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Circulating vitamin D level and mortality in prostate cancer patients: a dose-response meta-analysis

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Abstract

Previous studies investigating the association of circulating 25-hydroxyvitamin D level with prognosis of prostate cancer yielded controversial results. We conducted a dose-response meta-analysis to elucidate the relationship. PubMed and Embase were searched for eligible studies up to July 15, 2018. We performed a dose-response meta-analysis using random-effect model to calculate the summary hazard ratio (HR) and 95% confidence interval (CI) of mortality in patients with prostate cancer. Seven eligible cohort studies with 7,808 participants were included. The results indicated that higher vitamin D level could reduce the risk of death among prostate cancer patients. The summary HR of prostate cancer-specific mortality correlated with an increment of every 20 nmol/L in circulating vitamin D level was 0.91, with 95% CI 0.87-0.97, P=0.002. The HR for all-cause mortality with the increase of 20 nmol/L vitamin D was 0.91 (95% CI: 0.84-0.98, P=0.01). Sensitivity analysis suggested the pooled HRs were stable and not obviously changed by any single study. No evidence of publications bias was observed. This meta-analysis suggested that higher 25-hydroxyvitamin D level was associated with a reduction of mortality in prostate cancer patients and vitamin D is an important protective factor in the progression and prognosis of prostate cancer.

Keywords: Vitamin D; Mortality; Prostate cancer; Meta-analysis

Introduction

Prostate cancer (PCa) is one of the most common malignant tumors in male. In 2017, American Cancer Society reported 161,360 cases of newly diagnosed PCa, accounting for 20% of male tumors. Furthermore, its incidence and mortality ranked the first place and third respectively [1]. The mortality of PCa was proposed to be associated with obesity, physical

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activity, smoking, antioxidants, etc. [2]. At present, the treatment of PCa have caused serious economic burden [3]. More useful treatment measures are urgently needed by people to improve the survival rate of prostate cancer patients.

The major circulating form of vitamin D in human body is 25-hydroxyvitamin D (25(OH)D), which comes from vitamin D via 25-hydroxylation process in the liver. 25(OH)D can be converted into $1,25(OH)_2D$ by 1α-hydroxylase, which is the most active hormonal metabolite of vitamin D. As a hormone, $1,25(OH)_2D$ binds to vitamin D receptor located in nucleus and functions. It's reported to play an important role in cellular proliferation [4], differentiation, apoptosis [5], angiogenesis [6] and metastasis [7]. All these processes may regulate the development and progression of cancer.

A number of researches have been done to clarify the association between vitamin D and PCa. Some experimental studies indicated that vitamin D might play a crucial role in the occurrence and progression of PCa. One study demonstrated mutations of vitamin D receptor gene were associated with Gleason score [8]. Furthermore, study showed that genetic variants in the vitamin D pathway had effects on the risk of progression, prostate cancer-specific mortality and recurrence of PCa [9]. Recent studies have reported controversial results about the association of vitamin D with the survival rate of prostate cancer. For example, in newly diagnosed stage IV prostate cancer patients, no significant association of 25-hydroxyvitamin D with the prognosis of them was found [10]. In contrast, other studies reported that higher 25-hydroxyvitamin D was related to improved prostate cancer prognosis [11, 12].

Therefore, it's still unclear the relationship between 25-hydroxyvitamin D level and mortality of PCa. Hence, we conducted this analysis to explore whether circulating

25-hydroxyvitamin D level was correlated with the survival of PCa through a dose-response meta-analysis.

Materials and Methods

Search strategy

We searched PubMed and Embase databases from inception to July 15, 2018 for eligible studies on the relationship between vitamin D and mortality in prostate cancer patients. The terms used to retrieve literatures were the following: (vitamin D OR 25-hydroxyvitamin D OR 25(OH)D) and (prostate cancer OR prostate carcinoma). We also referred to the reference lists from reviews or relevant papers to get more eligible researches. There was no language restriction.

Selection criteria

Reports were included in this dose–response meta-analysis if they met the criteria as follows: (1) the association between vitamin D and mortality in prostate cancer patients was reported; (2) the study type was cohort; (3) The risk estimates of mortality in prostate cancer patients, like hazard ratio (HR) and 95% confidence interval (CI) were reported. If the same data were used in several studies, we selected the publication with the largest number of cases or more details.

Data extraction

Data were extracted from eligible studies by two researchers independently. The information collected from each study contained of the first author's last name, publication year, country, follow-up time, number of cases and person-year, risk estimates with corresponding 95% confidence intervals and confounding factors adjusted in multivariable

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89 analysis. We extracted the risk estimates from the most completed adjusted model to decrease
90 the risk of possible confounding. Disagreements were resolved by consensus among authors.

91 Quality assessment

92 We evaluated the quality of studies by use of the Newcastle Ottawa Scale (NOS) [13].
93 According to its criteria, studies were assessed on basis of three perspectives: selection,
94 comparability and outcomes. If studies got 7 or more stars, they were regarded as high quality.
95 Differences were resolved by discussion.

