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Alcohol and folate intake association with breast cancer: a metanalysis.

Asociación del consumo de alcohol y folatos con el cáncer de mama: un metaanálisis.

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Abstract

Background: The relationship between alcohol and folate intake with breast cancer is still controversial. The present meta-analysis studies the effect of alcohol and folate intake on breast cancer. Methods: A PubMed, Web of Science and Scopus-Database search was conducted to include all papers published with the keywords "BREAST CANCER" AND "ALCOHOL" AND "FOLATE" OR "FOLIC ACID" with at least one reported relative risk (RR) or odds ratio (OR). In total twenty-two studies has been analyzed. Information about type of study, type of folate intake and menopausal status was retrieved. A pooled OR has been estimated by weighting individual OR/RR by the inverse of their variance. Results: Our study showed an increased risk of breast cancer in women with high alcohol and low folate intake compared with low alcohol and high folate intake in all (OR=1.22, CI: 1.09-1.36) and postmenopausal women (OR=1.45, CI: 1.19-1.79); while this risk disappears in all women (OR=0.80, CI: 0.40-1.62) and decrease in postmenopausal women (OR=1.12; CI: 1.0001-1.26) when comparing high alcohol and folate intake with low alcohol and folate intake. Conclusion: our results show an increased alcohol carcinogenic effect in low folate intake especially in postmenopausal women.

Keywords: breast cancer, folate intake, folate blood levels, alcohol intake.

Resumen

Contexto: la relación entre el alcohol y el folato con el cáncer de mama es todavía controvertida. Así, este metaanálisis estudia dicha asociación en el cáncer de mama. Métodos: se ha realizado una búsqueda sistemática en PubMed, Web of Science y Scopus incluyendo todos los artículos con las palabras clave: "BREAST CANCER" AND "ALCOHOL" AND "FOLATE" OR "FOLIC ACID" y que reportaran al menos un riesgo relativo (RR) u odds ratio (OR). En total, se han analizado 22 artículos. Se ha incluido información sobre el tipo de estudio, tipo de ingesta de folato y el estatus menopáusico. Se realizó una OR ponderada dividiendo cada OR/RR por el inverso de su varianza. Resultados: Nuestro estudio muestra un aumento de riesgo del cáncer de mama en mujeres con alta ingesta de alcohol y baja de folato tanto en todas las mujeres (OR=1,22, IC: 1,09-1,36) y en postmenopáusicas (OR=1,45, IC: 1,19-1,79); mientras que este riesgo desaparece en toda la población (OR=0,80, IC: 0,40-1,62) y disminuye en postmenopáusicas (OR=1,12, IC: 1,0001-1,26) cuando se compara la alta ingesta de alcohol y folatos frente a ambos consumos bajos. Conclusión: nuestros resultados muestran un aumento del efecto carcinogénico del alcohol con bajo consumo de folato, especialmente en mujeres postmenopáusicas.

Palabras clave: cáncer de mama, ingesta de folato, folato sanguíneo, ingesta de alcohol.

Introduction

Breast cancer is the most common cancer among women in Spain, with 25,215 cases in 2014(1). Although different hormonal risk factors have been found to be related to breast cancer development, the only dietary risk factor identified by the IARC is alcohol consumption. This is really important in our society as only 50% of the Spanish women are considered abstainers, although it is more than in the rest of our WHO region (Europe A) where abstainer women only account for the 23%(2).

Although alcohol has been considered a risk factor for many years, the physiopathology of the carcinogenesis is still unclear. At first alcohol was only considered a co-carcinogen since it failed to produce tumors in animals when given without other carcinogens. However, nowadays some experiments with mice have demonstrated the direct effect of alcohol without other cancer-inducing agents(3).

Diverse carcinogenesis mechanisms have been proposed, but in this work, we are going to focus on the interaction with folate metabolism, as it is one of the most discordant mechanism.

First, low folate levels seem to be linked with different cancers (uterine cervix, colorectal, lung and breast cancers) and although the exact mechanism is not well understood, the best candidates are the special roles of folate during biologic methylation and nucleotide synthesis. Moreover, alcohol interferes with different steps of folate metabolisms, so pro-carcinogenic effect is thought to be due to these modifications(4).

The main sources of folate are the vegetables with green leaves, but they are conjugated as polyglutamyl folates, so to be absorbed their deconjugation is need. However, this process is altered by alcohol. Therefore, people with chronic consumption of alcohol has low folate absorption. After that, folate needs to be transported across the luminal membrane of the enterocyte which is also inhibited by the alcohol consumption. Moreover, chronic and acute alcohol drinking is related to increase of folate renal excretion, but its biological implication is not yet known.

Alcohol also interferes with the one carbon metabolism where folate is implicated. The main effect of alcohol is inhibition of the methionine synthase, which leads to accumulation of homocysteine and methyl-THF.

Due to the inactivation of methionine synthase, the folate is transform into methyl-THF, which cannot be recycled to THF, which is known as folate trap. This trap is responsible for reduction of de novo thymidine synthesis which leads to alteration of DNA synthesis and introduction into the DNA of the thymidine precursor, uridine.

Consequently, some articles claim that high intake of folates can mitigate the carcinogenic effect of alcohol. However, others postulate that is not a direct effect, since other group B vitamins are also needed to reduce the folate trap, so the patient also need high levels of group B vitamins, specially methionine (5,6).

Finally, some experimental studies performed in animal models suggest that the excess of folate intake can produce alteration of the mammary gland proliferation (7,8), which also can enhance the alcohol carcinogenic effect. This was also observed in some observational studies, such as Cancer Prevention Study II Nutrition Cohort (9). However, two previous metanalysis (10,11) found reduced risk of breast cancer when evaluating the folate effect in women with high alcohol intake, while other found no differences (12), and other found reduced alcohol risk as higher folate intake is consumed (13); but the combined effect of both exposures (alcohol and folate intake) was not studied in previous metanalysis (Table 1).

Therefore, the aim of this study is to assess the effect of the interaction between folate and alcohol and the combined effect of both in the production of breast cancer.

Methodology

Search strategy

Firstly, our inclusion criteria were defined as follows: cohort or case-control studies performed in humans, with at least, one relative risk (RR) or odds ratio (OR) with 95%confidence interval (95% CI) where interaction between folate and alcohol intake or a combined effect of both was evaluated.

We performed a systematic literature search in Pub-Med, Web of Science (Science Citation Index Expanded) and SCOPUS database for epidemiological studies published before 1st of March 2018, with the terms “breast cancer” AND “alcohol” AND “folate” OR “folic acid” (n=153 n=286 and n=125, respectively). Finally, the references of the already selected studies were reviewed to include any missing relevant studies (only one relevant study was found). Only studies reported in English and Spanish were included in the search.

