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Article

The Effect of Follow-Up Period on the Relationship between Serum 25(OH)D Concentration and Risk of Stroke and Major Cardiovascular Event in Prospective Cohort Studies

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Abstract: Background/Objectives: Prospective cohort studies are useful for studying how biomolecular status affects risk of adverse health outcomes. Less well known is that the longer the follow-up time, the lower the apparent effect due to “regression dilution.” Here we evaluate how follow-up time affects the relationship between serum 25-hydroxyvitamin D [25(OH)D] concentration and incidence of stroke and major cardiovascular events (MCEs). Methods: Findings regarding the relative risk (RR) of stroke and MCEs with respect to serum 25(OH)D concentrations at baseline from prospective cohort studies were plotted against mean follow-up time. Fifteen studies from mainly European countries and the United States were used for stroke, with nine studies for MCEs. Linear regression analyses were performed for follow-up periods of up to 10 years. Results: For stroke, the linear regression fit for 1–10 years is $RR = 0.34 + (0.065 \times \text{follow-up [years]})$, $r = 0.84$, adjusted $r^2 = 0.67$, $p = 20 \text{ ng/mL}$ should be recommended for everyone likely to be at risk for stroke or MCE and indeed in the general population.

Keywords: Cardiovascular disease; causality; follow-up period/time; heart failure; hemorrhagic; hypertension; ischemic; prospective cohort study; stroke; vitamin D

1. Introduction

A type of observational study commonly used to assess the effect of dietary and lifestyle factors and biological parameters on health outcomes is the prospective cohort study. In this approach, participants are recruited and enrolled, information relevant to the study is obtained from each participant, the participants are followed for some period, and health outcomes are recorded. Afterwards, the health outcomes are compared statistically with respect to data obtained at the time of enrollment. Most such studies do not remeasure any of the parameters during the follow-up period. As a consequence, there is generally an underestimation of risk associations due to “regression dilution” in long-term follow-up of prospective studies as outlined by Clarke et al. in 1999 [1]. In that article, they reported repeated measurements over 25 years for systolic and diastolic blood pressure and blood cholesterol for participants in the Framingham Study. They demonstrated that the range from high to low for the first and fifth quantile shrunk by 65%, 75%, and 57%, respectively. While this article had 897 citations by August 31, 2024 according to Google Scholar, it seems not to have had much impact on conduct of prospective cohort studies or, more importantly, meta-analyses of such studies. The effect of changes in serum 25-hydroxyvitamin D [25(OH)D] has been known for cancer since 2011 [2] and all-cause mortality rate since 2012 [3]. Yet the effect was overlooked in a highly-cited meta-analysis of risk of colorectal cancer with respect to serum 25(OH)D concentration in 2019 [4], as pointed out in 2022 [5].

Recently, it was demonstrated that the same effect is found for risk of cognitive impairment, dementia, and Alzheimer’s disease. The 2024 meta-analyses included 15 prospective studies regarding dementia and/or Alzheimer’s disease and nine regarding cognitive impairment [6]. As shown in plots of risk ratio for low vs. high 25(OH)D concentration vs. follow-up period, there were linear decreases in the regression fit to the data from near 2.0 for the shortest follow-up periods (near four-to-five years) to near 1.0 for follow-up periods near 13 years (Grant, submitted).

When a 2021 meta-analysis of prospective cohort studies of risk of stroke with respect to serum 25(OH)D [7] was found, it was decided to do a similar analysis. A related 2024 meta-analysis [8] was also consulted.

2. Materials and Methods

The data used in this article are the prospective cohort studies in Su et al. [7]. Table 1 lists the studies in ascending order of follow-up period. The table includes the OR/RR from Su et al. [7] and the follow-up period and 25(OH)D concentration comparison obtained from each article. Two studies did not have enough information on follow-up period and how 25(OH)D concentrations were compared. Two studies were based on dietary vitamin D intake. None of those four studies were included in the analysis reported here.

Data were analyzed using SigmaStat 4.0 (Grafiti, Palo Alto, CA, USA). Data plots were made using KaleidaGraph 4.5.4 (Synergy Software, Reading, PA, USA).

Table 1. Data for stroke studies listed in Su et al. [7] and Xiong et al. [8].