96 Statistical analysis

97 We performed data analyses separately for two outcomes, namely all-cause mortality and
98 prostate cancer-specific mortality. Pooled hazard ratios (HRs) were calculated to assess the
99 impact of vitamin D level on the prognosis of patients. The method proposed by Greenland
100 and Longnecker [14] and Orsini [15] was used to estimate the HR per 20 nmol/L increase of
101 vitamin D level. Statistical heterogeneity among studies was evaluated with the use of Q and
102 I^2 statistic [16, 17]. For the Q statistic, we regarded P value < 0.10 as statistically significant
103 heterogeneity among studies. As to the I^2 statistic, I^2 more than 50% also suggested obvious
104 heterogeneity. We utilized the random-effects model to combine HRs from single studies if
105 obvious heterogeneity was observed [18]. In the sensitivity analysis, studies were omitted one
106 by one and the others were analyzed to evaluate the effect of single study on the summary risk
107 estimates. Publication bias was assessed with the use of funnel plot and the Egger's test [19].
108 We utilized Stata (Version 12.0) to perform this dose-response analysis. P value <0.05 was
109 reckoned as statistically significant difference.

110 Results

Study selection and characteristics

The selection process was showed in Figure 1. We retrieved 2,650 articles from PubMed and Embase databases (Figure 1). A majority of them were excluded from our analysis because they did not belong to cohort studies, or because outcomes were not associated with our analysis, leaving 19 articles for detailed evaluation by reading full-texts [20-38]. 12 studies were then removed after reading their full-texts. Two studies were excluded because of inadequate study design [22, 24]. Nine studies were excluded because they did not contain prognosis data among prostate cancer patients [20, 21, 26, 27, 29, 33, 36, 38]. One study was not qualified as a result of unusable data [37]. Finally, a total of 7 studies were included into our meta-analysis. The 7 studies were published between 2009 and 2016 and the total number of prostate cancer participants was 7,808. All of them were performed in developed countries, written in English (Table 1). Among them, three studies were conducted in USA [30, 31, 35], two in Norway [23, 32], one in Finland [28], one in Sweden [34]. All studies were prospective cohort type, except one from Tretli S. It's also a cohort study but hard to define it belongs to prospective or retrospective type. Meanwhile, the vitamin D assessments were performed after diagnosis in three studies, while the others were before diagnosis of prostate cancer. All studies reported adjusted HRs. Every research was adjusted for many confounding factors, such as age, BMI, drinking history and so forth. Participants were followed up from 4 to 21 years. Five studies contained HRs of all-cause mortality among prostate cancer patients, and six reported HRs of prostate cancer-specific mortality. The quality assessment of those studies according to NOS criteria was also presented in the Table 1.

25-hydroxyvitamin D and all-cause mortality

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We observed significant heterogeneity among 5 studies on all-cause mortality (I2=68.9%). Figure 2-A displayed the results of the dose-response analyses on all-cause mortality (Figure 2-A). A nonlinear relationship existed between 25-hydroxyvitamin D and risk of all-cause mortality in prostate cancer patients, suggesting higher 25-hydroxyvitamin D level was associated with decreased risk of death from all causes among prostate cancer patients (p=0.038). The summary HR of all-cause mortality correlated with an increment of every 20 nmol/L in circulating vitamin D level was 0.91 (95% CI: 0.84-0.98, P=0.01)(Figure 3-A). Sensitivity analysis suggested the pooled HRs were stable and not obviously changed by any individual study (Figure 4-A).

25-hydroxyvitamin D and prostate cancer-specific mortality

There was obvious heterogeneity observed among those 6 studies on prostate cancer-specific mortality (I^2=53.4%). A nonlinear relationship between 25-hydroxyvitamin D and risk of prostate cancer-specific mortality was also presented in Figure 2-B, indicating higher vitamin D level could decrease the mortality from prostate cancer (Figure 2-B). The summary HR of prostate cancer-specific mortality correlated with an increment of every 20 nmol/L in circulating vitamin D level were 0.91 (95% CI: 0.87-0.97, P=0.002) (Figure 3-B). The sensitivity analysis showed the summary HRs were not markedly changed by any individual study (Figure 4-B), indicating no significant influence of single study on the results.

Publication bias

No risk of publication bias was observed in the funnel plots (Figure 5). The outcomes from Egger's test also suggested that there were no publication bias for the analysis of

all-cause mortality (P=0.143) and prostate cancer-specific mortality (P=0.301).

Subgroup analysis and meta-regression

We conducted the subgroup analysis and meta-regression to detect the source of heterogeneity, which was presented in Table 2. Stratifying by the time of vitamin D assessment, the HR of prostate cancer-specific mortality was 0.91 (95% CI: 0.88-0.95) for prediagnosis studies and 0.84 (95% CI: 0.58-1.21) for postdiagnosis ones. The HR of all-cause mortality was 0.94(95% CI: 0.88-0.98) in prediagnosis subgroup. Restricting the analysis among more than 10 years follow-up yielded a HR of 0.92 (95% CI: 0.89, 0.96) and 0.94 (95% CI: 0.89-0.98) for prostate cancer-specific mortality and all-cause mortality respectively, which was slightly higher than the overall results. Moreover, there was no evidence of significant heterogeneity between subgroups with the use of meta-regression analyses.

