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Vitamin D exposure and risk of breast cancer: a meta-analysis

Exposición a la vitamina D y riesgo de cáncer de mama: meta-análisis

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ABSTRACT

Background: The relationship between vitamin D and breast cancer is still controversial. The present meta-analysis examines the effects of the 25(OH)D, 1.25(OH)D and vitamin D intake on breast cancer risk. Methods: A PubMed-database search was conducted to include all papers published with the keywords ‘‘BREAST CANCER” AND “VITAMIN D” with at least one reported relative risk (RR) or odds ratio (OR). In total fifty-eight studies published between 1998 and 2016 has been analyzed. Information about type of study, hormonal receptors and menopausal status was retrieved. A pooled OR or RR has been estimated by weighting individual OR/RR by the inverse of their variance. Results: Our study showed a protective effect between 25 (OH) D and breast cancer (OR=0.66, IC: 0.57-0.76) in case-control studies, although no association was observed when restricting the analysis to nested case-control studies (RR=0.91, IC: 0.82-1.01). However, a subgroup analysis on premenopausal women showed a consistent protective association in both case-control studies (0.68, IC: 0.53-0.87) and nested case-control studies (0.67, IC: 0.49-0.92). No significant association was found for vitamin D intake or 1.25(OH) D. Conclusion: This systematic review suggests a protective relationship between vitamin D (measured as 25(OH) D) and breast cancer development in premenopausal women.

Keywords: breast cancer. 25-hydroxyvitamin D. vitamin D intake. Supplements of vitamin D.

INTRODUCTION

Breast cancer is an important public health problem in developed countries as it is one of the most common cancers and the most one if we only consider female population (1). The incidence is increasing every year, which is partly due to early detection programs (2).

Recently, several studies have evaluated the role of vitamin D in the development of breast cancer, finding an inverse association between vitamin D levels and the risk of developing breast cancer (3). It has been demonstrated that treating breast cancer cells with 1.25(OH) 2D3 induce two beneficial effects: an anti-proliferative effect and a pro-apoptotic effect. The first one, linked to the suppression of growth stimulatory signals and the potentiation of growth inhibitory signals, and the second one, explained by the bcl-2 family proteins. The interaction between vitamin D and its receptors induces an expression of pro-apoptotic family member (4). In addition, the breast tissue contains the 1-α-hydroxylase, allowing to generate the active vitamin D metabolite (1.25 dihydroxyvitamin D) from the circulating precursor (25 hydroxyvitamin D). As vitamin D receptors are found in the breast (4), an autocrine role of vitamin D has been suggested (5).

In spite of this biological background, literature shows inconsistent results, as reflected by different meta-analyses (6-14) (Table 1). Several additional observational studies have appeared after the last meta-analysis publication, which only included articles until 2013. The main purpose of the present meta-analysis is to update the relationship between vitamin D exposure and breast cancer risk adding the studies published in the last years. In this way, the hypothesis of vitamin D being a protective factor for breast cancer is analyzed in this meta-analysis based on sixty observational studies, twenty-seven of which were case-control, twenty were nested case-control and the remaining thirteen were cohort studies.

METHODS

Search strategy

First, inclusion criteria were defined, we looked for cohort or case-control studies performed on humans, which report, at least, one relative risk (RR) or odds ratio (OR) with confidence interval at 95%. (95% CI).

We start our search in the Pub-Med database using “breast cancer” and “vitamin D” as keywords, finding 1560 articles. After reading the title and abstract, 1436 articles that did not meet the above criteria were eliminated. Next, we carried out a more exhaustive and complete reading, which allowed us to reject other additional 68 articles (Figure 1). Finally, sixty studies meeting our inclusion criteria were identified: forty-seven case-

control (15-59) and thirteen cohort studies (60-72). Tables 2 and 3 summarize the main characteristics of the included articles.

Data extraction

The following step was to create a database to extract all relevant information from each article: year of publication, author, journal, follow up, country, sample size, exposure levels, units of measure, data for the creation of the contingency table and RR/OR with 95% CI; as well as a section to assess the quality of the study using the STROBE scale (73).

Statistical analysis

The statistical analysis was performed separately for cohort and case-control studies. In the case control studies a sensitivity analysis was also carried-out including only nested case-control studies. We did separate analysis for any type of vitamin D exposition reported in at least three studies: 25-(OH)D, diet intake of vitamin D, 1.25 -(OH)D2 and supplements of vitamin D .

The ways that doses or levels of vitamin D were reported in each individual article were not standardized across studies (for instance, some papers reported vitamin D levels in quartiles; some others in tertiles, and so on), making it difficult to extract them in an analyzable form. Therefore, in order to provide a consistent criterion of comparability, we selected the OR or RR reported for the highest category compared with the lowest one.

According to the type of breast cancer, we analyzed all invasive breast cancers together, and breast cancer stratified according to the cancer estrogen receptor status and woman menopausal status. A pooled OR or RR has been estimated by weighting individual OR/RR by the inverse of their variance. OR or RR heterogeneity was measured using Q and I^2 statistics (74). A fixed-effect model was preferred if Q statistics were higher than 0.1 or I^2 lower than 25%, indicating no relevant heterogeneity; a random-effect model was chosen otherwise (75). The presence of small-study bias was explored with Rosenthal model and with Egger test (68) due to its low sensitivity, the cut-off was set at $p = 0.1$. Funnel plots (77) were applied to detect publication bias.

An analysis of influence was performed via re-estimating pooled OR/RR by removing one study at a time. Studies that, when removed, strongly changed the OR/RR would be considered as highly influential. Results are displayed as forest plots showing OR/RR and their 95% confidence intervals for each individual study and for the pooled result. Cumulative meta-analyses were carried out for knowing the stability of the OR/RR estimations. In order to do that, all studies considered were arranged from older to newer. Then an OR/RR estimation was obtained for the two eldest studies; another for the three eldest, and so on, adding a study each time. Results are reported as forest plots. Galbraith radial plots were used for studying heterogeneity.

All the statistical analyses were carried out with the package Stata 14/SE (Stata Corporation, College Station, TX, US).

RESULTS

Relationship between 25(OH)D and breast cancer

Twenty-seven case control studies were analyzed to study the relationship between 25 (OH) D and breast cancer (8, 17-21, 23, 25, 27-30, 32, 33, 36, 40, 42-44, 46, 47, 49, 53, 56-58) obtaining a pooled OR of 0.66 (95%CI: 0.57-0.76) (Figure 2a, Table 4). This value was calculated using the random effects model because of the high heterogeneity (I^2=86.3%) of the fixed-effect. Although Egger test cannot rule out a small-study effect (p = 0.002), no study shows a relevant influence. The funnel plot shows asymmetry (Supplementary Figure 1a), indicating either publication bias or heterogeneity that cannot be explained by a random-effect meta-analysis but Rosenthal model shows that 1141 negative studies would be needed to lose statistical significance. In order to further clarify the heterogeneous result, we carried out a sensitivity analysis including only nested case-control studies (19, 20, 23, 26, 29-32, 34, 35 39, 40, 43-45, 49, 53-55, 57) reaching pooled OR = 0.91 (0.82 – 1.01) (Figure 2b, Table 4) with I2 = 22.5%, Q-based p value = 0.22 and a very symmetrical-looking funnel plot (Supplementary Figure 1 b).

Only two cohort studies (69, 72) provided results on 25(OH)D and breast cancer relationship, from which we obtained a pooled RR of 1.09 (95% IC:0.81-1.47).

We have also analyzed the relationship between 25(OH) D and breast cancer, stratifying results by hormonal receptors (ER+/ER-) and menopausal status (postmenopausal or premenopausal). Regarding hormonal receptors (Table 4), we included five case-control studies (17, 30, 31, 40, 43). In both cases (ER+ and ER- tumors) statistical significance was not reached. With respect to menopausal status (Table 4), we obtained a protective effect in both groups: Fourteen case-control studies targeted postmenopausal women (16, 19, 26, 28, 32-34, 36, 39, 45, 47, 49, 53, 58) with a pooled OR of 0.74 (95%CI: 0.59-0.94), and ten focused on premenopausal (19, 24, 28, 32, 33, 36, 47, 49, 53, 58) obtaining a pooled OR of 0.68 (95%CI: 0.53-0.87). When carried out the sensitivity analysis including only nested case-control studies, the protective vitamin D – breast cancer association only remained in the premenopausal group (supplementary table 1). We did not find cohort studies that stratified results of 25(OH)D by menopausal status or hormonal receptor.

Relationship between 1.25(OH)D and breast cancer

Three case-control studies (23, 35, 37) have examined the relationship between circulating 1.25(OH)D and breast cancer; significant association was found neither in the whole analysis (pooled OR = 0.61 (0.33-1.16) nor in postmenopausal women (combined OR= 1.28 IC 95%: 0.98-1.67) (34, 35) (Table 4).

Relationship between dietary vitamin D and breast cancer

We found seven case-control studies (21, 36, 38, 48, 50, 51, 55) on the relationship between dietary vitamin D and breast cancer with a pooled OR of 0.95 (95%CI: 0.74-1.22) (Table 4, Supplementary Figure 2a). In addition, combining five cohort studies (60,

62, 64, 65, 66) we obtained an RR of 1.00 (95% CI 0.93-1.07) (Table 4, Supplementary Figure 2b).

Stratifying by menopausal status, three case-control (36, 38, 51) and five cohort studies (60, 67, 68, 70, 71) assessed the risk of breast cancer in postmenopausal women. The pooled OR for case-control studies was 0.79 (0.68-0.90) and the pooled RR for cohort studies was 0.95 (0.83-1.1) (Table 4). In both analyses, Egger test rejects the possibility of small study bias (p=0.414 in case-control studies and p=0.68 in cohort studies). On the other hand, three case-control studies (36, 38, 51) and three cohort studies (60, 63, 67) targeted premenopausal women; the pooled OR was 0.70 (95%CI:0.56-0.89) for case controls studies and the RR for cohort studies was 1.01 (95% CI: 0.86-1.18) (Table 4).

Relationship between supplements of vitamin D and breast cancer

We identified four case-control studies (21, 22, 41, 50) and two cohort studies (61, 65) that have evaluated the association between supplements of vitamin D and breast cancer risk. The pooled OR and RR were 0.85 (95% CI: 0.70-1.04)(Table 3) and 1.06(95% IC: 0.90-1.25) respectively (Table 4, Supplementary Figure 3a, 3b). Regarding menopausal status, Kim et al (39) published a study on five different populations of postmenopausal women; when combining all five results, we found no significant association (OR: 0.82 95%CI: 0.49-1.35).

Relationship between total vitamin D intake (dietary and supplements) and breast cancer

Finally, we found only two cohort studies (63, 65) and two case control studies (22, 36) on vitamin D intake (dietary plus supplemented) and breast cancer risk, providing no separate results on dietary / supplemented vitamin D origin. We obtained a combined RR =0.89 (95% CI: 0.74-1.07) for cohort studies, and a combined OR=0.79 (95% CI: 0.44-1.45) for case-control studies. Five cohort studies (63, 67, 68, 70, 71) provided results about postmenopausal women (RR= 0.95 95% CI: 0.86-1.04) and three cohort studies (63, 67, 71) about premenopausal women (RR=0.82 95% CI: 0.65-1.00) (Table 4).

DISCUSION

It is well established that there are vitamin D receptors in breast tissue (78) and several cellular and animal studies support a potential anticarcinogenic effect of vitamin D on breast cancer development (79). Nevertheless, prospective (cohort and nested case-control studies) and case control studies tend to show discrepant results: case-control studies usually show a protective effect while prospective studies rarely found it (80). This discrepancy would be due to several factors: First, it is well known that prospective studies are less prone to be affected by both information bias and reverse-causation bias. Second, several authors highlighted the season the vitamin D measurement was done as a potential limitation of case-control studies Eliassen et al (31) in a nested case-control study found an inverse association between serum 25(OH) D levels and breast

cancer limited only to summer measures. It can be assumed that people with low vitamin D levels in summer would also have low levels year-round; therefore, vitamin D levels in summer would be more adequate for analyzing vitamin D – breast cancer relationship than vitamin D levels in winter.

When stratifying by menopausal status, our meta-analysis show a consistent protective effect of 25(OH) D in both case-control and nested case-control studies, but only in premenopausal women. There are different explanations for the influence of menopausal status in the relationship between vitamin D and breast cancer. One of them may be related to the joint relationship between vitamin D and insulin-like growth factors (IGFs). IGF-I is a mitogenic and antiapoptotic peptide that can stimulate the proliferation of breast epithelial cells, increasing the risk of neoplasic transformation (81, 82). The active vitamin D metabolite is able to block the mitogenic effects of IFG-I, leading a decrease in proliferation and increase in apoptosis (83). As there is a physiological decline of the IGF with ageing (84), the interaction between IGF pathways and vitamin D is likely to be stronger for premenopausal women than for postmenopausal women, leading to greater risk reduction in premenopausal breast cancer (67, 85). Finally, high levels of vitamin D may reduce progesterone and estradiol, providing a potential mechanism to reduce breast cancer risk in young women (86).

Previous meta-analyses of prospective studies showed contradictory results. Kim et al (11) (who included 24 studies) found a slightly stronger inverse association among premenopausal than among postmenopausal women but without significant differences, whereas in the meta-analysis of Bauer et al (6) (nine studies included) the inverse association was only observed in postmenopausal women. In our meta-analysis, new prospective studies (29, 31, 39, 54, 55, 5, 61, 72) not included in previous reviews, have been added and this fact may explain the differences in the results.

Concerning hormonal receptors (ER+/ER-), it would be expected a decreased risk in ER+, since it seems that sensitivity to 1,25(OH)2D is generally reported as being higher in breast cancer cells that express the estrogen receptor than in those that do not (86, 87). It has been demonstrated that treating breast cancer cells ER+ with 1,25(OH)2D3 induces a cell cycle shutdown in GO/G1 (4, 79). Despite this fact, most studies found no significant difference (30, 32, 40, 43)or even decreased risk of ER- breast cancer regarding the serum levels of 25 (OH) D (16). In the same way, our study does not reach significant differences when the analysis was performed separately in ER+ or ER- subgroups.

No relationship was found between the level of circulating 1,25(OH)D and breast cancer. This result is consistent with previous studies (7), while Janowsky et al (37) found an inverse association. Several authors considered that 1,25(OH)D is not a good indicator of vitamin D status: First, 1.25(OH)D's half-life is only 4-6h, whereas 25(OH)D's half-life is 3 weeks; second, 1.25(OH)D is influenced by many factors (8), for instance, it can be elevated in patients with vitamin D deficiency as a result of hyperparathyroidism (88); finally, as 1.25(OH)D is metabolized by 1-α -hydroxylase in breast tissue, plasma levels may not adequately represent breast tissue levels (10, 12).

We do not find a relationship between vitamin D intake and breast cancer in the overall analysis. In contrast, when stratifying by menopausal status, a protective effect is observed in case-control studies in both premenopausal and postmenopausal women, whereas this association is not present in cohort studies. On the other hand, analyzing the influence of vitamin D supplements on breast cancer risk, we find a borderline protective effect.

In the relationship between vitamin D intake (dietary and/or supplements) and breast cancer, most observational studies showed non-significant differences; only two articles (15, 51) found a protective association. In a previous meta-analysis (11), this association was significant for neither vitamin D intake nor supplements.

A probable explanation for the lack of association observed in the analysis of dietary intake or supplements compared to the 25(OH)D levels may be due to the fact that the main source of vitamin D is sunlight rather than food or supplements.

In addition, the French E3N Cohort Study reported that high vitamin D intake is associated with lower breast cancer risk (10) in regions with high ultraviolet solar radiance; suggesting that the total amount of vitamin D needed to reach a protective effect on breast cancer is too high to be achieved in regions with low ultraviolet radiance as the vitamin D intake has to be higher than the usually recommended, eventually leading to side effects as hypercalcemia, constipation or muscle weakness.

Our study has some limitations; first each article uses different cutoff points according to serum levels of vitamin D. To analyze it we restricted our analysis to the comparison among the highest vs. lowest category of exposure. This analysis strategy does not allow for a dose-response analysis. Moreover, we carried out a sensitivity analysis excluding one study at a time, showing that no single study affected substantially the pooled RR/OR. Second, there is a huge variability in the literature on the type of vitamin D studied, which makes it difficult to perform the analysis. In addition levels of vitamin D depend on the season, so it would be advisable to take all samples at the same time, or at least refer to when they were collected (61). Finally, case-control studies are more prone to methodological issues, such as recall and selection biases, which limits the strength and quality of evidence. However, about half of the case-control studies included in our meta-analysis are nested in cohort studies, which minimizes the possibility of introducing biases.

Despite these limitations, our study has also several strengths; first, we have gathered all the observational studies published in the last twenty years. In addition, we have focused the analysis on different types of vitamin D exposure (diet, supplements and blood-levels of 25(OH)D and 1,25(OH)2D) whereas other meta-analysis are focused only on 25(OH)D levels (6, 7, 12, 13, 14, 8, 88) or vitamin D intake (10) .This strategy allows us to obtain a more detailed analysis of the relationship vitamin D- breast cancer.

In conclusion, our meta-analysis supports that high serum levels of 25(OH) vitamin D has a protective effect on breast cancer risk in premenopausal women; we cannot draw the same conclusion regarding vitamin D intake or supplements of vitamin D since the number of studies are still limited and publication biases cannot be excluded.

Conflict of interest: The authors declare that they have no competing interests

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TABLES AND FIGURES

Table 1. Results of previous meta-analysis.

Source	Type of vitamin D	Number of studies included	Type of studies included	RR (95%IC)
Bauer SR et al. (2013)	25(OH)D	9	Cohort and nested case-control studies	0.99 (0.97-1.00)
Chen P et al. (2010)	25(OH)D	21	Case control, cohort, and cross-sectional studies	0.55 (0.38-0.80)
	Intake of vitamin D			0.91 (0.85-0.97)
	1,25(OH)D			0.99 (0.68-1.44).
Chen P et al. (2013)	25(OH)D	21	Nested case-control and retrospective studies	0.86(0.75-1.00)
			Population based case control studies	0.35(0.24-0.52)
			Hospital based case-control studies	0.08(0.08-0.33)
Gandini S et al. (2011)	25(OH)D	10	Case-control	83 (0.79-0.87)
			Nested case-control and cohort studies	0.97 (0.92-1.03)
Gissel T et al. (2008)	Intake of vitamin D	6	Cross sectional, Case-control, cohort and randomized-control trials	0.98 (0.93-1.03)
Kim Y et al. (2014)	Intake of vitamin D	24	Cohort and nested case-control studies	0.95 (0.88-1.01)
	25(OH)D			0.92 (0.83-1.02)
Mohr SB et al. (2011)	25(OH)D	11	All	0.61 (0.47-0.80)
			Case-control studies	0.87 (0.77-0.99)
			Nested case-control studies	0.41(0.31-0.56)
Wang D et al. (2013)	25(OH)D	14	Cohort and nested case-control studies	0.845 (0.75-0.95)
Yin Y et al. (2010)	25(OH)D	9	All	0.73 (0.60-0.88)
			Nested case-control studies	0.92 (0.82-1.04)
			Case- control studies	0.59 (0.48-0.73)

Table 2: Case –control studies included in our meta-analyses with the OR and IC of breast cancer for any type of vitamin D

Study	Country	Exposition	Group	OR 95%IC	N
Abba S et al. (2009)	Germany	25(OH)D	All	0.45(0.29-0.70)	473
			ER +	0.56(0.31-1.00)	394
			ER -	0.40(0.20-0.81)	367
Abbas S et al. (2008)	Germany	25 (OH)D	postmenopausal	0.31(0.24-0.42)	1066
Alipour S et al. (2014)	Iran	25 (OH)D	All	0,33(0.12-0.91)	360
Almquist M et al.(2010)*	Sweden	25(OH)D3	All	0.99(0.72-1.36)	810
		25(OH)D3+ D2	All	1.01(0.73-1.40)	764
		25(OH)D3	Premenopausal	1.58(0.77-3.25)	
			postmenopausal	0.88(0.60-1.28)	
		25(OH)D3+ D2	Premenopausal	1.74(0.84-3.60)	
			postmenopausal	0.88(0.60-1.29)	
Amir E et al. (2012)*	China	25(OH)D	All	0.86(0.62-1.21)	1087
Anderson LN et al. (2010)	Canada	Total vitamin D intake[1]	All	0.99(0.78-1.26)	2176
		Dietary Vitamin D	All	1.13(0.88-1.45)	2008
		Vitamin D supplement	All	0.76(0.59-0.98)	3938
Anderson LN et al. (2011)	Canada	Vitamin D supplement	Caucasian women in Ontario	0.80(0.60-1.08)	1824
		Total Vitamin D intake[1]	Caucasian women in Ontario	0.87(0.71-1.06)	1659

Bertone-Johnson ER et al. (2005)*	USA	25(OH)D	All	0.73(0.49-1.07)	562
		1,25(OH)D	All	0.76(0.52-1.11)	520
		25(OH)D	<60	0.92(0.57-1.48)	337
			>=60	0.57(0.31-1.04)	239
		1,25(OH)D	<60	0.88(0.56-1.40)	326
			>=60	0.72(0.40-1.32)	213
Bidgoli SA et al. (2014)	Iran	25(OH)D	Premenopausal	1.12(1.05-1.19)	176
Bilinski K et al. (2012)	Australia	25(OH)D	All	0.43(0.23-0.77)	
			<50	0.29(0.08-1.00)	
			>= 50	0.45(0.23-0.71)	
Chen P et al.(2010)	China	25(OH)D	All	0.11(0.07-1.17)	654
Chlebowski RT et al. (2008)*	USA	25(OH)D	Postmenopausal	0.82(0.60-1.12)	
Colagar AH et al. (2015)	Iran	25(OH)D	All	0.26(0.13-0.50)	171
Crew KD et al. (2009)	Germany	25(OH)D	All	0.56(0.41-0.78)	958
			Premenopausal	0.83(0.36-1.30)	330
			Postmenopausal	0.46(0.09-0.83)	592
Deschasaux M et al. (2016)*	France	25(OH)D	All	0.98(0.60-1.61)	350
Eliassen AH et al. (2011)*	USA	25(OH)D	All	1.20(0.88-1.63)	923
			ER+	1.21(0.84-1.75)	785
			ER-	1.31(0.63-2.74)	642
Eliassen AH et al.(2016)*	USA	25(OH)D	All	0.84(0.58-1.21)	586
			ER+	0.89(0.74-1.08)	1141

			ER-	0.87(0.63-1.20)	261
Engel P et al. (2010)*	France	25(OH)D	All	0.73(0.55-0.96)	1233
			Premenopausal	0.37(0.12-1.15)	368
			Postmenopausal	0.80(0.60-1.07)	958
			<53	0.60(0.37-0.98)	380
			53-60	0.71(0.46-1.10)	432
			>60	1.09(0.70-1.71)	421
Fedirko V et al. (2012)	Mexico	25(OH)D3	All	0.53(0.36-0.78)	848
			Premenopausal	0.40(0.30-0.81)	309
			postmenopausal	0.55(0.33-0.90)	520
Freedman M et al. (2008)*	USA	25(OH)D	postmenopausal	1.04(0.72-1.51)	368
Hiatt RA et al. (1998)*	USA	1,25(OH)D	All	1.00(0.20-1.00)	
Jamshidinaein Y et al. (2016)	Iran	Dietary vitamin D	Postmenopausal	0.40(0.15-1.12)	
		Total vitamin D intake[1]	All	0.52(0.25-1.14)	132
			Premenopausal	0.36(0.13-1.06)	
			Postmenopausal	0.70(0.27-1.82)	
		25(OH)D	All	0.26-(0.12-0.59)	135
			Premenopausal	0.25(0.09-0.69)	
			Postmenopausal	0.42(0.15-1.17)	
Janowsky EC et al. (1999)	USA	1,25(OH)D	All	0.31(0.17-0.59)	
			Black women	2.00(0.37-10.00)	
			White women	0.19(0.07-0.48)	

Kawase T et al. (2010)	Japan	Dietary Vitamin D	All	0.76(0.63-0.90)	2634
			Premenopausal	0.65(0.50-0.86)	1291
			Postmenopausal	0.83(0.64-1.07)	1389
Kim Y et al.(2014)*	USA	Vitamin D supplement	whites.postmenopausal	1.29(0.75-2.23)	294
			African-American.postmenopausal	0.29(0.12-0.70)	212
			Native Hawaiian.postmenopausal	0.46(0.16-1.34)	136
			Japanese.postmenopausal	1.32(0.90-1.93)	508
			Latino.postmenopausal	0.85(0.46-1.56)	264
		25(OH)D	whites.postmenopausal	0.13(0.03-0.71)	294
			African-American.postmenopausal	1.35(0.65-2.78)	212
			Native Hawaiian.postmenopausal	1.35(0.23-7.69)	136
			Japanese.postmenopausal	1.04(0.51-2.13)	508
			Latino.postmenopausal	1.11(0.51-2.44)	264
Kühn T et al.(2013)*	Denmark	25(OH)D	All	1.07(0.85-1.36)	1405
			ER+	0.97(0.67-1.38)	649
			ER-	0.97(0.66-1.42)	553
Levi F et al.(2001)	Sweden	Vitamin D supplement	All	1.43(0.90-2.26)	
Lowe LC et al.(2005)	UK	25(OH)D	All	0.17(0.07-0.43)	113
McCullough ML et al.(2009)*	USA	25(OH)D	All	1.09(0.70-1.68)	391
			ER+	1.15(0.80-1.65)	578
			ER-	0.95(0.43-2.06)	389

Mohr SB et al. (2013)*	USA	25(OH)D	All	0.84(0.56-1.25)	496
Neuhouser ML et al. (2012)*	USA	25(OH)D	Postmenopausal	0.94(0.70-1.28)	311
Nogueira Oliveira CM et al. (2016)	Brazil	25(OH)D	All	0.34(0.16-1.71)	125
Park S et al. (2015)	Korea	25(OH)D	All	0.82(0.75-0.90)	20767
			Premenopausal	0.84(0.74-0.96)	10470
			Postmenopausal	0.82(0.73-0.93)	9756
Potischman N et al. (1999)	USA	Dietary Vitamin D	All	0.98(0.80-1.20)	1337
Rejnmark L et al. (2009)*	Denmark	25(OH)D	All	0.52(0.32-0.85)	
			Premenopausal	0.38(0.15-0.97)	
			Postmenopausal	0.71(0.38-1.30)	
Rollison DE et al. (2012)	US	Dietary Vitamin D	All	1.35(1.15-1.60)	2378
		Vitamin D supplement	All	0.79(0.65-0.96)	2443
Rossi M et al. (2009).	Italy	Dietary Vitamin D	All	0.76(0.58-1.00)	1031
			premenopausal	0.80(0.64-0.99)	
			Postmenopausal	0.78(0.66-0.92)	
Salarabadi A et al. (2015)	Iran	Vitamin D supplement	Premenopausal	0.53(0.14-1.96)	152
Scarmo S et al. (2013)*	USA	25(OH)D	All	0.94(0.76-1.16)	1775
			Premenopausal	0.67(0.48-0.92)	731
			Postmenopausal	1.21(0.92-1.58)	1044

Shirazi L et al. (2016)*	Sweden	25(OH)D3	All	0.97(0.75-1.25)	1036
Simard A et al. (1991)*	Canada	Dietary Vitamin D	All	2.79(0.85-9.15)	
Sofi NY et al. (2016)	India	25(OH)D	All	0.40(0.14-1.11)	200
Wang J et al. (2014)*	USA	25(OH)D	All	0.95(0.67-1.36)	604
Yao S et al. (2011)	USA	25(OH)D	All	0.37(0.27-0.51)	709
			Premenopausal	0.57(0.34-0.93)	297
			Postmenopausal	0.29(0.19-0.45)	412
Yousef FM et al. (2013)	USA	25(OH)D	Saudi Arabia women	0.16(0.07-0.42)	160

*Nested case-control studies

[1] Total vitamin D = dietary + supplements

Table 3: Cohort studies included in our meta-analyses with the RR and IC of breast cancer for any type of vitamin D

Study	Country	Exposition	Group	RR 95%IC	N
John ME et al. (1999)	USA	Dietary vitamin D	All	0.85(0.59-1.24)	126
		Vitamin D supplement	All	0.89(0.60-1.32)	164
		Total vitamin D intake	All	0.86(0.61-1.2)	136
Shin MH et al. (2002)	USA	Total vitamin D intake[1]	Premenopausal	0.89(0.68-1.15)	392
			Postmenopausicas	0.93(0.8-1.08)	930
		Dietary Vitamin D	Premenopausal	0.84(0.59-1.18)	120
			Postmenopausicas	0.86(0.7-1.05)	343
Lin J et al. (2007)	USA	Total vitamin D intake[1]	Premenopausal	0.65(0.42-1)	124
			Postmenopausicas	1.3(0.97-1.73)	257
		Dietary vitamin D	Premenopausal	1.02(0.69-1.53)	102
			Postmenopausal	1.22(0.95-1.55)	280
		Vitamin D supplement	Premenopausal	0.76(0.5-1.17)	241
			Postmenopausal	0.87(0.68-1.12)	649
Robien K et al. (2007)	EEUU	Vitamin D supplement	Postmenopausal	0.89(0.74-1.08)	23700
		Dietary Vitamin D	All	0.55(0.24-1.22)	29422
		Total vitamin D intake[1]	Postmenopausal	0.89(0.77-1.03)	23461
Kuper H et al. (2016)	Sweden	Dietary vitamin D	All	0.9(0.80-1.1)	404
Cadeau C et al. (2015)	France	Vitamin D supplement	All	1.1(0.92-1.31)	2256
			ER+	1.23(1-1.51)	1543
			ER-	0.93(0.55-1.55)	332
Abbas S et al. (2013)	UK	Dietary vitamin D	All	1.04(0.94-1.14)	
			Premenopausal	1.07(0.87-1.32)	

			Postmenopausal	1.02(0.9-1.16)	
Skaaby T et al. (2014)	Denmark	25(OH)D	All	1.1(0.7-1.71)	
McCullough ML et al. (2005)	USA	Total vitamin D intake[1]	Postmenopausal	0.94(0.8-1.1)	17821
		Dietary vitamin D	Postmenopausal	0.87(0.75-1)	25706
Edvarsen K et al. (2011)	Norway	Dietary vitamin D	All	1.07(0.87-1.32)	417
Engel P et al. (2010)	Norway	Total vitamin D intake[1]	All	0.9(0.72-1.12)	1037
			Premenopausal	0.68(0.25-1.87)	216
			Postmenopausal	0.91(0.73-1.14)	821
Frazier et al. (2004)	USA	Dietary vitamin D	All	0.92(0.66-1.27)	145
Ordonez-Mena JM et al. (2013)	Germany	25(OH)D	All	1.08(0.72-1.6)	2310

[1] total vitamin D =dietary + supplements

Table 4. Results from this meta-analysis

Exposition	Group	Type of study	OR/RR (95% CI)	I^2
25(OH)D	All	Case-control	0.66 (0.57-0.76)	41.78%
	All	Cohort	1.09(0.81-1.47)	0%
	ER+	Case-control	0.96 (0.80-1.16)	13.33%
	ER -	Case-control	0.86(0.64-1.15)	15.60%
	Postmenopausal	Case-control	0.74 (0.59-0.94)	16.96%
	Premenopausal	Case-control	0.68 (0.53-0.87)	16.43%
Dietary vitamin D	All	Case-control	0.95(0.74-1.22)	24.14%
	All	Cohort	1.00(0.93-1.07)	0%
	Postmenopausal	Case-control	0.79(0.68-0.90)	0%
	Postmenopausal	Cohort	0.95(0.83-1.09)	19.13%
	Premenopausal	Case-Control	0.70(0.56-0.89)	34.35%
	Premenopausal	Cohort	1.01(0.86-1.18)	0%
Vitamin D supplement	All	Case-control	0.85(0.70-1.04)	28.03%
	All	Cohort	1.06(0.90-1.25)	0%
Total Vitamin D intake (dietary + supplements)	All	Case-control	0.79(0.44-1.45)	0%
	All	Cohort	0.89(0.74-1.07)	0%
	Postmenopausal	Cohort	0.95(0.86-1.04)	13.59%
	Premenopausal	Cohort	0.82(0.65-1.01)	0%

Figure1: Flow diagram of the literature search preocess

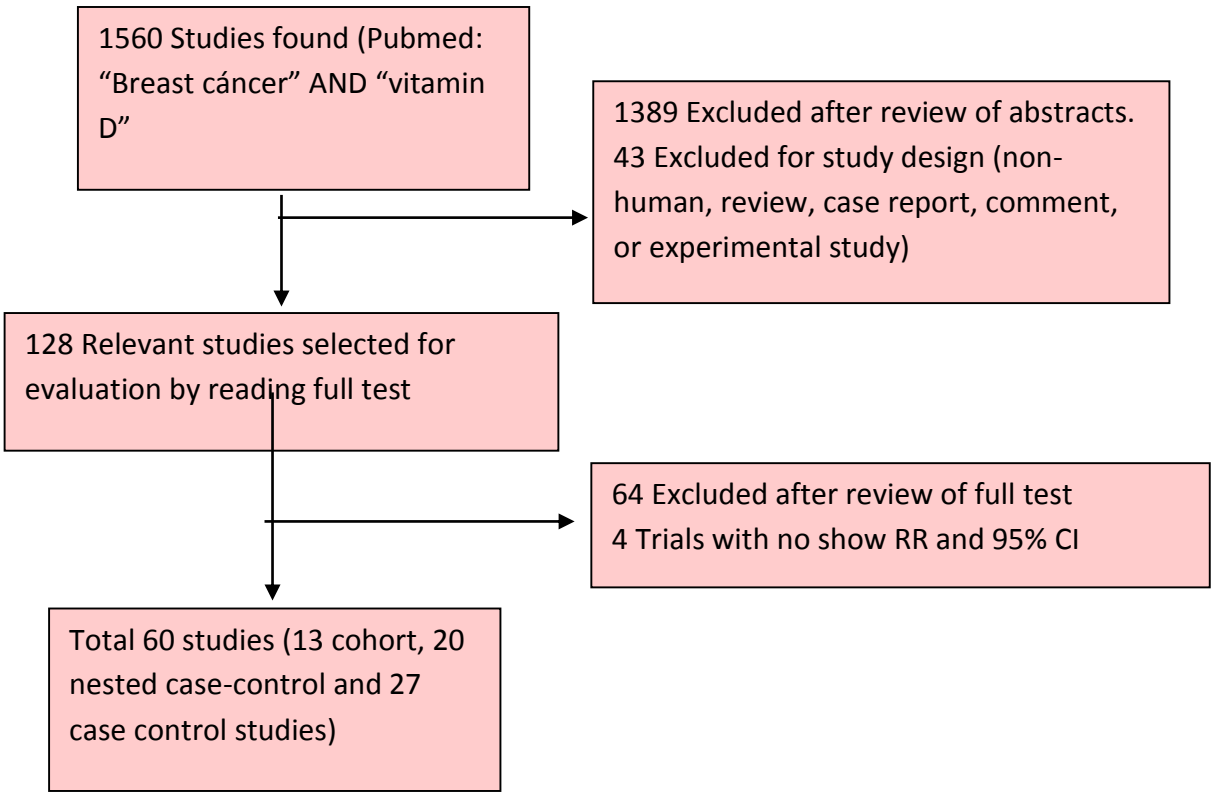
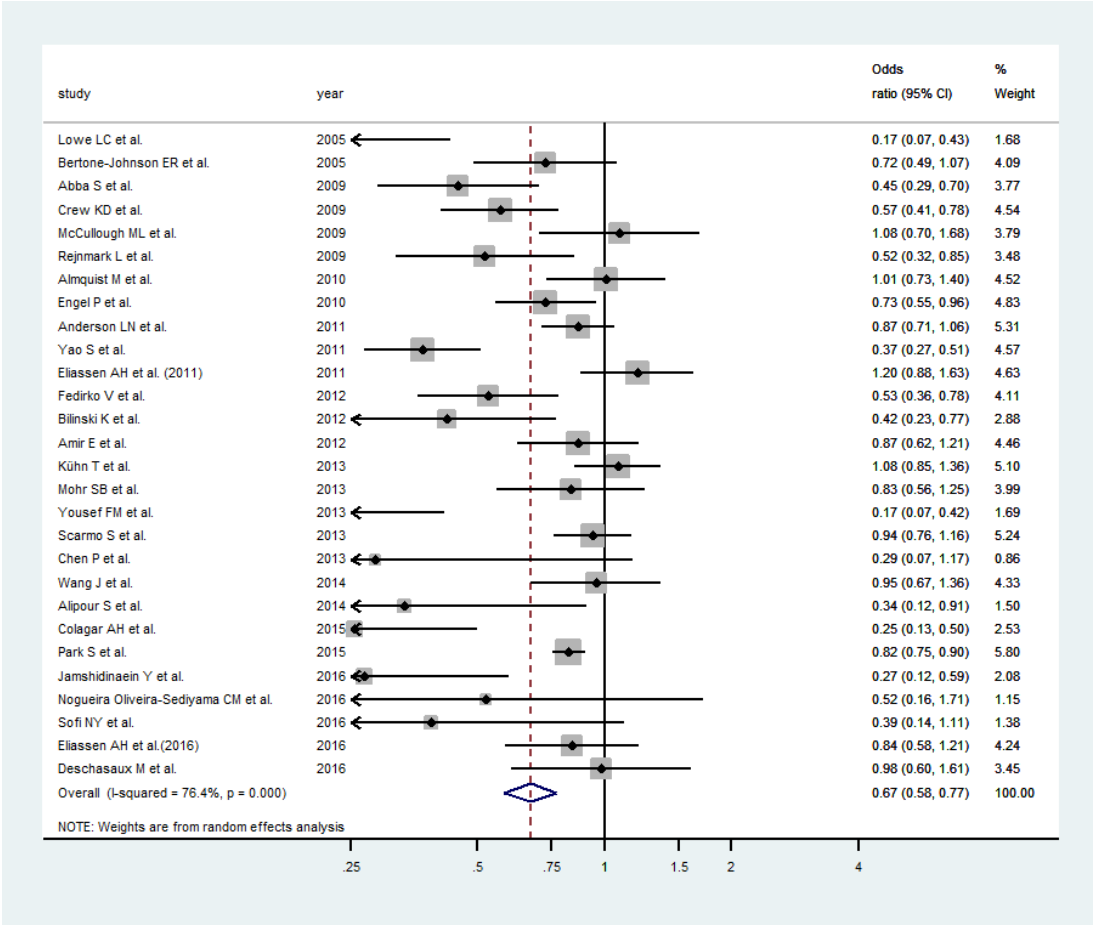


Figure 2.-Forest plot for the relationship between 25(OH)D and breast cancer

a) Case control studies.



b) Nested case control studies.

