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Article

Circulating 25-hydroxyviamin D levels and Risk of Incident Stroke: An Updated Meta-analysis

Jong-Myon Bae [1,*]

[1] Department of Preventive Medicine, Jeju National University College of Medicine 1; jmbae@jejunu.ac.kr

* Correspondence: jmbae@jejunu.ac.kr; Tel.: +82-64-758-3230

Abstract: A recent systematic review for 19 selected articles after searching through to 30 September 2017 showed vitamin D deficiency was associated with ischemic stroke (IS), not hemorrhagic stroke (HS). But a heterogeneity would be introduced with comparing the lowest and highest category of vitamin D. The aim of this article was to conduct an updated meta-analysis (UMA) with searching through to 31 March 2019. An interval collapsing method as information extraction was applied in order to decrease a heterogeneity among studies. Additional articles were selected from cited lists from 19 selected articles using citation discovery tools. Random effect model was applied if I-squared value was over 50%. A funnel plot and Egger's test were used to detect a publication bias. After 5 new studies were added, the summary RRs [and their 95% confidence intervals] (I-squared value) were 1.52 [1.33-1.74] (0.0%) in IS, and 2.44 [1.34-4.46] (69.7%) in HS. This UMA supported the hypothesis that serum vitamin D deficiency was associated with an increased risk of HS as well as IS. Diverse public health programs against vitamin D deficiency status would be needed for higher risk group, especially elderly people.

Keywords: Vitamin D; Stroke; Meta-analysis

1. Introduction

As stoke is a leading case of mortality and disability globally [1], the economic burden is substantial [2,3]. Although hypertension, diabetes mellitus, obesity, and stroke are well known as important risk factors of stroke, the exploration of unknown risk factors is still needed [2,4].

Several studies reported that the incidence of first-ever stroke (FES) is higher on winter and spring [5]. As like as tuberculosis [6] or depression [7] showing seasonal variation of occurrence, a hypothesis of the association between vitamin D deficiency and risk of FES has been suggested [8-10]. And Zhou et al. [4] conducted a quantitative systematic review using 19 relevant articles [11-29] published through to 30 September 2017. Authors concluded that vitamin D level was associated with ischemic stroke (IS), but not hemorrhagic stroke (HS).

However, the following two problems were found in Zhou et al. [4] First, they did not distinguish the measuring method of vitamin D from blood sampling or intake amounts. Among 19 selected articles, Kojima et al. [15] and Ford et al. [22] evaluated the vitamin D level of subjects through food frequency questionnaire and supplement intake, respectively. The remaining articles assessed the vitamin D level by measuring serum 25-hydroxyvitamin D [25(OH)D]. Second, Michos et al. [16] having the outcome as mortality was selected for meta-analysis, even though the aim of Zhou et al. [4] was to verify the association between vitamin D and the 'incidence' of stroke. Thus, it is necessary to carry out an updated meta-analysis (UMA) in order to clarify the results in Zhou et al. [4]. Thus, the aim of this UMA was to evaluate the hypothesis that lower level of circulating 25(OH)D was associated

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with an increased risk of stroke.

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2. Materials and Methods

As Zhou et al. [4] selected the relevant articles that were published through to 30 September 2017, it is necessary to add relevant studies that were published till 31 March 2019. A search list was created through the citation discovery tools (CDT) of "cited by" provided by PubMed [30] from 19 articles selected by Zhou et al. [4]. The selection criteria were analytic epidemiological studies that measured circulating 25(OH)D level of cohort participants and identified the risk of HS as well as IS and overall stroke (OS).

Instead of 'highest versus lowest' method (HLM) used by Zhou et al., [4] 'interval collapsing method' (ICM) was used to extract information of each selected article in order to make full use of the suggested information of selected articles [31,32]. The logarithm relative risk (logRR) and its standard error of logRR (SElogR) of each article was calculated from the extracted RR and 95% confidence intervals (CI).