After avoiding repeated studies, we found 405 studies for further analysis. First, though reading the title and abstract we excluded 221 and 126 studies respectively, so 56 relevant studies where found for complete reading (Figure 1). Finally, only 22 studies meet our inclusion criteria: fifteen cohort, six case control and two nested-case and control studies. Eventually, one study (14) had to be eliminated as the reference was a medium level of folate intake (150-299ug/d), which made it impossible to compare with other studies. Also, other two studies (15,16) could not be included in the analysis as they were the only ones where the alcohol and folate interaction was evaluated stratified by hormonal status.

Tables 3a, 3b and 3c summarize the main characteristics of the included articles.

Data extraction

In order to create our database, we extracted all the relevant information from each article, which includes: year of publication, journal, author, country, years of follow-up, sample size, exposure levels of alcohol and folate, units of measure, stratification by menopausal status, familiar history of breast cancer and hormonal receptor status (when available), and RR/OR with 95% CI.

Finally, we have analyzed separately three kinds of studies:

Firstly: studies in which the alcohol consumption is the main exposure and the folate level is a secondary variable (Table 3a).

Secondly: studies where the folate intake is considered main exposure and the alcohol consumption is studied as a secondary variable (Table 3b).

Thirdly: studies which explore the exposure to alcohol/folate jointly as a unique variable, hereinafter called *combined exposure* (Table 2). The joint exposure has been subdivided into different categories according to the study exposure and the reference category (Table 3c).

Statistical analysis

The statistical analysis was performed including all studies (cohort and case-control studies). A sensitivity analysis was carried-out including only the prospective studies (cohort and nested-case control studies).

The ways folate and alcohol intake or folate blood levels were reported in each article were not standardized (neither the number of categories nor the cut-off levels) which makes difficult the analysis. Therefore, to provide a reliable 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 cancer together, stratified according to women menopausal status and cancer estrogen and progesterone receptor status (when enough studies where available).

According to folate intake, we analyzed all types of folate exposure together, and performed separate analyses for the different types of exposure (dietary folate, total folate intake and folate blood level) when reported in at least two studies.

During the analysis of the combined effect, some results needed to be inverted to increase the number of studies included in each analysis: two studies (17,18) when comparing high alcohol & low folate intake vs low alcohol & high folate intake; one study (18) when comparing high alcohol & low folate intake vs low alcohol & low folate intake; and two studies (19,20) when comparing low alcohol & high folate intake vs low alcohol & low folate intake.

A pooled OR or RR has been estimated by weighting individual OR/RR by the inverse of their variance. OR/RR heterogeneity was measured using Q and I^2 statistics. A fixed-effect model was preferred if Q statistics where higher than 0.1 and I^2 lower than 25% indicating low heterogeneity; otherwise random effect model was conducted.

Funnel plots and the Egger test were applied to detect publication bias.

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

Results

Relationship between alcohol intake and breast cancer

Seven studies evaluate the relationship between alcohol intake and breast cancer. These results are shown in the Table 4a.

Four studies reported association between alcohol and breast cancer in the whole population (17,21–23) with a pooled OR of 1.12 (95%CI: 1.03-1.23) and three (17,24,25) did the same only in postmenopausal women with a pooled OR of 1.29 (95%CI: 1.18-1.41).

Also, analyses evaluating the relationship between alcohol and breast cancer stratified by folate intake and type of folate intake (dietary or total folate intake including supplements) were conducted.

Four studies (21–23,26) evaluated the relationship of alcohol intake and breast cancer in the whole population with low folate intake (Fig. 2a) with statistical significance (OR: 1.56 (95%CI: 1.12-2.17)) while when stratifying by high folate intake (Fig. 2b) no relationship was found (OR: 1.00 (0.86-1.17).

When the same analysis was made in postmenopausal women, four studies (17,21–26) evaluate the relationship stratified by low folate intake (Fig. 3a) with statistical significance (OR:1.30 (95%CI: 1.13-1.50)). Analyzing stratified by high folate intake (Fig. 3b) this risk is reduced, with a pooled OR of 1.22 (95%CI: 1.04-1.43). Selecting studies which work with folate intake (diet + supplements), this positive association is only found in postmenopausal (OR: 1.26 95%CI (1.06-1.43).

Relationship between folate intake and breast cancer risk

Four studies evaluated the relationship between folate intake and breast cancer risk. These results are shown in the table 4a.

First, three studies (27–29) were analyzed to assess the relationship between folate intake and breast cancer in the whole population and four studies (25,28,30) in postmenopausal women. In both analysis no effect was found. The same happen when reanalyzed these studies including only dietary folate intake; both in the whole population (27,28) and in postmenopausal women (25,28).

In addition, considering the level of alcohol consumption, three studies (27–29) were included to analyze the effect of folate intake in the whole population with low alcohol intake. Statistical significance was not found neither with all the studies (pooled OR 0.94, 95%CI: 0.67-1.33) nor only including dietary folate intake (27,28): OR: 1.10 (95%CI 0.91-1.32). When, evaluating menopausal population only two studies were found without statistical significance (pooled OR 0.47; 95%CI 0.19-1.18). Note that these studies evaluated folate exposure in two different way: dietary intake (28) and plasma folate level (30), and no study evaluated total folate intake with supplements.

Finally, when evaluating the same studies with high alcohol intake (27–30) statistical significance was not reached in the whole population neither evaluating all the studies (pooled OR 0.65; 95%CI: 0.33-1.28) nor when only dietary folate intake is considered (OR: 0.64 (95%CI 0.19-2.16). However, an inverse association was found in the postmenopausal study (pooled OR 0.25; 95%CI 0.13-0.47).

Relationship between the combined effect of alcohol and folate intake exposure and breast cancer risk

Eleven studies reported a combined effect of alcohol and folate intake in breast cancer. These results are shown in the table 4b. Also, a stratified analysis by type folate intake is available in the appendix (Table 1).

High alcohol & folate intake

Eight studies evaluated the relationship between high alcohol & folate intake versus low intake of both and BC risk, five of them in postmenopausal women (9,31–34) and the other three in the whole population (34–36) (Figure 4a and 5a). A positive association was observed but restricted to the postmenopausal group (OR: 1.12 (95%CI: 1.0001-1.26)).

High alcohol & low folate

Regarding the effect of the exposure to high alcohol& low folate intake on BC risk, eleven studies were included.

In postmenopausal women a positive association was observed regardless of the reference category. The five studies (9,31–34) using as reference (low alcohol & folate intake) found a pooled OR of 1.33 (95%CI: 1.10-1.63) while the two (19,20) using (low alcohol & high folate intake) a OR of 1.46 (95%CI: 1.52-1.85).

On the other hand, in the whole population a significant risk effect was obtained (OR:1.22 CI95% (1.09-1.35)) only using low alcohol & high folate intake as reference (17,18) (Figures 4b and 5b).