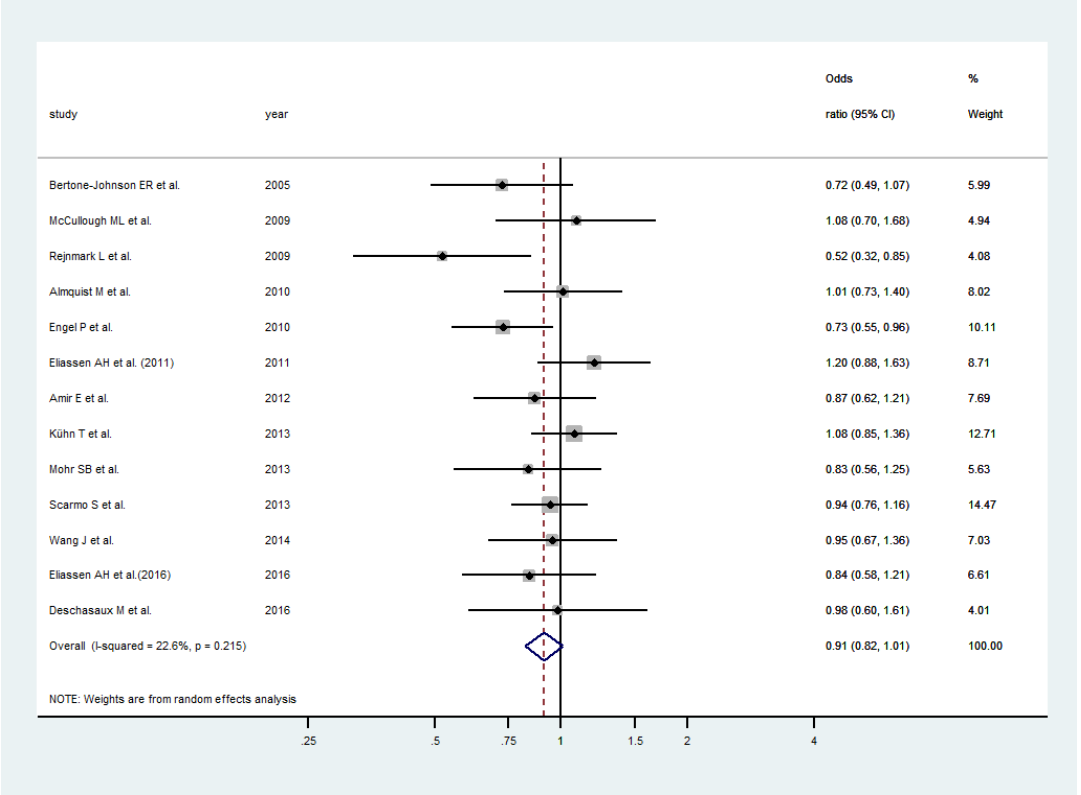
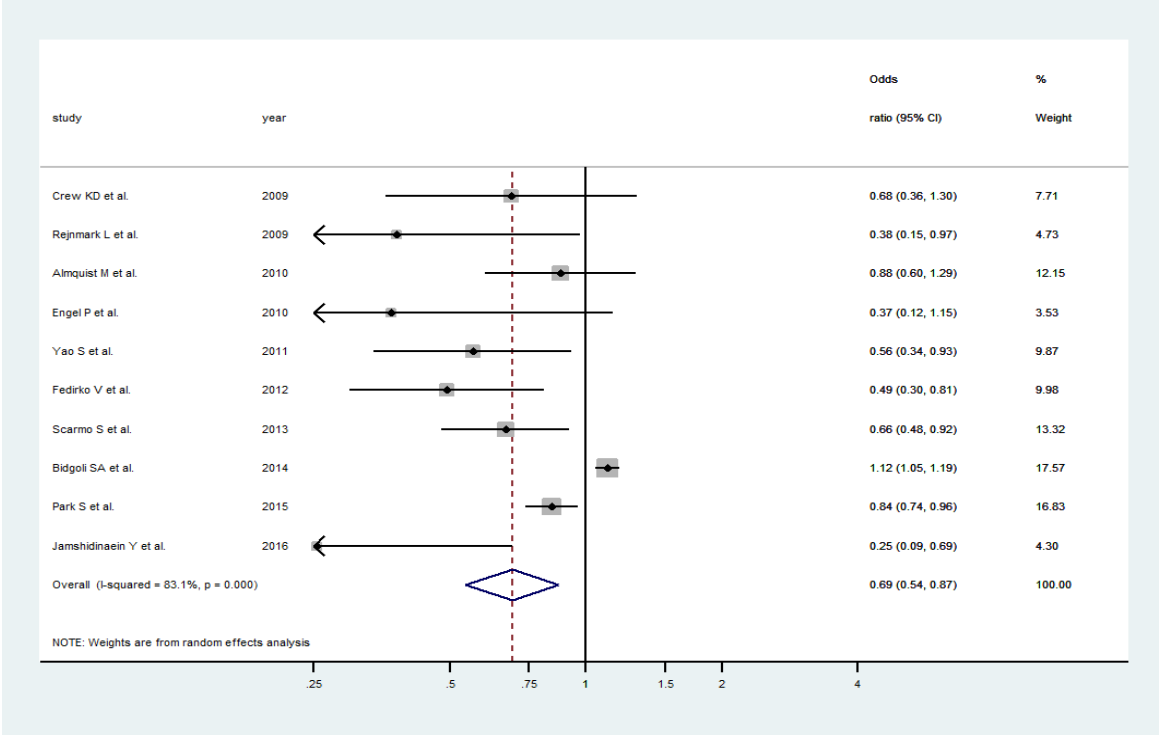
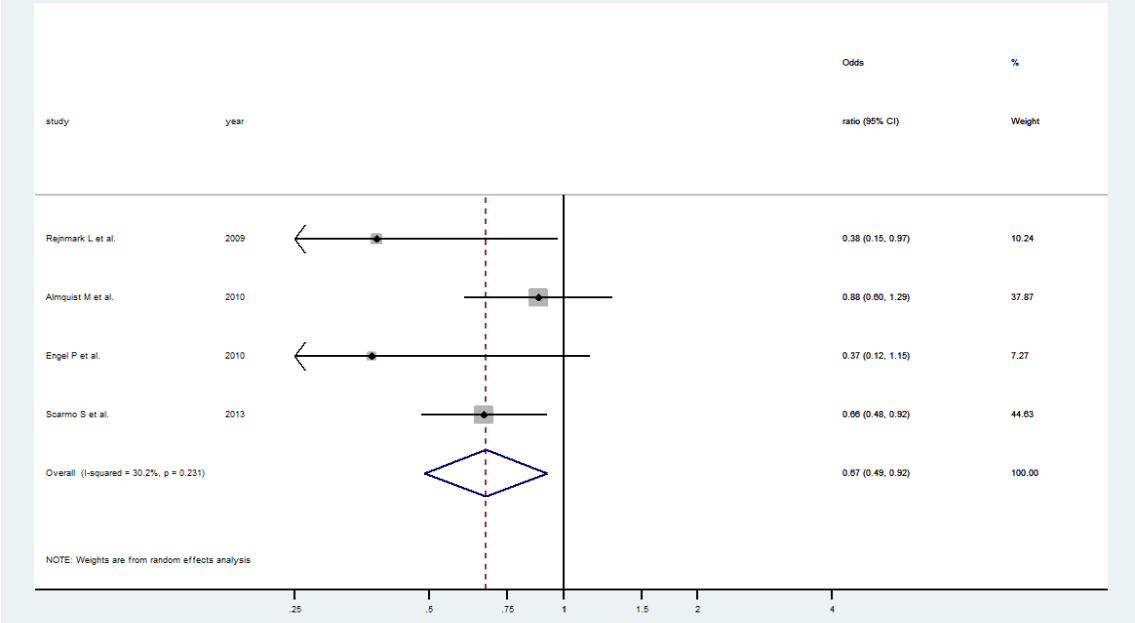


Figure 3: Forest plot for the relationship between 25(OH)D exposure and breast cancer in premenopausal women.

a) Case control studies



b) Nested case control studies



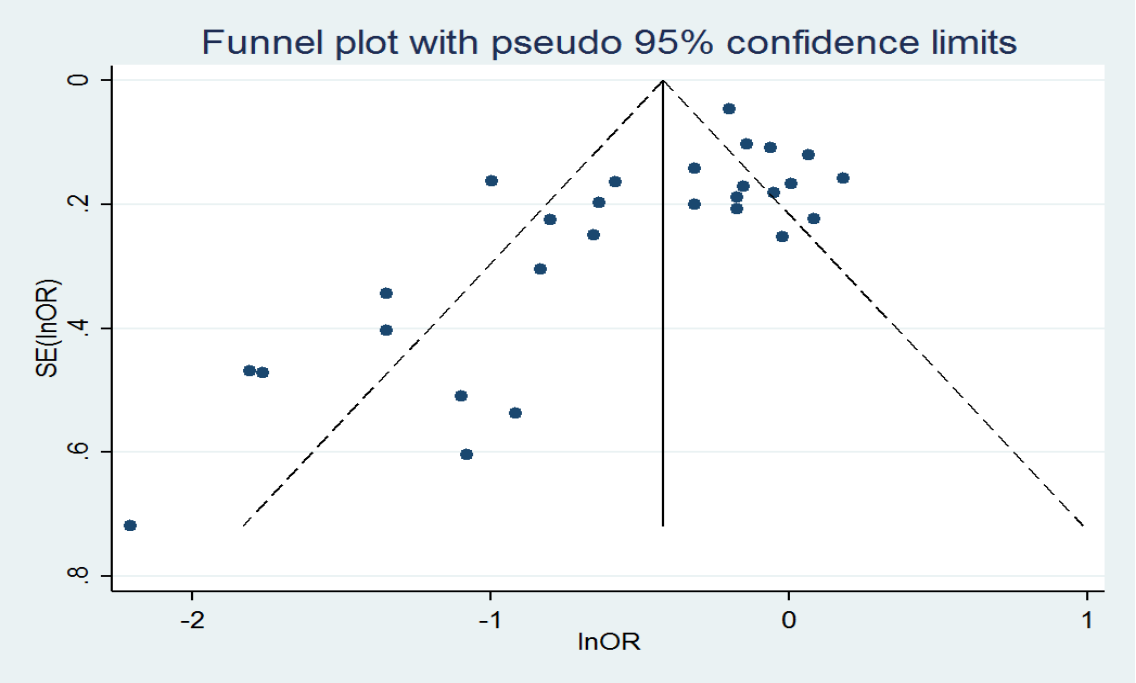
SUPPLEMENTARY MATERIAL

Table 1: Comparing results of global case-control studies versus nested case-control studies

Exposition	Group	OR case-control and nested case control studies. Number of studies included	OR nested case-control studies. Number of studies included
25(OH)D	All	0.66 (0.57-0.76) N=29	0.91 (0.82-1.01) *N=14*
	ER+	0.96 (0.80-1.16) *N=5*	0.98 (0.85-1.13) *N=4*
	ER -	0.86(0.64-1.15) *N=5*	0.94 (0.76-1.18) *N=4*
	Postmenopausal	0.74 (0.59-0.94) *N=18*	0.97 (0.82-1.14) *N=12*
	Premenopausal	0.68(0.53-0.87) N=10	0.67 (0.49-0.92) *N=4*
Dietary vitamin D	All	0.95(0.74-1.22) *N=7*	2.79(0.85-9.15) N=1
	Postmenopausal	0.79(0.68-0.90) *N=3*	NO STUDIES
	Premenopausal	0.70(0.56-0.89) N=3	NO STUDIES
Vitamin D supplement	All	0.85(0.70-1.04) N=4	NO STUDIES
	Postmenopausal	OR: 0.82 (0.49-1.35) N=1	0.82 (0.49-1.35) N=1
Total Vitamin D intake (dietary + supplements)	All	0.79(0.44-1.45) N=2	NO STUDIES

Figure 1. Funnel plot for the relationship between 25(OH)D and breast cancer

a) case control studies



b) Nested case control studies

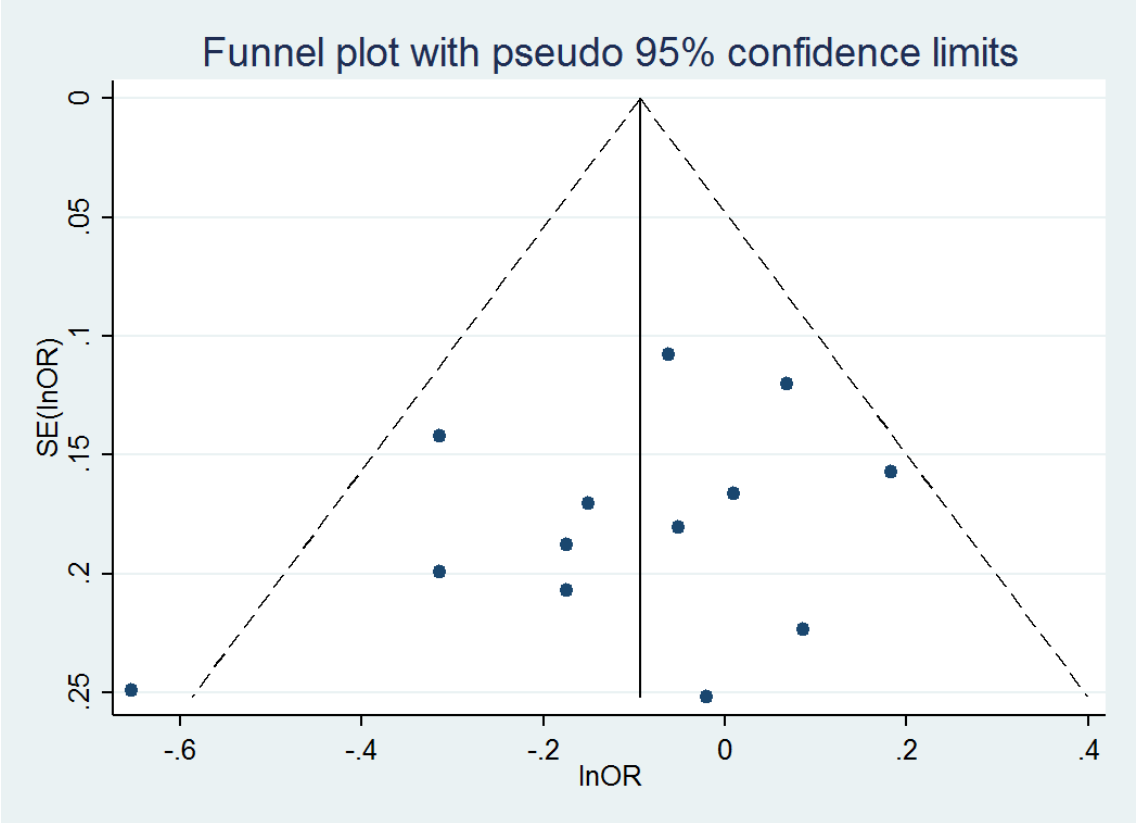
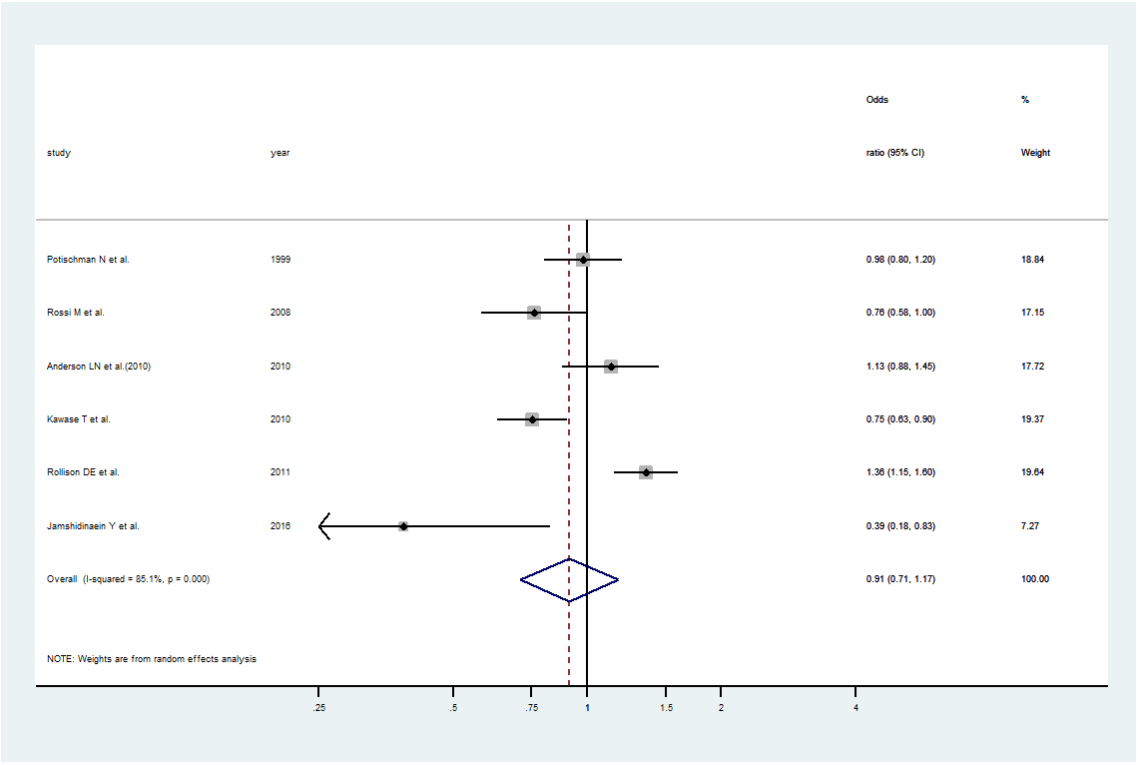


Figure 2: Forestplot for the relationship between diet vitamin D and breast cancer

a) Case control studies



b) Cohort studies

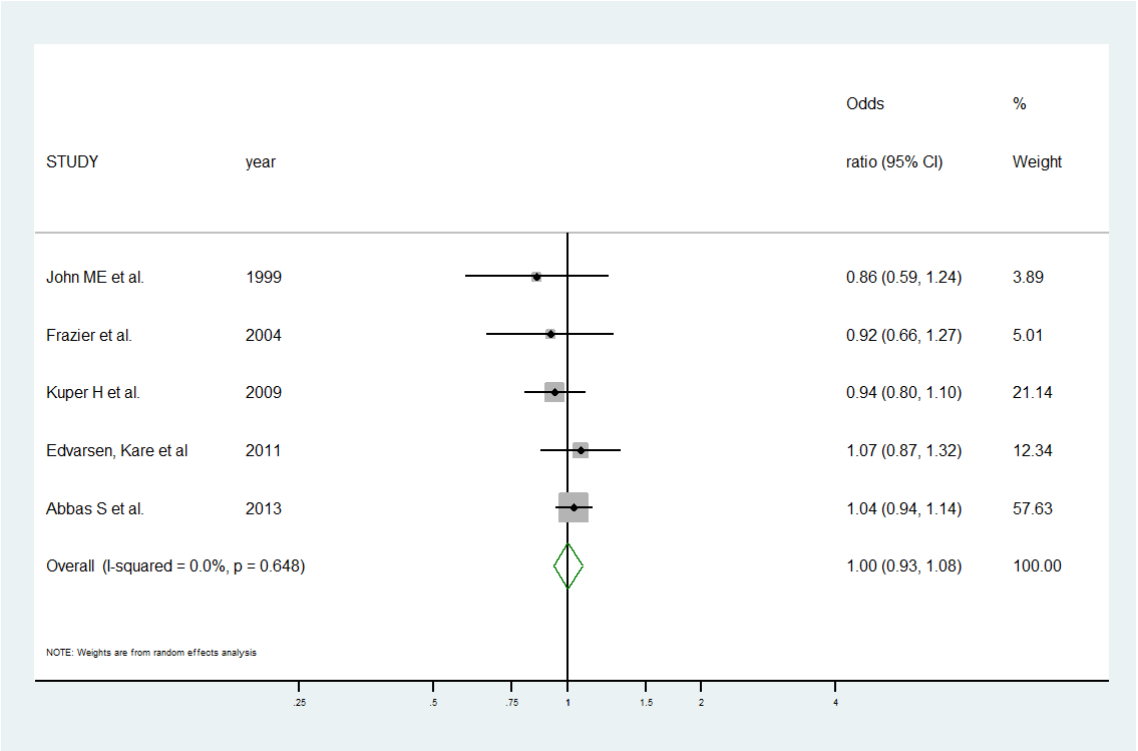
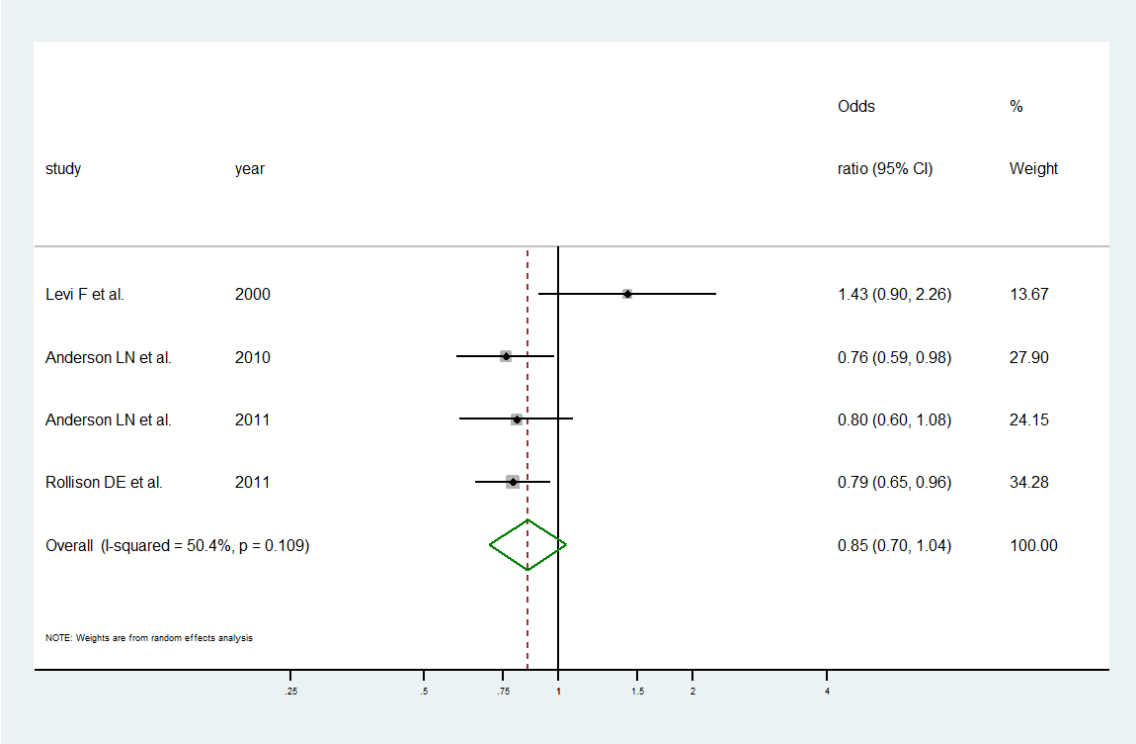
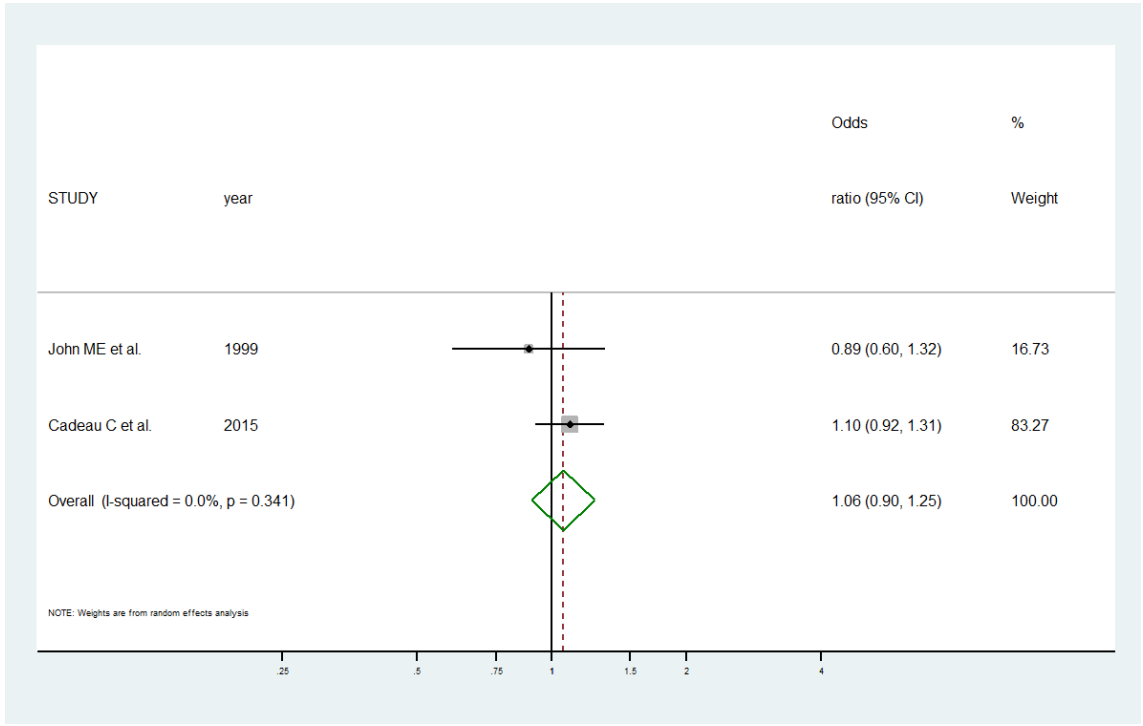


Figure 3: Forestplot for the relationship between vitamin D supplements and breast cancer

a) in case control studies



b) Cohort studies



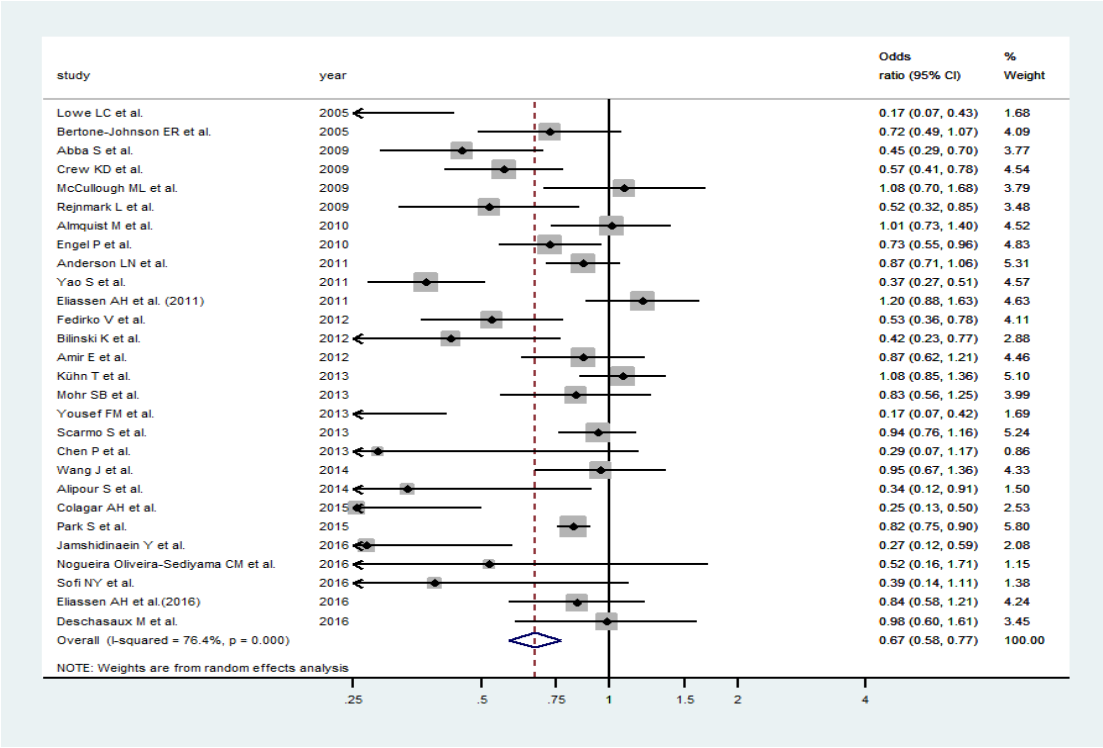
APPENDIX

The most representative figures of this meta-analysis are included below to facilitate the reader´s comprehension (we have included the figure if there were 3 or more articles for each exposition).

25(OH)D exposure and breast cancer

Figure 1. Forest plot for the relationship between 25(OH)D exposure and breast cancer.

a) Case control studies.



b) Nested case control studies.

