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Special Article – Vitamin D

Circulating 25-Hydroxyvitamin D levels and Risk of Incident Stroke: An Updated Meta-Analysis

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Abstract

A recent systematic review that selected 19 relevant articles that were published up until September 30, 2017 showed that vitamin D deficiency was associated with Ischemic Stroke (IS) but not Hemorrhagic Stroke (HS). However, heterogeneity would be introduced when comparing the lowest and highest categories of vitamin D. The aim of this article was to conduct an Updated Meta-Analysis (UMA) that involved searching for relevant articles published up until March 31, 2019. An interval collapsing method was applied for information extraction to decrease heterogeneity among studies. Additional articles were selected from cited lists from 19 selected articles using citation discovery tools. The random effect model was applied if the I-squared value exceeded 50%. A funnel plot and Egger's test were used to detect publication bias. After the addition of five new studies, the relative risks [and their 95% confidence intervals] (and I-squared value) were 1.52 [1.33-1.74] (0.0%) for IS and 2.44 [1.34-4.46] (69.7%) for 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 targeting vitamin D deficiency are needed for higher-risk groups, such as the older population.

Keywords: Vitamin D; Stroke; Risk factors; Systematic Review; Meta-analysis

Abbreviations

25(OH)D: 25-Hydroxyvitamin D; CDT: Citation Discovery Tools; CI: Confidence Interval; FES: First-Ever Stroke; HLM: Highest Versus Lowest Method; HS: Hemorrhagic Stroke; ICM: Interval Collapsing Method; IS: Ischemic Stroke (IS); logRR: Logarithm Relative Risk; OS: Overall Stroke; RR: Relative Risk; SElogRR: Standard Error of Logarithm Relative Risk; sRR: Summary Relative Risk

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 in winter and spring [5]. Similar to tuberculosis [6] or suicide [7] that show seasonal variation of occurrence, the hypothetical association between vitamin D deficiency and risk of FES has been suggested [8-10]. Zhou et al. [4] conducted a quantitative systematic review of 19 relevant articles [11-29] published up to 30 September 2017, and concluded that vitamin D level was associated with Ischemic Stroke (IS), but not Hemorrhagic Stroke (HS).

However, the following two issues were identified with the study by Zhou et al [4]. First, they did not specify the method by which vitamin D was measured from blood sampling or intake amounts. Among the 19 selected articles, Kojima et al. [15] and Ford et al. [22] evaluated the vitamin D level of subjects using a food frequency questionnaire and supplement intake data, respectively. The remaining articles assessed vitamin D levels 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 level and the 'incidence' of stroke. Thus, it is necessary to perform an Updated Meta-Analysis (UMA) to clarify the results in Zhou et al [4]. The aim of this UMA was to evaluate the hypothesis that lower level of circulating 25(OH) D are associated with an increased risk of stroke.

Materials and Methods

As Zhou et al. [4] selected relevant articles that were published up to September 30, 2017, it is necessary to add relevant studies that have been published up until 31 March 2019. A search list was created through the Citation Discovery Tools (CDT) of "cited by" provided by PubMed [30] from the 19 articles selected by Zhou et al [4]. The inclusion and exclusion criteria were as same as the study by Zhou et al [4]. In other words, the selection criteria were analytic epidemiological studies that measured the circulating 25(OH)D levels of cohort participants and identified the risk of HS as well as IS and Overall Stroke (OS).

Instead of the 'highest versus lowest' method (HLM) used by Zhou et al. [4], an 'Interval Collapsing Method' (ICM) was used to extract information from each selected article to make full use of the information in the selected articles [31,32]. The Logarithm Relative Risk (log RR) and the standard error of log RR (SE log R) for each article were calculated from the extracted Relative Risk (RR) and 95% confidence intervals (CI).