Finally, analyzing separately the effect of dietary folate significance was reached only in postmenopausal women OR of 1.46 (95%CI: 1.52-1.85) (using low alcohol & high folate as reference).

High folate & low alcohol intake

Finally, high folate & low alcohol intake (versus low alcohol & low folate) showed a protective effect against BC risk in the whole population (OR: 0.55 (95%CI: 0.32-0.94). (34,36,37), but this effect disappeared in the postmenopausal group (OR:0.98 (95%CI: 0.90-1.07). (9,19,20,31–34).

Discussion

Our study shows a higher risk of BC development in women exposed to high alcohol consumption and low folate intake (compared to low alcohol & high folate intake) than in those with high alcohol consume and high folate intake, especially in postmenopausal women. These results are consistent with previous knowledge. It is known that alcohol consumption decreases the intestinal absorption and increases the renal excretion of folate intake (4); so patients with higher intake of alcohol are supposed to require more intake of folate to supply the basic needs of this vitamin, which could prevent from the proposed carcinogenic effect of folate over-intake (38). Furthermore, the most important carcinogenic effect of alcohol intake is the alteration of folate metabolism, so the increase of folate intake can improve the bioavailability of folate of the thiamine synthesis. Also, other alcohol mechanism of carcinogenesis is the hypermethylation of p16 promoter, which is prevented when high amount of folate is intake, as is one of the most important factors for a correct gene methylation and expression (39).

Folate intake act as an effect modifier of alcohol exposure on BC risk. The relationship between alcohol consumption and breast cancer is stronger in those with low folate intake, especially in the analysis of the whole population (pre and postmenopausal women). These results are consistent with those found in previous meta-analyses (40,41). In hormone-dependent tumors this interaction seems to be higher, maybe due to its ability to increase the circulating levels of estrogens (38), but this relation has not been explored in our study because of the low number of articles including this information (15,16).

On the other hand, analyzing the effect of folate intake on breast cancer risk, no relationship was found in the whole analysis, but stratifying by alcohol intake a strong protection, restricted to the high alcohol consumers, was observed in postmenopausal women. However, only two studies were included (28,30), and both use different folate source (dietary and plasma). It is remarkable that plasma folate is less influenced by the alcohol intake. Moreover, this last study used as a cut-off level of 14ug/mL, which is lower than the higher levels of other studies where folate intake was associated as a risk factor (42,43), so this cut-off could be too low to see the real effect of high folate blood levels. One possible explanation of the lack of association could be the “J” effect that produces no difference comparing high and low levels (11,44). In addition, the reduced number of studies included in the meta-analysis make it difficult to obtain association.

To date, the relationship between folate exposure and breast cancer remains inconsistent, a previous meta-analysis fails to obtain association (12), while others found a protective effect of folate exposure in patients with high alcohol intake (10,11). We have to take into consideration that the aforementioned studies (10–12) did not perform stratification by menopausal status, which can lead to mistaken conclusions, as the tumors in premenopausal and postmenopausal women have different pathogenesis. Premenopausal women's most important factor for cancer development is genetic risk (45), so high folate intake can ameliorate the division of this altered cells preventing them from cancer development (46). There are even some SNP polymorphisms of folate metabolism related to breast cancer in premenopausal women (47,48), showing the important factor this nutrient can have in the breast cancer development. In contrast, postmenopausal women are more influenced by hormonal factors, so increased levels of folate can produce two antagonistic actions (49), which leads to a neutral interaction. Firstly, folate prevents from producing de novo DNA alterations by other external factors, and secondly, folates promote the proliferation of an initial tumor as soon as it is produced.

Despite of this protective effect, other studies in both pre- and postmenopausal women have found mutations related to folate metabolism, where high intake of folate is related to increased risk of breast cancer (50,51). Consequently, preventive recommendations of folate supplementation to increase its intake has to be used in very concrete situations specially, in premenopausal women, only when high risk situations are identified.

Finally, analyzing the effect of folate type, we found no statistical differences neither in the studies analyzing the exposure to folate stratified by alcohol nor in the combined analysis, but very low number of studies where included to observe differences. These results were different from the ones found in previous metanalysis, where, although, no high differences were found, total folate intake had higher risk than only dietary folate intake without evaluating the alcohol intake (10,11). These contradictory findings can be understood, because we are evaluating two different characteristics of the folate supplements. Firstly, supplements have a better absorption, been approximately 1.7 times more bioavailable than natural folates (18). Therefore, women with this intake can have a better folate status than women with only dietary folate intake. Secondly, there are two kinds of folate transporters: reduced folate carrier, which prefers dietary folate and supply all cells; and folate receptor, which has 1000 more times ability to transport synthetic folate and is expressed in almost no body tissues, but tumors cells (9). Therefore, supplementary folate will bind better to this last receptor, which increase the proliferation of any tumor cell from the very beginning of the tumor. This can explain an increased risk of cancer when using supplements of folate as is suggested by different metanalysis (52,53). Also, Baggott (54) found in rats that giving supplements produced an increase of the number of mammary tumors and decreased the time to development. Therefore, more analysis are needed to found the real interaction of different types of folate intake and breast cancer.

Our study has some limitations; first each study uses different cut-off points according to folate and alcohol intake. To analyze it we restricted our analysis to the comparison between the highest to the lowest category of exposure. This prevented us from performing a dose-response analysis. Also, this analysis can reduce the real effect of folate intake as both low and high intake are considered to have increased risk of developing breast cancer.

Secondly, most of the studies included in the metanalysis only reported the folate intake with a FFQ at the beginning of the study (19,20,25,26,33,55), which makes it difficult to take into considerations the modification of diet during the follow-up. Also, only one study (9) considered the change of folate fortification in cereals that became mandatory in United States in 1998, reporting levels lower than reals (34).

Finally, the alcohol level misclassification is a problem that can produce biases when assessing the real risk of breast cancer and alcohol intake, especially when occasional drinkers are classified together with non-drinkers (56).

Despite these limitations, our study has also several strengths, as it is the first metanalysis evaluating the combined association of alcohol and folate intake with breast cancer. Also, we have evaluated different factors that could modify this interaction, such as menopausal status and type of folate intake; whereas other metanalysis were only focused on the relationship between alcohol and breast cancer stratified by folate intake (13), or vice versa (10,12,38). Therefore, our study can help to understand better the complex interaction of these two factors in the pathogenesis of breast cancer. Lastly, our meta-analysis included new prospective not analyzed in previous reviews (21–24,30).

In conclusion, our results support the interaction of alcohol and folate intake on breast cancer development. The effect of alcohol is increased in those women with low folate intake and vice versa. Further research is needed to improve the knowledge of the influence of the type of folate and menopausal status in this association.