Discussion

The role of circulating 25-hydroxyvitamin D and survival outcomes among prostate cancer patients remains unclear and controversial. This meta-analysis is the first one to focus on the relationship between 25-hydroxyvitamin D and mortality in prostate cancer, involving 7,808 participants with survival outcomes. The results calculated from 7 eligible studies indicated higher vitamin D level was significantly associated with decreased all-cause mortality and prostate cancer-specific mortality. Further dose-response analysis showed that every 20nmol/L increment in 25-hydroxyvitamin D level was associated with a 9% lower risk of all-cause mortality and prostate cancer-specific mortality. By conducted the subgroup analysis, we found the results were consistent in prediagnosis and more-than 10 years follow-up subgroups. The assessment of vitamin D before diagnosis was more likely to get rid

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of the influence of prostate cancer on the level of vitamin D and long follow-up time enabled researchers to calculate the outcome events more precisely. Based on the above findings, we conclude that higher circulating vitamin D level is associated with a lower risk of death from prostate cancer.

Numerous experimental studies have been done to elucidate the mechanism by which vitamin D affect the prostate cancer survival. According to previous studies, $1,25(OH)_2D$ could cause cell cycle arrest and induce apoptosis, inhibiting cell proliferation in several prostate cancer cell lines [39-41]. $1,25(OH)_2D$ played a protective role in preventing normal human prostate epithelial cell lines from oxidative stress in since it increased both the expression and activity of antioxidants, such as Glucose-6-phosphate dehydrogenase and glutathione [42]. Ben-Shoshan and colleagues demonstrated that $1,25(OH)_2D$ inhibited angiogenesis by reducing HIF-1α expression in various human prostate cancer cell lines [43]. In terms of animal model evidence, Ray and colleagues indicated that a diet deficient in vitamin D rather than vitamin D-sufficient diet accelerated growth of human prostate cancers insensitive to androgen therapy in athymic mice [44]. Another study reported that a higher vitamin D3-supplemented diet led to significant tumor shrinkage in mice bearing PC-3 prostate cancer xenografts [45]. Moreover, vitamin D could prevent the metastasis of prostate cancer according to several animal and cell experiments [46, 47]. Therefore, there is some evidence supporting the protective effect of vitamin D in prostate cancer. However, the underlying molecular mechanisms are still not fully clarified, and more studies are needed to explore them.

Some studies reported that 25-hydroxyvitamin D concentration was correlated with

prostate cancer pathology. Researchers found lower 25-hydroxyvitamin D concentrations were positively correlated with higher Gleason grade and tumor stage [48, 49]. The findings above provide some explanations for the prognostic role of 25-hydroxyvitamin D in prostate cancer.

Previous studies reported conflicting results about the vitamin D and prostate cancer incidence. One meta-analysis showed positive association between high level of vitamin D and increased incidence of prostate cancer [50]. Some studies also suggested that high incidence of aggressive prostate cancer in African Americans might be partly due to deficient concentrations of serum vitamin D [51, 52]. In the contrast, one Mendelian randomization study showed null relationship between vitamin D and risk of prostate cancer [53]. Other studies also failed to find a positive relationship between vitamin D and prostate cancer risk [48, 54]. The conflicting findings in the relationship between vitamin D and prostate cancer risk may result from the some factors, such as different populations, various study design, and different confounding factors. The findings in our study suggest that vitamin D is more likely to be a suppressive and protective factor during the development of prostate cancer. Therefore, there is still controversy on the role of vitamin D in prostate cancer, which need to be elucidated in future researches.

There is also some evidence from clinical trials on the roles of vitamin D in prostate cancer. In a clinical trial, low-grade prostate cancer patients took 4000 IU of vitamin D3 every day for a whole year and had a biopsy after the supplementation [55]. Results of biopsy revealed a decreased number of positive cores and no increase in Gleason Score [55]. Several randomized clinical trials showed that oral vitamin D3 modestly decreased the level of PSA

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[56], and reduced the PSA rise rate [57, 58]. However, a vitamin D supplementation trial showed no influence on free or total PSA level in African American population [59]. At present, the evidence from clinical trials on the roles of vitamin D in prostate cancer is still limited, and more clinical trials are needed.

There are potential limitations existing in our study which should be considered. For one thing, although all studies adjusted for confounding factors, some potential confounding factors related to vitamin D remained residual. For another, some studies included in our meta-analysis tested the circulating vitamin D level post-diagnosis or post-treatment, thus it's difficult to get rid of the possibility of reverse causality. What's more, the limited number of included studies restricted us to find the source of heterogeneity.

Based on the results mentioned above, we can draw the conclusion that higher vitamin D level is significantly associated with a risk reduction of all-cause mortality and prostate cancer-specific mortality, indicating vitamin D may exert a protective effect in the progression and prognosis of prostate cancer. More cohort studies and randomized clinical trial are needed to further illustrate the role of vitamin D in the pathogenesis and prognosis of prostate cancer.