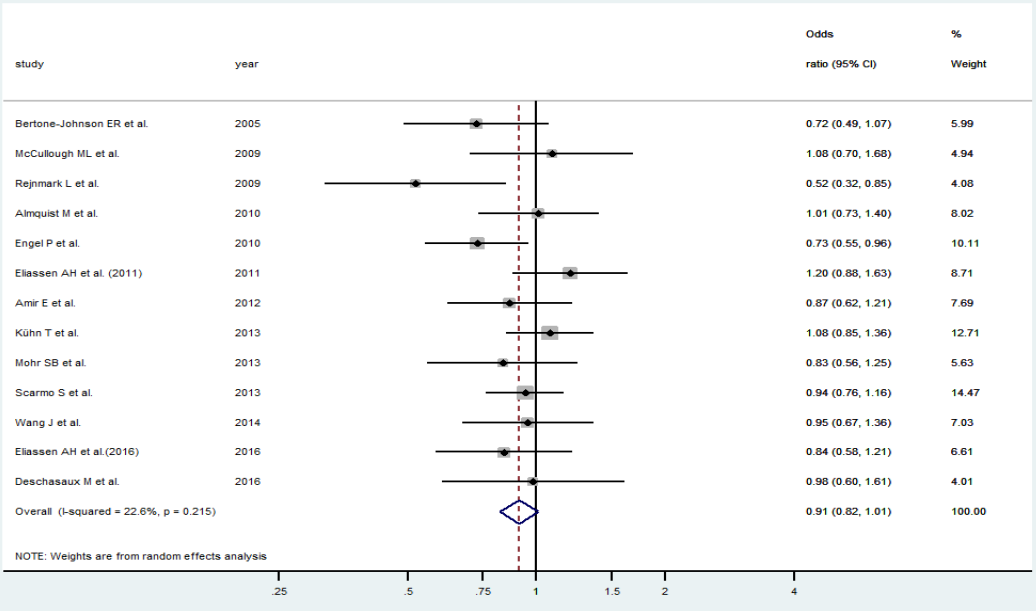
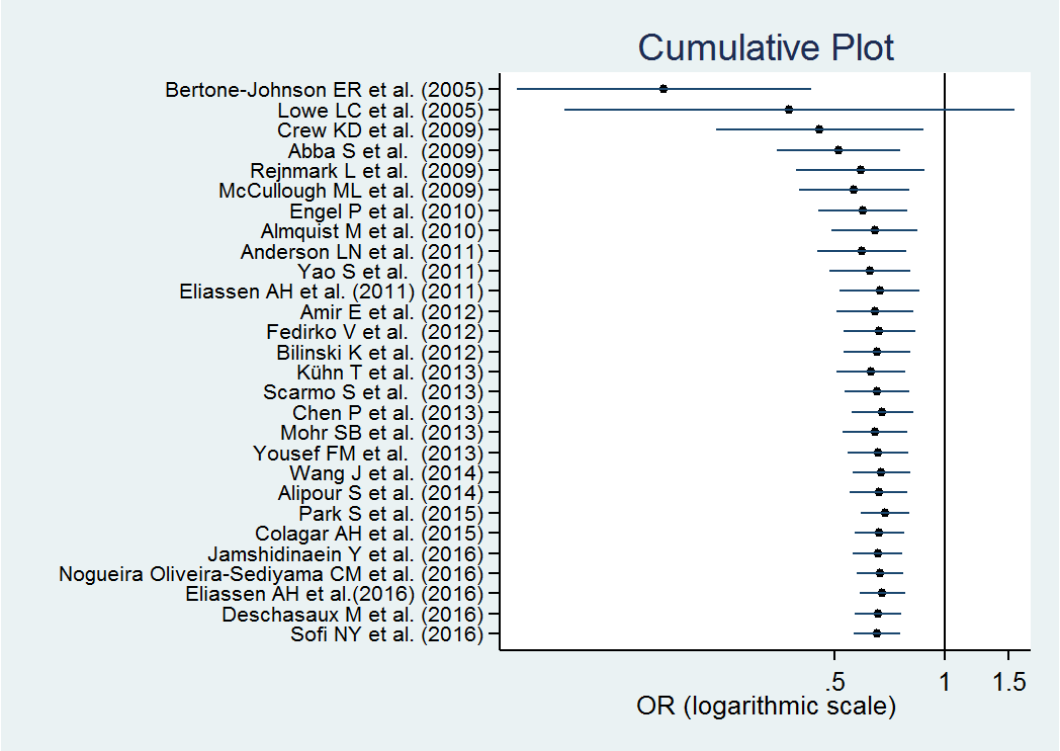


Figure 2. Cumulative plot for the relationship between 25(OH)D exposure and breast cancer.

a) Case control studies.



b) Nested case control studies.

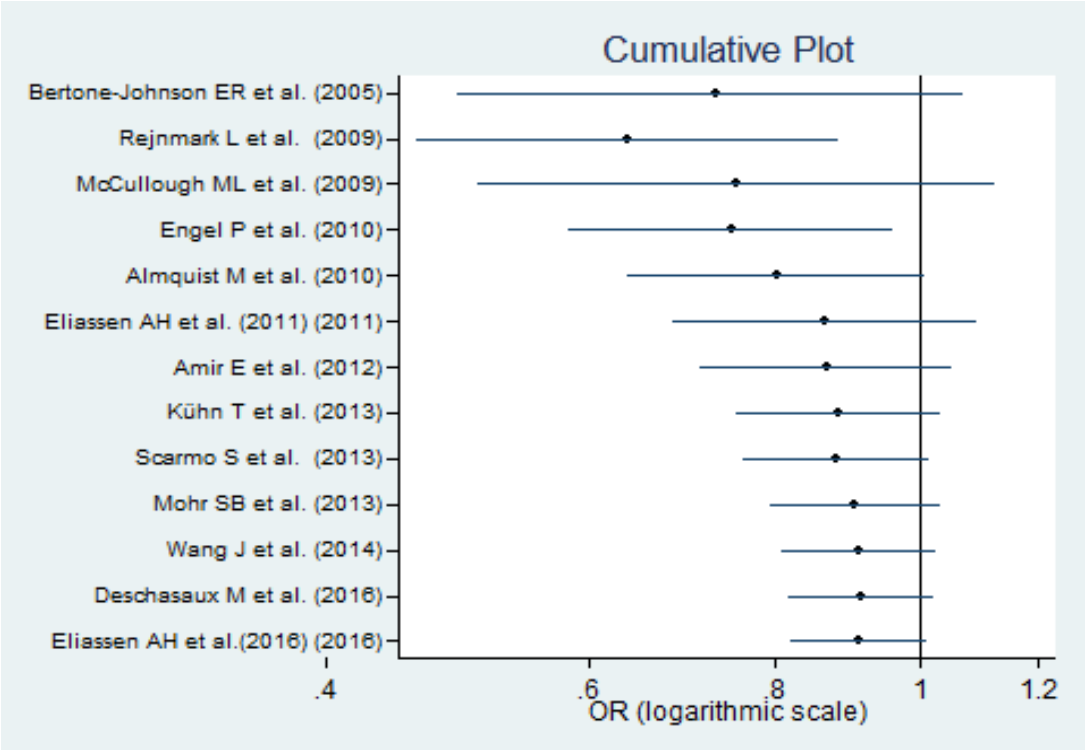
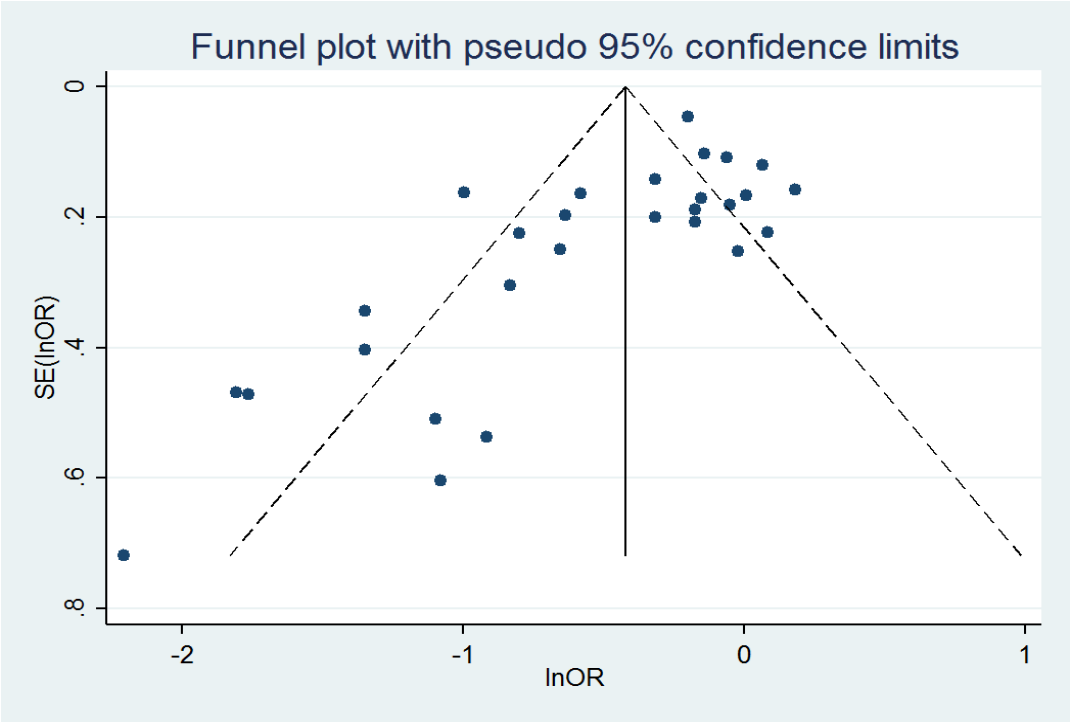


Figure 3. Funnel plot for the relationship between 25(OH)D exposure and breast cancer.

a)Case control studies.



b) Nested case control studies.

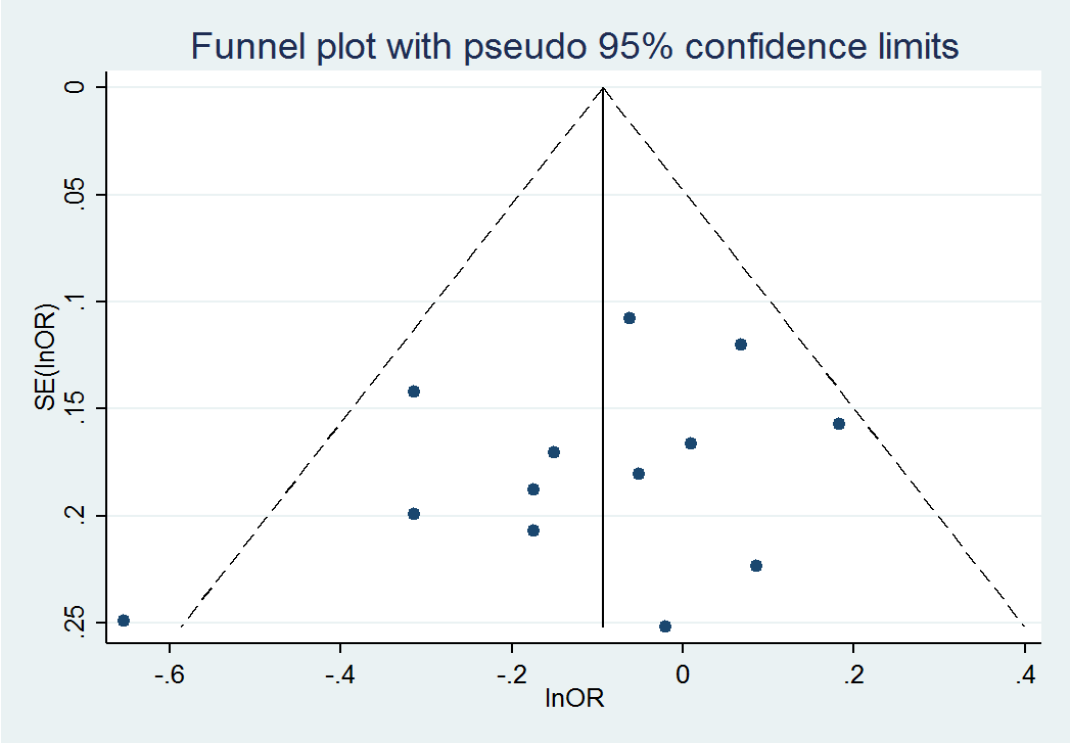
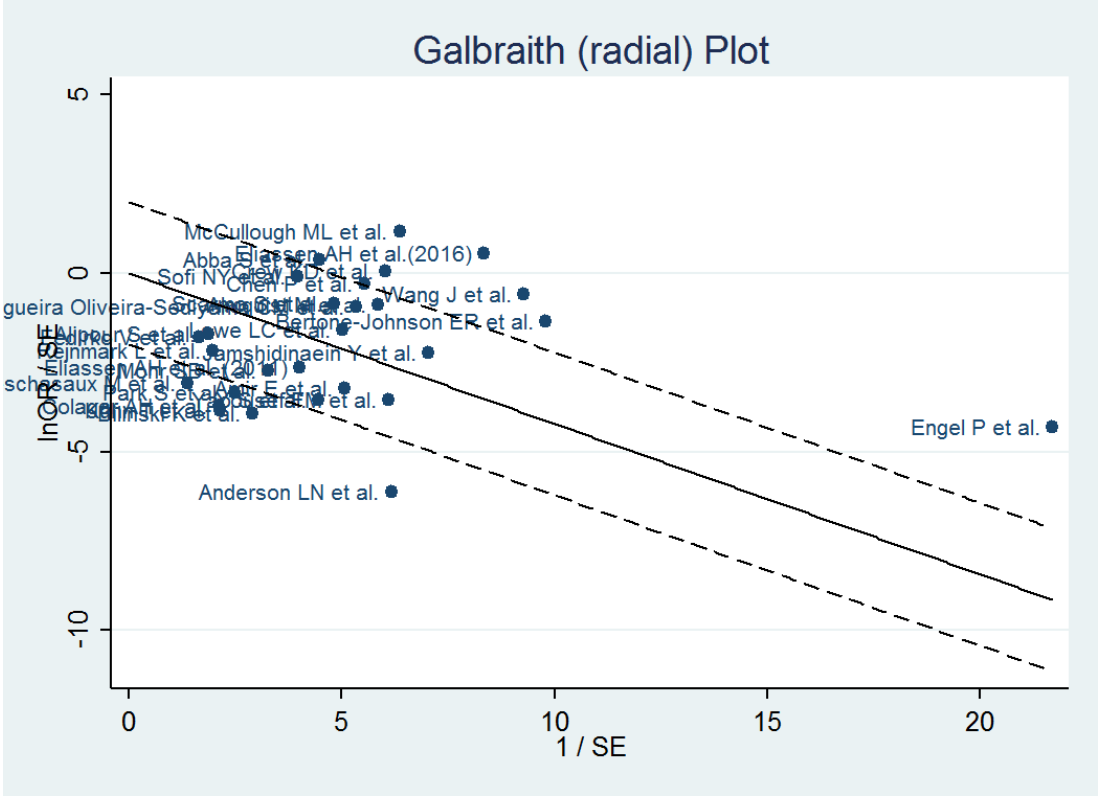
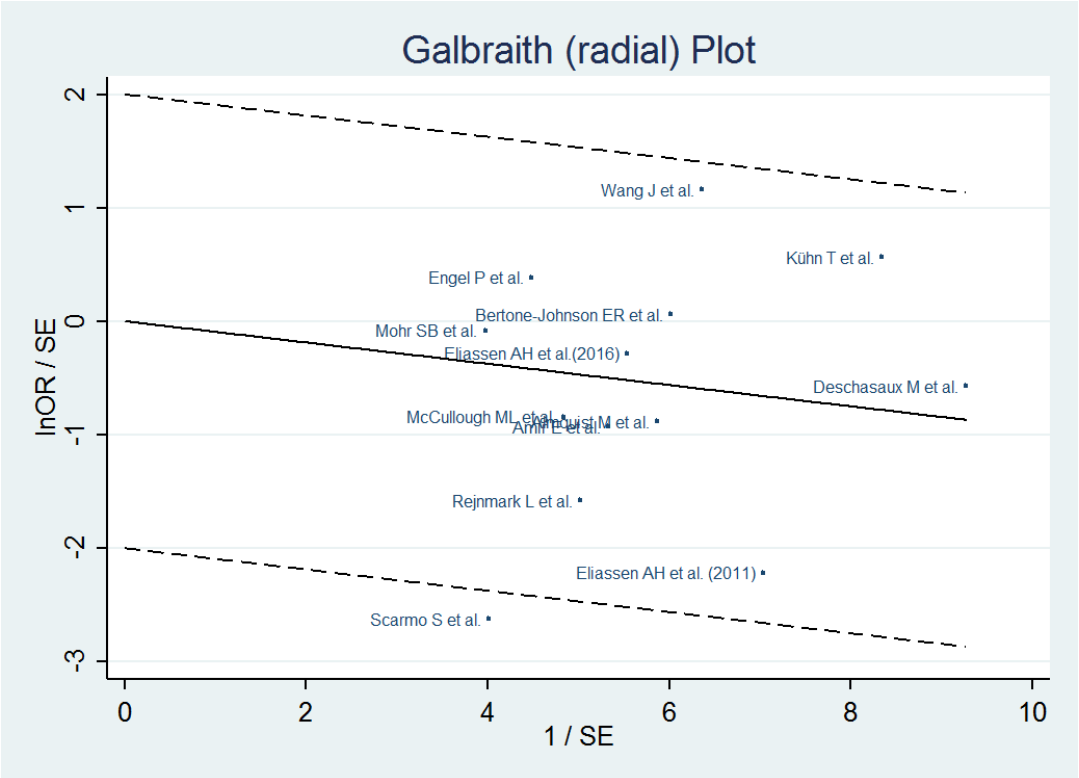


Figure 4. Galbraith plot for the relationship between 25(OH)D exposure and breast cancer.

a) Case control studies .



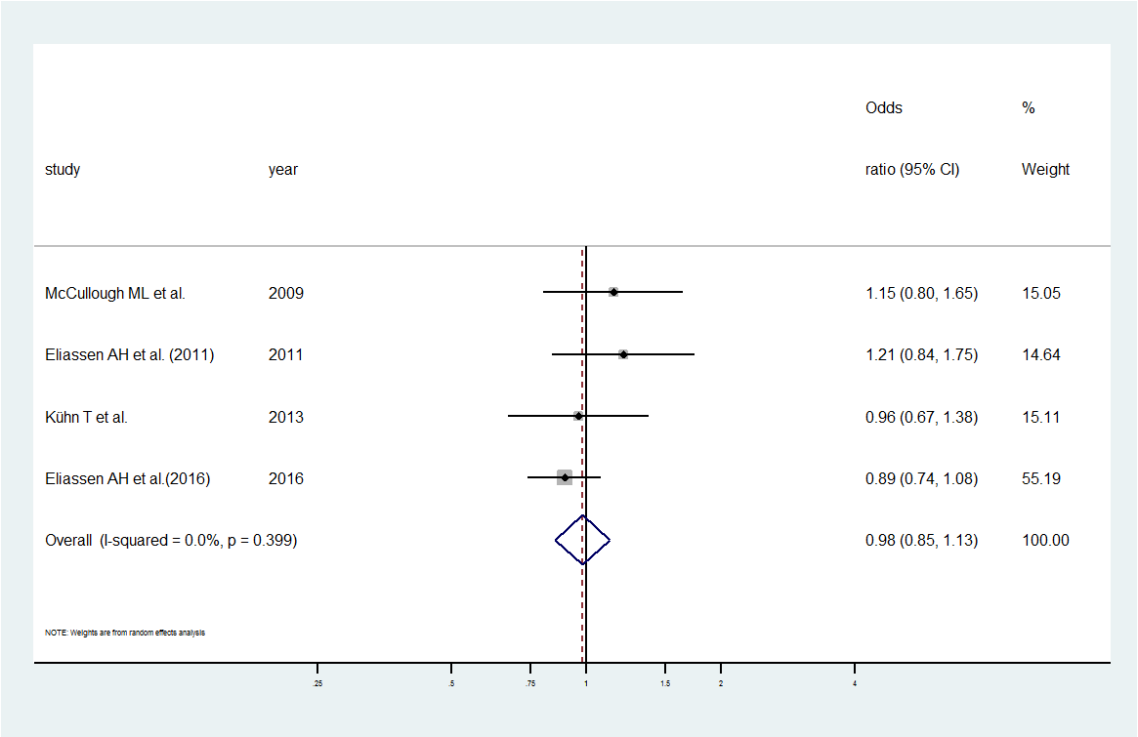
b) Nested case control studies.



25(OH)D exposure and breast cancer according ER status

Figure 5. Forest plot for the relationship between 25(OH)D exposure and ER+ breast cancer.

a) Case control studies.



b) Nested case control studies.

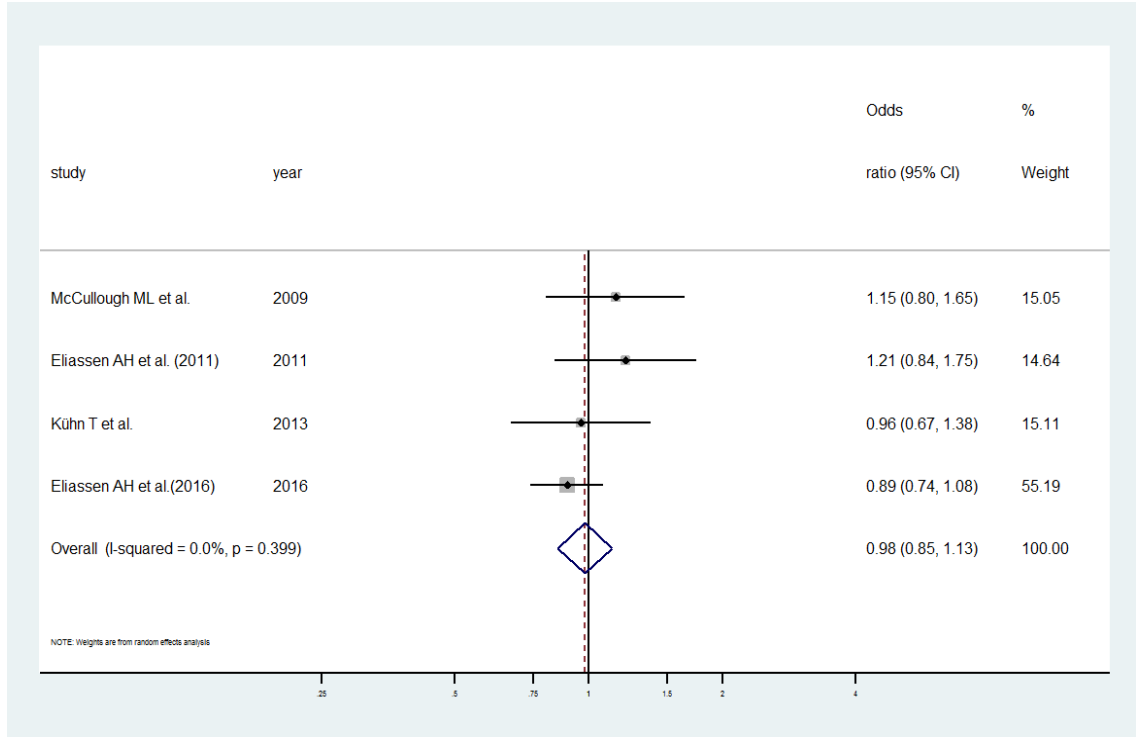
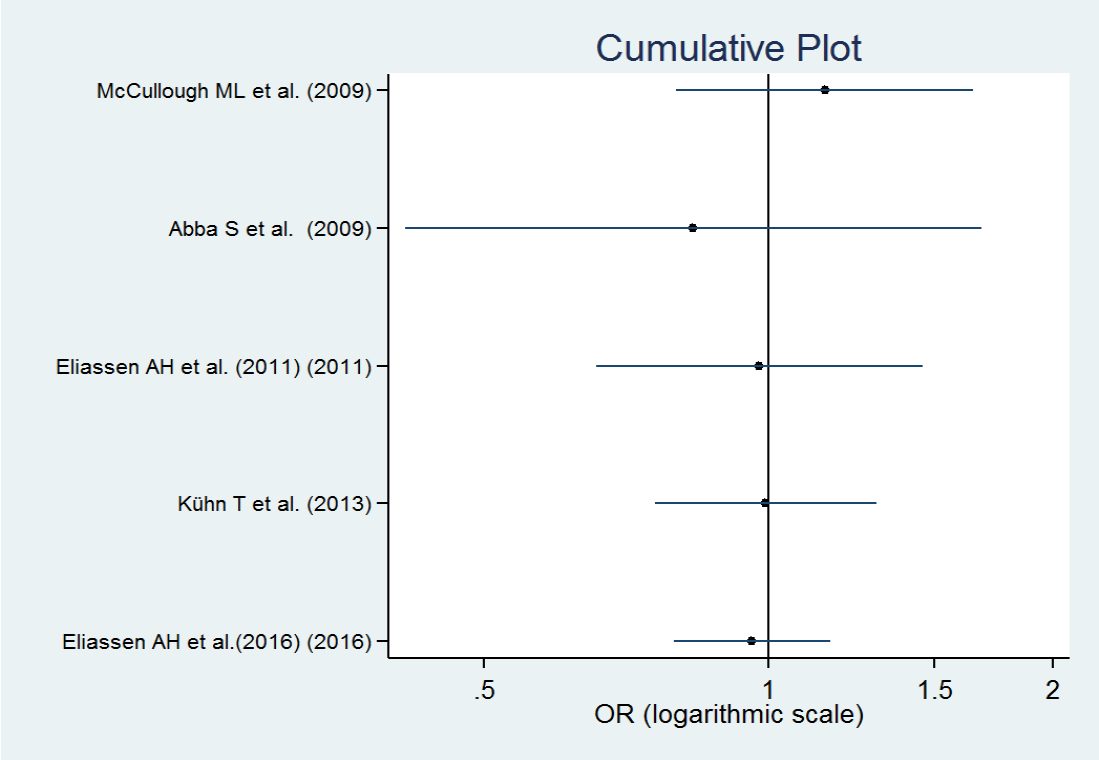


Figure 6. Cumulative plot for the relationship between 25(OH)D exposure and ER+ breast cancer.

a) Case control studies.



b) Nested case control studies.

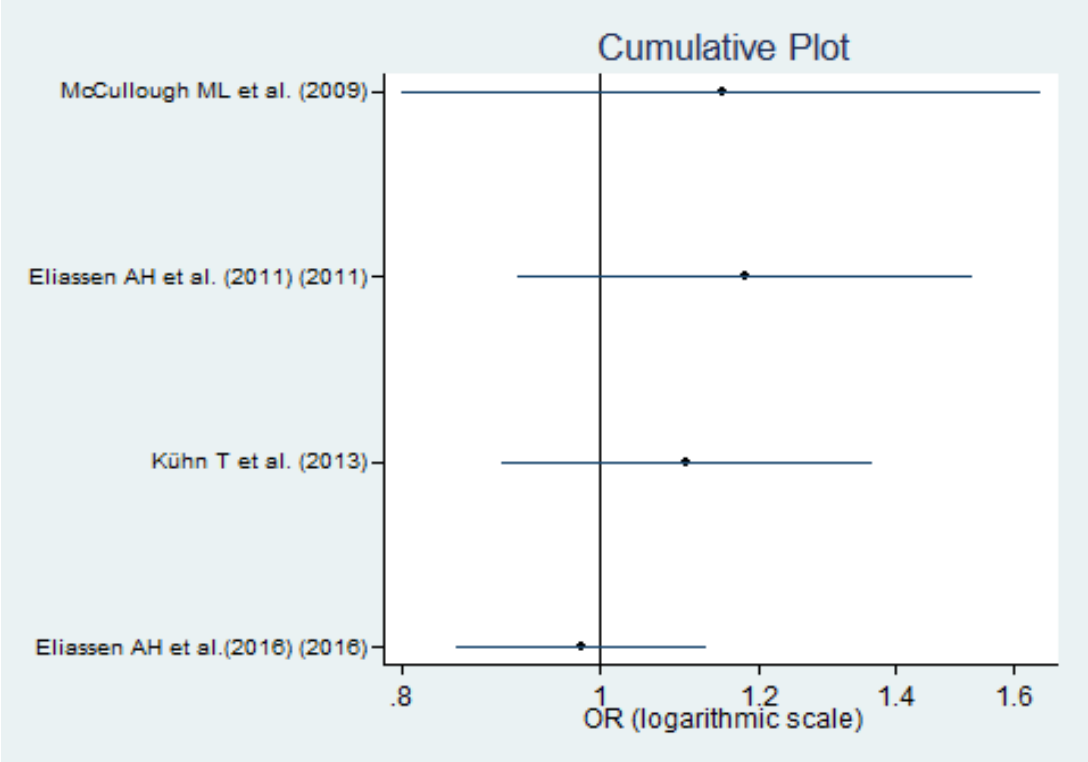
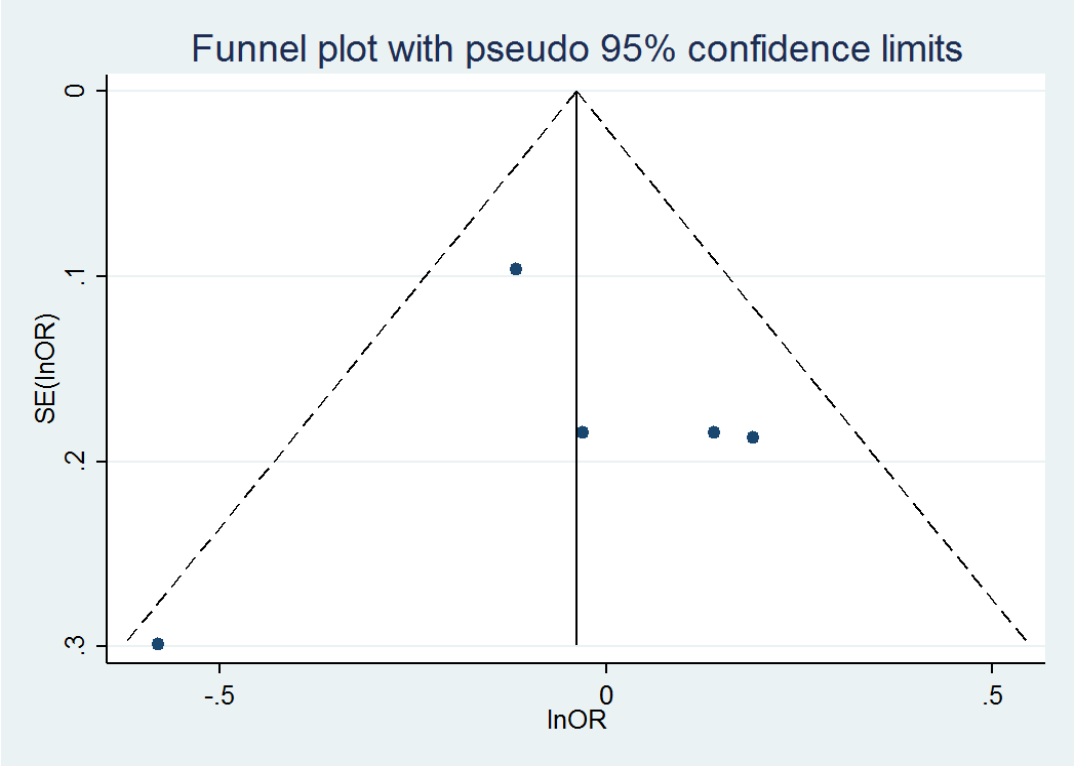


Figure 7: Funnel plot for the relationship between 25(OH)D exposure and ER+ breast cancer.

a) Case-control studies.



b) Nested case control studies.