Heterogeneity of articles was assessed with I-squared value (%). A random effect model was used when I-squared value was above 50% and if not, fixed effect model was used [33]. Subgroup analyses were conducted by study design such as cohort and case-control. Publication bias was evaluated by funnel plot and Egger's test. If a publication bias was confirmed, a sensitivity analysis was performed with limiting SElogRR. The level of statistical significance was set to 0.05.

3. Results

A total of 359 studies were retrieved from the 19 studies selected by Zhou et al. [4] using PubMed's CDT. Five studies among them were additionally selected [34-38]. Zhang et al. [34] and Manouchehri et al. [35] were published after 30 September 2017. With adding 16 studies [11-14, 17-21, 23-29], 21 studies were finally selected for meta-analysis (Table 1). There were 14 cohort studies [11-14,17,19-21,23-26,28,34] and 7 case-control studies [18,27,29,35-38].

Table 1. Summary table of the extracted information from 21 selected studies[1]

Reference number	First Author	Year	Design	Types of stroke	logRR	SElogRR	Study or Nation
11	Marniemi	2005	COS	OS	-0.07	0.23	Finland
12	Anderson	2010	COS	OS	0.41	0.13	IHC
13	Bolland	2010	COS	OS	0.34	0.29	New Zealand
14	Drechsler	2010	COS	OS	0.9	0.36	4D
17	Schierbeck	2012	COS	OS	0.52	0.22	DOPS
18	Sun	2012	CCS	IS	0.31	0.13	NHS
19	Kuhn	2013	COS	OS	-0.05	0.14	EPIC Germany
20	Perna	2013	COS	OS	0.22	0.10	ESTHER
21	Skaaby	2013	COS	OS	-0.12	0.10	Monica10&Inter99
23	Schneider	2015	COS	OS	0.11	0.06	ARIC

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24	Judd	2016	COS	OS	0.43	0.15	REGARDS
				IS	0.37	0.16	
				HS	0.49	0.24	
25	Zittermann	2016	COS	OS	0.89	0.41	Germany
				IS	0.86	0.57	
				HS	0.65	0.54	
26	Afzal	2017	COS	OS	0.13	0.07	CCHS
27	Alfieri	2017	CCS	IS	1.5	1.29	Brazil
28	Leung	2017	COS	OS	0.38	0.11	Hong Kong
				IS	0.36	0.12	
				HS	0.46	0.23	
29	Tan	2017	CCS	OS	1.47	1.08	China
				IS	1.42	1.04	
				HS	1.55	1.14	
34	Zhang	2019	COS	OS	-0.09	0.10	WHI-OS
35	Manouchehri	2017	CCS	HS	1.97	0.39	Iran
36	Afshari	2015	CCS	IS	1.26	0.64	Iran
37	Gupta	2014	CCS	IS	0.3	0.29	India
38	Chaudhuri	2014	CCS	IS	0.72	0.19	India

[1] CCS: case-control study; CI: confidence interval; COS: cohort study logRR: logarithm relative risk; HS: hemorrhagic stroke; IS: ischemic stroke; OS: overall stroke: SElogRR: standard error of logarithm relative risk

From the 21 studies, sRR [95% CI] (I-squared value, %) of OS, IS, and HS were 1.36 [1.19-1.55] (74.3%), 1.52 [1.33-1.74] (0.0%), and 2.44 [1.34-4.46] (69.7%), respectively (Table 2) (Figure 1). When subgroup analyses were conducted, the results from 3 cohort studies 2 case-control studies for risk of HS showed statistical significance.