Follow-up (years)	Type of stroke	Inc or Mor	OR/RR (95% CI)	25(OH)D comparison (ng/mL)	Reference
--			1.41 (0.64–3.13)		(Guo, 2017*) [9]
--			1.19 (0.79–1.79)		(Leu Agelii, 2017*) [10]
1		inc	0.42 (0.14–1.28)	≥10 vs. <10	(Zittermann, 2016) [11]
1.3		inc	0.56 (0.38–0.84)	>30 vs. ≤15	(Anderson, 2010) [12]
3.1		inc	0.54 (0.34–0.85)	>30 vs. <20	(Judd, 2016) [13]
4		inc	0.33 (0.15–0.73)	>30 vs. ≤10	(Drechsler, 2010) [14]
5		inc	0.71 (0.40–1.25)	≥20 vs. <20	(Bolland, 2010) [15]
6.8		inc + mor	0.91 (0.81–1.02)	per +10	(Perna, 2013) [16]
6.8		inc + mor	0.76 (0.55–1.05)	<12 vs. ≥20	
7.6		inc	0.60 (0.59–1.09)	Q4 (27 median) vs. Q1 (12 median)	(Kuhn, 2013) [17]
7.6		inc	0.65 (0.49–0.95)	≥20 vs. <10	
8.0		inc	0.93 (0.46–1.85)	≥20 vs. <20	(Welles, 2014) [18]
9.3	I	inc	0.81 (0.70–0.94)	≥20 vs. <10	(Afzal, 2017) [19]

10		inc + mor	1.00 (0.51– 1.94)	High vs. low tertile	(Marniemi, 2005) [20]
10			0.88 (0.49– 1.61)	Middle vs. low tertile	
10		inc	1.13 (0.80– 1.59)	Fourth vs. first quartile	(Skaaby, 2013[21])
10.3	All	inc	0.56 (0.36– 0.86)	Lowest vs. highest quintile	(Leung, 2017[22])
10.3	I		0.55 (0.35– 0.86)	Lowest vs. highest quintile	
10.6		inc	0.91 (0.75– 1.11)	One 25(OH)D SD increase	(Berghout, 2019) [23]
14.1	All, W	mor	0.47 (0.22– 0.99)	>15 vs. <15	(Michos, 2012) [24]
14.1	All, B	mor	1.07 (0.56– 2.04)	>15 vs. <15	
14.1		mor	0.57 (0.31– 1.06)	>15 vs. <15	
16		inc or mor	0.60 (0.39– 0.91)	≥20 vs. <20	(Schierbeck, 2012) [25]
19.3			0.66 (0.49– 0.89)	>440 vs. <110 IU/day vitamin D	(Sheerah, 2018*) [26]
20		inc	0.75 (0.58– 0.94)	≥31 vs. <17	(Schneider, 2015) [27]
34			0.82 (0.68– 0.99)	>4 vs. <1.1 µg/day	(Kojima, 2012*) [28]

(*) omitted from the graph; B, Black; I, ischemic; Inc, incidence; mor, mortality; W, White.

Table 2. Baseline data for stroke studies listed in Su et al. [7] and Xiong et al. [8].

Country	Patient characteristics	Mean Age (± SD) or range (years)	BMI (± SD) (kg/m ²)	M, F (%)	Type of Stroke	N _s	N _c	Reference
Germany	Left ventricular assist device implants	62 (37– 81)	23 ± 3	100, 0	All	25		(Zittermann, 2016) [11]
		57 (49– 66)	26 ± 5	85, 15			129	
USA	Community hospital	55 ± 21	NA	25, 75	All	208	25,818	(Anderson, 2010) [12]
USA	B and W community- dwelling				I	536	1069	(Judd, 2016) [13]
Germany	Diabetic haemodialysis	66 ± 8		60, 40	All	89	1019	(Drechsler, 2010) [14]