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Tables and Figures

Table 1.- Results of previous meta-analysis

Source	Type of folic acid	Adjustment of alcohol	Number of included studies	Type of included studies	RR (95%IC)
Liu M et al. (2014)	Dietary folate intake	Non-adjusted	16	Prospective studies	0.98 (0.90-1.05)
		Low alcohol intake	6		1.05 (0.95-1.15)
		High alcohol intake	6		0.94 (0.80-1.08)
Chen P et al. (2014)	Total folate intake	Non-adjusted	3	Prospective studies	1.06 (0.95-1.19)
		Adjusted	8		0.97 (0.91-1.03)
	Dietary folate intake	High alcohol intake	6		0.60 (0.45-0.82)
		Low alcohol intake	6		0.92 (0.79-1.07)
	Supplement folate intake	Non-adjusted	3		1.07 (0.96-1.19)
	Dietary folate intake	Non-adjusted	17	Case control studies	0.74 (0.60-0.92)
		Adjusted	8		0.84 (0.66-1.06)
Larsson SC et al. (2007)	Dietary folate intake	High alcohol intake	4	Prospective and case-control studies	0.51 (0.41-0.63)
		Low alcohol intake	4		0.95 (0.78-1.15)
		Non-adjusted	3	Prospective studies	0.99 (0.87-1.13)
			10	Case-control studies	0.84 (0.66-1.08)
	Serum folate intake	Non-adjusted	2	Case-control studies	0.41 (0.15-1.10)
			3	Prospective studies	0.81 (0.59-1.10)

Source	Alcohol exposure	Folate stratification		Number of included studies	Type of included studies	RR (95%IC)
Jung S et al. (2016)	Increase of 10g/d of alcohol intake	Total folate intake	<200ug/d	20	Cohort studies	1.12 (1.06-1.19)
			200-400ug/d			1.10 (1.07-1.13)
			400-600ug/d			1.12 (1.07-1.17)
			>600ug/d			1.08 (1.05-1.12)

Table 2.- Combined exposition to alcohol and folate intake: Exposure category and reference level

Exposure	Reference
High alcohol &low folate intake	Low alcohol&high folate
	Low alcohol&low folate
High alcohol &high folate intake	Low alcohol&low folate
Low alcohol &high folate intake	Low alcohol&low folate

Table 3 a.- Studies included in our meta-analysis of folate intake and breast cancer risk according alcohol intake

Type of Study	Study	Country	N	Alcohol intake	Folate intake	Folate exposition	Group	OR 95% CI
Cohort study	Kim Hk et al. (2017)	USA	93835	≥10g/d vs non drinkers	≥400ug/d	Dietary Folate	Premenopausal	1,01 (0,86-1,20)
					<400ug/d			1,19 (0,95-1,47)
Cohort study	Fagherazzi et al (2014)	France	66481	≥2 drinks/d vs Non drinkers	<411ug/d	Dietary Folate	Postmenopausal	1,35 (1,10-1,67)
					≥411ug/d			1,16 (0,94-1,44)
Cohort study with HR	Kawai M et al. (2011)	Japan	4994	≥15g/d vs Non drinkers	<219 ug/d	Dietary Folate	All	1,58 (0,65-3,86)
					≥219ug/d			0,28 (0,04-2,03
Cohort study with HR	Baglietto L et al. (2005)	Australia	17447	≥40g/d vs non-drinkers	200ug/d	Dietary Folate	All	2,00 (1,14-3,49)
					330ug/d			1,08 (0,60-1,93)
					400ug/d			0,77 (0,33-1,80)
Cohort study	Feigelson HS et al. (2003)	USA	66561	≥15g/d vs Non-drinkers	<178ug/d	Dietary Folate	Postmenopausal	1,40 (1,00-1,99)
					<230,9ug/d			1,11 (0,76-1,61)
					<294,3ug/d			1,55 (1,07-2,23)
					≥294,3ug/d			0,93 (0,56-1,54)
					<209,8ug/d	Total folate intake		1,33 (0,94-1,88)
					<319,8ug/d			1,19 (0,79-1,80)
					<603,7ug/d			1,05 (0,72-1,53)
					≥603,7ug/d			1,50 (1,02-2,22)
Cohort study	Lew JQ et al. (2009)	USA	184418	>35g/d vs Non-drinkers	<300ug/d	Total folate intake	Postmenopausal	1,06 (0,77-1,51)
					<600ug/d			1,28 (0,96-1,67)
					<800ug/d			1,54 (1,20-1,96)
					≥800ug/d			1,41 (0,91-2,17)
Case and control study	Beasley JM et al. (2010)	Mexico	2074	Drinkers vs Non drinkers	197 +/- 47	Total folate intake	All	1,99 (1,26-3,16)
					317 +/- 36			1,70 (1,10-2,63)
					532 +/- 145			1,12 (0,69-1,83)

Table 3 b.- Studies included in our meta-analysis of alcohol intake and breast cancer risk according folate intake

Type of Study	Study	Country	Folate	Upper cut off levels of Alcohol	Group	OR 95% CI	N
Cohort study	Larsson SC et al. (2008)	Sweden	Dietary Folate	Non drinkers	All	1,01 (0,81-1,27)	61433
				<10g/d		0,99 (0,86-1,15)	
				=>10g/d		1,18 (0,67-2,07)	
Cohort study	Rohan TE et al. (2000)	Canada	Dietary Folate	=<14g/d	All	1,22 (0,94-1,58)	5681
				>14g/d		0,34 (0,18-0,61)	
				=<14g/d	Premenopausal	1,31 (0,70-2,47)	
				>14g/d		0,47 (0,04-6,01)	
				=<14g/d	Postmenopausal	1,15 (0,86-1,54)	
				>14g/d		0,28 (0,14-0,55)	
Case and controls	Levi F et al. (2001)	Switzerland	Dietary Folate	Non drinkers	All	0,67 (0,40-1,12)	731
				Drinkers		0,55 (0,33-0,92)	
Nested case-control study	Zhang SM et al. (2003)	USA	Plasma folate	<15g/d	Postmenopausal	0,72 (0,49-1,05)	1424
				=>15g/d		0,11 (0,02-0,59)	

Table 3 c.- Studies included in our meta-analysis of joint effect alcohol-folate intake on breast cancer risk