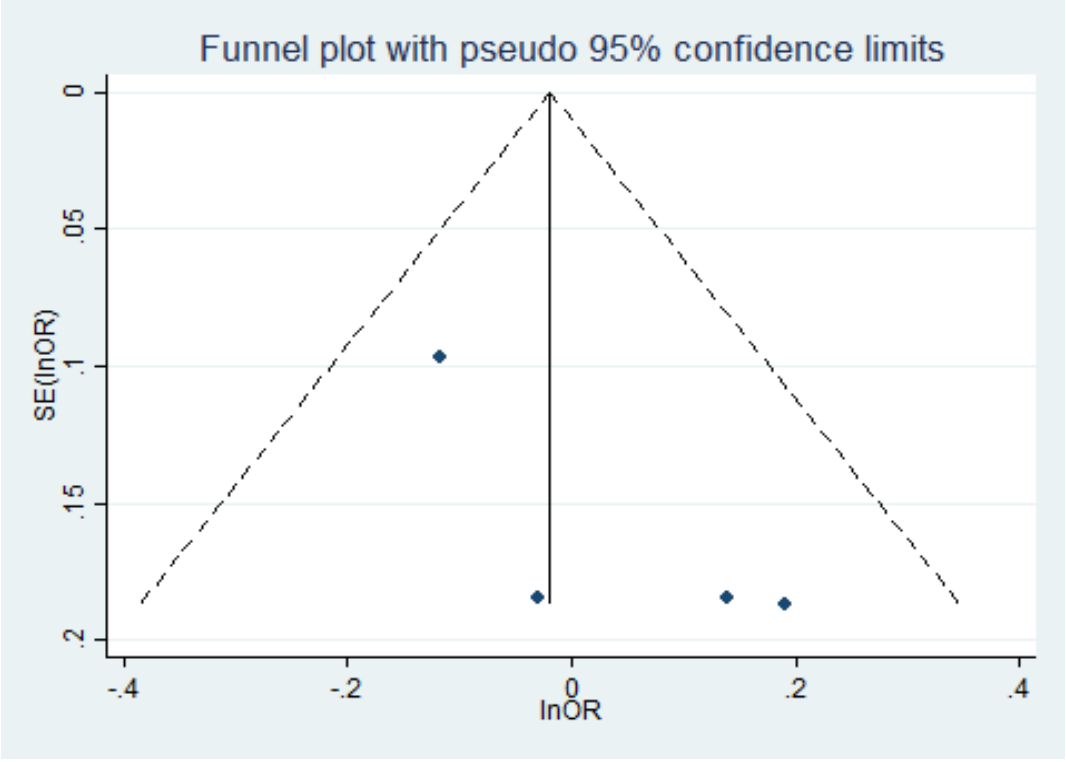
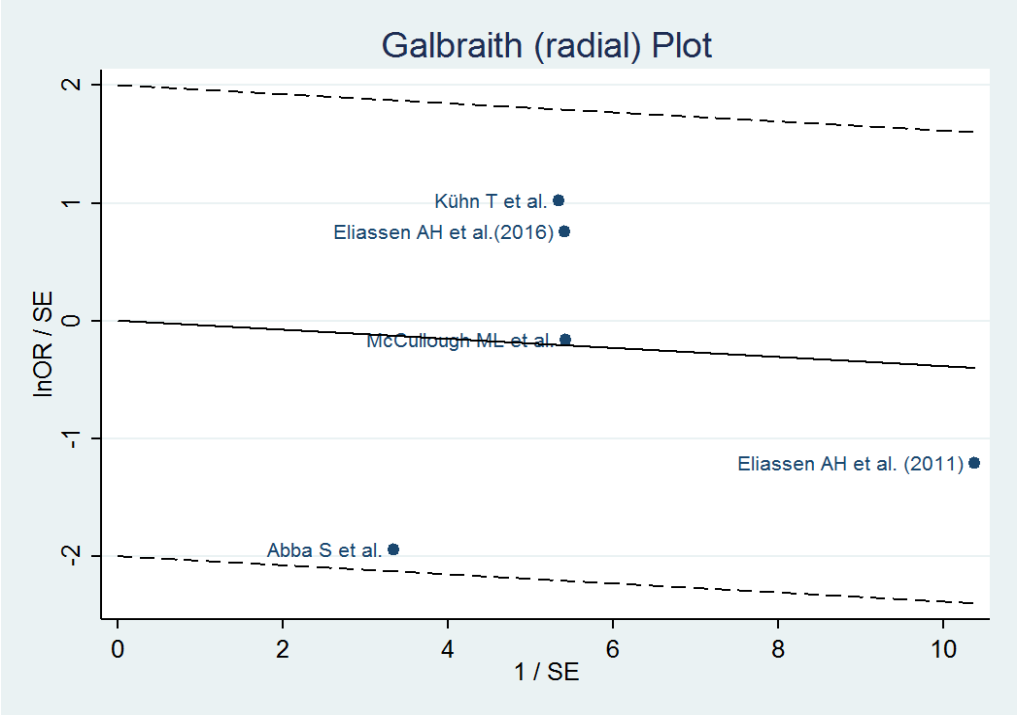


Figure 8. Galbraith plot for the relationship between 25(OH)D exposure and ER+ breast cancer.

a) case-control studies.



b) Nested case control studies.

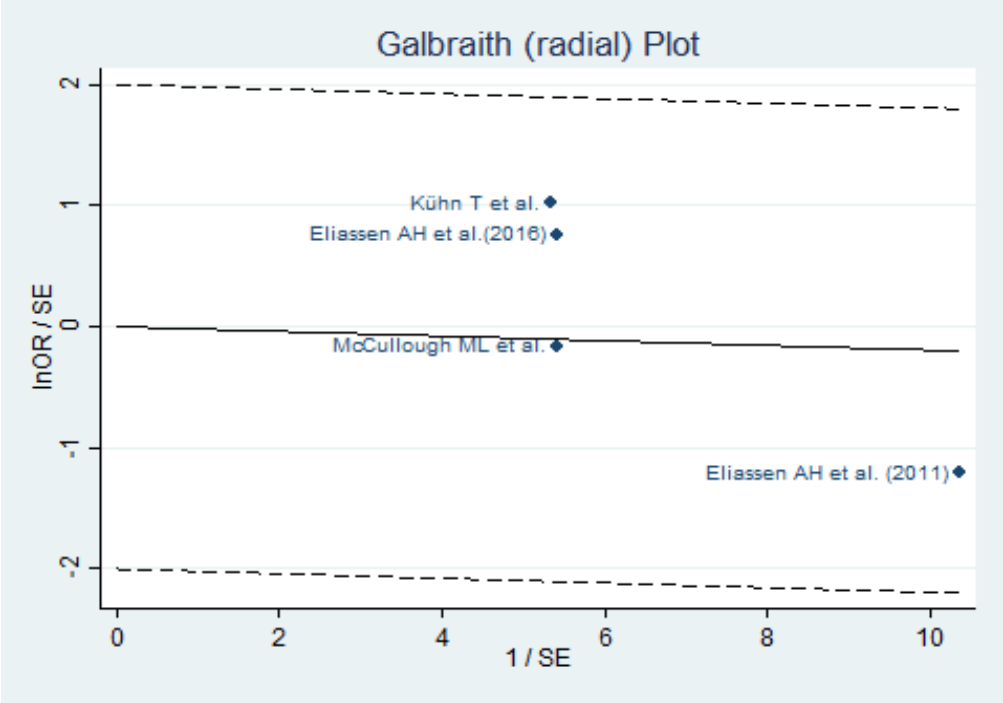
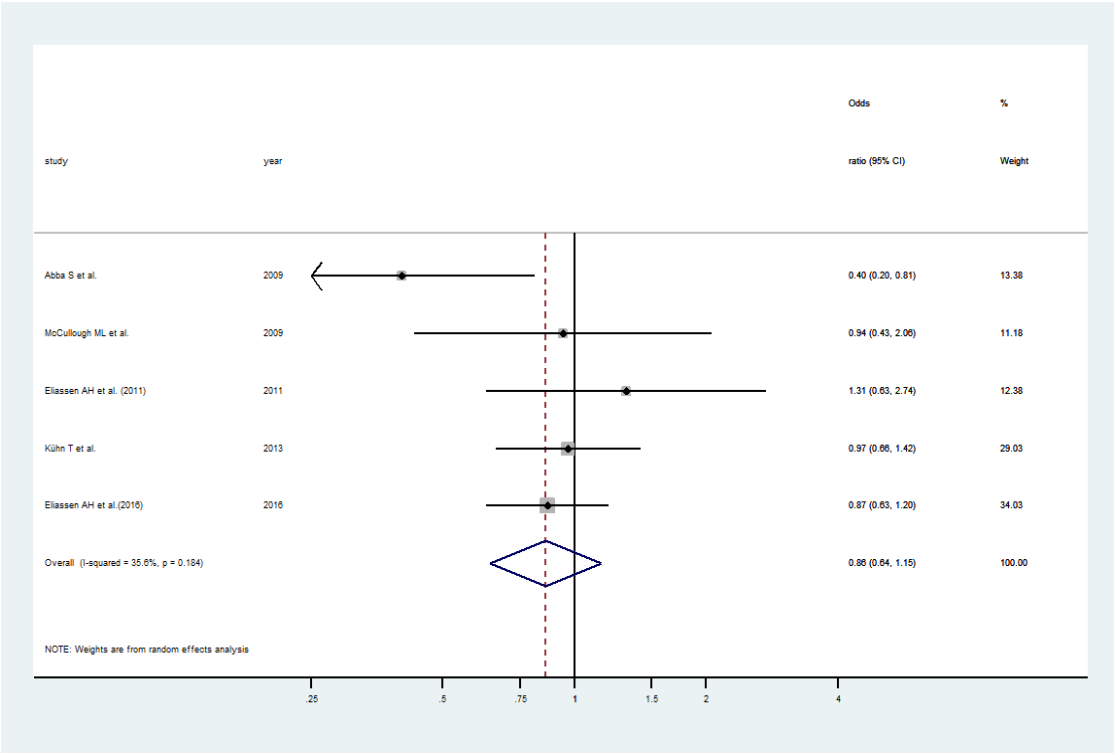


Figure 9. Forest plot for the relationship between 25(OH)D exposure and ER- breast cancer.

a) Case-control studies.



b) Nested case control studies.

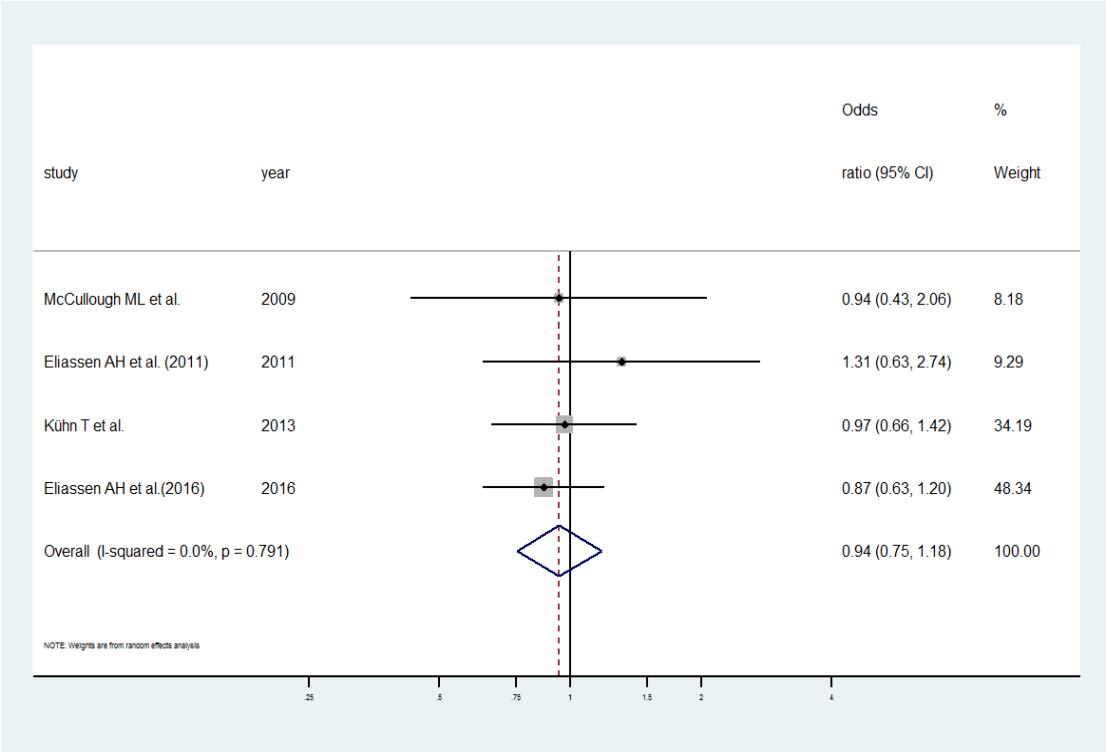
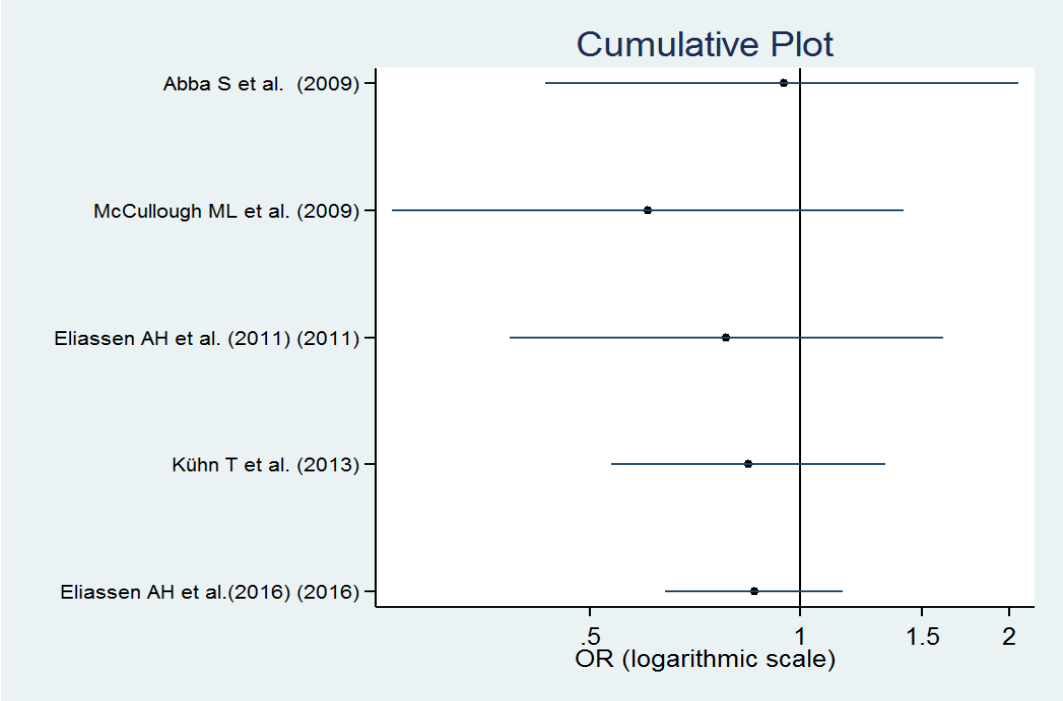


Figure 10. Cumulative plot for the relationship between 25(OH)D exposure and ER- breast cancer.

a) Case control studies.



b) Nested case control studies.

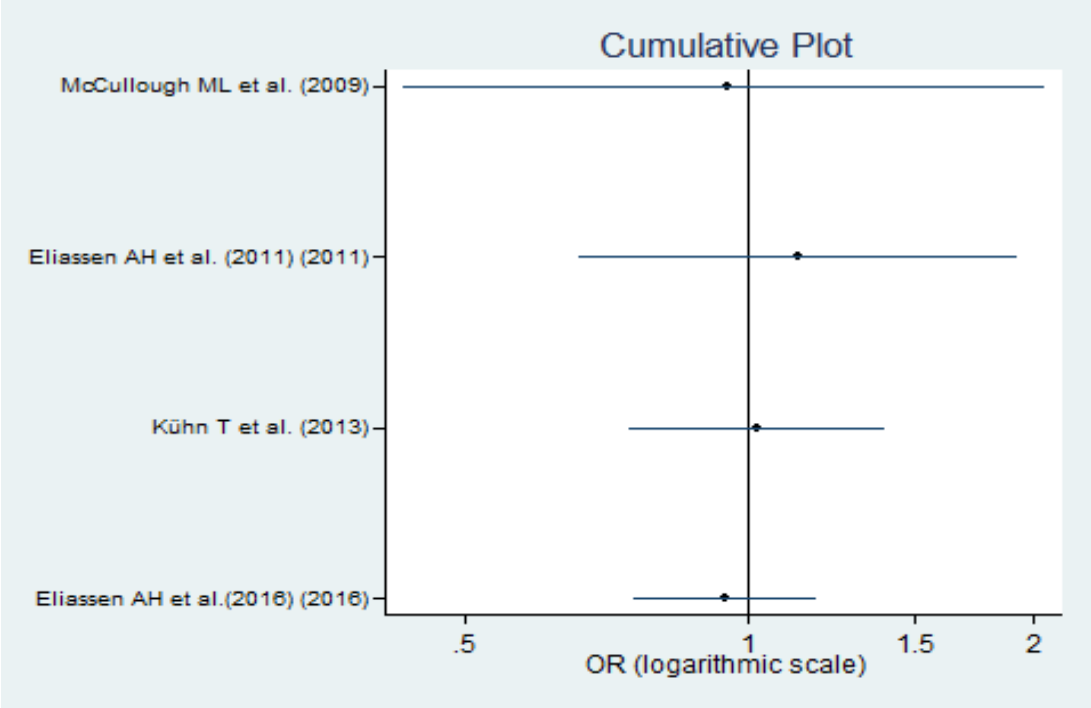
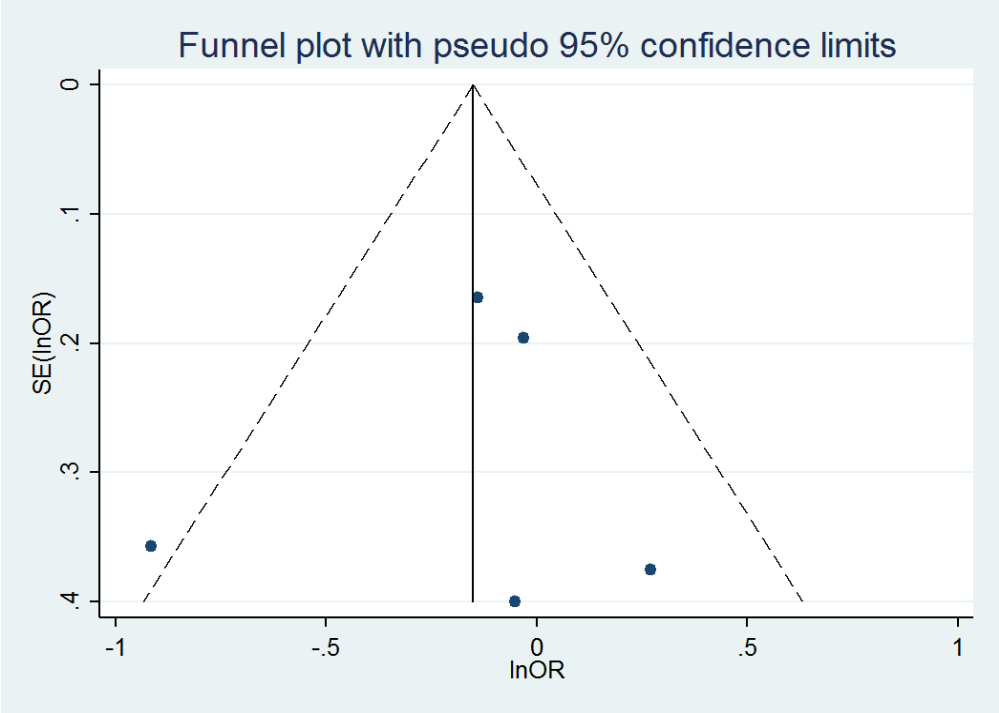


Figure 11. Funnel plot for the relationship between 25(OH)D exposure and ER- breast cancer.

a) Case control studies.



b) Nested case control studies.

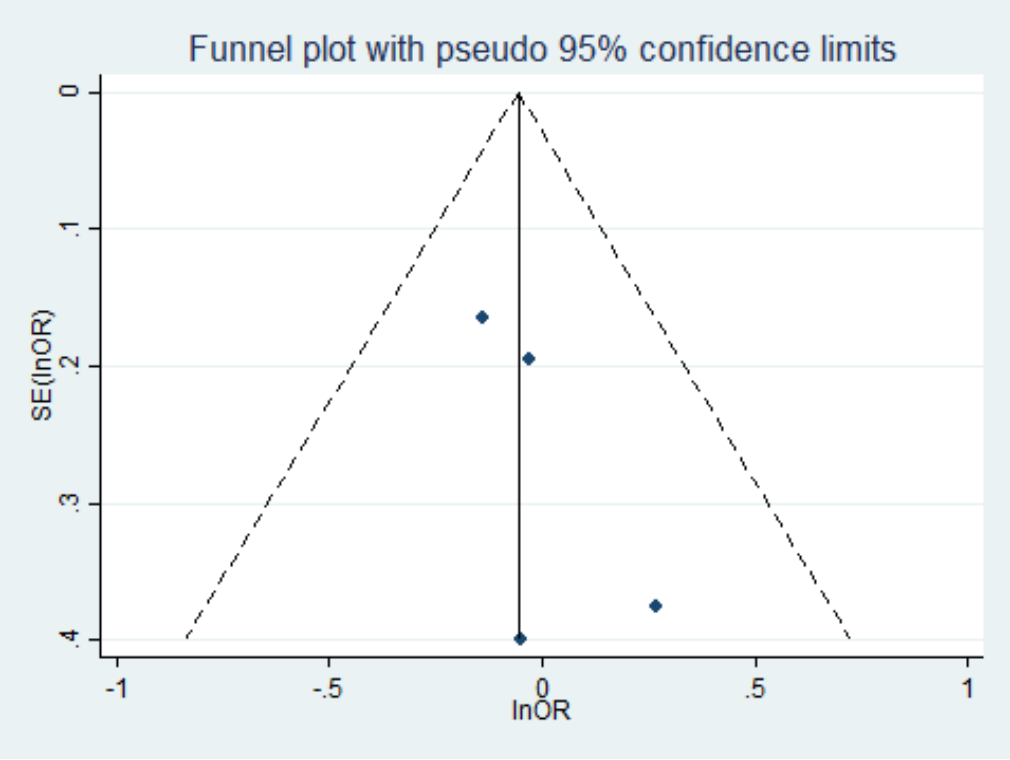
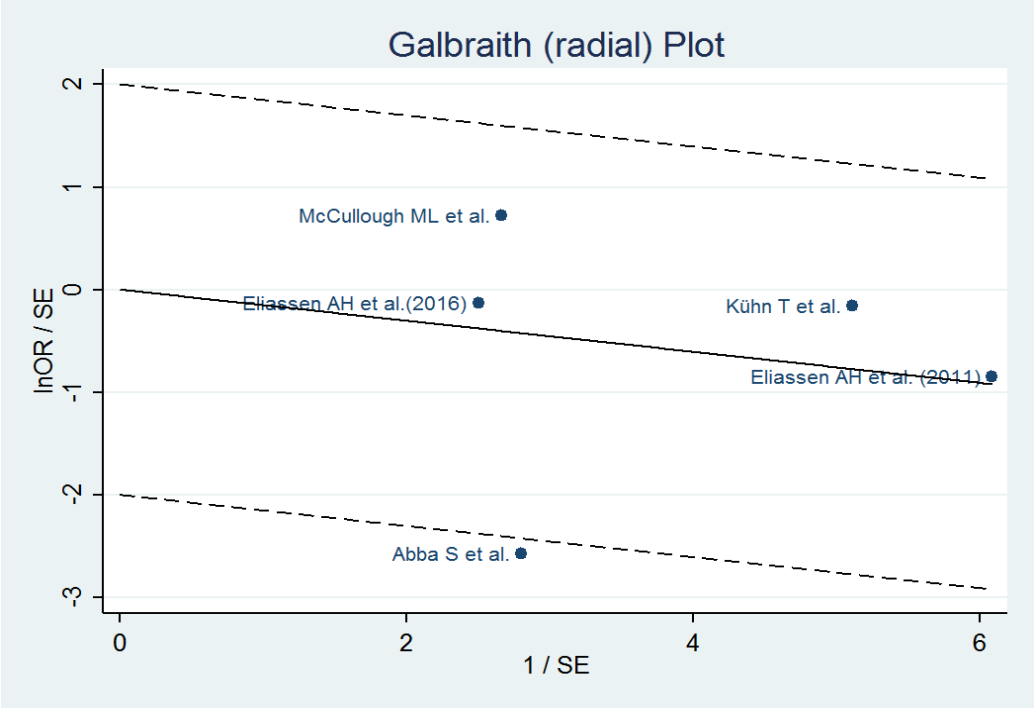
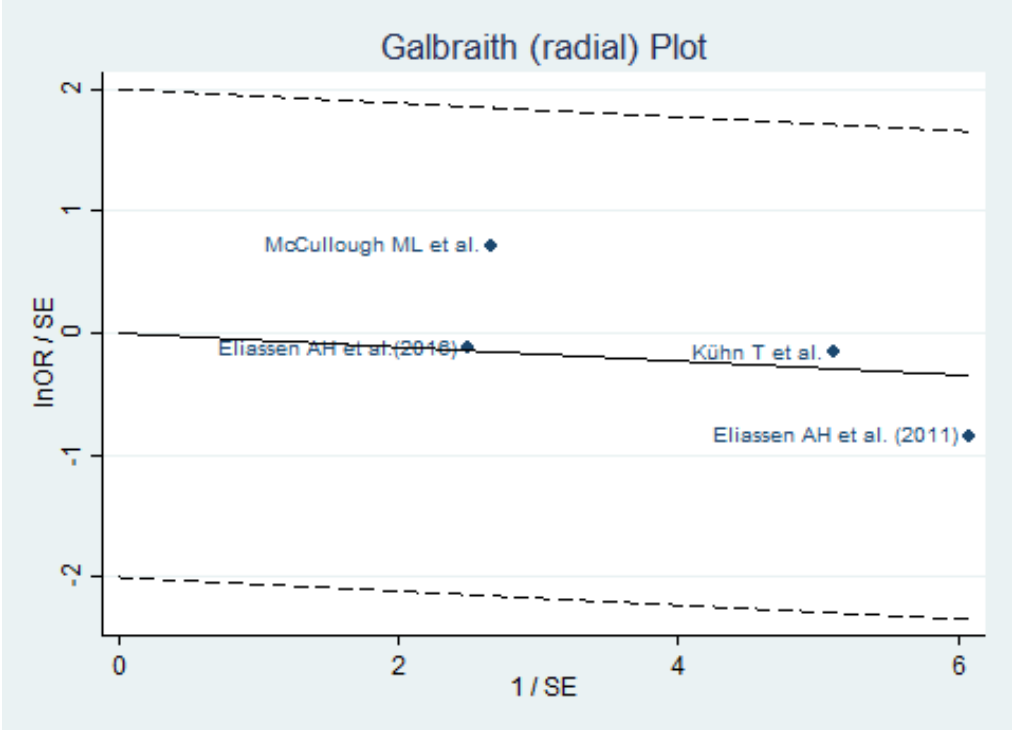


Figure 12. Galbraith plot for the relationship between 25(OH)D exposure and ER- breast cancer.

a) case-control studies.



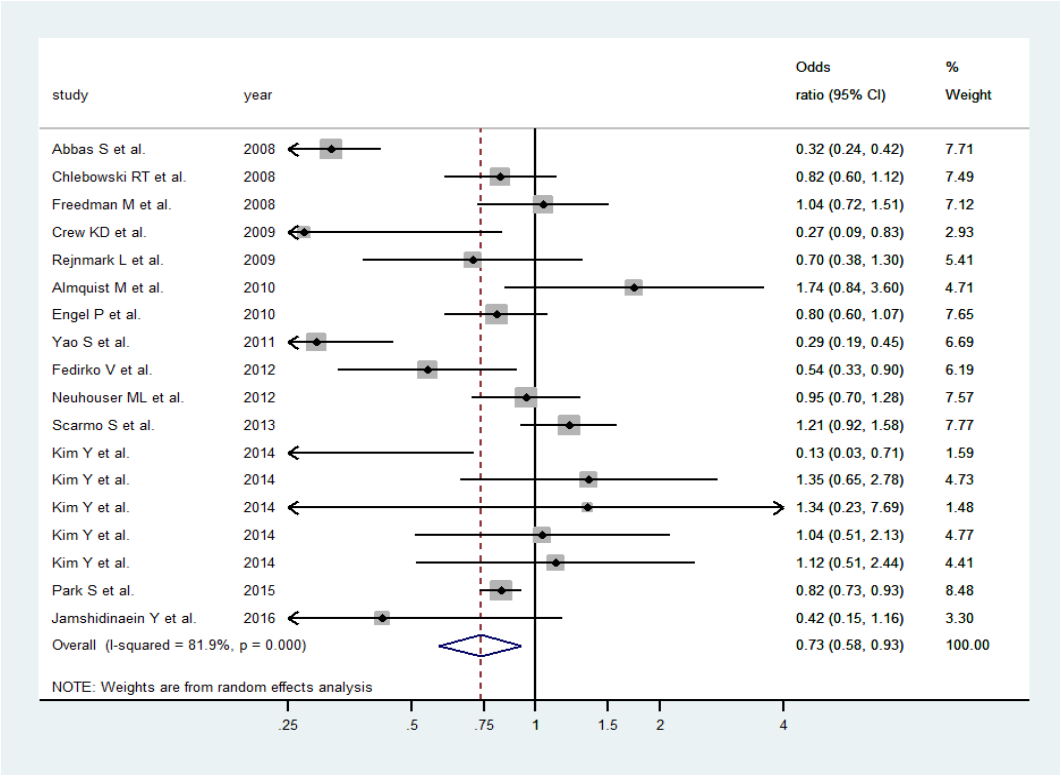
b) Nested case control studies.



25(OH)D exposure and breast cancer according menopausal status

Figure 13. Forest plot for the relationship between 25(OH)D exposure and breast cancer in postmenopausal women.

a) case control studies.



b) Nested case control studies.

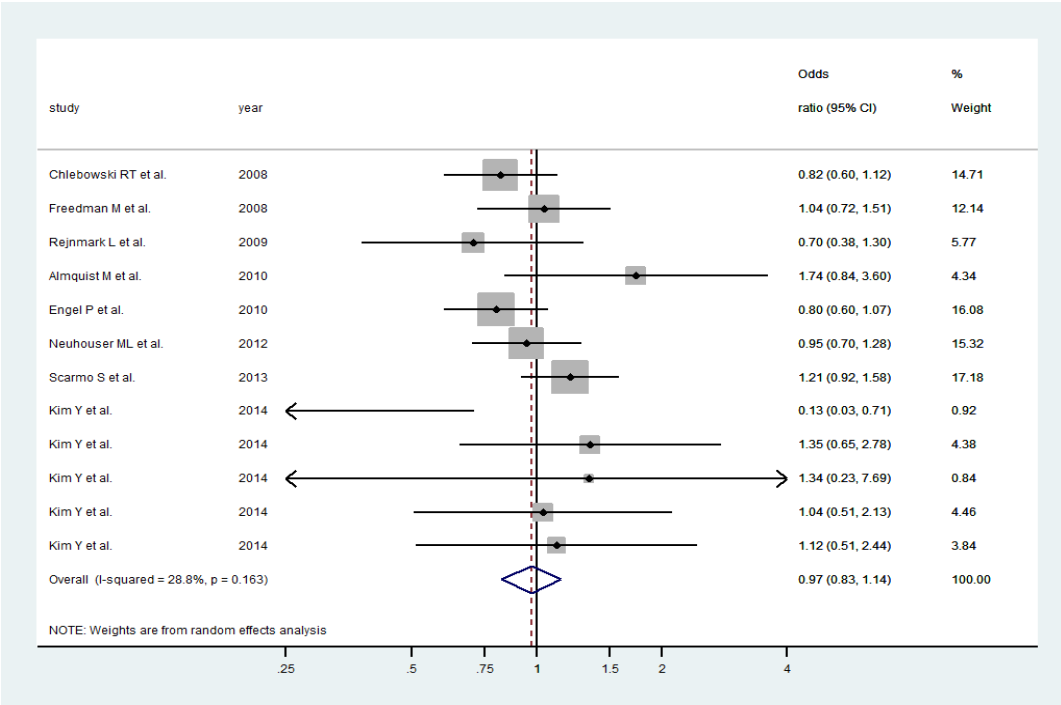
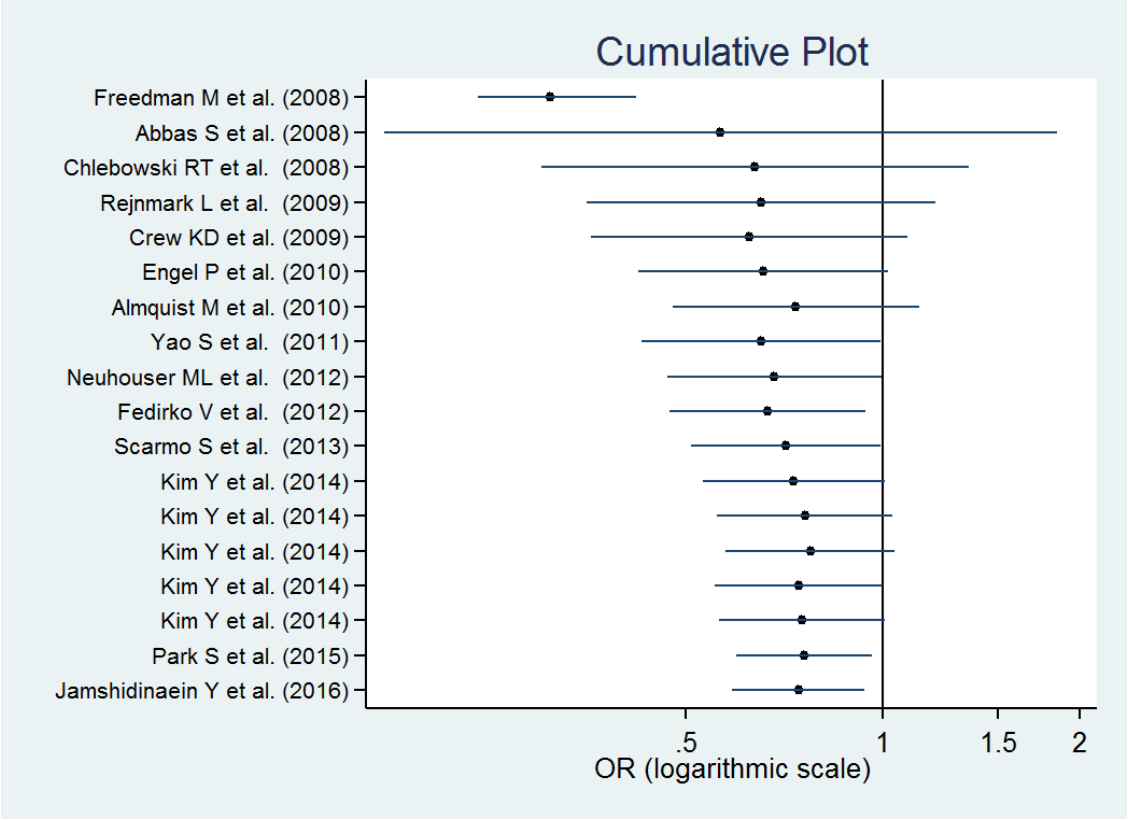


Figure 14. Cumulative plot for the relationship between 25(OH)D exposure and breast cancer in postmenopausal women.

a) Case control studies.



b) Nested case control studies.