Author contributions

Zhen-yu Song designed the study. Qiuming Yao, Zhi-yuan Zhuo and Zhe Ma extracted the

data. Zhen-yu Song and Qiuming Yao performed the analyses. Zhen-yu Song wrote the draft. Gang Chen revised it critically.

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Conflict of interests

The authors declare no conflicts of interests. They are all responsible for the content of the paper.

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Figure 1 Flowchart of study selection in the meta-analysis

Figure2-A Risk estimates with 95% CI for the association between 25(OH)D and all-cause mortality

Figure2-B Risk estimates with 95% CI for the association between 25(OH)D and prostate cancer-specific mortality

Figure 2 Dose-response relationships between 25(OH)D and risk estimates of all-cause mortality and prostate cancer-specific mortality

Figure 3-A Funnel plot of risk estimates of all-cause mortality of prostate cancer with the increment of 20 nmol/L in 25(OH)D level

Figure 3-B Funnel plot of risk estimates of prostate cancer-specific mortality with the increment of 20 nmol/L in 25(OH)D level

Figure 3 Summary risk estimates of mortality in prostate cancer patients associated with 20 nmol/L increment in 25(OH)D level

Figure 4-A Sensitivity analysis of the association between 25(OH)D and all-cause mortality of prostate cancer

Figure 4-B Sensitivity analysis of the association between 25(OH)D and prostate cancer-specific mortality

Figure 4 Sensitivity analysis by excluding studies by turns suggested that the pooled HRs were not significantly changed by any individual study

Figure 5-A Publication bias of the association between 25(OH)D and all-cause mortality of prostate cancer

Figure 5-B Publication bias of the association between 25(OH)D and prostate cancer-specific mortality

Figure 5 Publication bias

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Table 1 The main characteristics of the included studies in the meta-analysis

Study	Country	Study design	Time of vitamin D assessment	Participants	Follow-up	Outcomes	Age at diagnosis (years)	Adjustments	Quality
Tretli S 2009	Norway	Cohort	postdiagnosis	160	44 months	ACM; PCSM	64.5	patient group and age，tumor differentiation grade and the patient functional status at the time of blood collection	7
Fang F 2011	USA	Prospective cohort	prediagnosis	1822	10 years	ACM; PCSM	68.9	age at diagnosis, body mass index, physical activity, and smoking, Gleason score, and TNM stage	9
Holt SK 2013	USA	Prospective cohort	postdiagnosis	1476	10.8 years	PCSM	60	season of blood draw, age and race, BMI, smoking status, and weekly exercise stage, Gleason score and primary treatment	9
Gupta D 2015	USA	Prospective cohort	postdiagnosis	125	31 months	ACM; PCSM	60	age, ECOG performance status, body mass index(BMI), prostate specific antigen (PSA), season of blood draw, CTCA hospital, serum albumin, corrected serum calcium, bone metastasis and nutritional status	7
Mondul AM 2016	Finland	Prospective cohort	prediagnosis	1000	23 years	PCSM	69.2	age, physical activity, cigarettes per day, and family history of prostate cancer	9
Meyer HE 2016	Norway	Prospective cohort	prediagnosis	2282	21.2 years	ACM	NA	age, month of blood sampling and examination physical activity, BMI, smoking and education	9
Brandstedt J 2016	Sweden	Prospective cohort	prediagnosis	943	16.6 years	ACM; PCSM	69.3	season and year of inclusion, age at baseline, age at diagnosis, body mass index (BMI), and tumor characteristics (TNM and Gleason score)	9

Abbreviation: (ACM, all-cause mortality; PCSM, prostate cancer-specific mortality; BMI, body mass index; PSA, prostate specific antigen; ECOG, Eastern Cooperative Oncology Group; CTCA, Cancer Treatment Centers of America; NA, not available)

Table 2. Summary risk estimates of the associations between vitamin D level and prostate cancer mortality

Study characteristics	No. of studies	HR	95% CI	I^2 (%)	p-Value 1	p-Value 2
Studies of PCM	6	0.91	0.87-0.97	53.4	0.057	
Country						0.294
Europe	4	0.88	0.81-0.95	57.9	0.068	
USA	2	0.96	0.90-1.03	0	0.389	
Time of vitamin D assessment						0.36
postdiagnosis	2	0.84	0.58-1.21	89.1	0.002	
prediagnosis	4	0.91	0.88-0.95	0	0.675	
Follow-up						0.055
Less than 10 years	1					
More than 10 years	5	0.92	0.89-0.96	0	0.479	
Studies of ACM	5	0.91	0.84-0.98	68.9	0.012	
Country						0.295
Europe	3	0.87	0.79	68.5	0.042	
USA	2	0.98	0.93-1.03	0	0.576	
Time of vitamin D assessment						0.246
postdiagnosis	2	0.83	0.66-1.04	71.5	0.061	
prediagnosis	3	0.94	0.89-0.98	53.9	0.114	
Follow-up						0.246
Less than 10 years	2	0.83	0.66-1.04	71.5	0.061	
More than 10 years	3	0.94	0.89-0.98	53.9	0.114	

p-Value 1 for heterogeneity within each subgroup. p-Value 2 for heterogeneity between subgroups with meta-regression analysis.