New Zealand	Healthy community-dwelling	74 ± 4	NA	0, 100	All	59	1412	(Bolland, 2010) [15]
Germany	Population-based	65% 50–65; 35% 65–74	27 ± 5	41, 59	All	353	7356	(Perna, 2013) [16]
Germany	Population-based	51	NA	42, 58	All	471	1661	(Kuhn, 2013) [17]
USA	Stable CVD disease	66 ± 11	29	81, 19	All	49	897	(Welles, 2014) [18]
Denmark	General population	58 (48–68)	26 ± 3	48, 52	I	960	~115,000	(Afzal, 2017) [19]
Finland	Population-based	65-99	NA	48, 52	All	70	685	(Marniemi, 2005) [20]
Denmark	General population	49 (41-73)	26	50, 50	All	316	8830	(Skaaby, 2013[21]
Hong Kong	Osteoporosis study, Chinese	63 ± 10		37, 63	All	244	3214	(Leung, 2017[22]
		63 ± 10		37, 63	I	205	3253	
The Netherlands	Population-based	65 ± 10	27 ± 4	43, 57	All	735	8603	(Berghout, 2019) [23]
USA	Population-based, W*	73 (SE, 1)	27 (SE, 0.5)	35, 65	All	116	4885	(Michos, 2012) [24]
USA	Population-based, B*	68 (SE, 2)	28 (SE, 0.8)	34, 66	All	60	2920	(Michos, 2012) [24]
Denmark	Osteoporosis study	50 ± 2	25 ± 5	0, 100	All	89	1924	(Schierbeck, 2012) [25]
USA	Population-based	57	NA	43, 57	All	804	11,354	(Schneider, 2015) [27]

(*), data for those with incident stroke: B, Black; CVD, cardiovascular disease; I, ischemic; NA, not available; Nc, number of controls; Ns, number with incident stroke; SE, standard error; W, White.

Table 3. Major cardiovascular disease event in prospective cohort studies based on studies in Grandi, 2010 [29] and Zhang, 2022 [30].

Follow-up (years)	RR (95% CI)	25(OH)D comparison (ng/mL)	Reference
1.0	1.85 (1.25–2.75)	<9 vs. >9	(de Metrio, 2015) [31]
1.0	1.20 (0.72–2.00)	<12 vs. >12	(Beska, 2019) [32]
1.25	7.24 (0.99–53.50)	<30 vs. >30	(Siasos, 2013) [33]
1.5	1.61 (1.15–2.27)	<7.3 vs. >7.3	(Ng, 2013) [34]
2.2	1.30 (1.04–1.64)	<20 vs. >20	(Aleksova, 2020) [35]
2.7	1.32 (1.07–1.63)	<12.7; 12.7–21.59; ≥21.6	(Verdoia, 2021) [36]
5	1.2 (0.7–2.2)	<20 vs. ≥20	(Bolland, 2010) [15]
5.8	1.84 (1.36–2.50)		(Gerling, 2016) [37]
6.7	1.36 (0.88–2.12)		(Yu, 2018) [38]
7.0	1.27 (0.92–1.75)		(Naesgaard, 2015) [39]
7.6	1.62 (1.11–2.36)	<15 vs. >15	(Wang, 2008) [40]

7.7	1.77 (1.47–2.13)		(Lerchbaum, 2012) [41]
8.0	1.11 (0.85–1.44)	≥20 vs. <20	(Welles, 2014) [18]
8.1	0.83 (0.37–1.86)	Quartiles	(Grandi, 2010) [42]
10			(Giovannucci,
10			(Marniemi
11.9	1.94 (1.66–2.27)		(Degerud, 2018) [43]

Note: Studies highlighted in gray will be omitted since they relate to mortality.

Table 4. Major cardiovascular disease event in prospective cohort studies based on studies in Grandi, 2010 [29] and Zhang, 2022 [30].