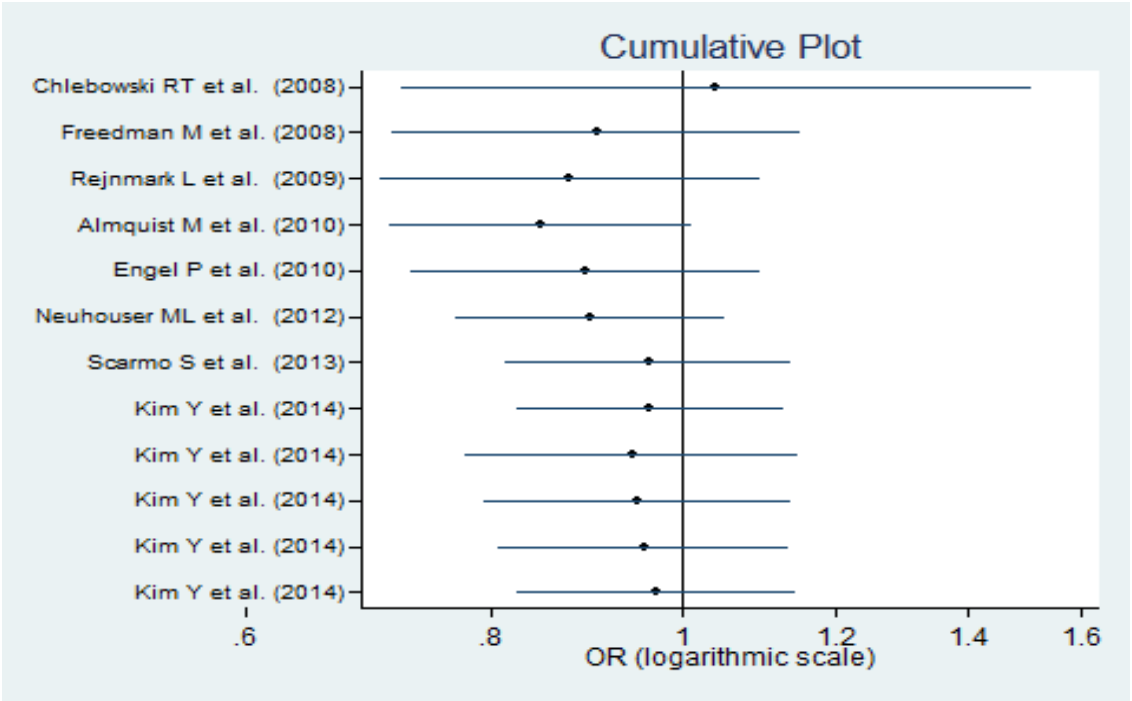
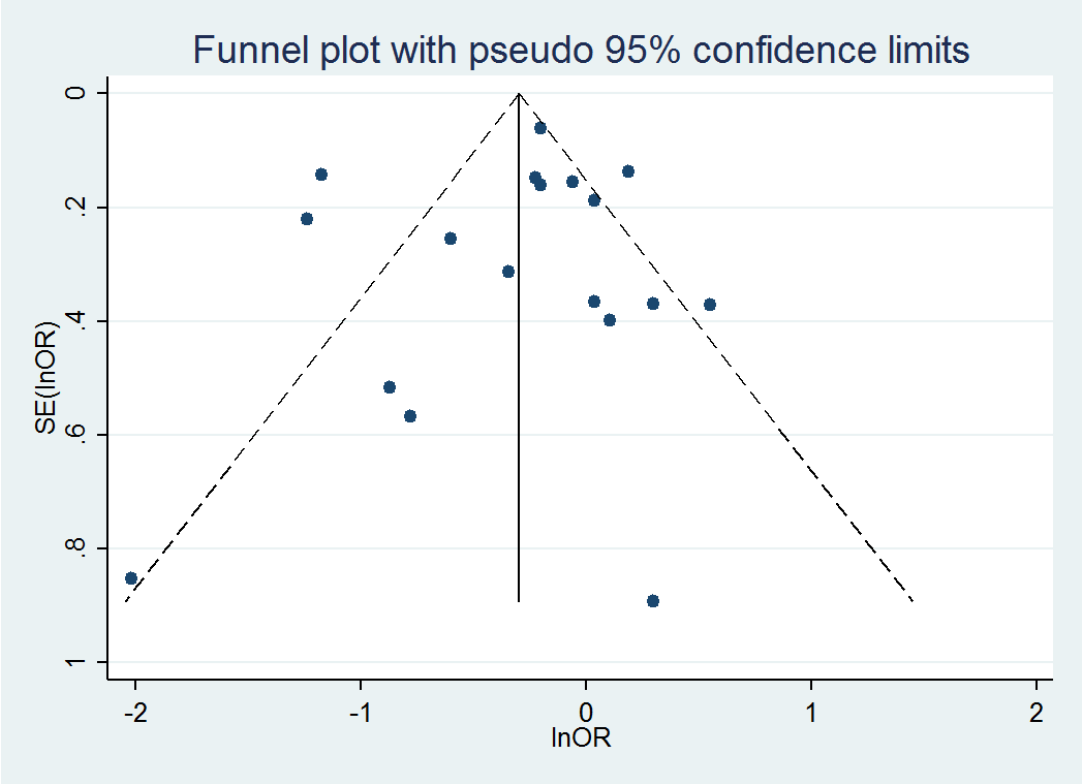


Figure 15. Funnel plot for the relationship between 25(OH)D exposure and breast cancer in postmenopausal women.

a) case control studies.



b) Nested case control studies.

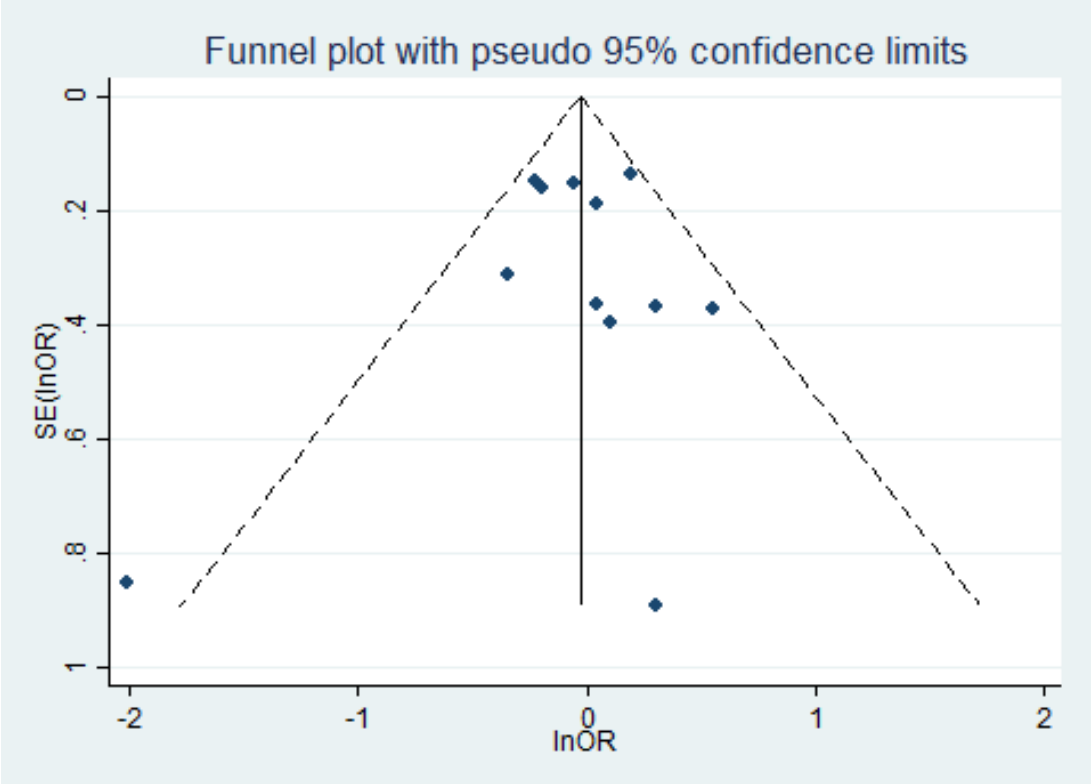
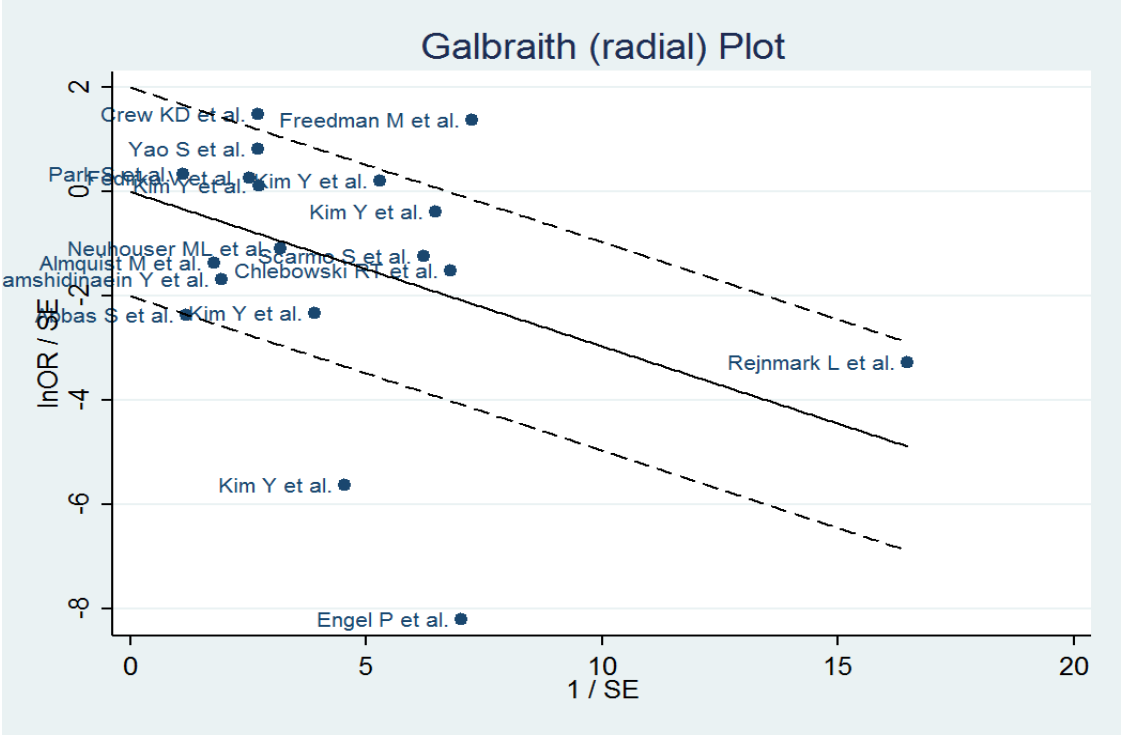


Figure 16. Galbraith plot for the relationship between 25(OH)D exposure and breast cancer in postmenopausal women.

a) Case control studies.



b) Nested case control studies.

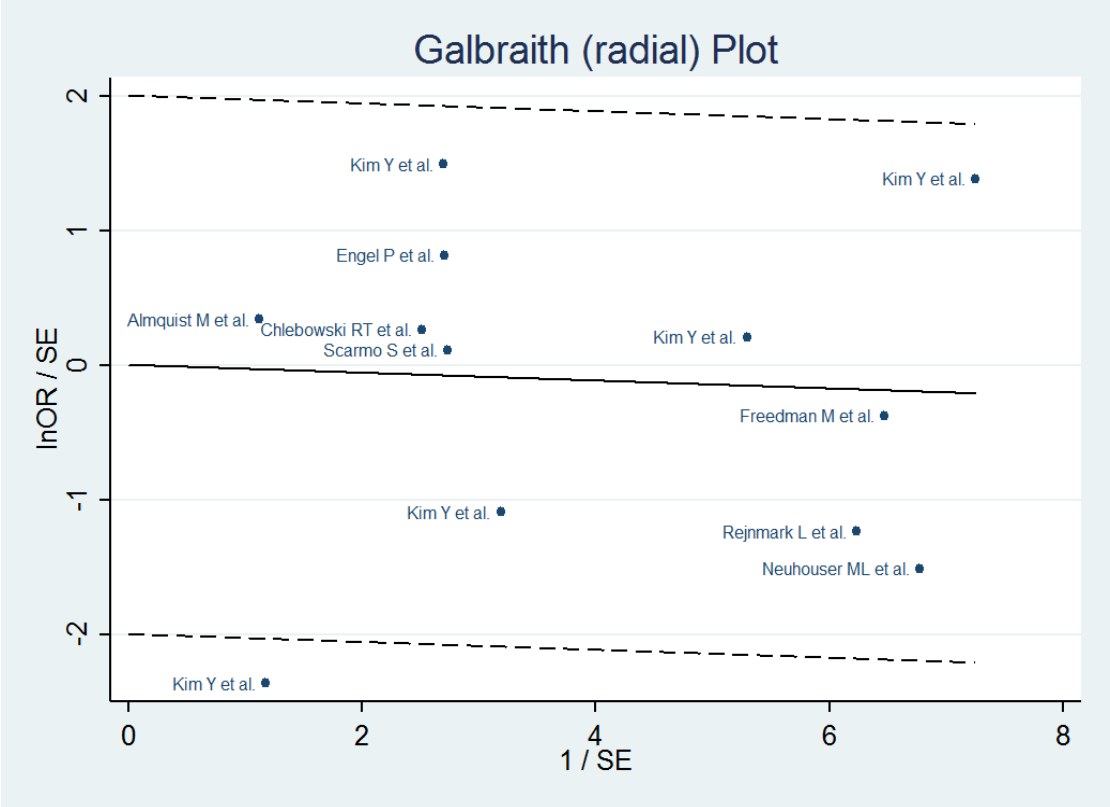
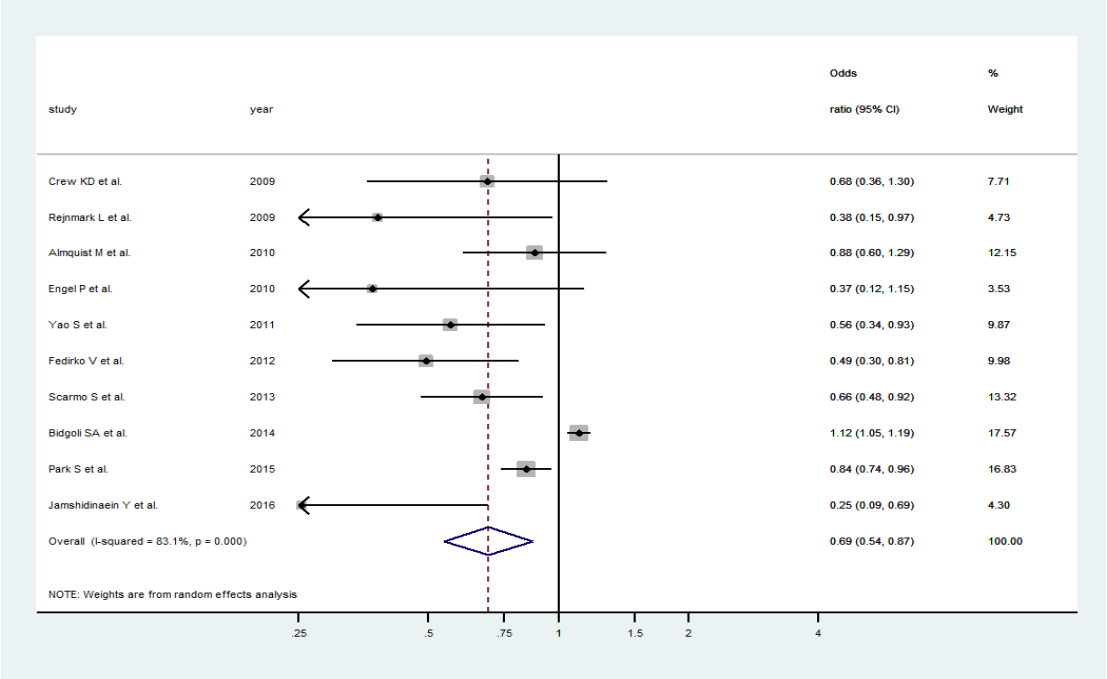


Figure 17. Forest plot for the relationship between 25(OH)D exposure and breast cancer in premenopausal women.

a) Case control studies.



b) Nested case control studies.

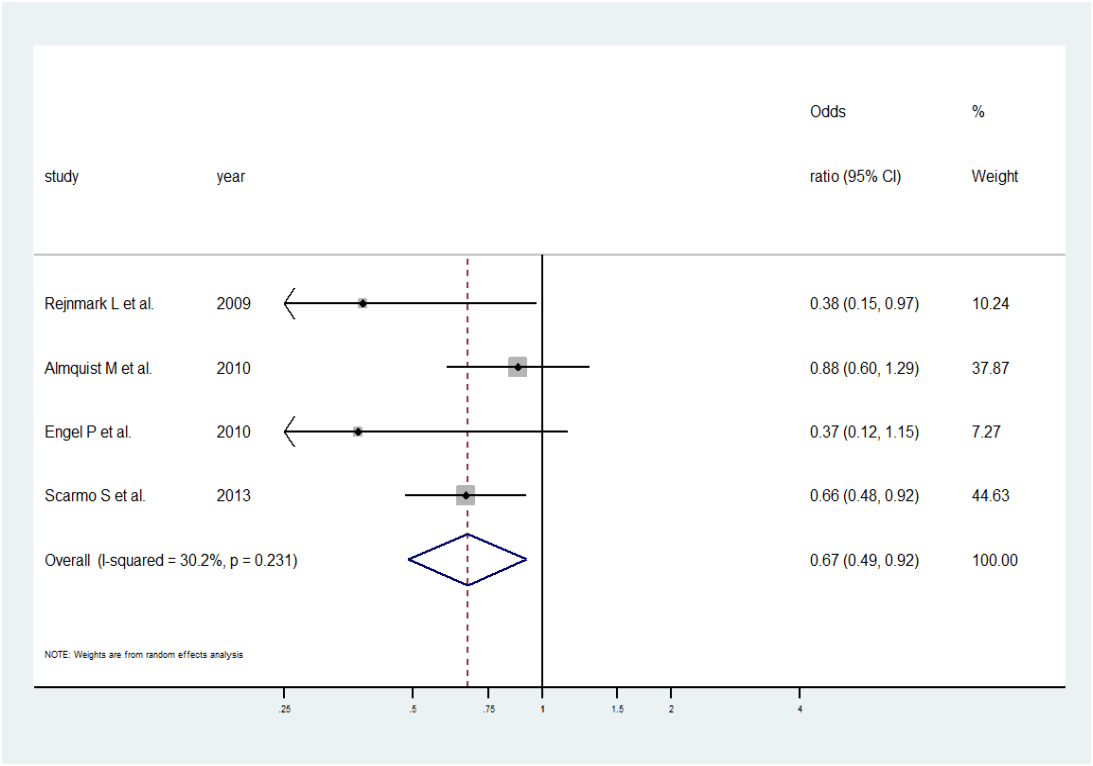
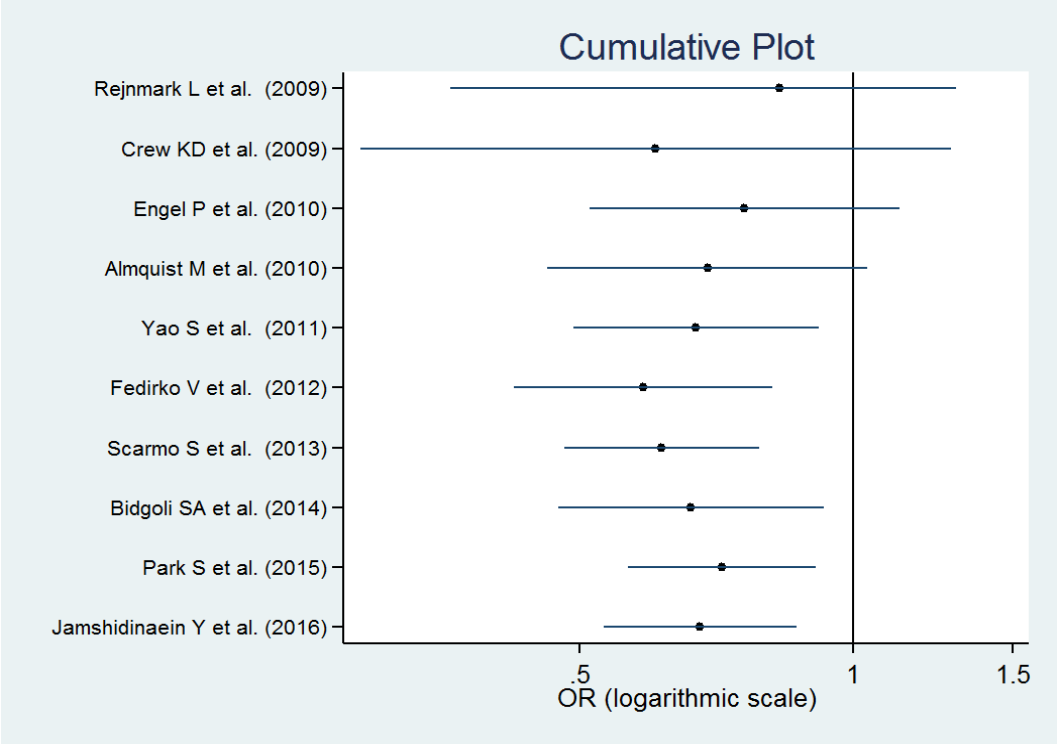


Figure 18. Cumulative plot for the relationship between 25(OH)D exposure and breast cancer in premenopausal women.

a) Case control studies.



b) Nested case control studies.

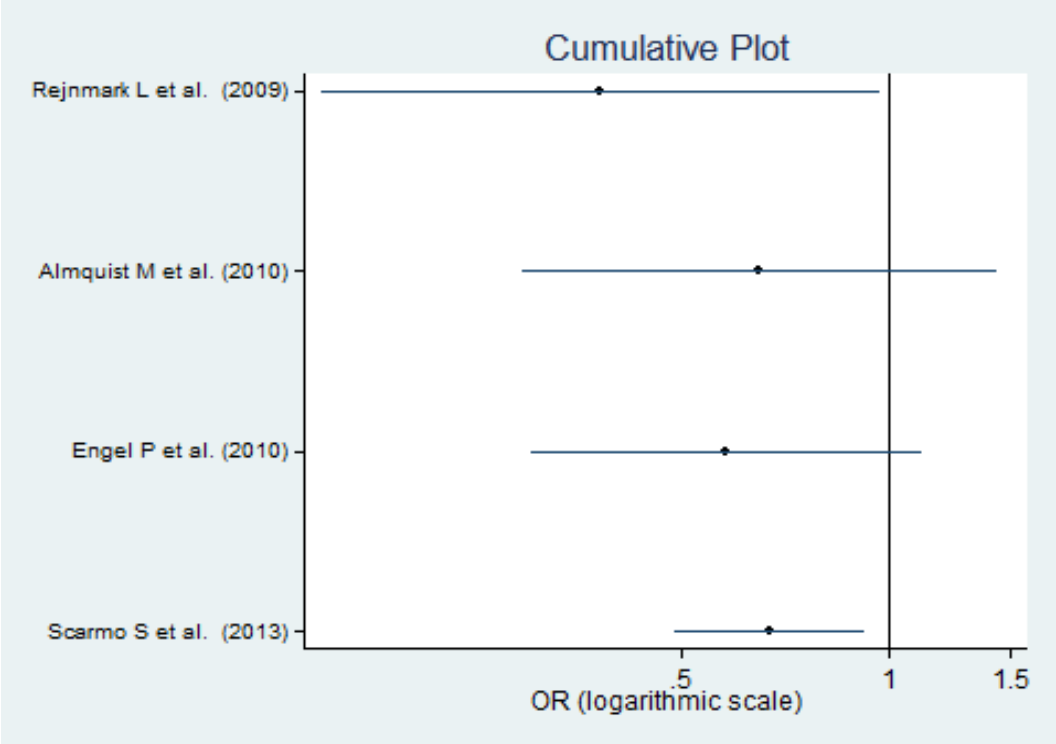
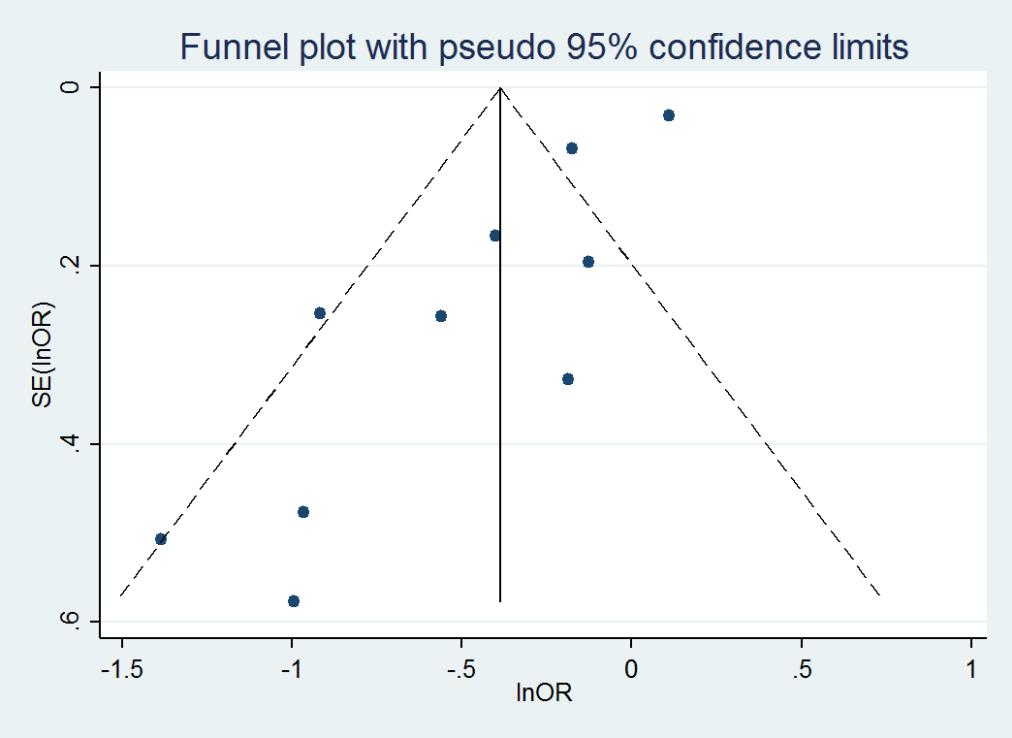


Figure 19. Funnel plot for the relationship between 25(OH)D exposure and breast cancer in premenopausal women.

a) Case control studies .



b) Nested case control studies.

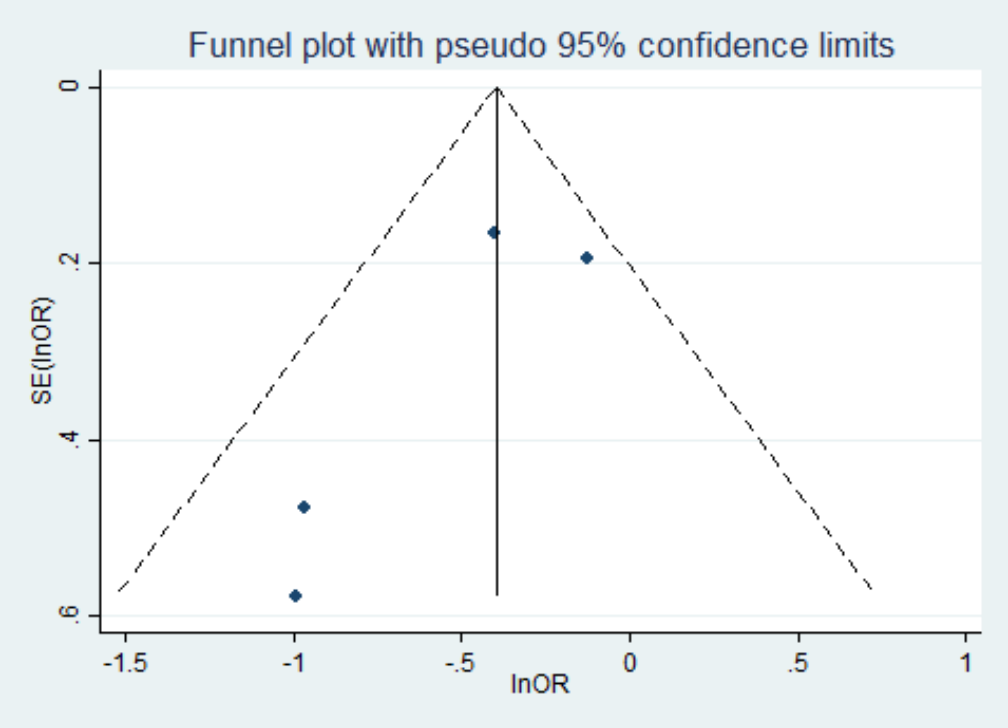
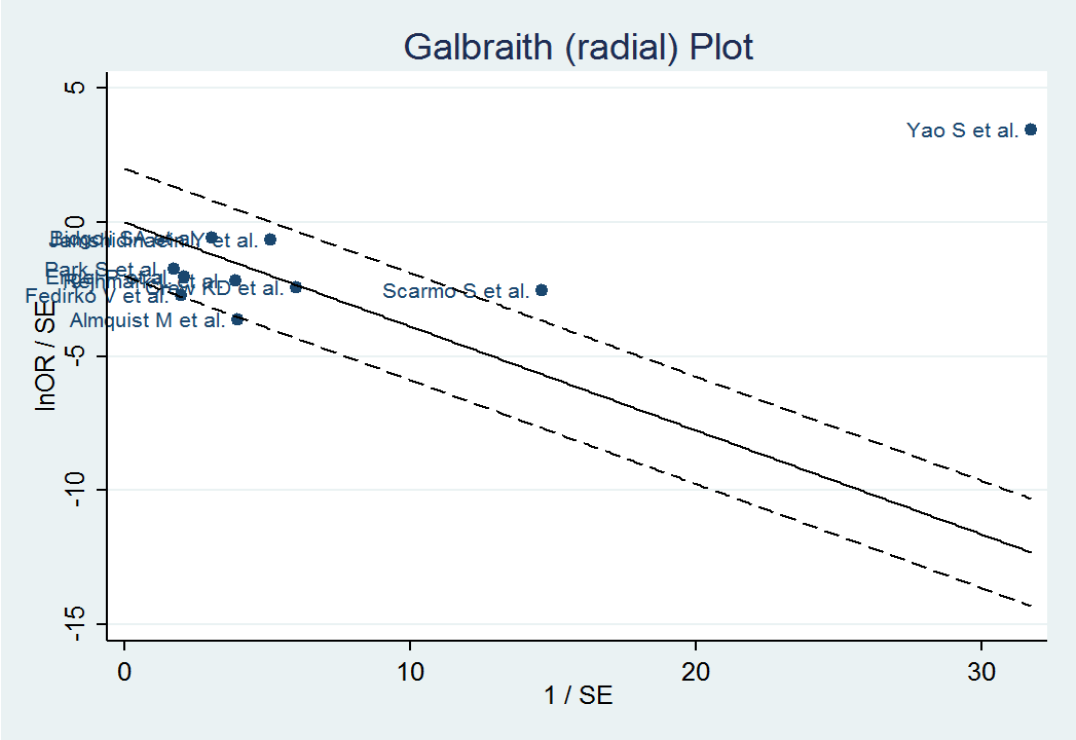
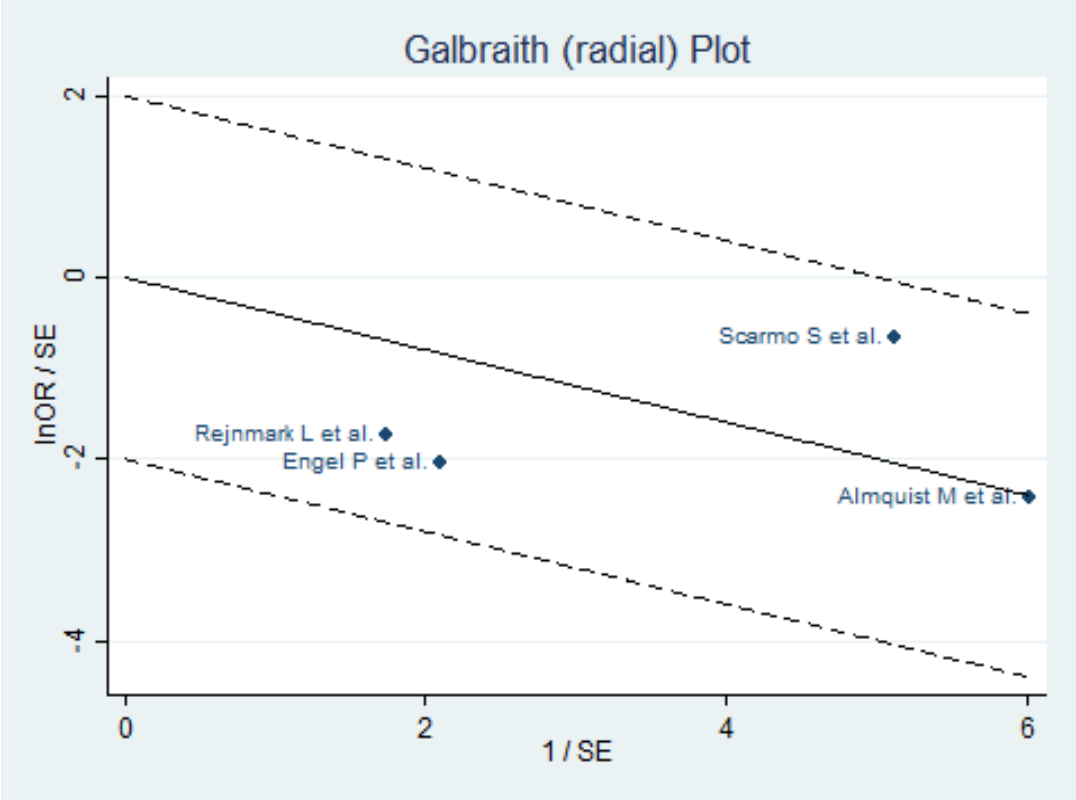


Figure 20. Galbraith plot for the relationship between 25(OH)D exposure and breast cancer in premenopausal women.

a) Case control studies.