Type of Study	Study	Country	N	Folate	Alcohol	Group	OR 95% CI
Cohort study with HR	Duffy CM et al. (2009)	USA	88530	Total folate intake	g/day	Postmenopausal	1,09 (0,88-1,14)
Cohort study with HR	Stolzenberg-Solomon RZ et al. (2006)	USA	25400	Total folate intake	g/day	Postmenopausal	1,23 (0,93-1,62)
Cohort study with HR	de Batlle J et al. (2014)	10 European countries	334848	Dietary Folate	drinks/ week	All	0,83 (0,74-0,93)
Cohort study	Sellers TA et al. (2001)	USA	34387	Total folate intake	g/day	Postmenopausal	1,45 (0,95-2,23)
				Dietary Folate			1,59 (1,05-2,41)
Cohort study	Sellers TA et al. (2004)	USA	33552	Dietary Folate	g/day	Non Family Hx of Breast Cancer (postmenopausal)	1,40 (1,05-1,86)
						Family Hx of Breast Cancer (postmenopausal)	2,39 (1,36-4,20)
Cohort study	Maruti SS et al. (2009)	USA	35023	DFE/d	g/day	Postmenopausal	1,05 (0,73-1,50)
Cohort study	Stevens VL et al. (2010)	USA	69855	Dietary Folate	drinks/ week	Postmenopausal	1,30 (0,85-2,00)
Case and controls	Islam T et al. (2013)	Japan	5181	Dietary Folate	g/day	All	1,19 (0,58-1,94)
			2611			Premenopausal	0,93 (0,43-2,47)
			2570			Postmenopausal	1,90 (0,27-1,72)
Case and controls	Gong Z et al. (2014)	USA	804	Dietary Folate	g/week	Premenopausal African American	1,11 (0,62-1,99)
Case and controls	Zhang M et al. (2011)	China	2018	Dietary Folate	g/day	All	0,38 (0,20-0,72)
Nested case-control study	Matejcic M et al. (2017)	10 European countries	5012	Plasma folate	g/day	All	0,75 (0,54-1,04)

Table 4a. Results from the stratified meta-analysis

Main exposition		Secondary exposition	Group	OR/RR (95%CI)	I2	Articles included
Alcohol consumption		None	All	1.12 (1.03-1.23)	0.00%	4
		Low folate		1.56 (1.12-2.17)	0.00%	4
		High folate		1.00 (0.86-1.17)	0.00%	4
		None	Postmenopausal	1.29 (1.18-1.41)	0.00%	3
		Low folate		1.30 (1.13-1.50)	0.00%	4
		High folate		1.22 (1.04-1.43)	0.00%	4
		High dietary folate	All	0.96 (0.64-1.45)	0.00%	3
		High diet + supplements folate	Postmenopausal	1.26 (1.06-1.49)	0.00%	3
Folate	Any folate	None	All	1.01 (0.91-1.12)	0.00%	3
		Low alcohol intake		0.94 (0.67-1.33)	0.00%	3
		High alcohol intake		0.65 (0.33-1.28)	0.00%	3
		None	Postmenopausal	1.01 (0.88-1.15)	14.13%	4
		Low alcohol intake		0.47 (0.19-1.18)	0.00%	2
		High alcohol intake		0.25 (0.13-0.47)	0.00%	2
	Dietary folate	None	All	1.01 (0.91-1.11)	0.00%	2
		Low alcohol intake		1.10 (0.91-1.32)	0.00%	2
		High alcohol intake		0.64 (0.19-2.16)	0.00%	2
		None	Postmenopausal	1.02 (0.89-1.18)	0.00%	2
		Low alcohol intake		.	.	*No studies*
		High alcohol intake		.	.	*No studies*

Table 4b. Results from the combined interaction meta-analysis

Alcohol exposure	Folate exposure	Group	OR/RR (95%CI)	I^2	Articles included
High vs low alcohol intake	Low vs high folate intake	All	1.22 (1.09-1.36)	0.00%	2
		Postmenopausal	1.45 (1.19-1.79)	0.00%	2
	Low vs low folate intake	All	1.13 (0.74-1.84)	0.00%	4
		Postmenopausal	1.33 (1.10-1.63)	8.60%	5
	High vs low folate intake	All	0.80 (0.40-1.62)	4.04%	3
		Postmenopausal	1.12 (1.0001-1.26)	0.00%	5
Low vs low alcohol intake	High vs low folate intake	All	0.55 (0.32-0.94)	9,55%	3
		Postmenopausal	0.98 (0.90-1.07)	0.00%	7

Figure 1. Flow diagram of the literature search process

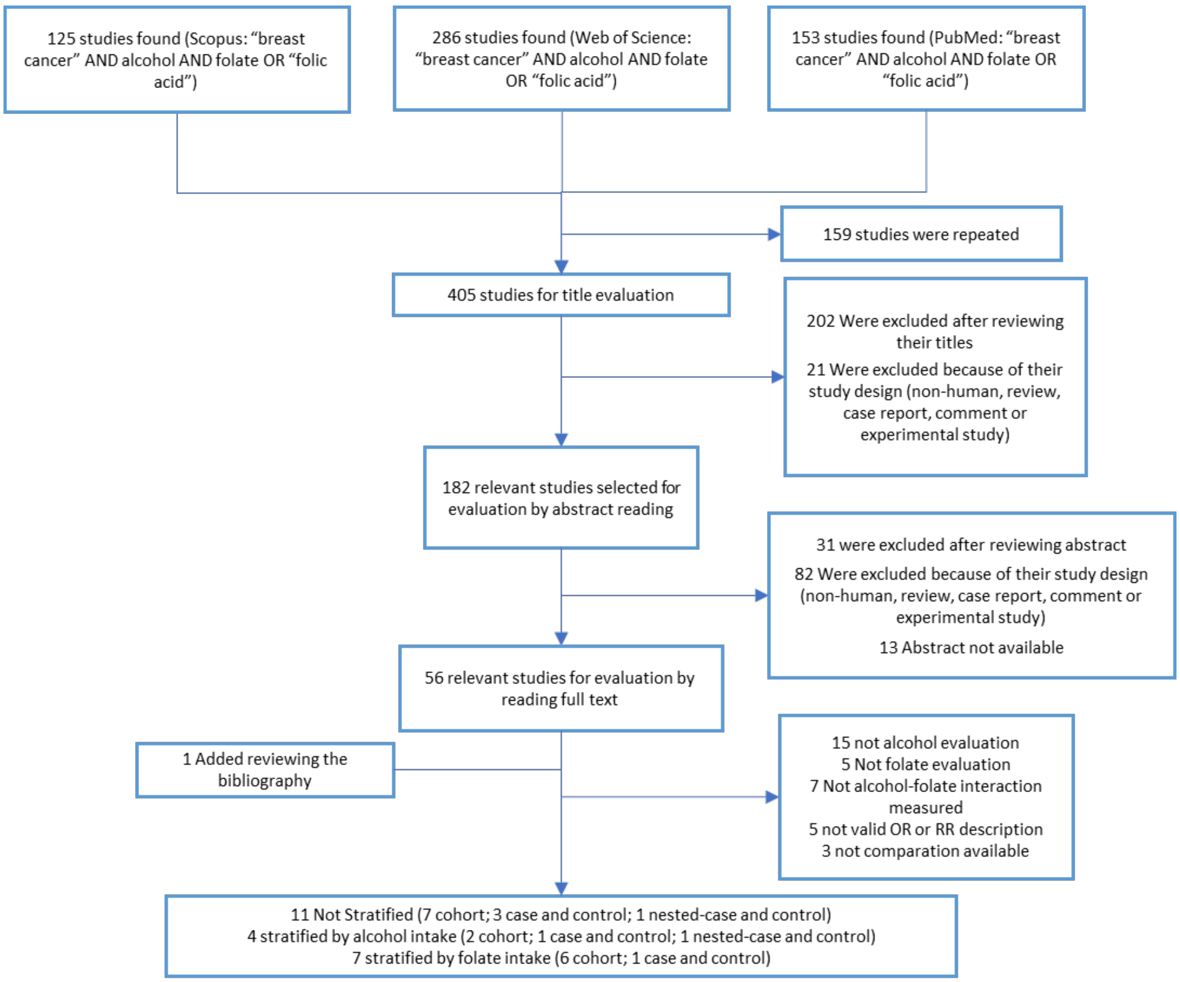


Fig 2a. Forest plot of alcohol relationship with breast cancer stratified by low folate intake in all women.