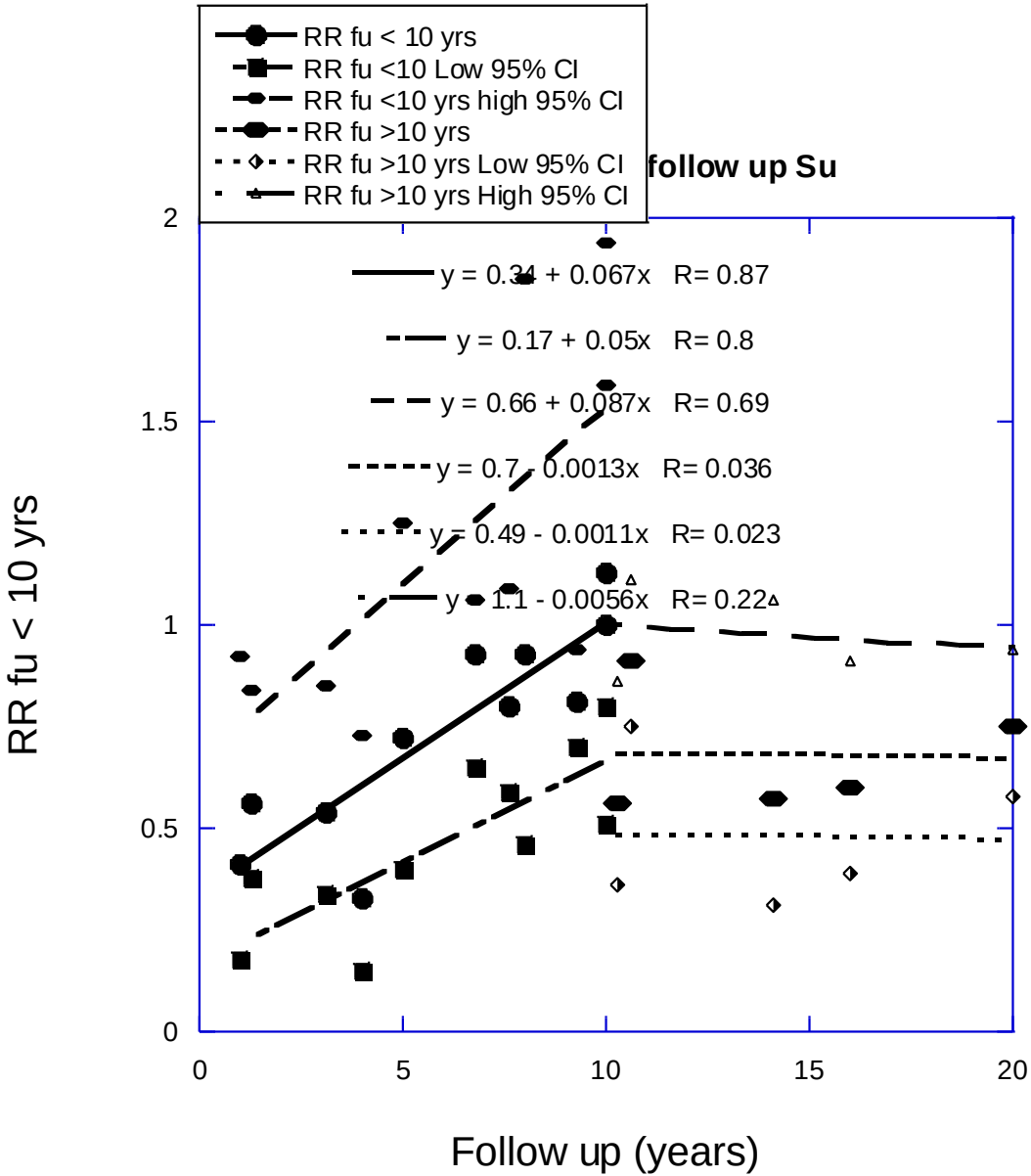
Country	Patient characteristics	Mean Age (± SD) or range (years)	BMI (± SD) (kg/m²)	M, F (%)	Type of event	N _{MCDE}	N _C	Reference
Italy	Acute coronary syndrome	67 ± 12	27 ± 4	72, 28	MACE	125	689	(de Metrio, 2015) [31]
UK	After non-ST elevation acute coronary syndrome	81 ± 5	27 ± 5	62, 38	MACE	76	224	(Beska, 2019) [32]
UK	Acute myocardial infarction	66 ± 13	NA	72, 28	non-fatal MACE	224	1035	(Ng, 2013) [34]
Italy	Myocardial infarction	67 ± 12	27 ± 4	71, 29	all-cause mortality, angina/MI, HF	391	690	(Aleksova, 2020) [35]
Italy	CAD undergoing percutaneous coronary intervention	68 ± 11	28 ± 5	73, 27	MACE	174	531	(Verdoia, 2021) [36]
New Zealand	Healthy community-dwelling	74 ± 4	NA	0, 100	MI	52	1419	(Bolland, 2010) [15]
					Death			(Gerling, 2016) [37]
					Death			(Yu, 2018) [38]
					Death			(Naesgaard, 2015) [39]
					Incident CVD			(Wang, 2008) [40]
					Death			(Lerchbaum, 2012) [41]
USA	Stable CVD disease	66 ± 11	29	81, 19	CVD events	49	897	(Welles, 2014) [18]
					CVD events	148	977	(Grandi, 2010) [42]