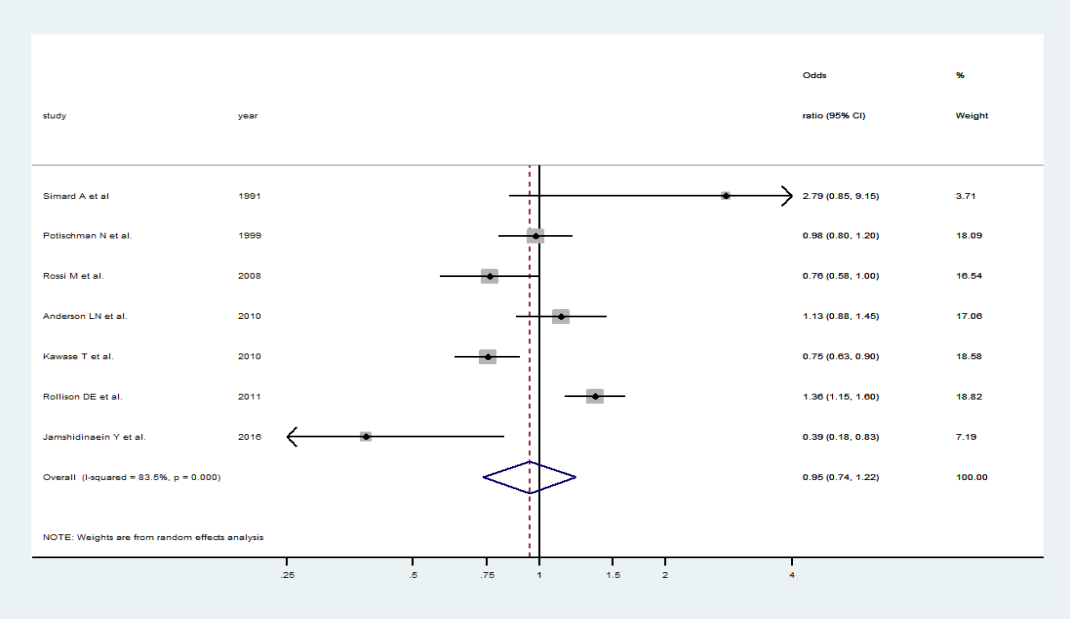
b) Nested case control studies.



Dietary vitamin D and breast cancer

Figure 21. Forest plot for the relationship between dietary vitamin D and breast cancer.

a) Case control studies.



b) Cohort studies.

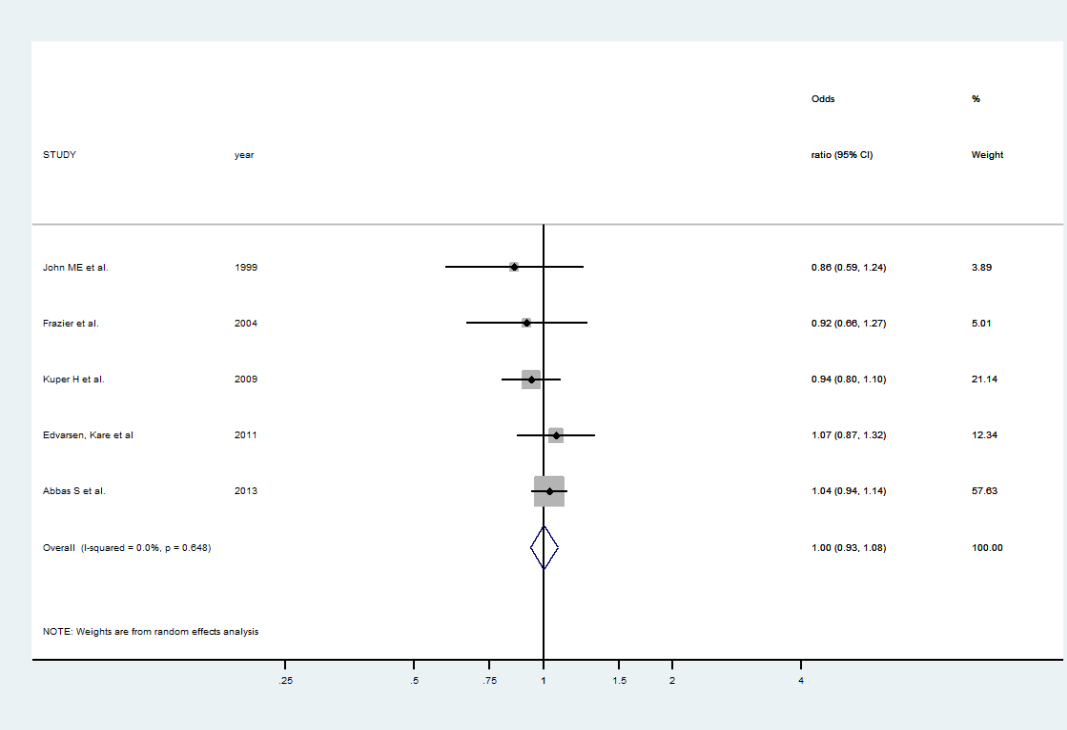
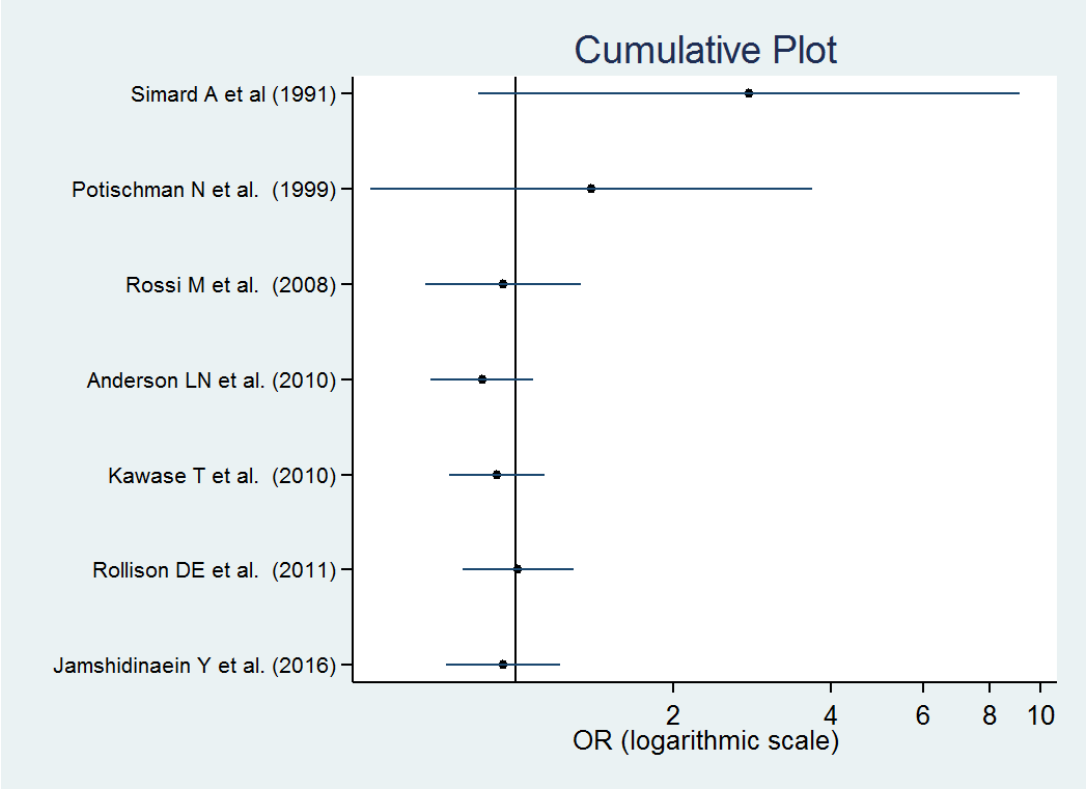


Figure 22. Cumulative plot for the relationship between dietary vitamin D and breast cancer.

a) Case control studies.



b) Cohort studies.

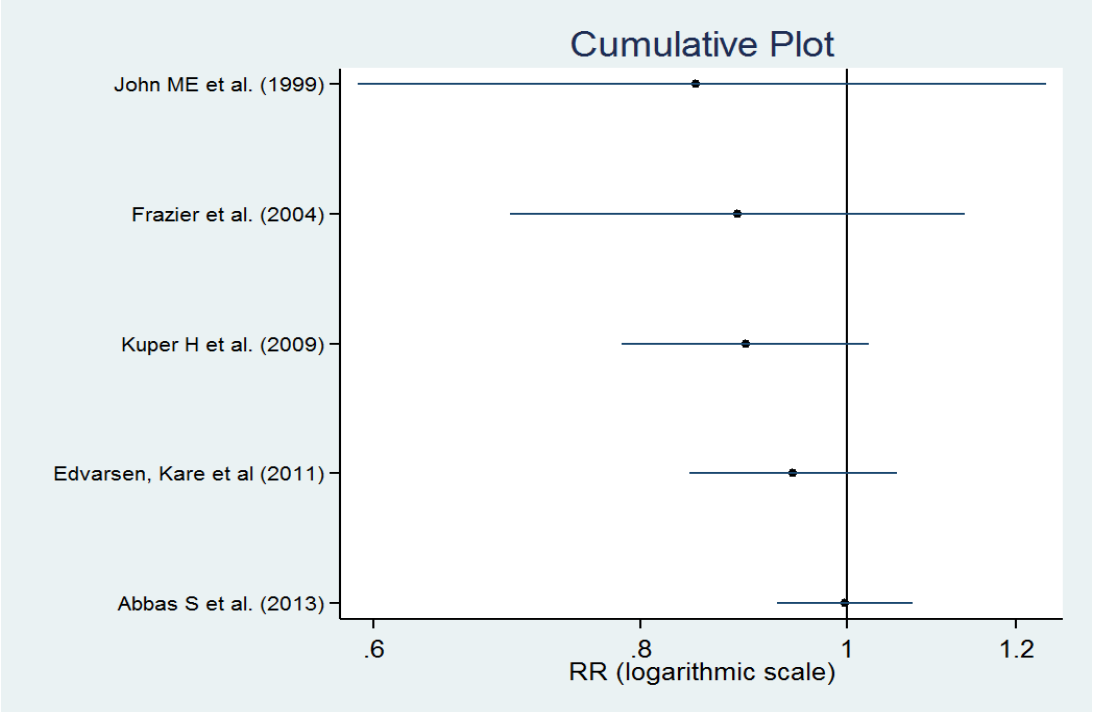
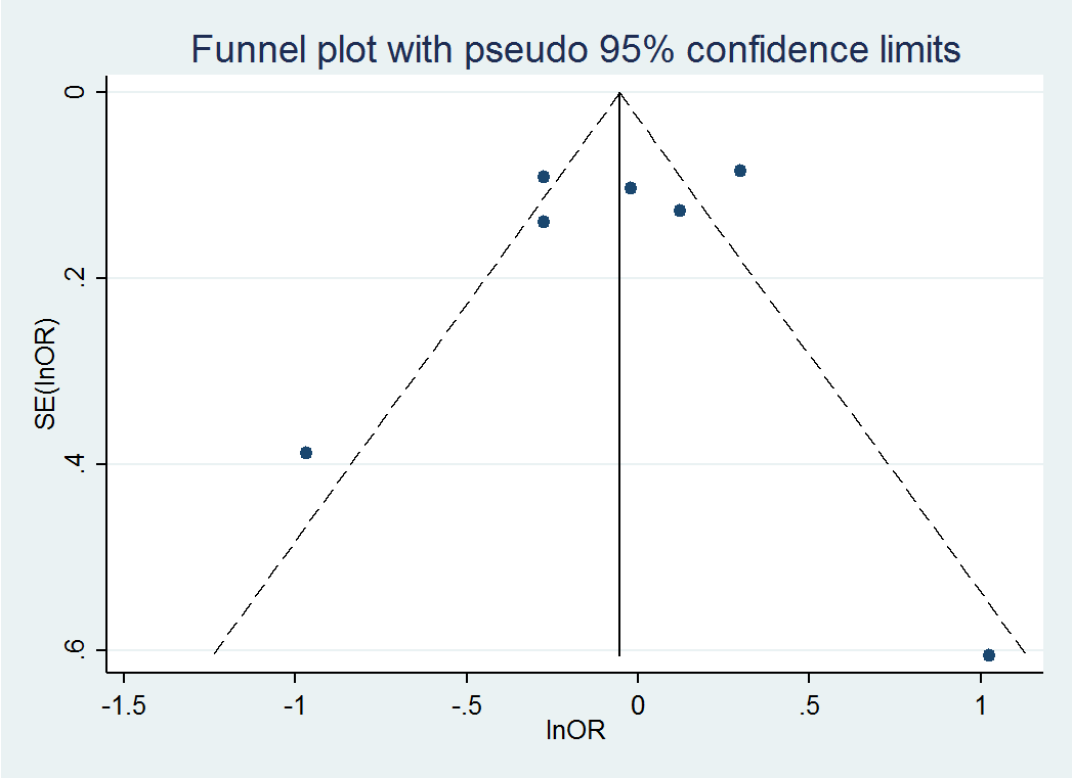


Figure 23. Funnel plot for the relationship between dietary vitamin D and breast cancer.

a) Case control studies.



b) Cohort studies.

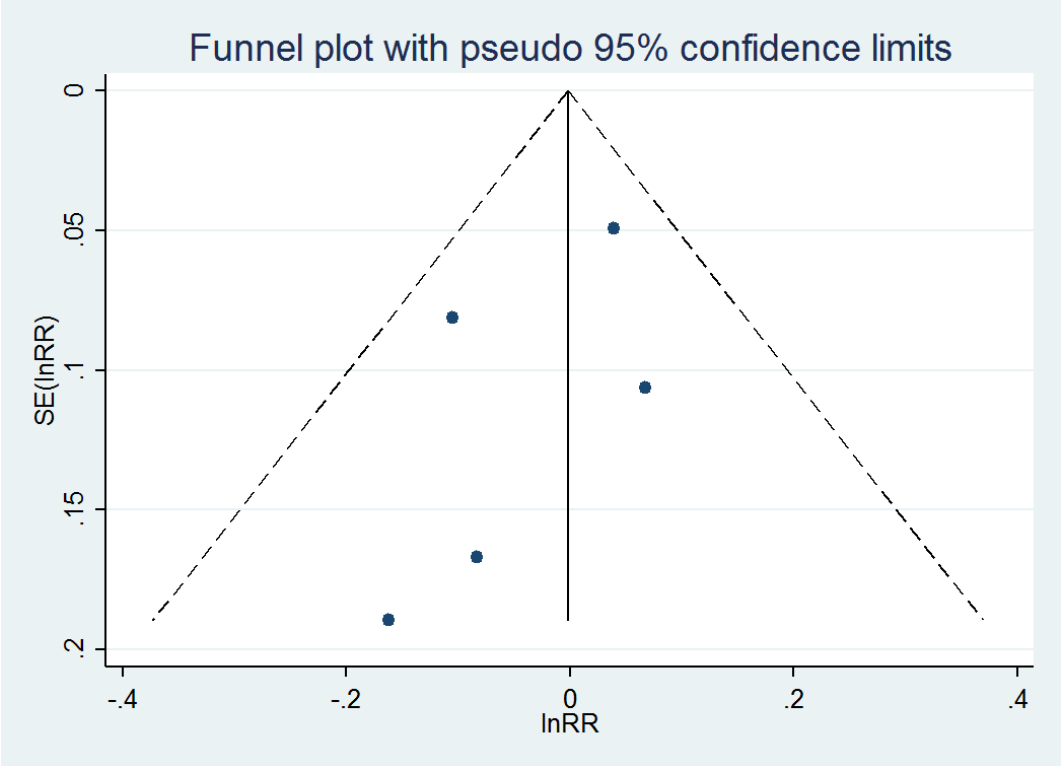
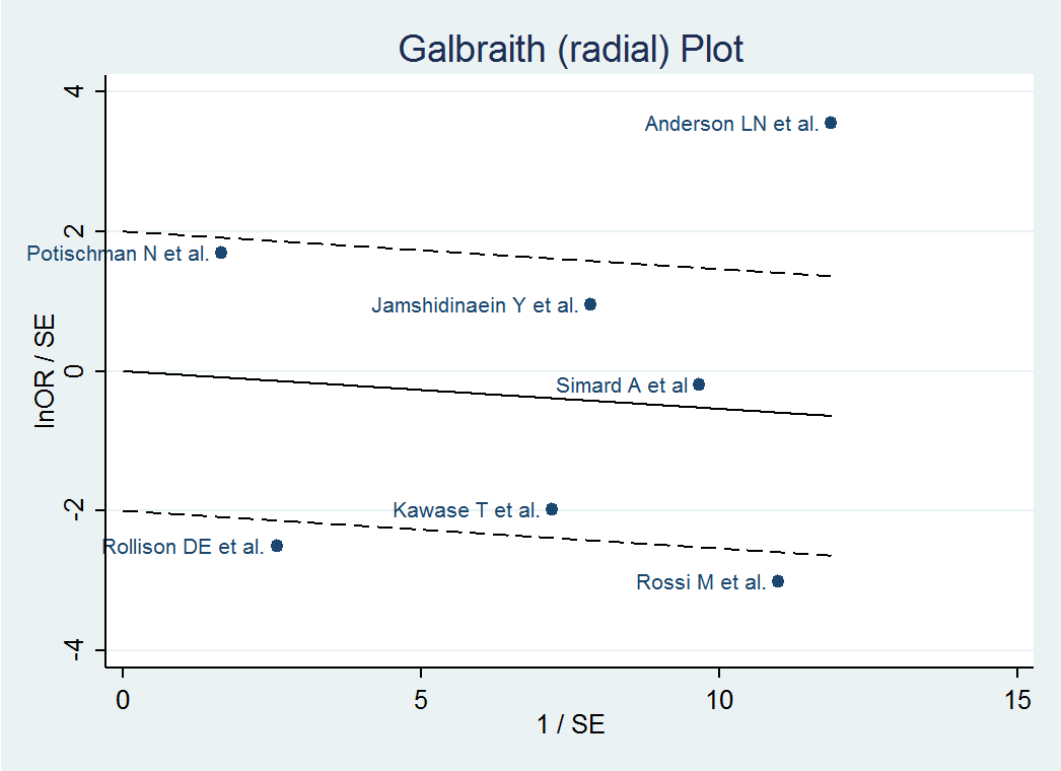
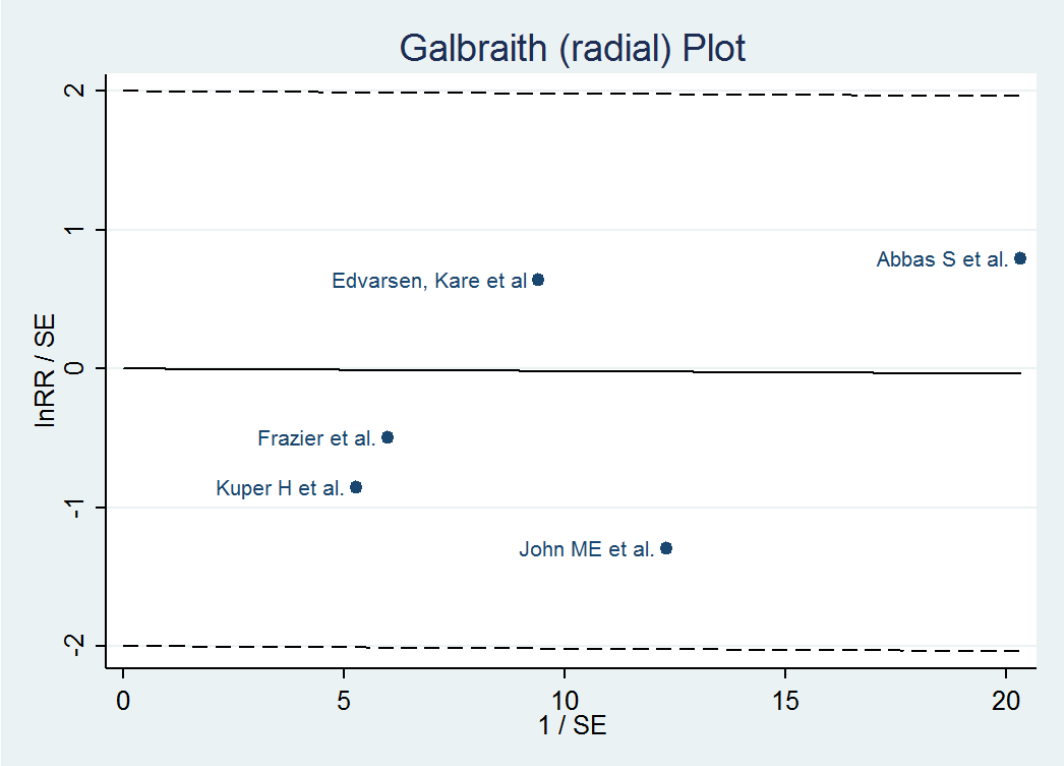


Figure 24. Galbraith plot for the relationship between dietary vitamin D and breast cancer.

a) Case control studies.



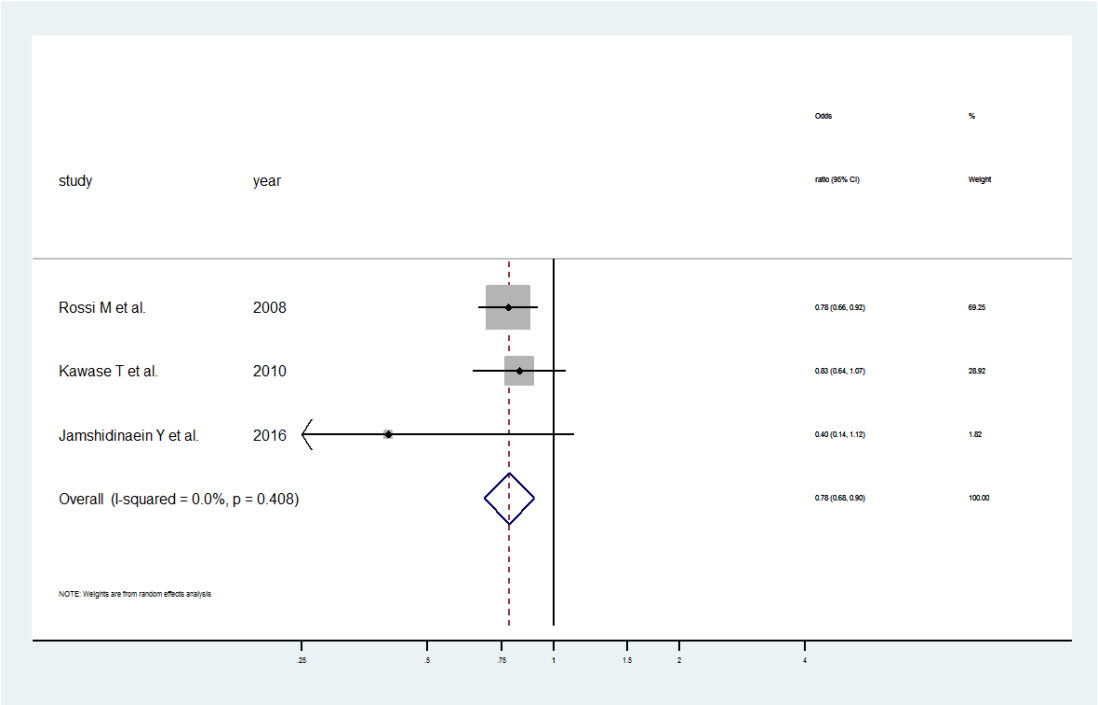
b) Cohort studies.



Dietary vitamin D and breast cancer according menopausal status

Figure 25. Forest plot for the relationship between dietary vitamin D and breast cancer in postmenopausal women.

a) Case control studies.



b) Cohort studies.

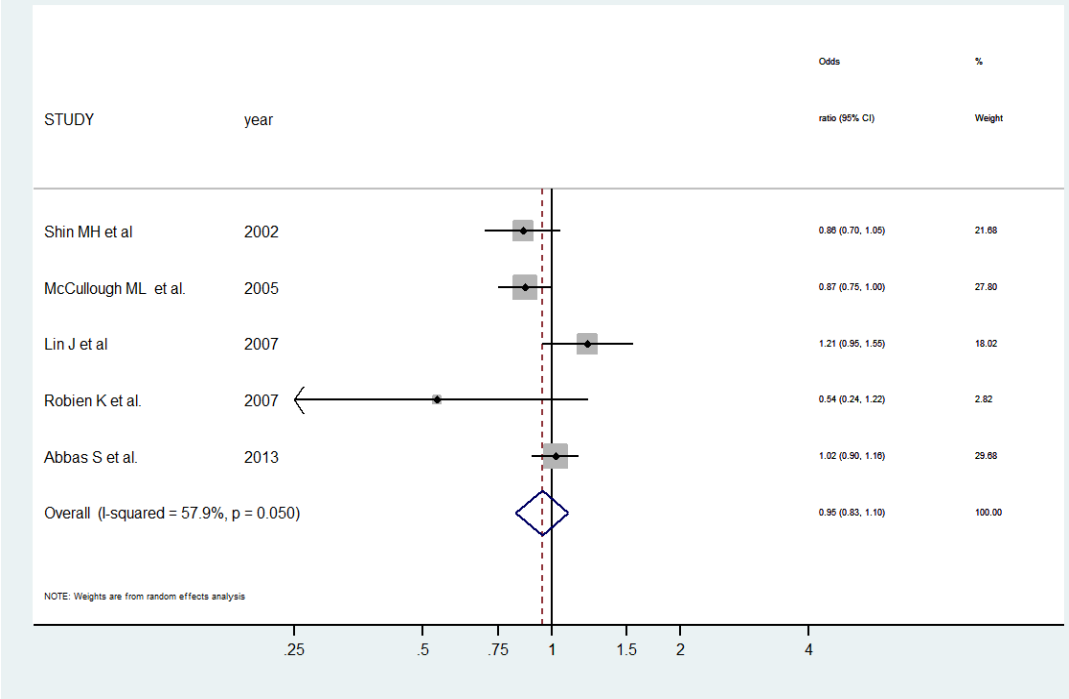
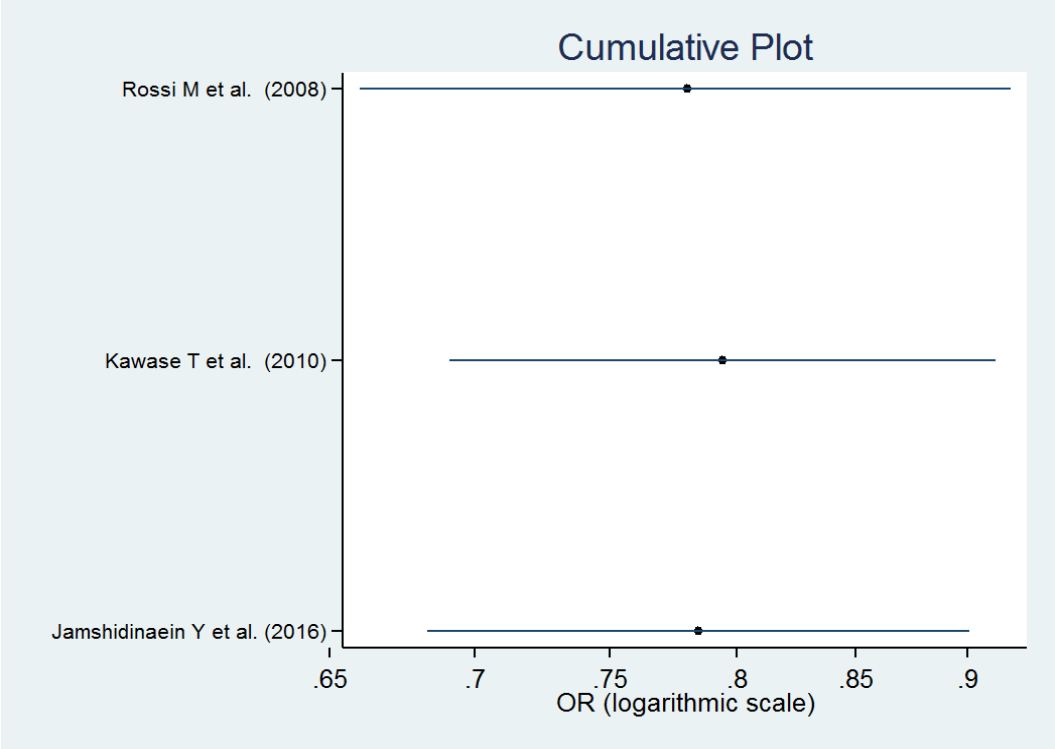


Figure 26. Cumulative plot for the relationship between dietary vitamin D and breast cancer in postmenopausal women.

a) Case control studies.



b) Cohort studies.

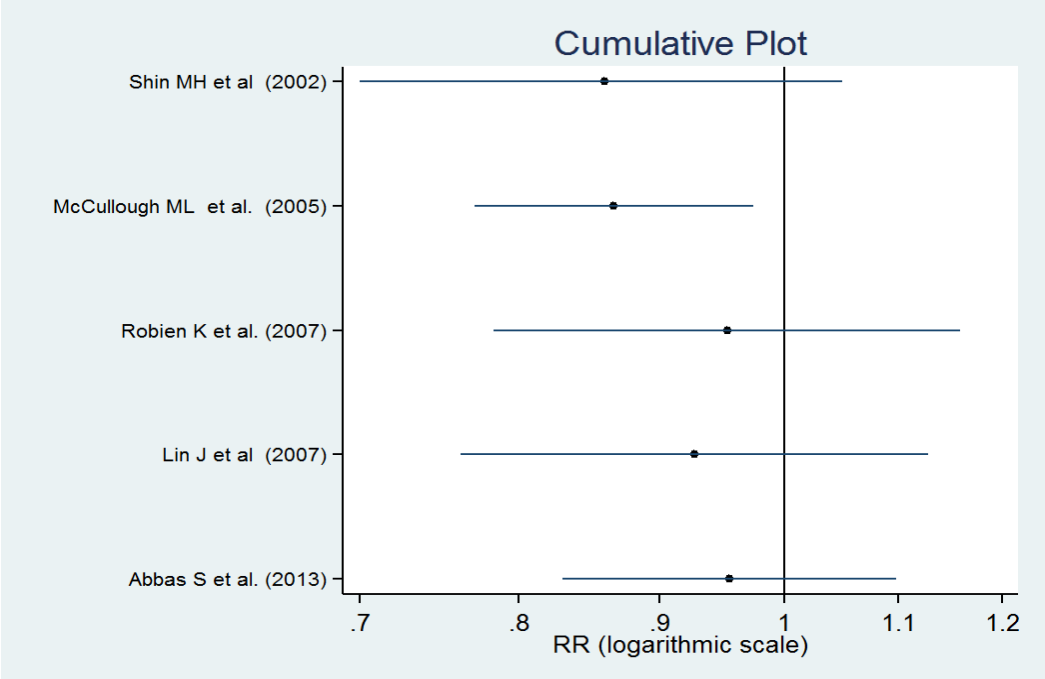
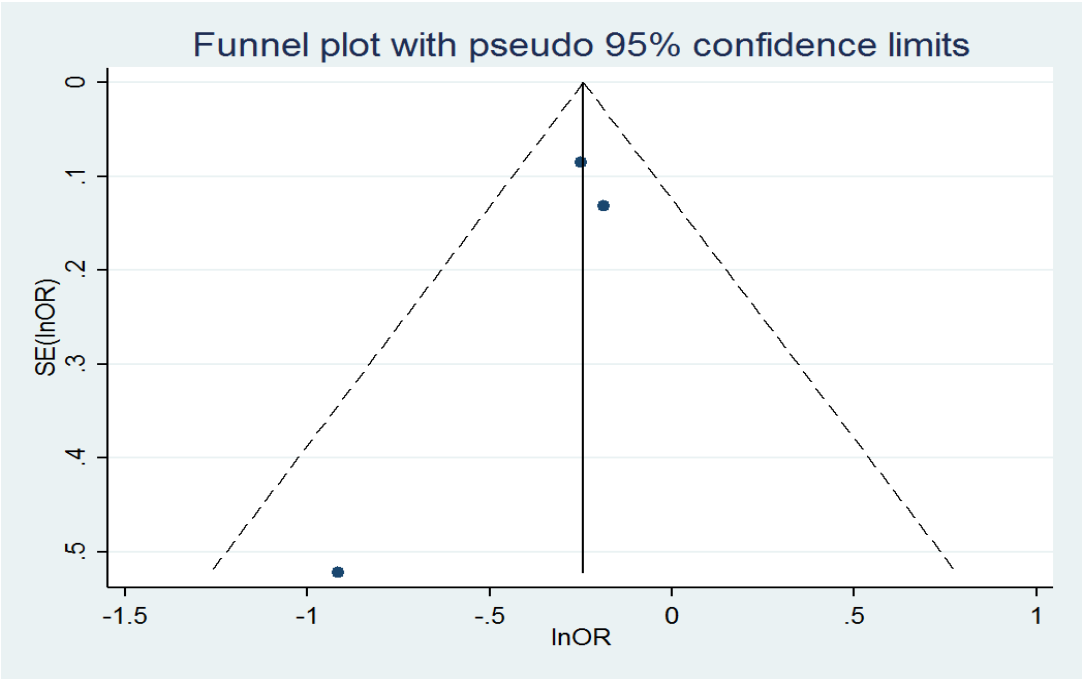


Figure 27. Funnel plot for the relationship between dietary vitamin D and breast cancer in postmenopausal women.

a) Case control studies.



b) Cohort studies.