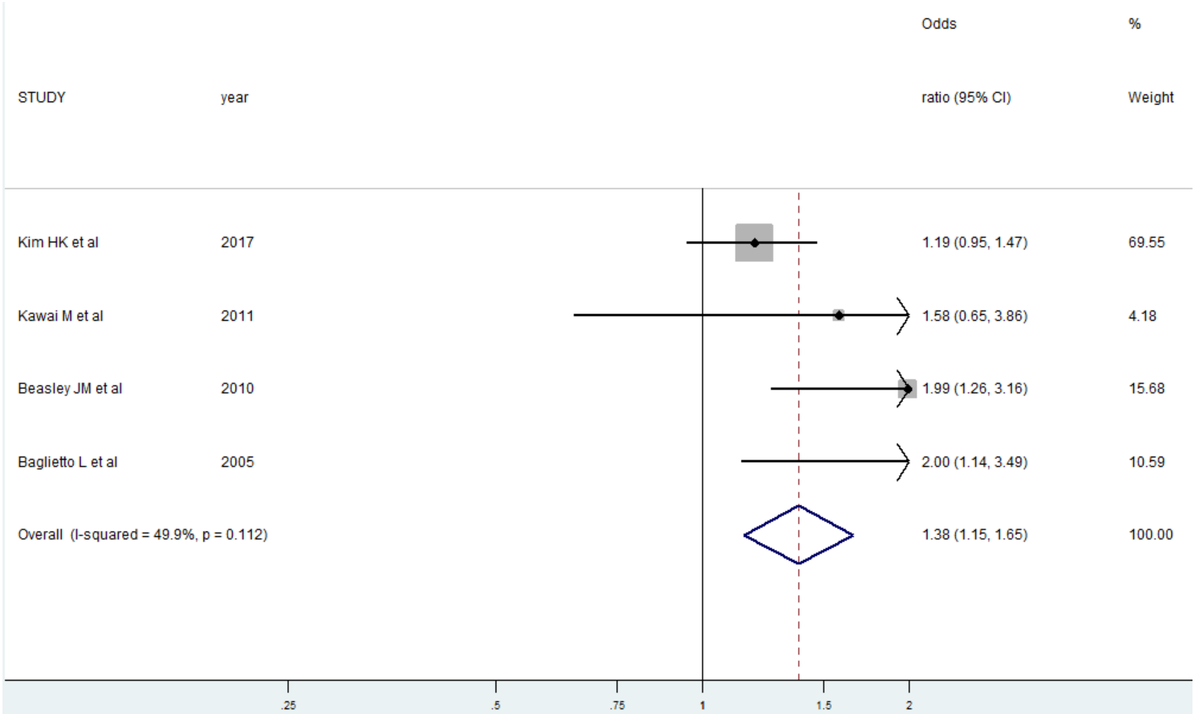


Fig 2b. Forest plot of alcohol relationship with breast cancer stratified by high folate intake in all women.

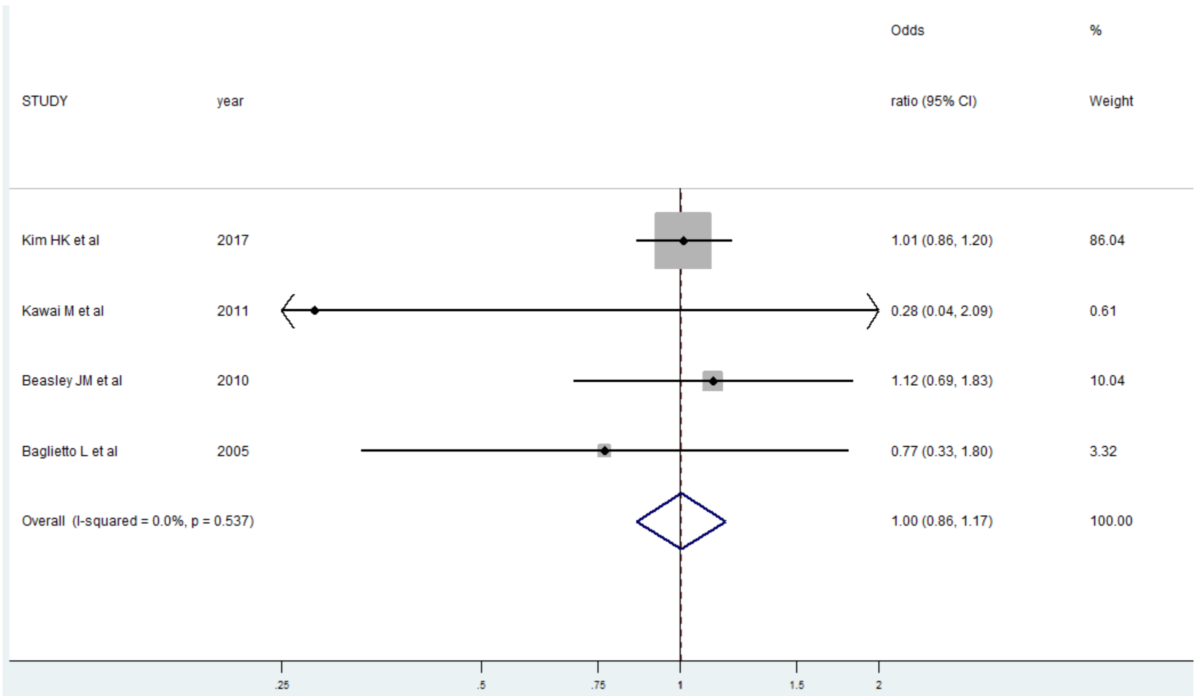


Fig 3a. Forest plot of alcohol relationship with breast cancer stratified by low folate intake in postmenopausal women.