Table 2. Summary relative risks [95% confidence intervals] (I-squared value, %) in {number} of selected articles by types of stroke

		Overall stroke	Ischemic stroke	Hemorrhagic stroke
All selected		1.36 [1.19-1.55] (74.3) {21}	1.52 [1.33-1.74] (0.0) {9}	2.44 [1.34-4.46] (69.7) {5}
	Cohort	1.21 [1.07-1.36] (67.3) {14}	1.46 [1.22-1.76] (0.0) {3}	1.63 [1.20-2.22] (0.0) {3}
	Case-control	2.32 [1.44-3.73] (71.4) {7}	1.59 [1.31-1.93] (25.1) {6}	6.87 [3.35-14.0] (0.0) {2}

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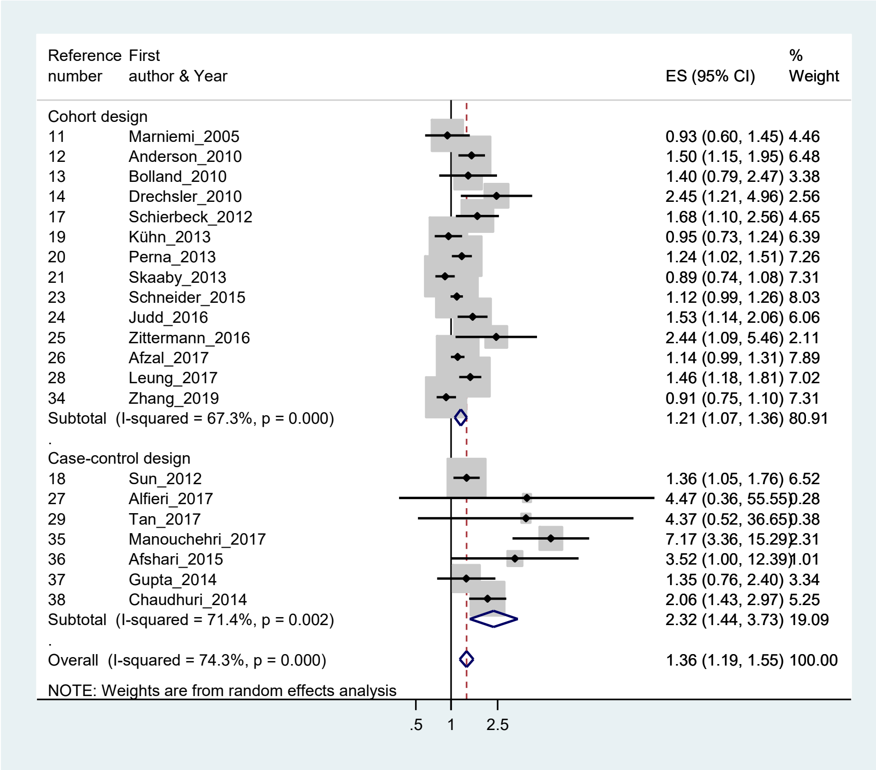

Figure 1. Forest plot for estimating the summary effect size (ES) in all 21 selected studies.

Egger's test on the 21 studies suggested a publication bias (P=0.003) (Table 3). When the test was performed to the 15 studies with SElogRR < 0.3, the publication bias disappeared (P=0.129) (Figure 2), and the sOR of OS remained statistically significant.

Table 3. Summary relative risks [95% confidence intervals] (I-squared value, %) in {number} of selected articles from restriction of standard error of log relative risk (SElogRR) and their P-value of Egger's test

Egger's test	All stroke	Ischemic stroke	Hemorrhagic stroke
P-value	0.003	0.026	0.379
P-value with SElogRR <0.3	0.129	0.639	-
summary effect size	1.23 [1.10-1.37] (67.7) {15}	1.49 [1.30-1.70] (0.0) {5}	-