							(Giovannucci,
					Death		(Marniemi,
							2005)
					Death		(Degerud,
							2018) [43]

CAD, coronary artery disease; HF, heath failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; NA, not available; N_{MCDE} , number with a major cardiovascular disease event; N_C , number of controls;.

3. Results

Figure 1 is a plot of the data from Table 1 along with the linear regression fits to the data. The data were divided into two groups, one to ten years and greater than ten years. The division was determined by inspection of the data plot. As can be seen, there is a good linear fit to the data for follow-up period one-to-ten years. The regression fit to those data is $RR = 0.34 + (0.067 \times \text{Follow-up [years]})$, $r = 0.87$, adjusted $r^2 = 0.73$, $p < 0.001$. The regression fit to the data with follow-up period >10 years is nearly flat with respect to follow-up period.



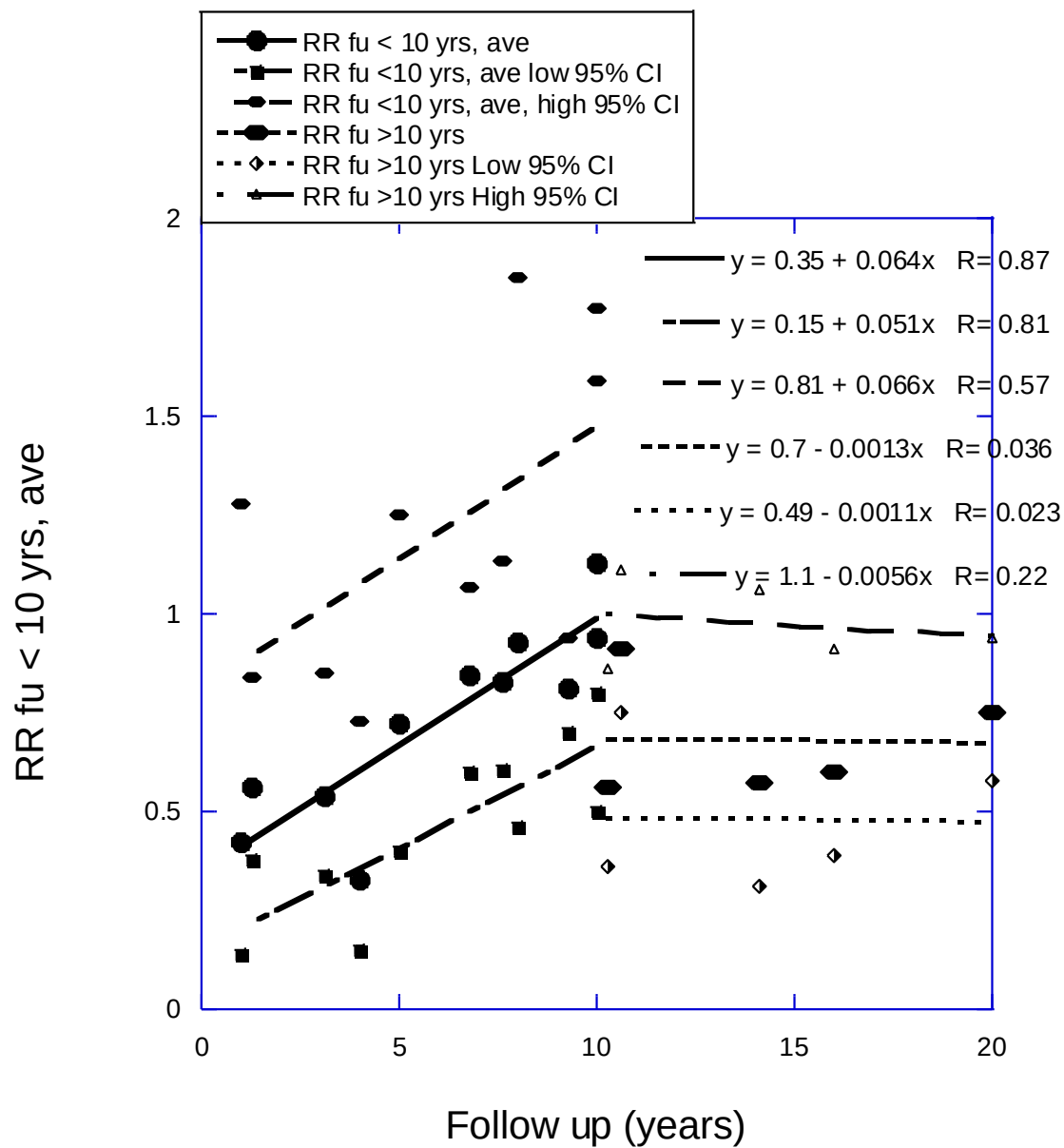


Figure 1. Plot of RR for ischemic stroke for high vs. low 25(OH)D concentration as a function of mean follow-up period in prospective cohort studies.

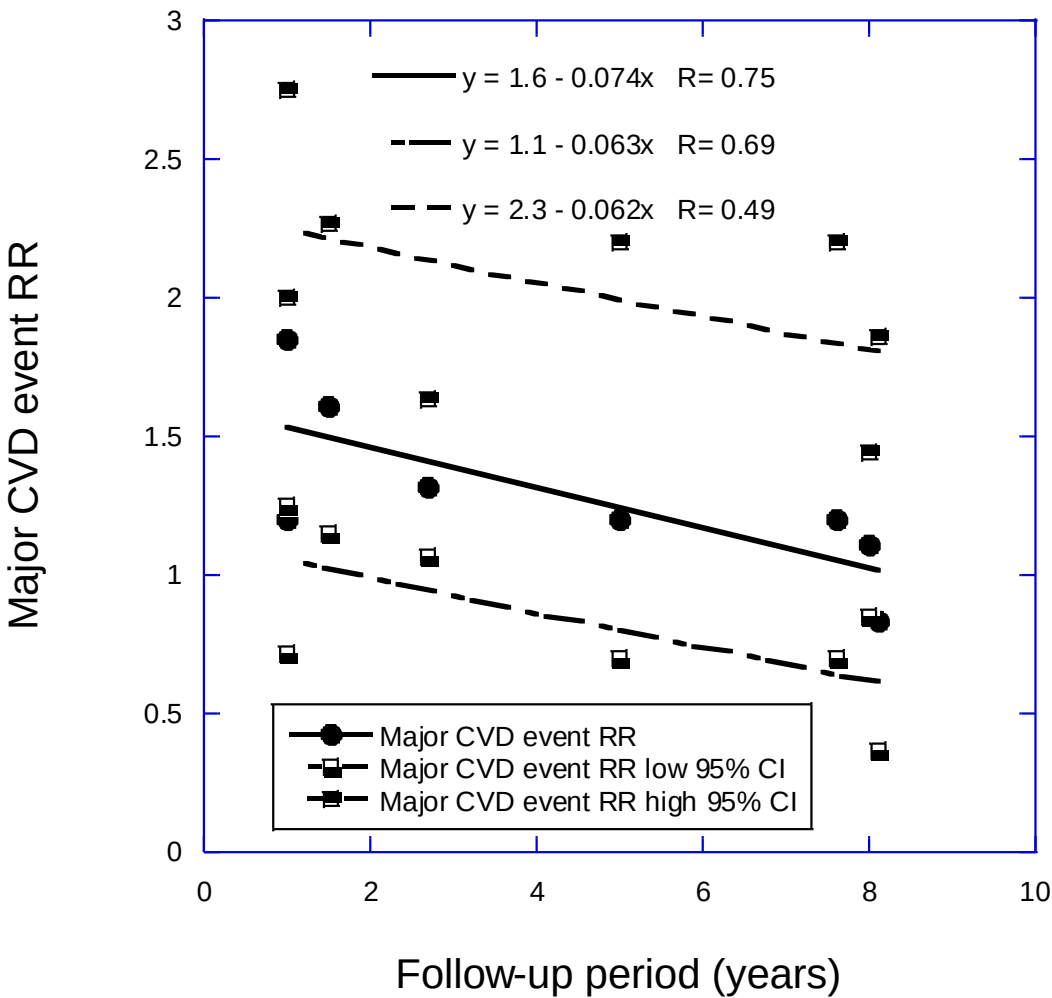


Figure 2. Plot of relative risk of major CVD event vs. mean follow-up period.