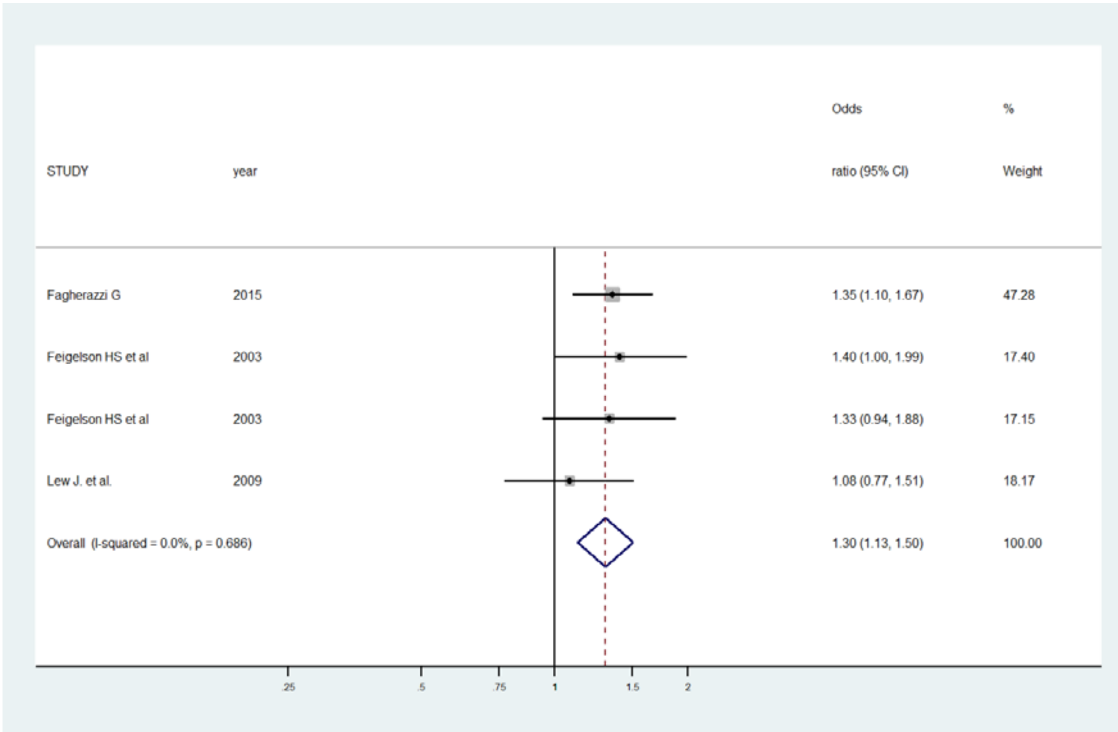


Fig 3b. Forest plot of alcohol relationship with breast cancer stratified by high folate intake in postmenopausal women.

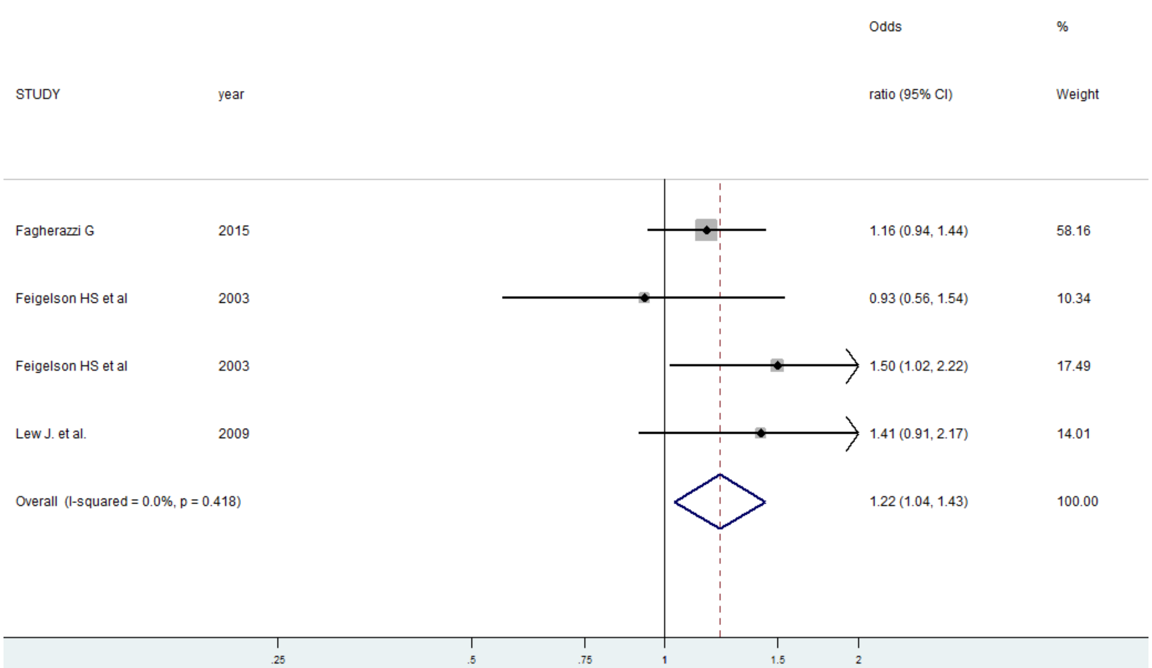


Fig 4a. Forest plot of high alcohol & high folate intake relationship with breast cancer compared with low alcohol & low folate intake in all women.