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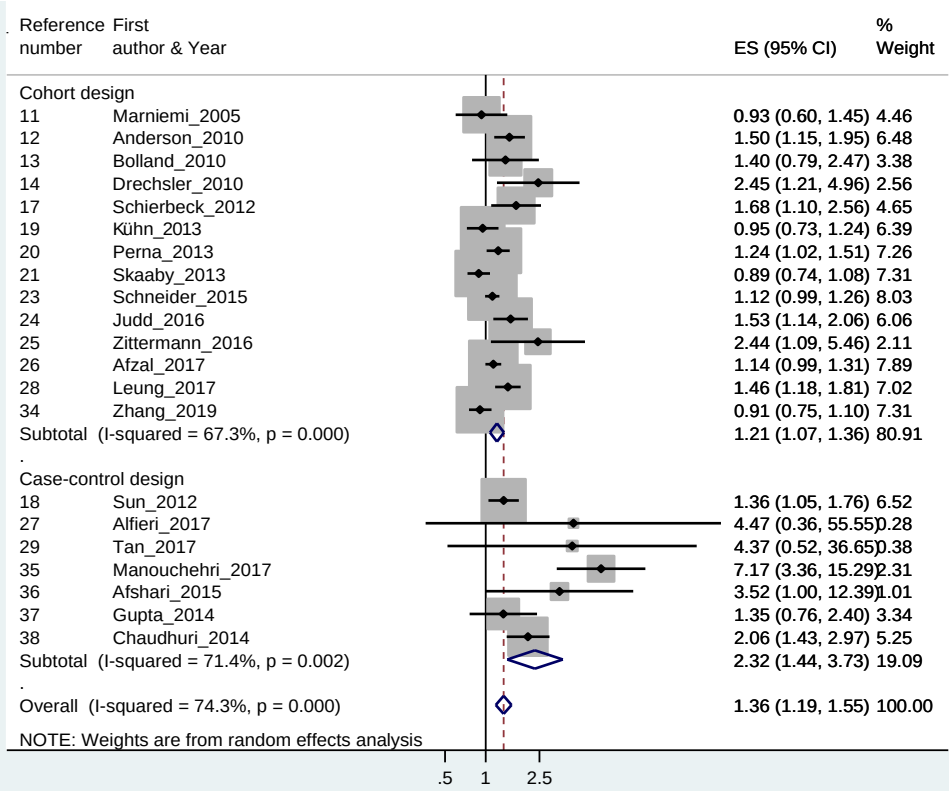

Figure 1: Forest plot for estimating the summary effect size (ES) in all 21 selected studies.

The heterogeneity of articles was assessed by the I-squared value (%). A random effect model was used when the I-squared value exceeded 50%, whereas if this value was below 50% a 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, sensitivity analysis was performed with limiting SElogRR. The level of statistical significance was set to 0.05.

Results

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

From the 21 studies, the summary RR (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 three cohort studies and two case-control studies showed statistical significance regarding the risk of HS.

Egger's test on the 21 studies suggested 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.

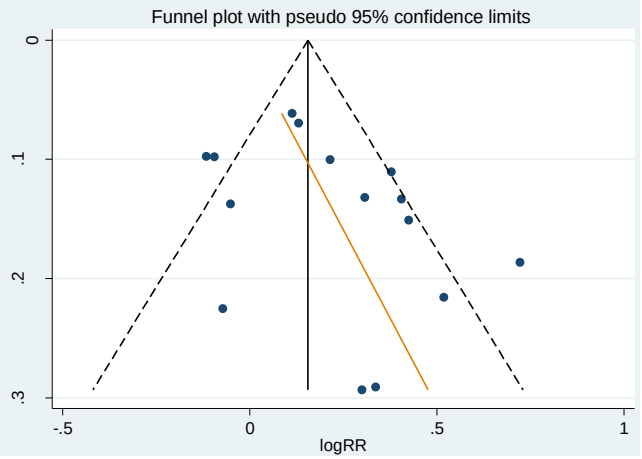

Figure 2: Funnel plot for 15 studies having standard error of log relative risk (s.e. of logRR) less than 0.3 (P-value of Egger's test = 0.129).