Abbreviation: (ACM, all-cause mortality; PCSM, prostate cancer-specific mortality; HR, summary hazard ratio; CI, confidence interval)

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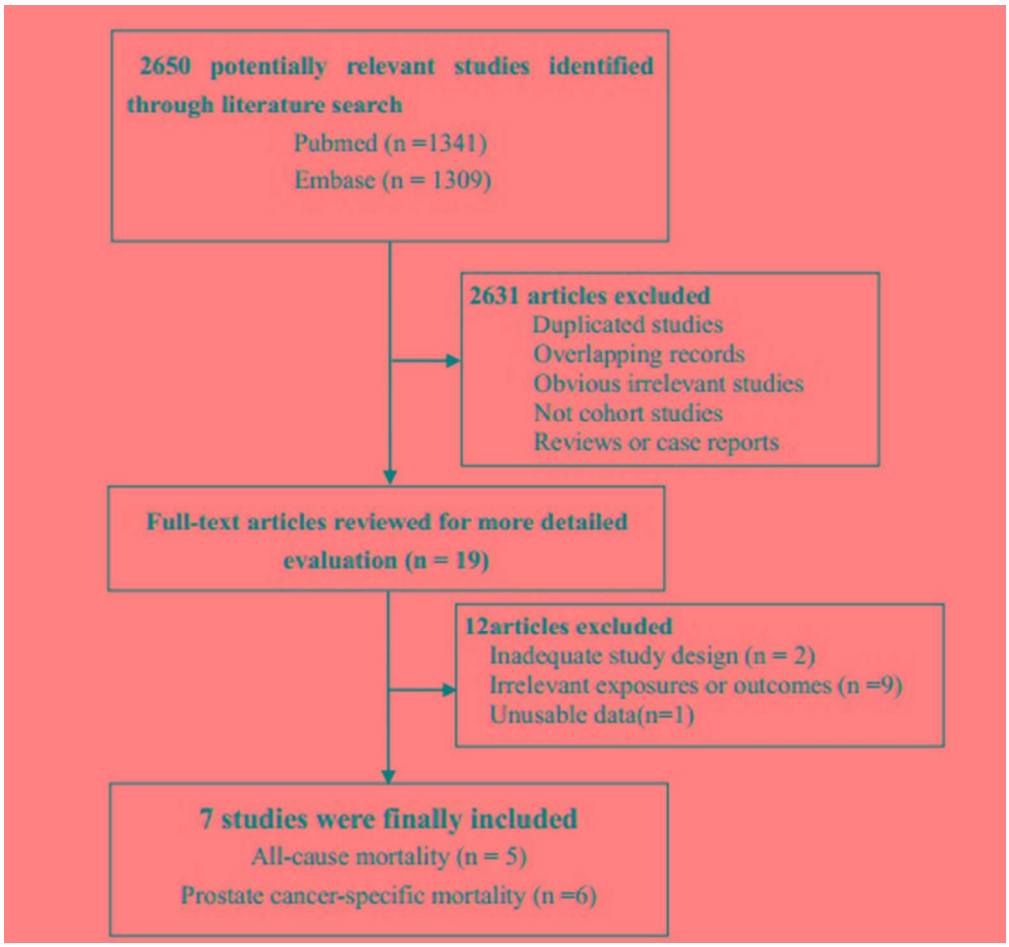

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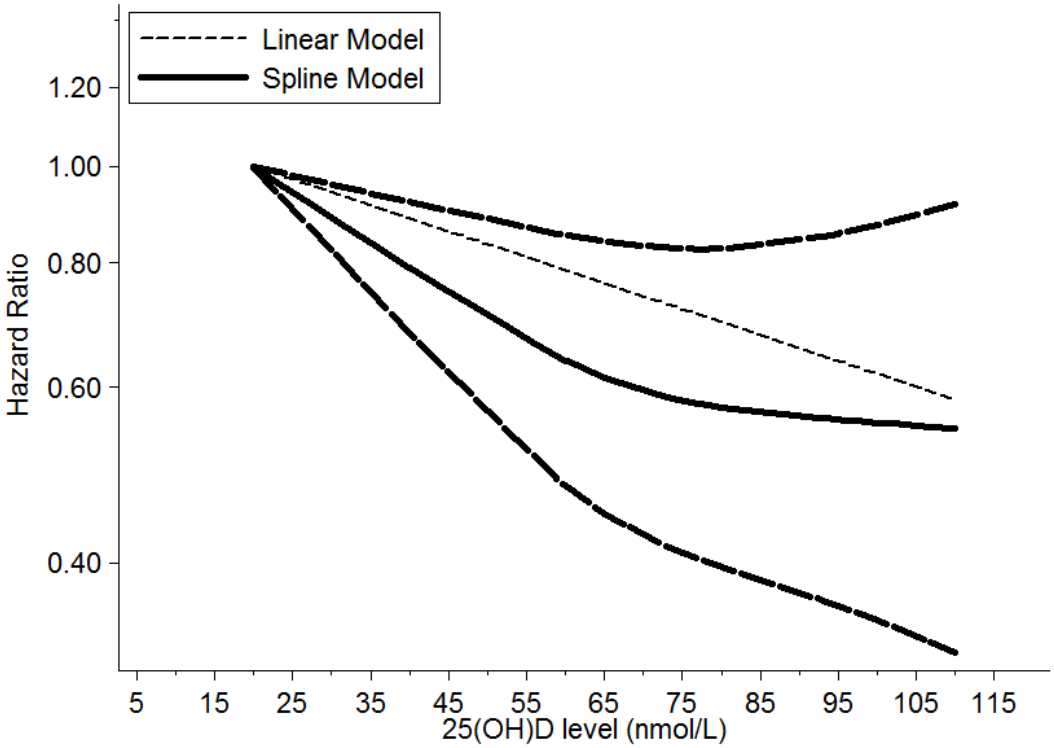