4. Discussion

The meta-analysis by Su et al. [7] found an average value of 0.78 (95% CI, 0.70–0.86). That is approximately half the reduction for the study with the one-year follow up and 44% as large as the regression fit to zero follow-up period. This finding provides more evidence that not considering the effect of follow-up period in doing meta-analyses of observational studies with long follow-up times can greatly underestimate the effect of the parameter studied. As a result, public policy recommendations are not as strong as they could be.

A 2020 article calculated the dose-response relationship for 25(OH)D concentration and risk of stroke (Shi, 2020) [44]. It used mostly the same observational studies as Su et al. [7]. The result, shown in Figure 2 in [44], was that risk decreased from near zero 25(OH)D concentration to about 20 ng/ml, then was flat out to 40 ng/mL with a reduction in risk of about 20%. However, due to not accounting for follow-up period, this analysis underestimates the reduction that can actually be achieved with vitamin D. On the other hand, it does show that the main change in risk is between very low and 10 to 15 ng/mL. Very few RCTs would enroll participants with mean 25(OH)D concentrations that low unless it was conducted in a country with low 25(OH)D concentrations. Such a country is Iran. Results

of a stratified randomized field trial of vitamin D supplementation in pregnant women reported that the mean baseline 25(OH)D concentration was 11 ng/mL [45]. By supplementing the women at one hospital with enough vitamin D to raise 25(OH)D concentration above 20 ng/mL, significant reductions were found for gestational diabetes, preeclampsia, and pre-term birth compared with outcomes in a similar but untreated hospital.

Will add a section on why the present knowledge is strong enough to say that 20 ng/mL reduces risk of stroke and CVD events.

An interesting question is how rapidly does vitamin D reduce risk of adverse brain and other health outcomes. As discussed in the analysis of follow-up period for cognitive function, an RCT demonstrated significant beneficial effects in improving cognitive function during one year of vitamin D supplementation [46]. To examine this question, Google Scholar was searched for representative RCTs that found a beneficial effect on brain health in less than one year. The findings are given in Table 2. As can be seen, significant benefits were found for depression and cognitive function. These studies provide evidence that raising serum 25(OH)D concentrations can produce significant improvements in brain health in less than a year. Interestingly, three of the papers dealt with studies from China, India, and/or Iran. In countries such as Iran, serum 25(OH)D concentrations are generally low, thus RCTs conducted there are more likely to show health benefits than studies done in countries with higher mean 25(OH)D concentrations.

Table 2. Results of short-term vitamin D supplementation on brain health.

Participants	Duration (weeks)	Condition	Intervention	Outcomes	Reference
Meta-analysis of nine clinical trials, China and Iran	8–52	Mental health	50,000 IU per week or two weeks or higher single dose	Beck Depression Inventory, weighted mean difference, -3.9 (95% CI, -5.2– -2.7)	[47]
46 patients, India Baseline 25(OH)D: N/A	12	Major depressive disorder	usual treatment or usual treatment plus 3 million IU vitamin D	Significantly greater improvement in depression score with vitamin D than placebo; also quality of life.	[48]
64 patients under methadone maintenance treatment, Iran. Baseline 25(OH)D: 14 ± 4 ng/mL	24	Cognitive function	50,000 IU or placebo every two weeks	Vitamin D treatment resulted in significant improvement in Iowa Gambling Task, Verbal Fluency Test, Reverse Digit Span, and visual working memory.	[49]
42 women, USA mean age 58 ± 6 years, BMI, 30.0 ± 3.5 kg/m², Baseline 25(OH)D: 23 ± 6 ng/mL	52	Cognitive outcome	600, 2000, or 4000 IU/d vitamin D ₃	2000 IU/d group had improved visual and working memory and learning; the 4000 IU/d group had slower attention reaction time	[50]

There are many reasons why serum 25(OH)D concentrations change with time over time scales from months to years. Table 3 lists a number of these reasons along with references that provide more information.