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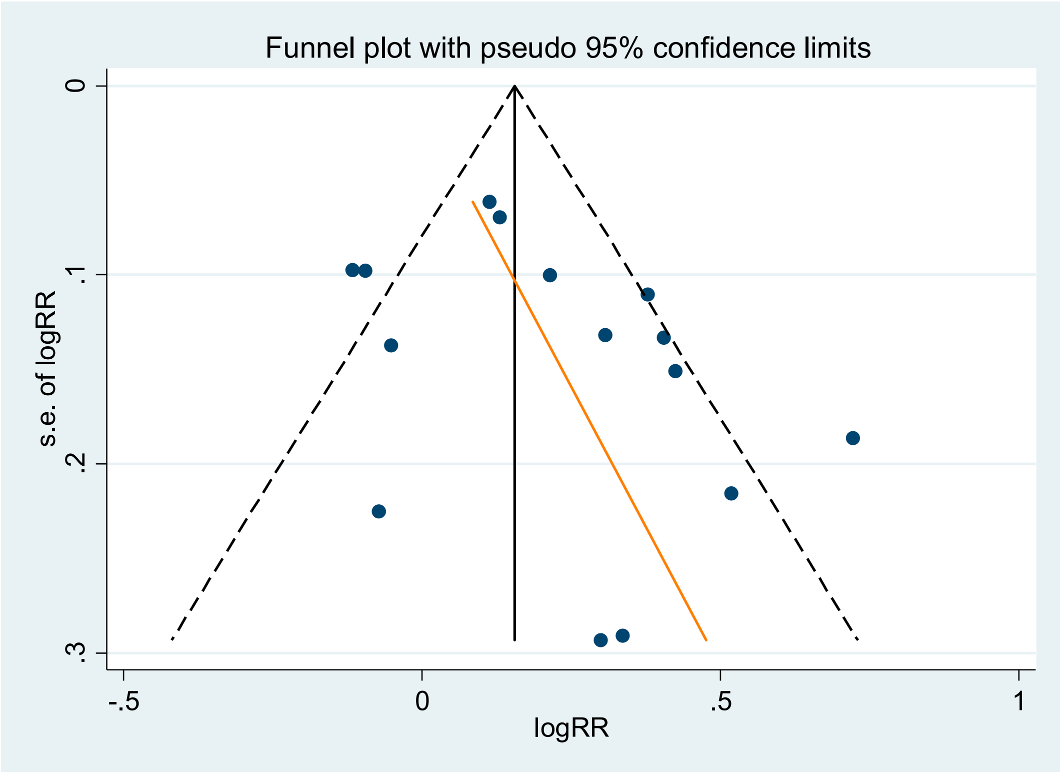

Figure 2. Funnel plot for 15 studies having standard error of log relative risk (s.e. of logRR) less than 0.3 (P-value of Egger's test = 0.129)

4. Discussion

The summary of results was that lower level of circulating 25(OH)D was associated with a significant, 1.36-fold in OS risk, 1.52-fold in IS risk, and 2.44-fold in HS risk. Statistical significance was maintained in subgroup analysis conducted by study design. Especially, this UMA showed that circulating vitamin D level was associated with HS through adding Manouchehri et al. [35] and using ICM [31,32], although Zhou et al. [4] did not show the statistically significant association between vitamin D and HS risk.

Based on these facts, this UMA had 2 advantages. First, five studies could be added using PubMed's CDT. Three [36-38] of them were published before 30 September 2017. In other word, they should be selected in Zhou et al. [4]. Thus. this fact suggested that adding new relevant studies using CDT would be efficient and valid methodology to conduct an UMA [30,39-41]. Second, ICM was used to make full use of the suggested information. That is more consistent with the original purpose of meta-analysis [42]. It is necessary to consider the ICM for the meta-analysis of nutritional epidemiological studies that categorize according to the overall distribution rather than the absolute criteria [31]. Because Zhou et al. [4] mentioned the limitation of heterogeneity introduced from using HLM.

Publication biases were in selected studies for OS and IS, except for HS. But they disappeared after restricting studies having SElogRR below 0.3 and the relationship between hypovitaminosis D and risk of OS and IS were significant. But, further analytically epidemiological studies for HS risk are needed

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because there is relatively little research on HS compared to IS.

5. Conclusions

In conclusion, this UMA derived the evidence that lower level of circulating vitamin D was associated with risk of HS as well as IS and OS. Thus, higher circulating vitamin D was one of protective factors for HS as well as IS. Diverse public health programs against vitamin D deficiency status would be needed for higher risk group, especially elderly people.

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Conflicts of Interest: The author declares no conflict of interest.

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