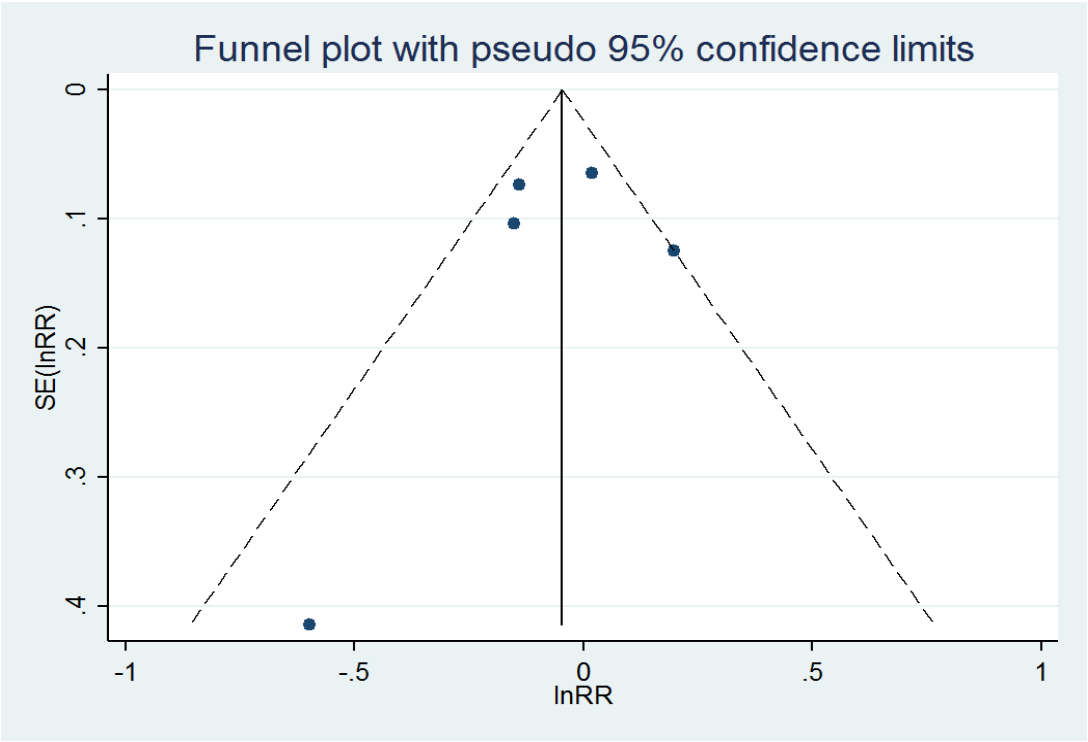
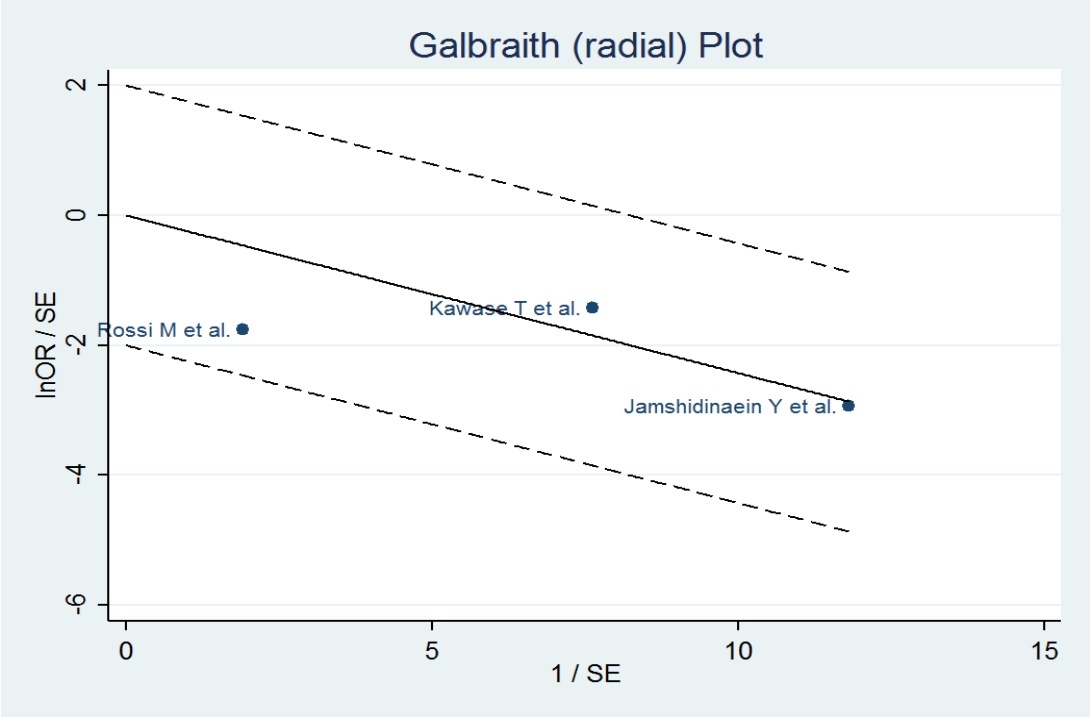


Figure 28. Galbraith plot for the relationship between dietary vitamin D and breast cancer in postmenopausal women.

a) Case control studies.



b) Cohort studies.

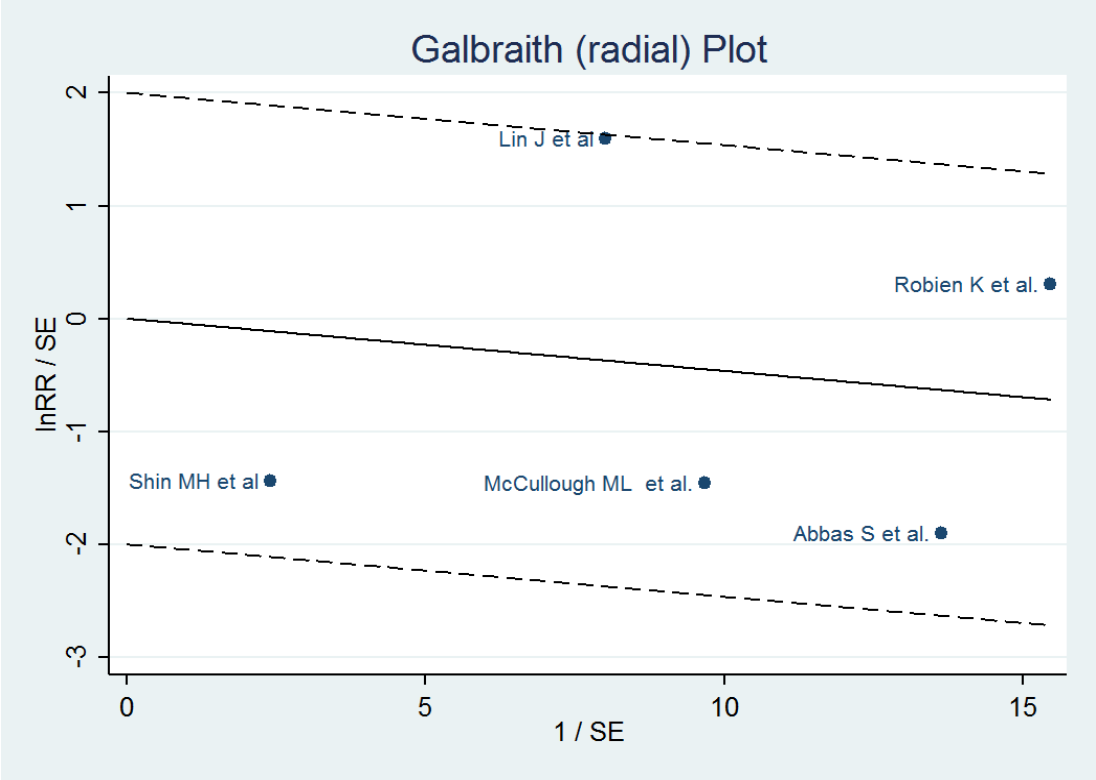
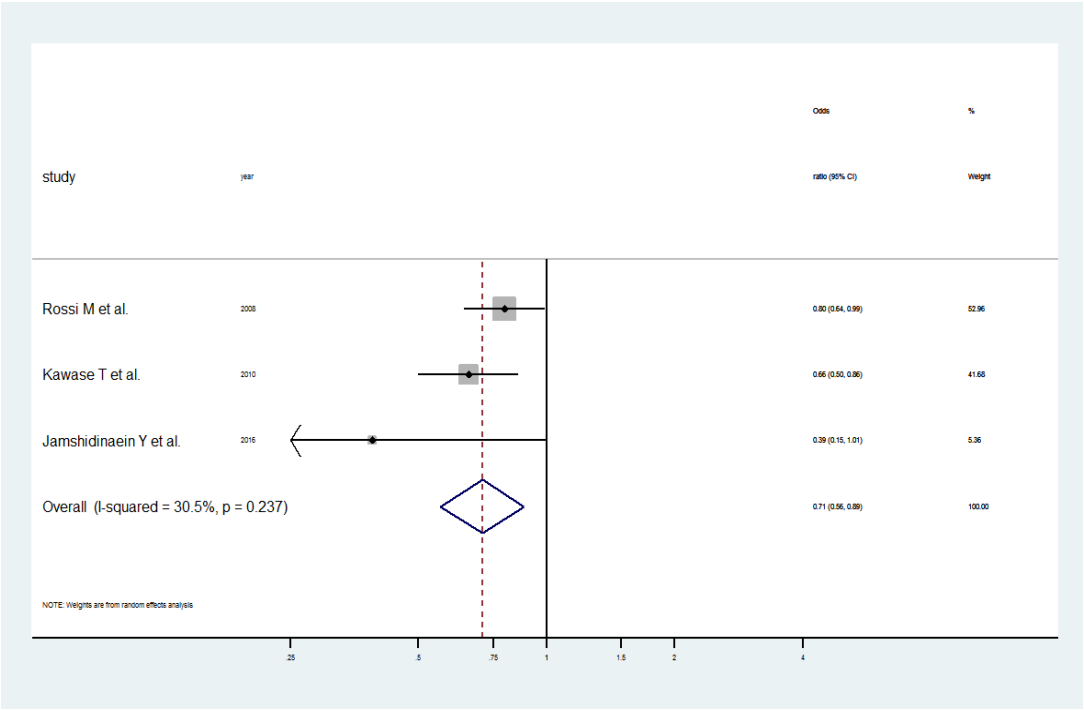


Figure 29. Forest plot for the relationship between dietary vitamin D and breast cancer in premenopausal women.

a) Case control studies.



b) Cohort studies.

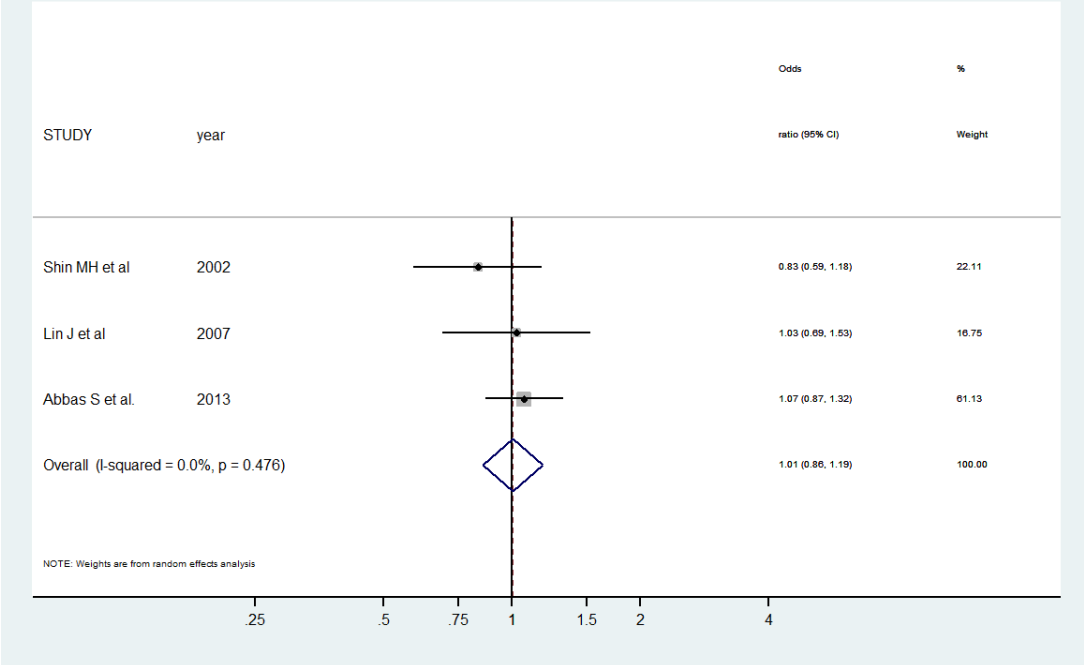
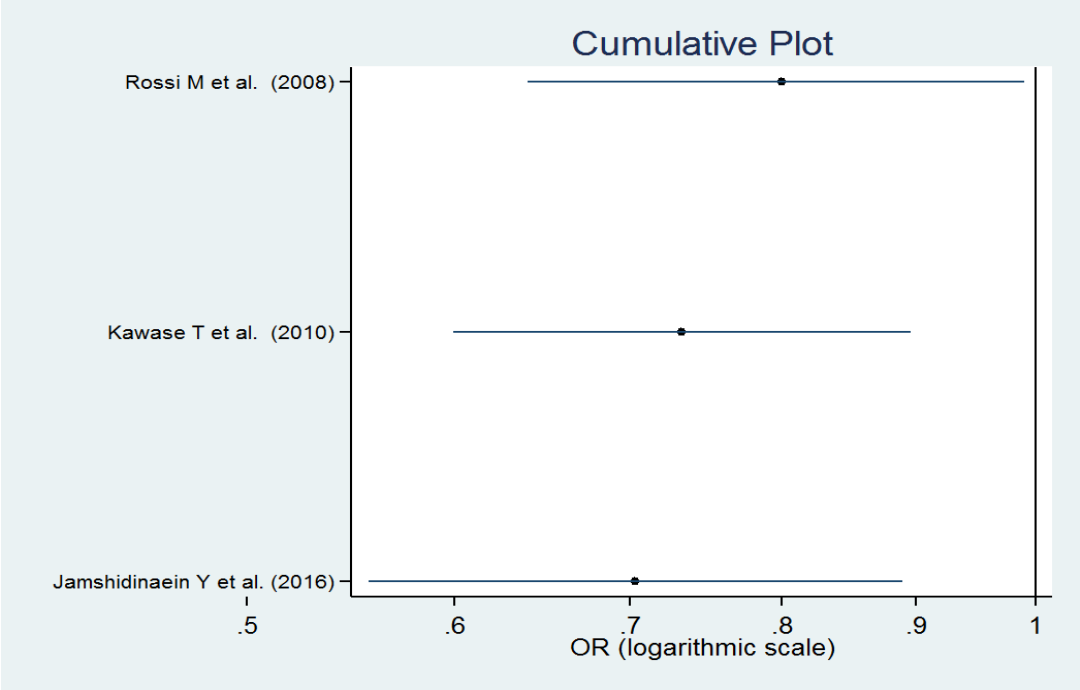


Figure 30. Cumulative plot for the relationship between dietary vitamin D intake and breast cancer in premenopausal women.

a) Case control studies.



b) Cohort studies.

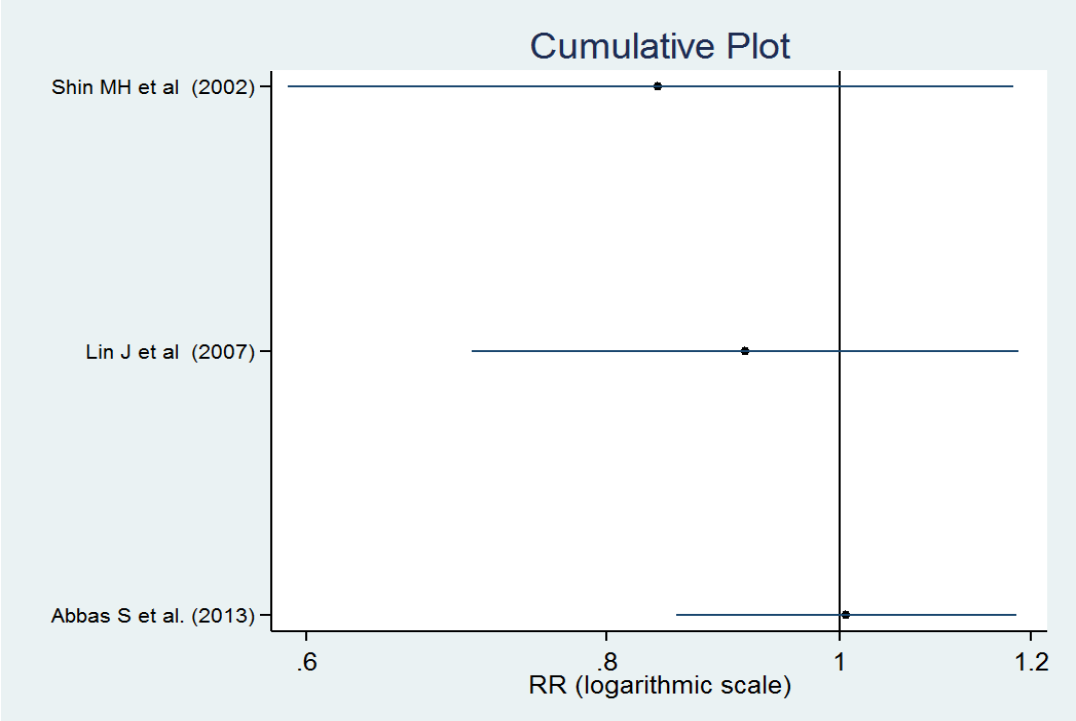
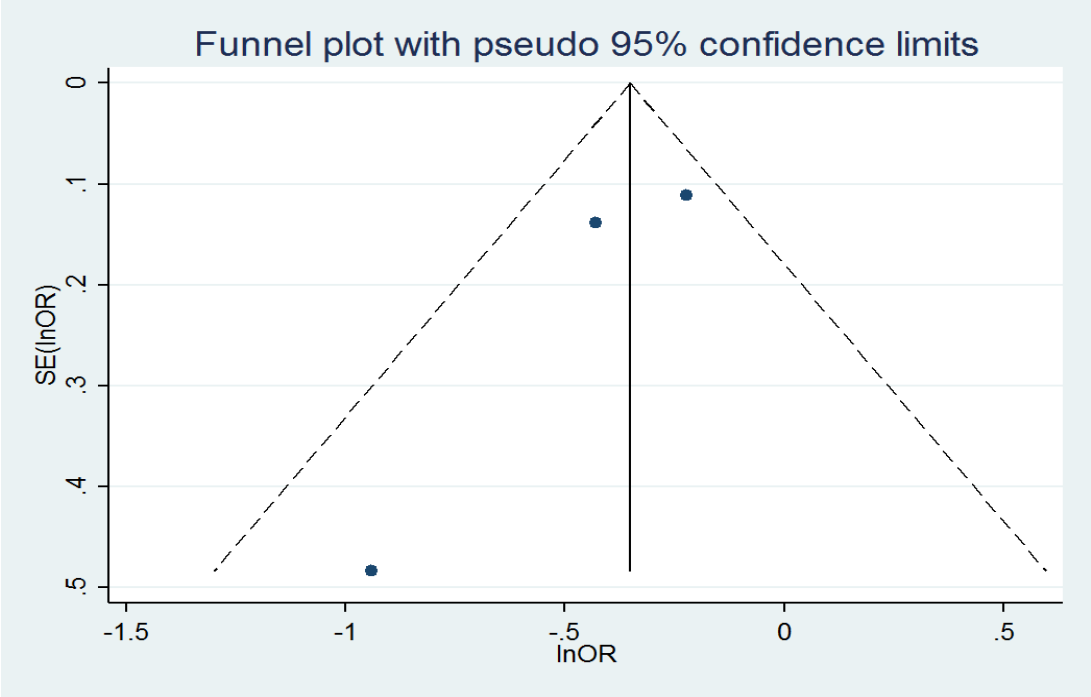


Figure 31. Funnel plot for the relationship between dietary vitamin D intake and breast cancer in premenopausal women.

a) Case control studies.



b) Cohort studies.

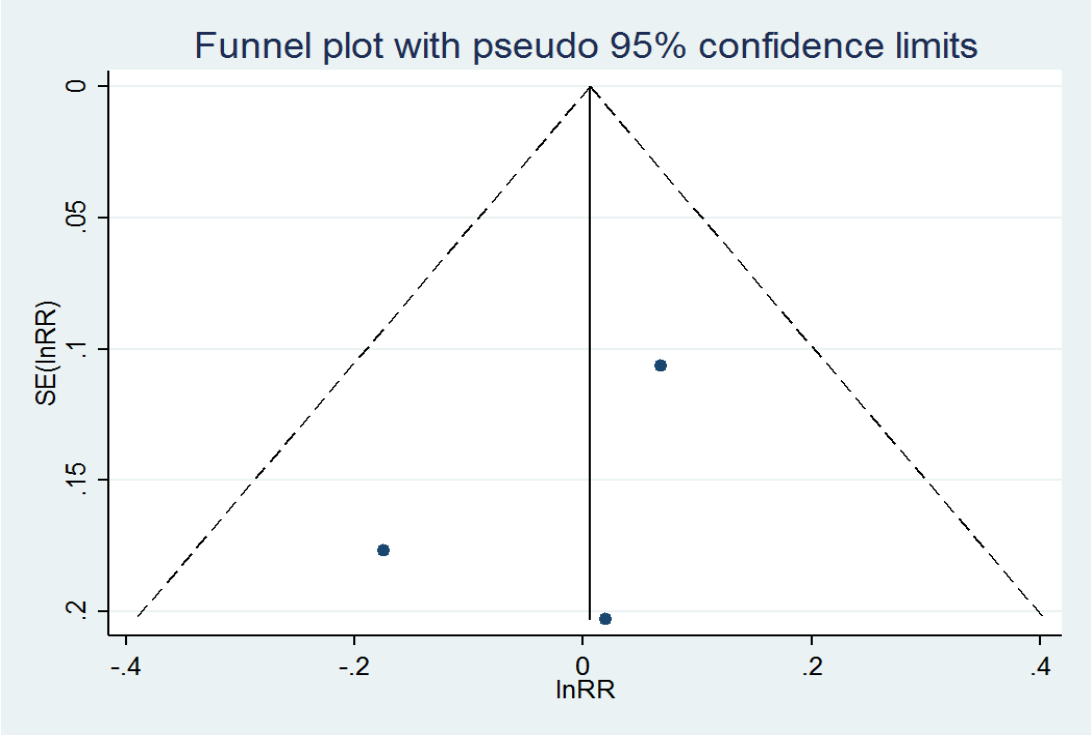
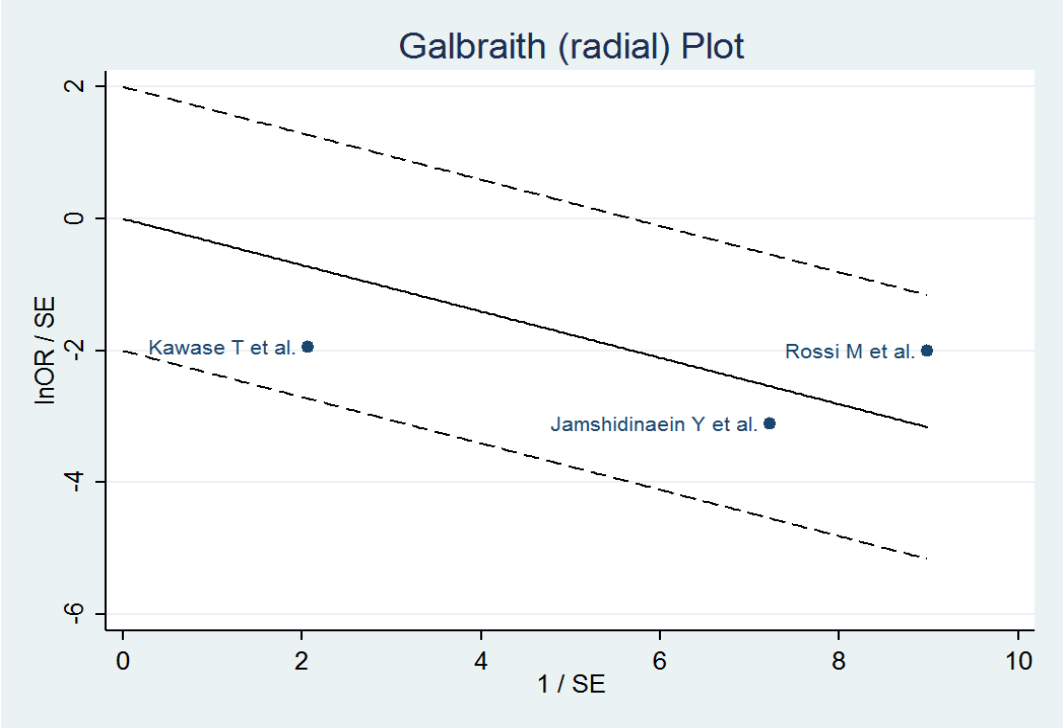
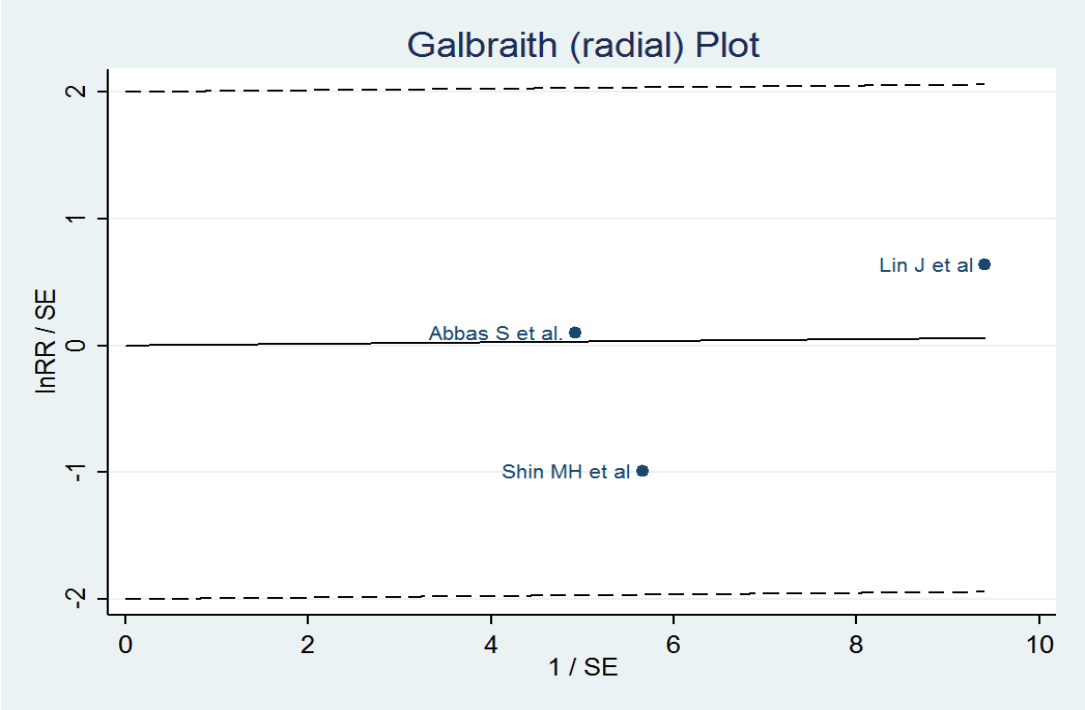


Figure 32. Galbraith plot for the relationship between dietary vitamin D intake and breast cancer in premenopausal women.

a) Case control studies.



b) Cohort studies.



Supplements of vitamin D and breast cancer

Figure 33. Forest plot for the relationship between supplements of vitamin D and breast cancer in case control studies.

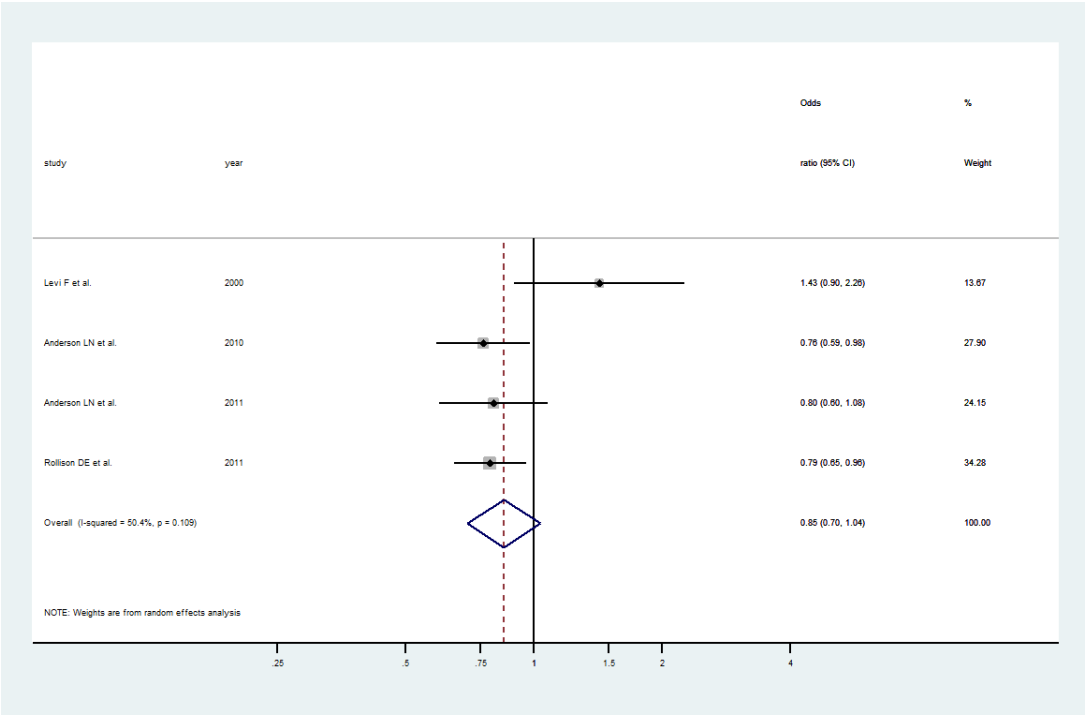


Figure 34. Cumulative plot for the relationship between supplements of vitamin D and breast cancer in case- control studies.

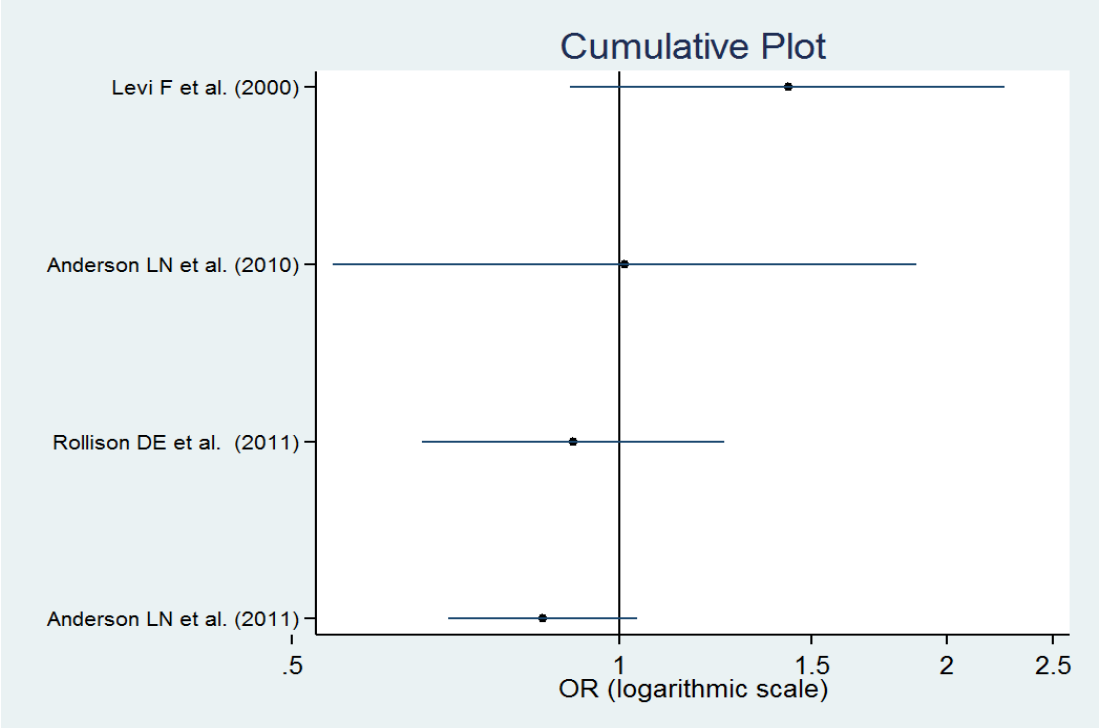


Figure 35. Funnel plot for the relationship between supplements of vitamin D and breast cancer in case control studies.