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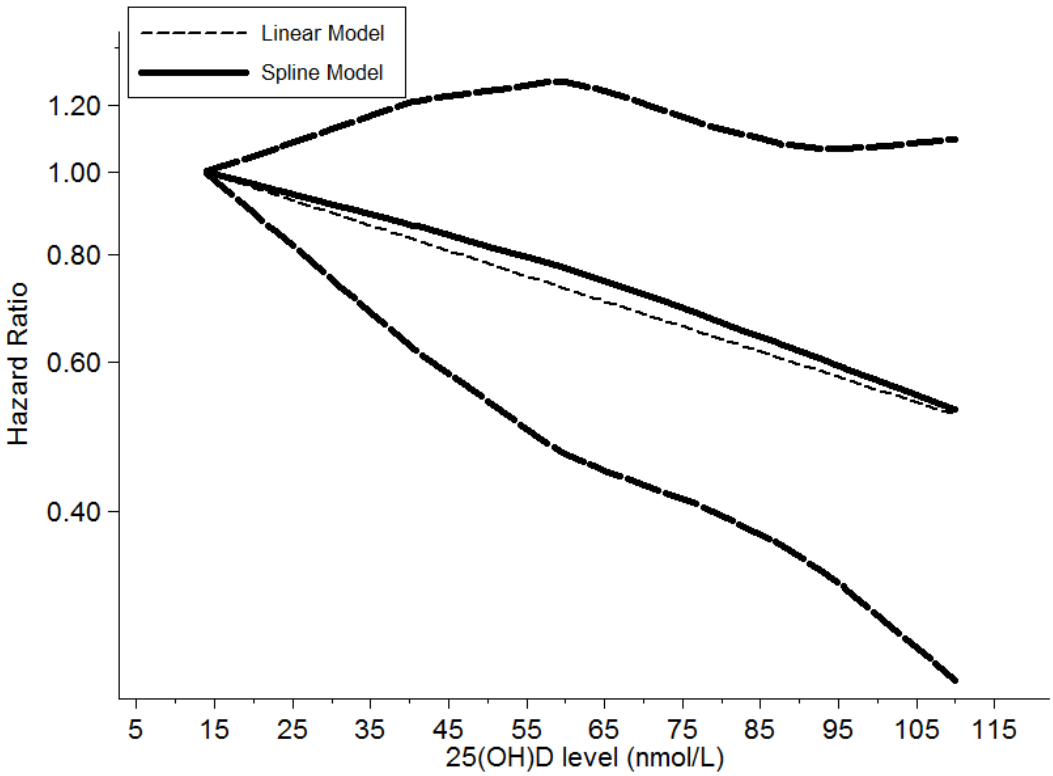

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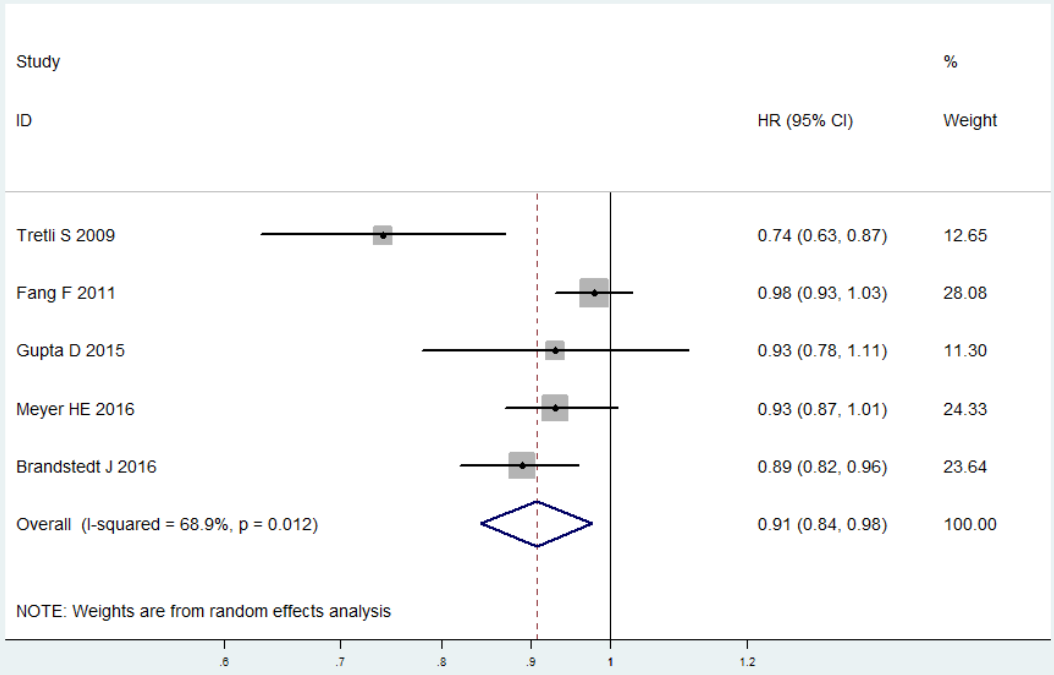