Table 3. Why 25(OH)D concentrations may change over time (should order be changed?).

Reason	Reference
Decline with age due to reduced production from solar UVB	[51]
Increased awareness of the overall benefits of vitamin D	[52]
Change amount of omega-3 fatty acid supplementation	[53]
Change geographic location	[54]
Retire from work	
Change in diet with reduced meat, fish consumption	[55]
Change in body mass	[56]
Change in physical activity	[57]
Change in use of sunscreen/sunblock, clothing when in sunlight	[58]
Increased use of sunscreen in cosmetics	[59]
Season	[60,61]
Increased vitamin D supplementation after menopause	[62]
Vitamin D fortification of food instituted country wide	[63]

Reviews

Topic	
Vitamin D mechanisms	(Yarlagadda, 2020) [64]
Post-stroke, 25(OH)D at time of stroke	(Marek, 2022) [65]
Risk of recurrent stroke	(Vergatti, 2023) [66]
Review, association, mechanisms, 25(OH)D, oral intake	(Cui, 2024) [67]

Mechanisms whereby vitamin D reduces risk of stroke

RCTs have not supported the role of vitamin D in reducing risk of stroke. A 2020 systematic review and meta-analysis of vitamin D supplementation and incidence of stroke included 13 RCTs [68]. The mean age was 66 years and the mean follow-up time was 3.1 years. The mean baseline 25(OH)D concentration for studies that reported values was 19.4 ng/mL (range: 8.8–25.4 ng/mL). The percentage of participants in these 13 trials was 2.1% in both treatment and control arm, resulting RR for stroke = 1.00 (95% CI, 0.91–1.10). Inspection of the baseline characteristics of participants in these trials in Table 1 in Nudy [68] finds that participants were being studied regarding various adverse health effects including arthritis index pain, asthma exacerbations, progression to type 2 diabetes mellitus, falls and fractures, insulin sensitivity, or renal function. In other words, none of the trials was established specifically to evaluate the role of vitamin D supplementation in the risk of stroke incidence.

A 2024 review included a different set of five vitamin D RCTs regarding ischemic stroke risk [67]. Mean baseline 25(OH)D concentrations were from 66 ± 23 ng/mL to 77 ± 25 ng/mL in four trials and 38 ± 16 ng/mL in one trial. Follow-up duration ranged from 3.3 to 5.3 years. All of these trials had cardiovascular disease outcome as a primary outcome. Again, no significant difference in stroke risk was found between the vitamin D treatment and control arms.

Even if the trials had been set up to test for stroke incidence, it is unlikely that they would have found a beneficial effect. There are two reasons. First, nearly all vitamin D RCTs have been based on guidelines for pharmaceutical drugs. In such trials, the control arm does not receive any of the drug. That is not the case for vitamin D trials since vitamin D is a naturally occurring substance required for life. Robert Heaney outlined guidelines for trials regarding nutrients in 2014 [69]. The main steps appropriate for vitamin D [70] are: 1, measure 25(OH)D concentrations and include those with low concentrations appropriate for the outcome of interest; 2, give a vitamin D dose large enough to raise 25(OH)D concentrations to where beneficial effects are expected; 3, measure achieved 25(OH)D concentrations; 4, analyze results with respect to achieved vitamin D concentrations. The second reason for poor results from vitamin D RCTs is that the enroll people with relatively high 25(OH)D concentrations, give relatively low doses and permit participants in the control arm to take moderate

vitamin D supplements, and analyze with respect to intention to treat. These failures have been discussed in two 2022 reviews [71,72].

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Institutional Review Board Statement: Not applicable.

Data Availability Statement: The original contributions presented in the study are included in the article or in the references provided. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: W.B.G. has had funding from Bio-Tech Pharmacal, Inc., (Fayetteville, AR, USA). The funder had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results. P.M. has no conflicts of interest to declare.

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