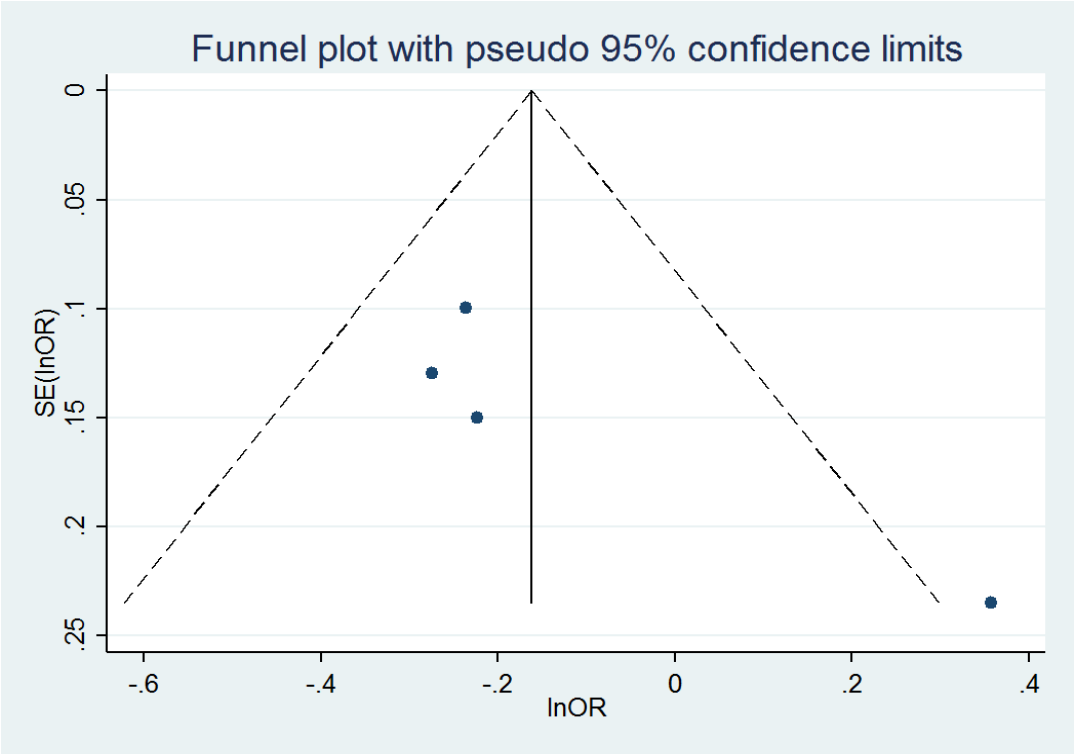
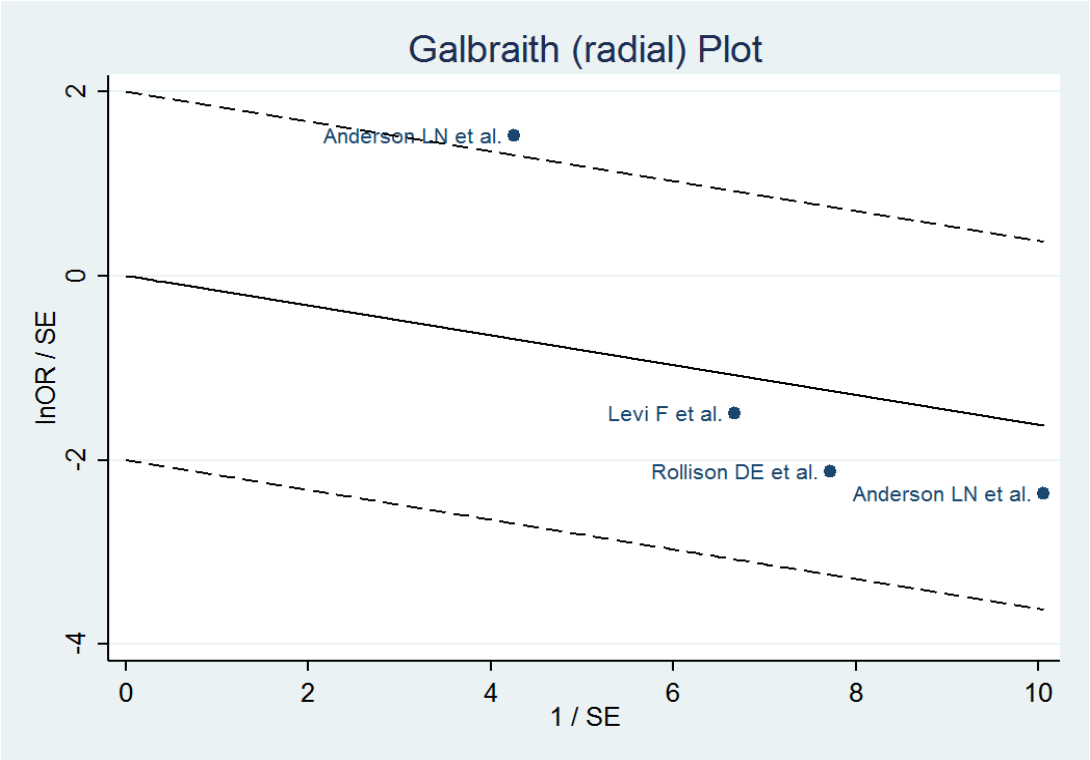


Figure 36. Galbraith plot for the relationship between supplements of vitamin D and breast cancer in case-control studies.



Dietary and supplements of vitamin D and breast cancer according menopausal status

Figure 37. Forest plot for the relationship between dietary and supplements of vitamin D and breast cancer in postmenopausal women. Cohort studies.

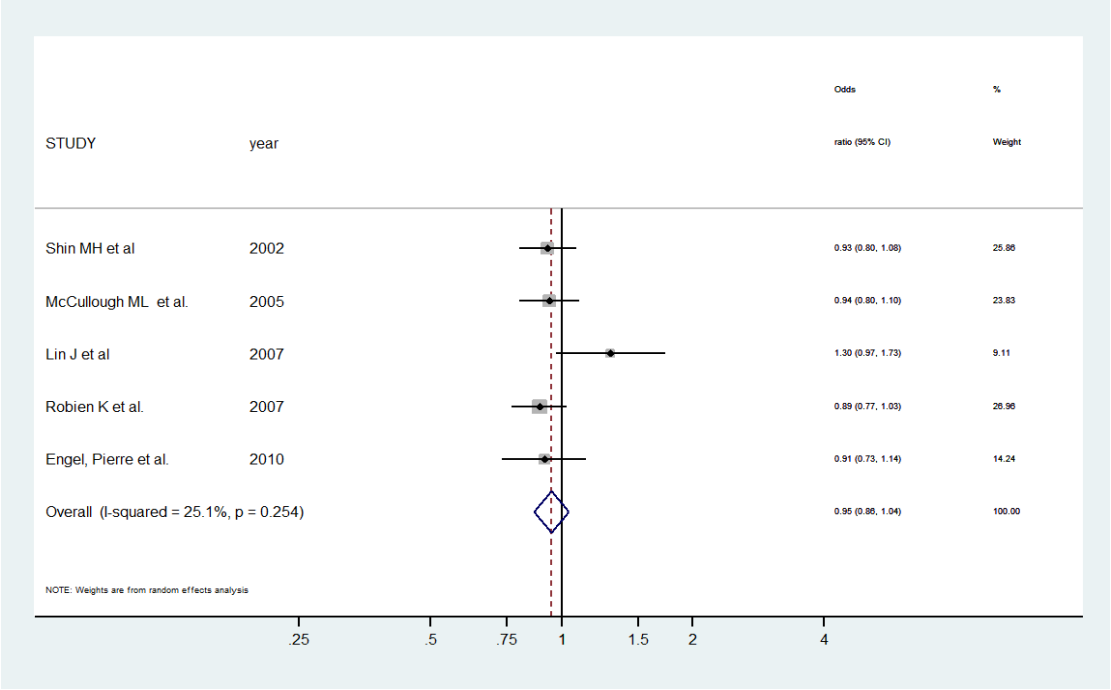


Figure 38. Cumulative plot for the relationship between dietary and supplements of vitamin D and breast cancer in postmenopausal women. Cohort studies.

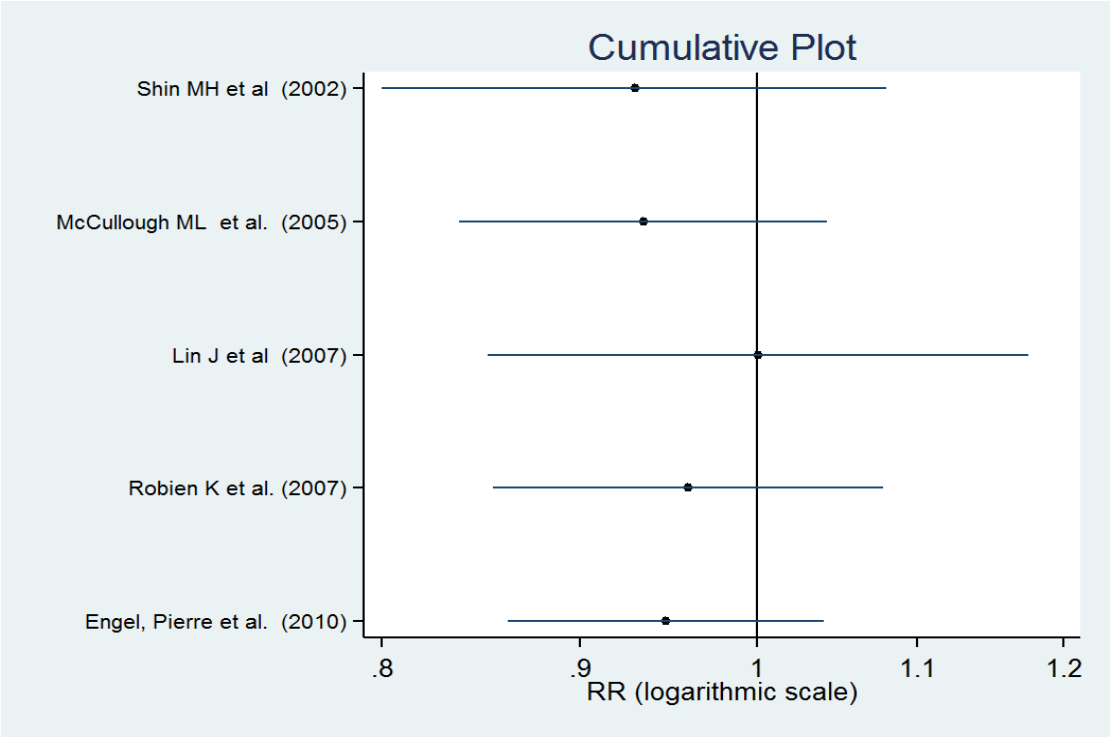


Figure 39. Funnel plot for the relationship between dietary and supplements of vitamin D and breast cancer in postmenopausal women. Cohort studies.

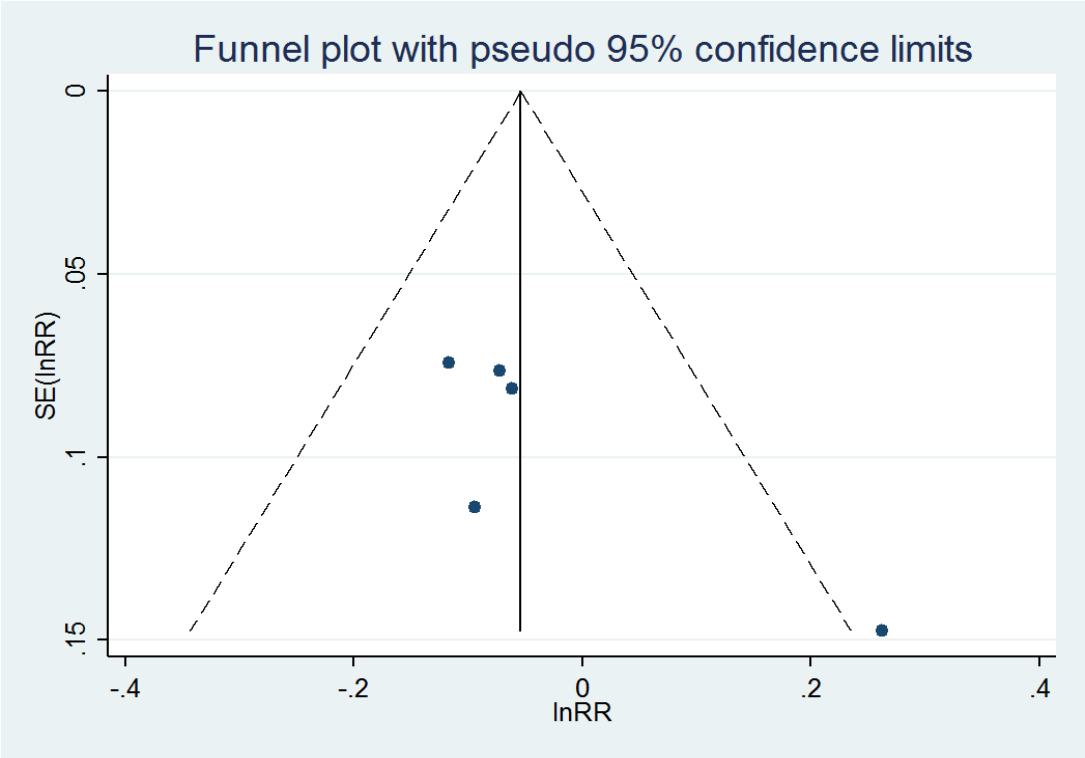


Figure 40. Galbraith plot for the relationship between dietary and supplements of vitamin D and breast cancer in postmenopausal women. Cohort studies.

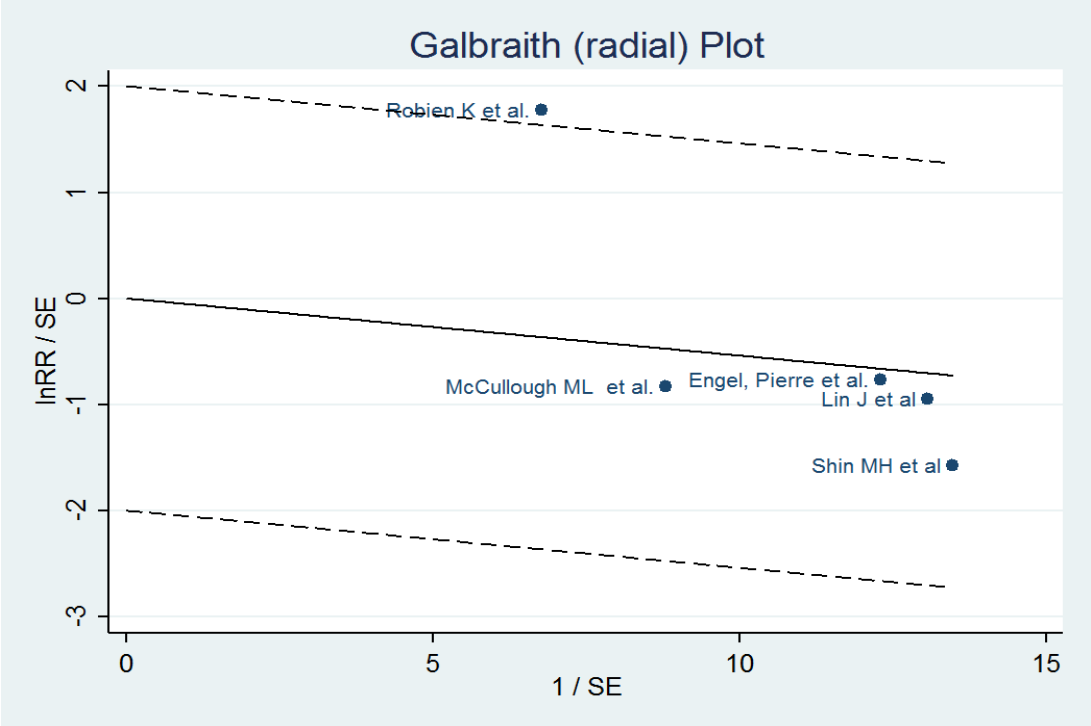


Figure 41. Forest plot for the relationship between dietary and supplements of vitamin D and breast cancer in premenopausal women. Cohort studies.

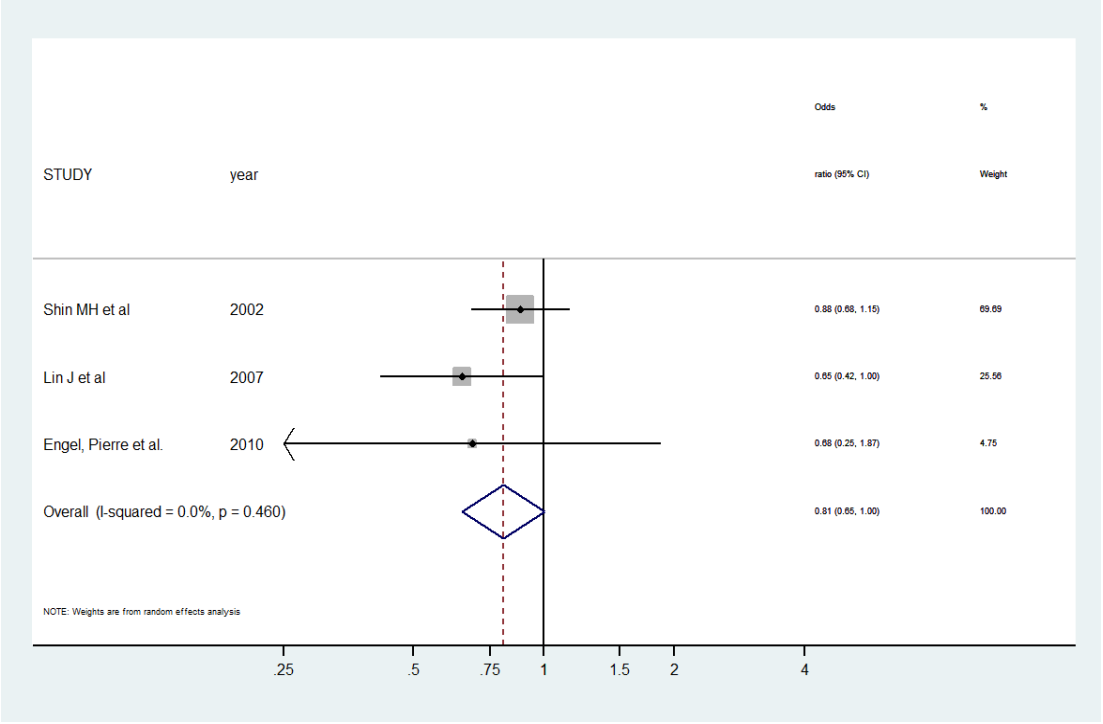


Figure 42. Cumulative plot for the relationship between dietary and supplements of vitamin D and breast cancer in premenopausal women. Cohort studies.

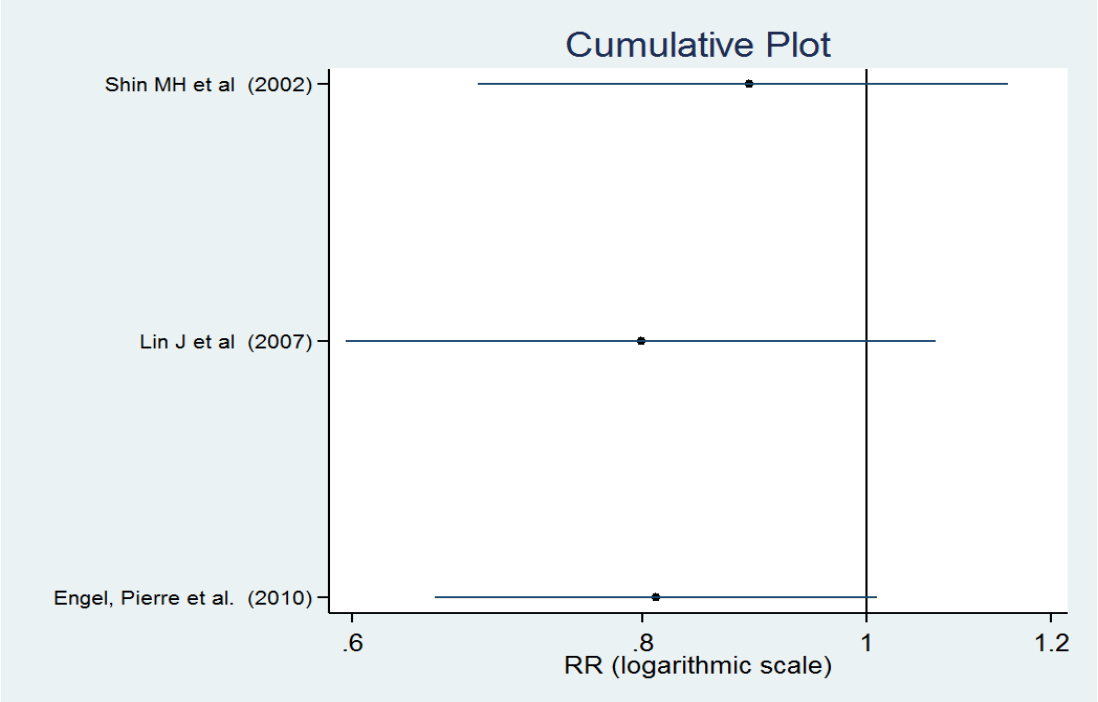


Figure 44. Funnel plot for the relationship between dietary and supplements of vitamin D and breast cancer in premenopausal women. Cohort studies.

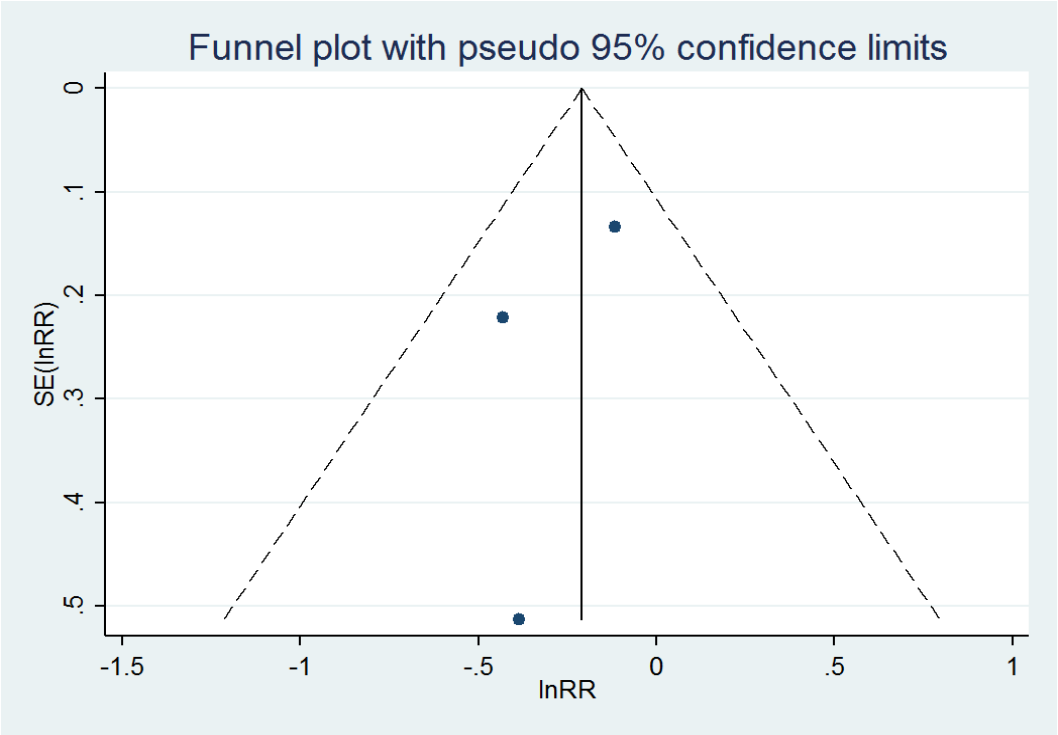
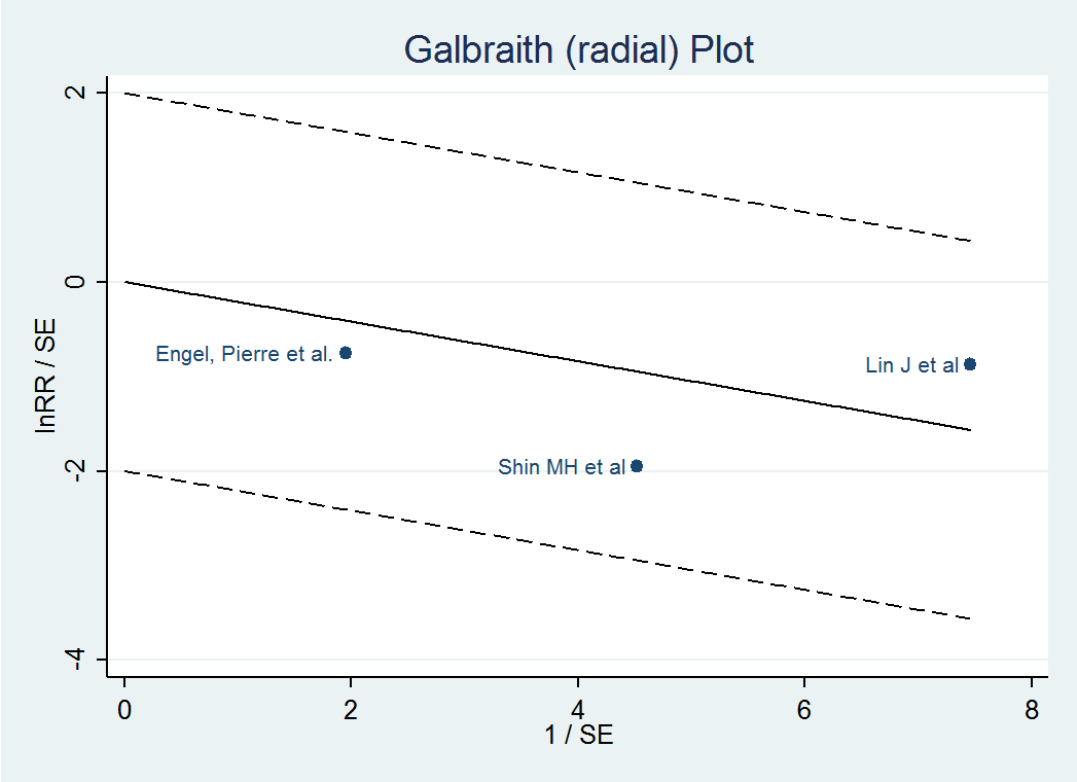


Figure 45. Galbraith plot for the relationship between dietary and supplements of vitamin D and breast cancer in premenopausal women. Cohort studies.



1,25(OH)D exposure and breast cancer

Figure 46. Forest plot for the relationship between 1,25(OH)D exposure and breast cancer in case control studies.

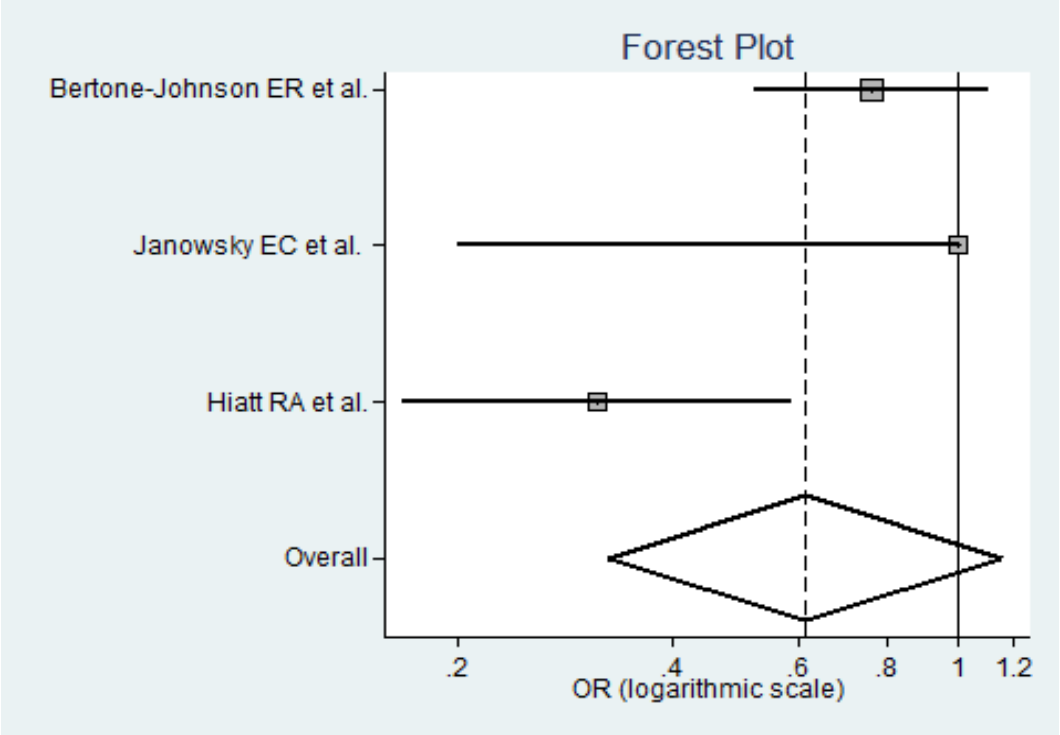


Figure 47. Cumulative plot for the relationship between 1,25(OH)D exposure and breast cancer in case control studies.

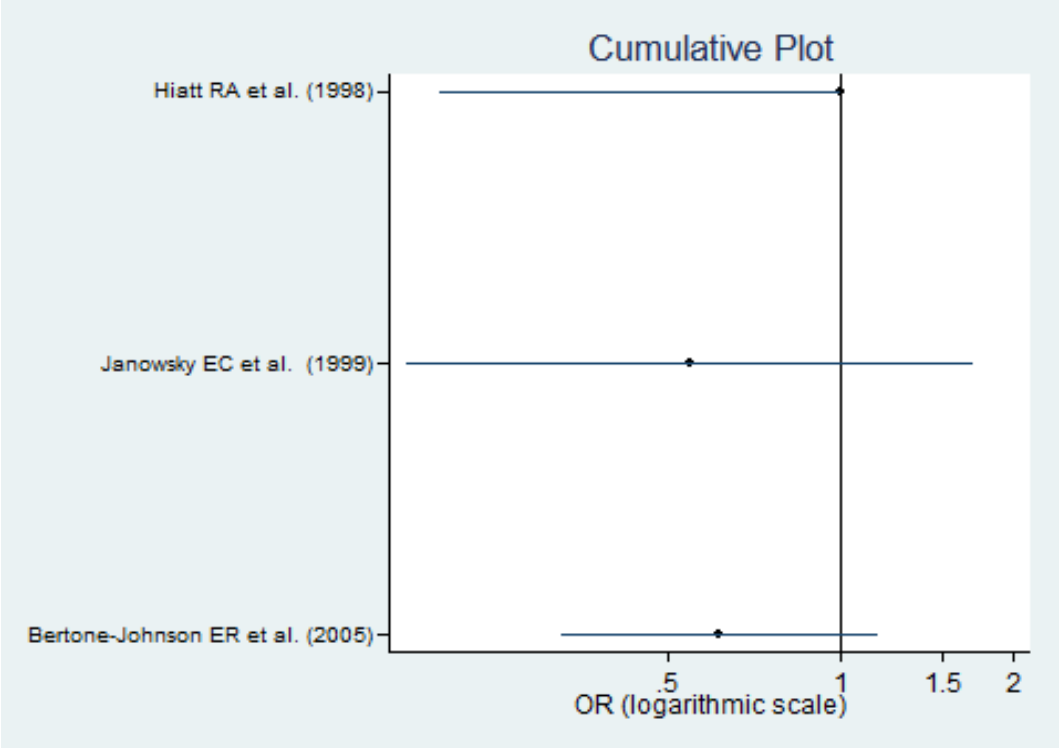


Figure 48. Funnel plot for the relationship between 1,25(OH)D exposure and breast cancer in case control studies.

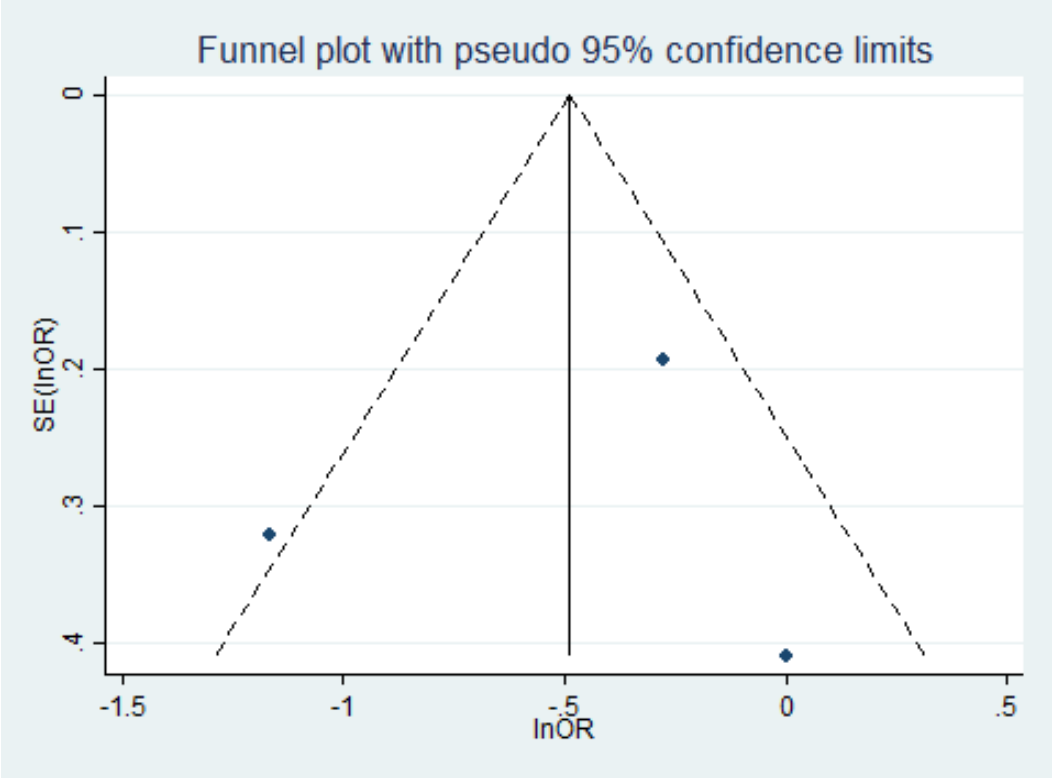


Figure 49. Galbraith for the relationship between 1,25(OH)D exposure and breast cancer in case control studies.