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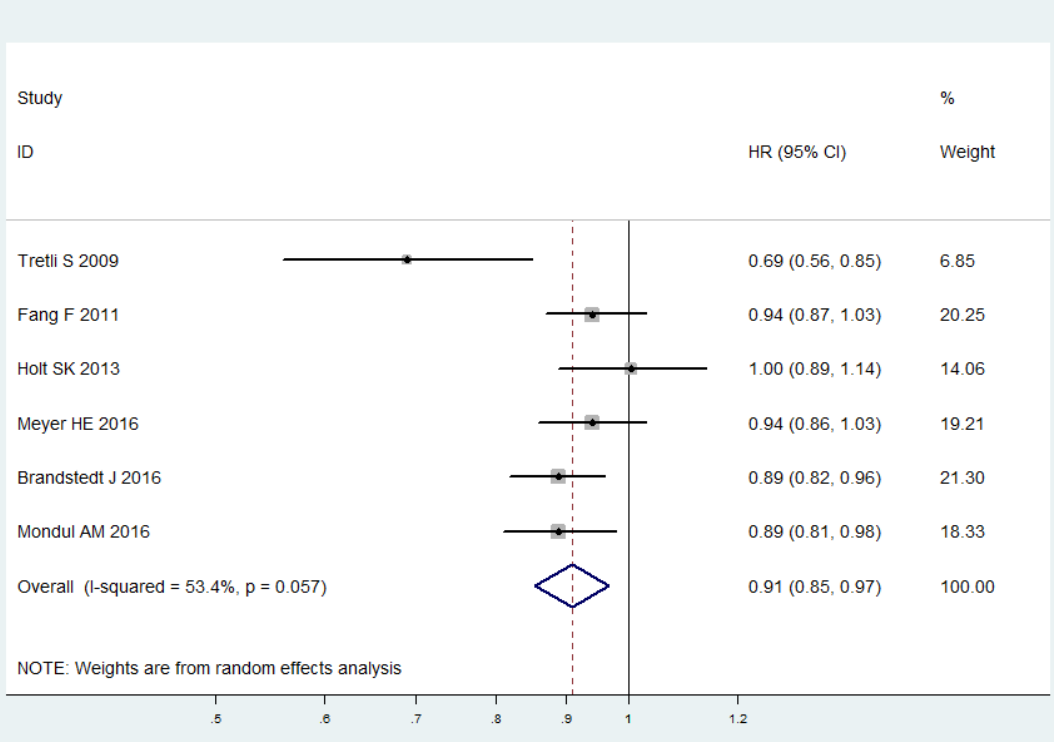

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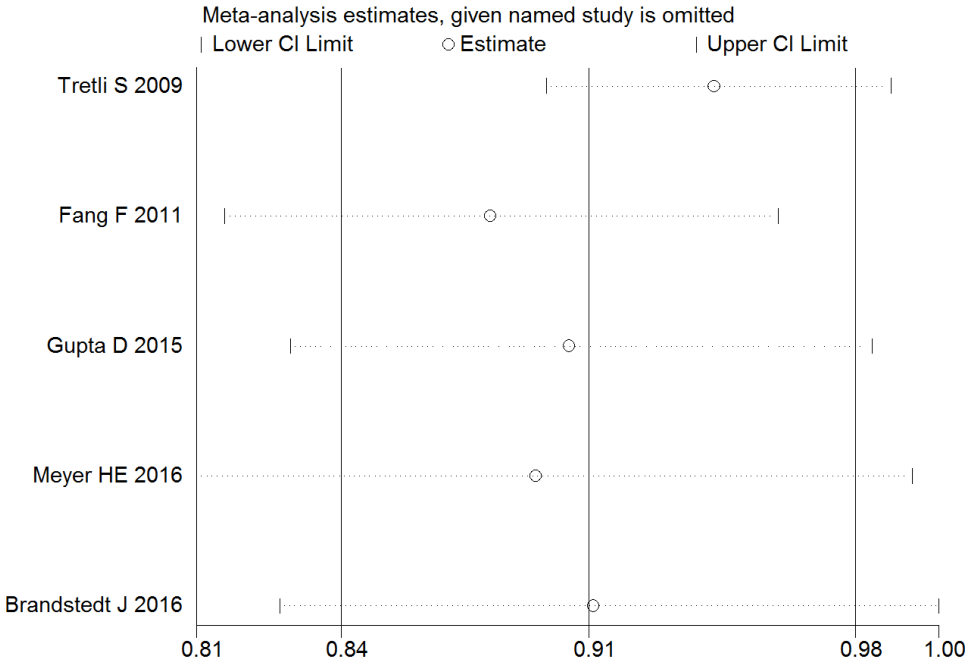