Discussion

Taken together, the results indicated that a lower level of circulating 25(OH)D was associated with a significant increase of 1.36-fold for the risk of OS, 1.52-fold for the risk of IS, and 2.44-fold for the risk of HS. Statistical significance was maintained in subgroup analysis conducted according to study design. In particular, this UMA showed that circulating vitamin D levels were associated with HS through adding Manouchehri et al. [35] and using ICM [31,32]. Zhou et al. [4] did not show the statistically significant association

Table 1: Summary table of the extracted information from 21 selected studies*.

Reference number	First Author	Year	Design	Types of stroke	No. of Subjects	logRR	SElogRR	Study or Nation
11	Marniemi	2005	COS	OS	755	-0.07	0.23	Finland
12	Anderson	2010	COS	OS	41 504	0.41	0.13	IHC
13	Bolland	2010	COS	OS	1471	0.34	0.29	New Zealand
14	Drechsler	2010	COS	OS	1108	0.9	0.36	4D
17	Schierbeck	2012	COS	OS	2 016	0.52	0.22	DOPS
18	Sun	2012	CCS	IS	928	0.31	0.13	NHS
19	Kuhn	2013	COS	OS	3 115	-0.05	0.14	EPIC Germany
20	Perna	2013	COS	OS	9949	0.22	0.1	ESTHER
21	Skaaby	2013	COS	OS	9146	-0.12	0.1	Monica 10 & Inter 99
23	Schneider	2015	COS	OS	12 158	0.11	0.06	ARIC
24	Judd	2016	COS	OS	1 547	0.43	0.15	REGARDS
				IS		0.37	0.16	
				HS		0.49	0.24	
25	Zittermann	2016	COS	OS	154	0.89	0.41	Germany
				IS		0.86	0.57	
				HS		0.65	0.54	
26	Afzal	2017	COS	OS	116 655	0.13	0.07	CCHS
27	Alfieri	2017	CCS	IS	286	1.5	1.29	Brazil
28	Leung	2017	COS	OS	3458	0.38	0.11	Hong Kong
				IS		0.36	0.12	
				HS		0.46	0.23	
29	Tan	2017	CCS	OS	404	1.47	1.08	China
				IS		1.42	1.04	
				HS		1.55	1.14	
34	Zhang	2019	COS	OS	4 808	-0.09	0.1	WHI-OS
35	Manouchehri	2017	CCS	HS	150	1.97	0.39	Iran
36	Afshari	2015	CCS	IS	72	1.26	0.64	Iran
37	Gupta	2014	CCS	IS	143	0.3	0.29	India
38	Chaudhuri	2014	CCS	IS	500	0.72	0.19	India

*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

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}

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}	-

between vitamin D and HS risk.

Based on the findings, this UMA has two advantages. First, five studies were added using PubMed's CDT, three [36-38] of which were published before 30 September 2017. In other words, they should have been selected in the analysis of Zhou et al [4]. This suggests that adding new relevant studies using CDT would be an efficient

and valid methodology to conduct an UMA [30,39-41]. Second, ICM was employed to make full use of the suggested information, which was consistent with the original purpose of the meta-analysis [42]. It is necessary to consider ICM for 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 that a limitation was the heterogeneity introduced by using HLM.

The major limitations and suggestion of this UMA are as follows. First, author did not evaluate the quality of selected articles using the Newcastle-Ottawa Scale (NOS) or Grading of recommendation, assessment, development and evaluation. Instead, author did conduct subgroup analyses by study design for observational studies in nutritional epidemiology. The reason was based on the suggestion by Bae JM [43], which concluded that 'it is more reasonable to control for quality level by performing subgroup analysis according to study design rather than by using high quality based on the NOS quality assessment tool. "Second, publication biases was detected in selected studies for OS and IS, but not HS, but this was removed by restricting studies that had a SElogRR of below 0.3. The relationship between hypovitaminosis D and the risk of OS and IS was significant. Further analytical epidemiological studies for HS risk are needed because of the lack of research on HS compared to IS.

Conclusion

Despite above limitations, this UMA provided that a lower level of circulating vitamin D was associated with the risk of HS, as well as IS and OS. Thus, higher levels of circulating vitamin D might be a protective factor for HS, as well as IS.

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