamin D_2. Vitamin D_2 was described as halving the rate of primary tooth decay by a physician who was described as having industry connections[19,58,59] and being a "wheeler-dealer, a publicity genius."[100] Design and analysis issues other than conflict of interest, such as intent-to-treat, proper randomization techniques, and statistical power calculations, can similarly bias findings and were largely unknown before 1950.

A second weakness is that the majority of the evidence stems from populations growing up between the First and the Second World Wars and whose health, nutrition, and lifestyle are not representative of the current situation. When compared with current lifestyles, the interwar institutionalized populations consumed more animal fats,[15,70] had lower fluoride exposure, had a lower carbohydrate and phosphate intake, and grew up during an era when sun exposure was considered essential to health.[101] These factors may have increased serum vitamin D levels[102–105] and may explain the low caries rates in institutionalized populations of that time.[6,66] The health of noninstitutionalized populations in the interwar era depended on geographical location and was, in some instances, much different from the institutionalized populations. For instance, the prevalence of rickets among poor noninstitutionalized children in New York was 9%, suggesting that malnutrition was still common in some urban settings.[73] In contrast, the current population of noninstitutionalized US children may have a growing epidemic of vitamin D deficiency[106,107] mixed with a 25% prevalence of fluoride overdose[108] and a 5% prevalence of severe obesity.[109] These differences in nutrition, fluoride exposures, and lifestyle factors make inferences from one time era to another tenuous.

Remaining weaknesses included the need for imputations for incomplete caries data, the absence of individual patient data, the heterogeneity of the findings, the inability to identify a dose-response relationship, and the lack of serum vitamin D levels. The significant heterogeneity of the effectiveness of vitamin D_3, vitamin D_2, and UV therapy was partly explained by factors such as study setting and age of enrolled children. The lack of dose-response effects may be due to the large difference in UV or dietary doses studied, the possibility of U-shaped dose-response curves, and the difficulty in controlling factors that influence dietary absorption of vitamin D.

In summary, this systematic review of CCTs suggests that vitamin D exposures in early life may play a role in caries prevention. This promising evidence base may be relevant to current challenges in improving health, as vitamin D levels in the US population are decreasing[106,107,110] and dental caries among US children is increasing.[111] Current and ongoing investigations on the role of vitamin D intake could help rectify this situation by assessing both dental caries and periodontal disease[112] as part of overall research aims.

Acknowledgments

The inspiration for this work came in part from reading a draft of Martin Renner's doctoral dissertation entitled "Conservative Nutrition: The Industrial Food Supply and Its Critics, 1915–1985." A controlled trial on UV supplementation (Hathaway, *Journal of Educational Research*, 1995: 88; 228–242) was identified after manuscript acceptance and changed the overall relative rate for caries prevention associated from 0.53 (95% confidence interval: 0.43–0.65) to 0.52 (95% confidence interval: 0.43–0.63) and the UV-specific relative rate from 0.36 (95% confidence interval: 0.17–0.78) to 0.35 (95% confidence interval: 0.19–0.65).

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Details on search strategies.
Appendix S2 Caries abstraction (location of primary evidence in published literature).
Appendix S3 Baseline caries scores across compared groups.
Appendix S4 Details on caries counts.
Appendix S5 Funnel plot.
Appendix S6 Details on two excluded vitamin D trials.
Appendix S7 Influence analyses.