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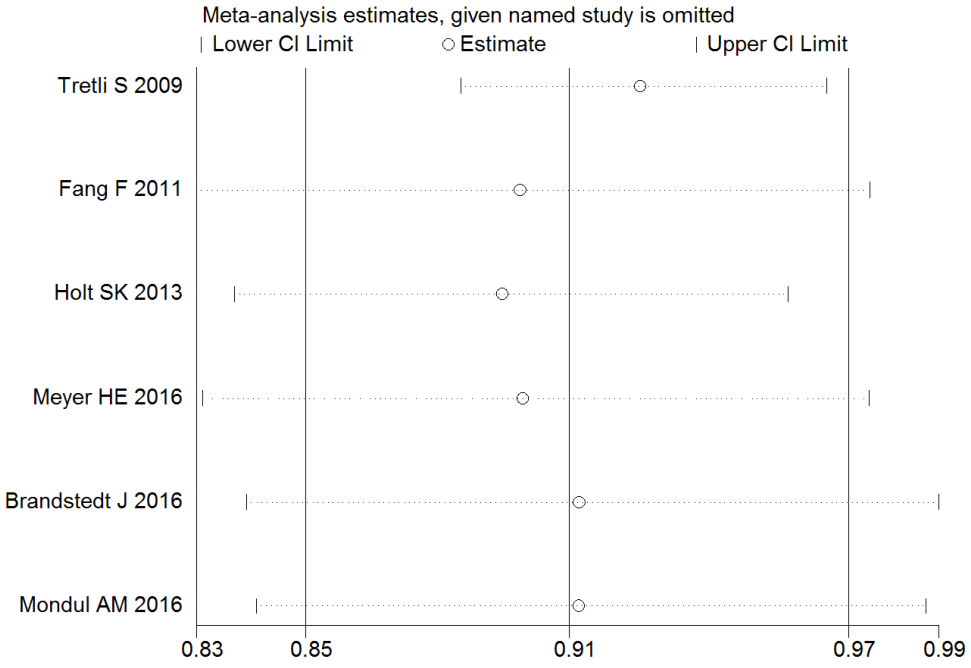

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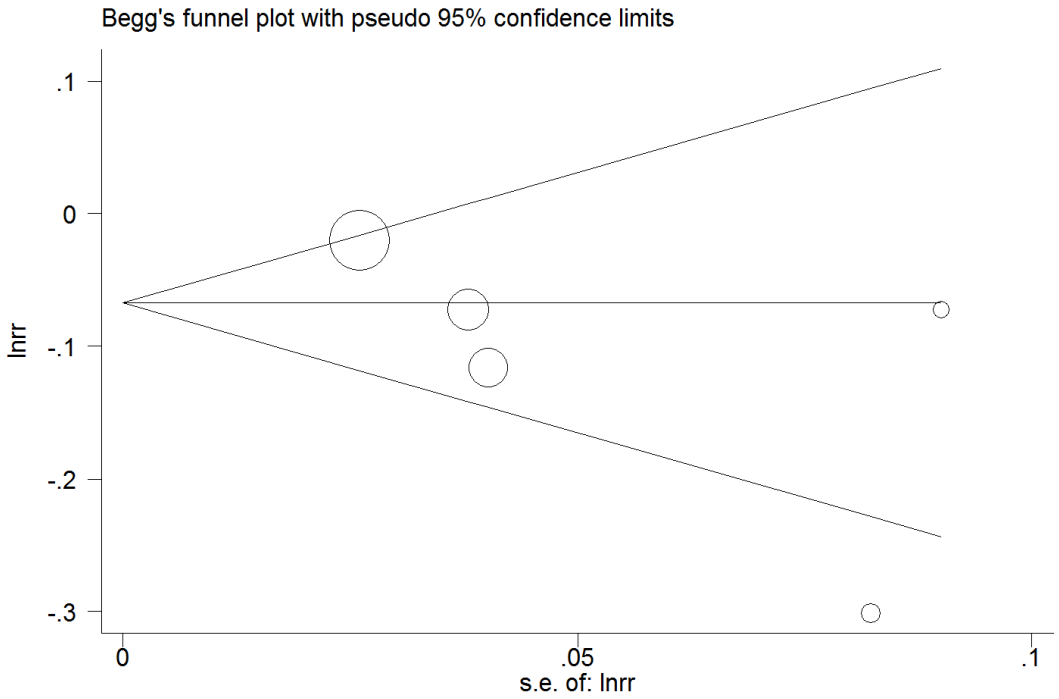

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