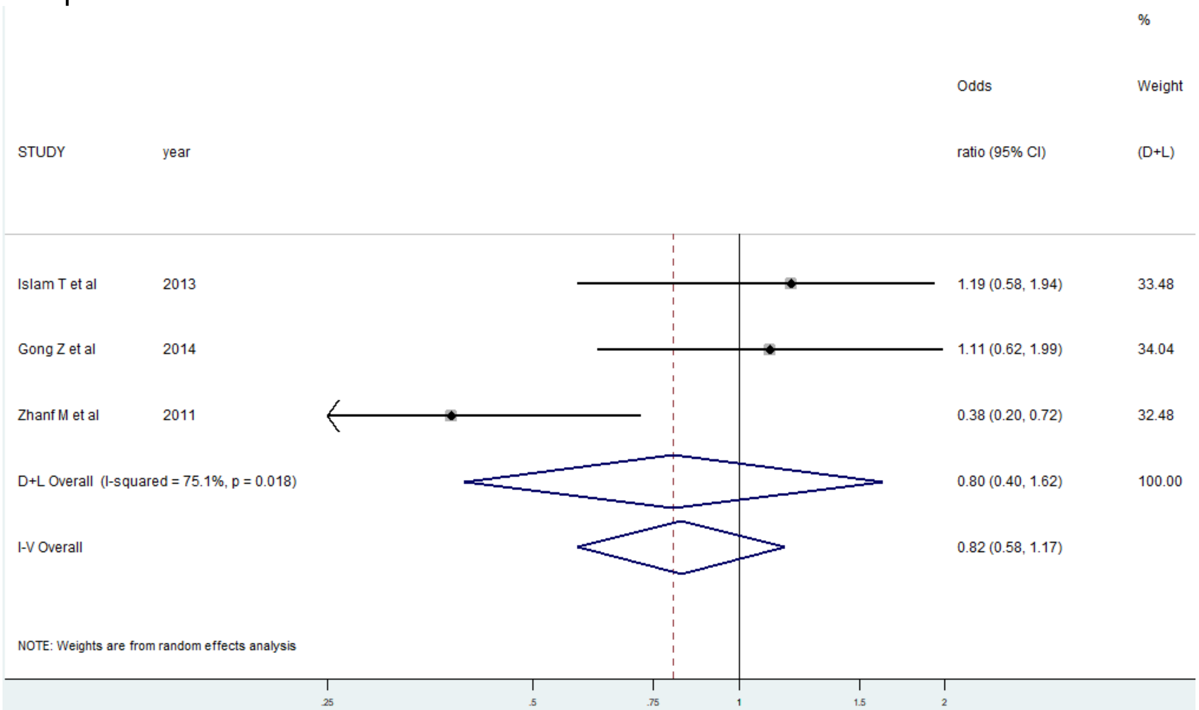


Fig 4b. Forest plot of high alcohol & low folate intake relationship with breast cancer compared with low alcohol & high folate intake in all women.

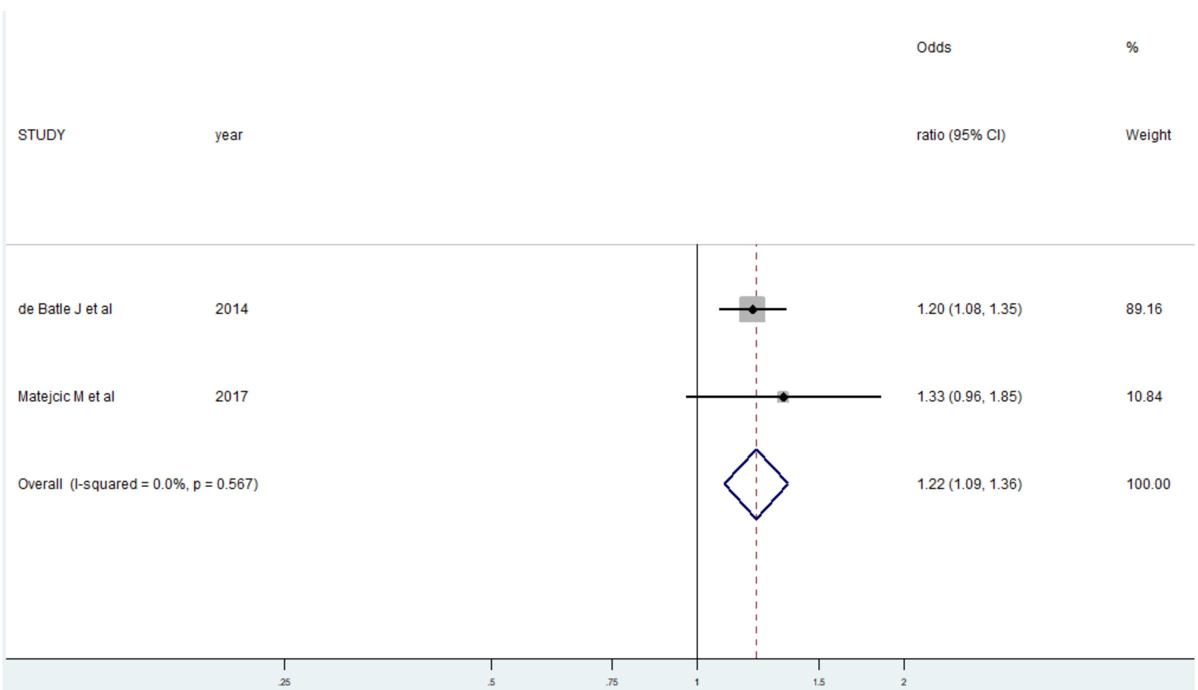


Fig 5a. Forest plot of high alcohol & high folate intake relationship with breast cancer compared with low alcohol & low folate intake in postmenopausal women.

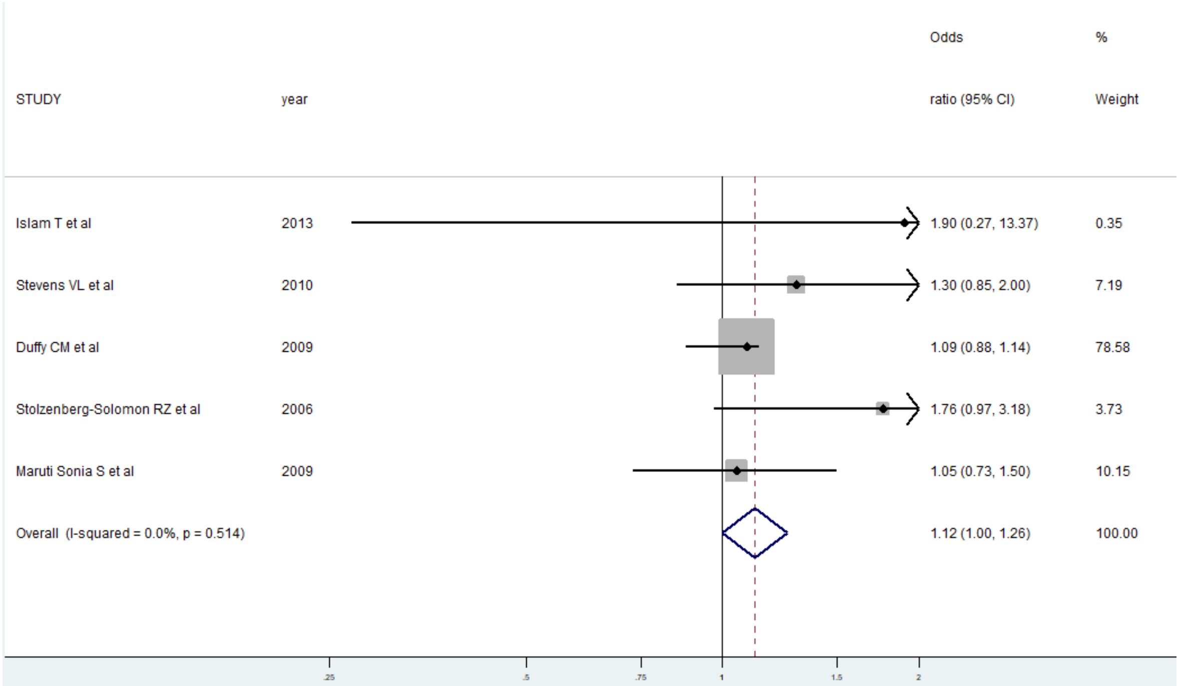
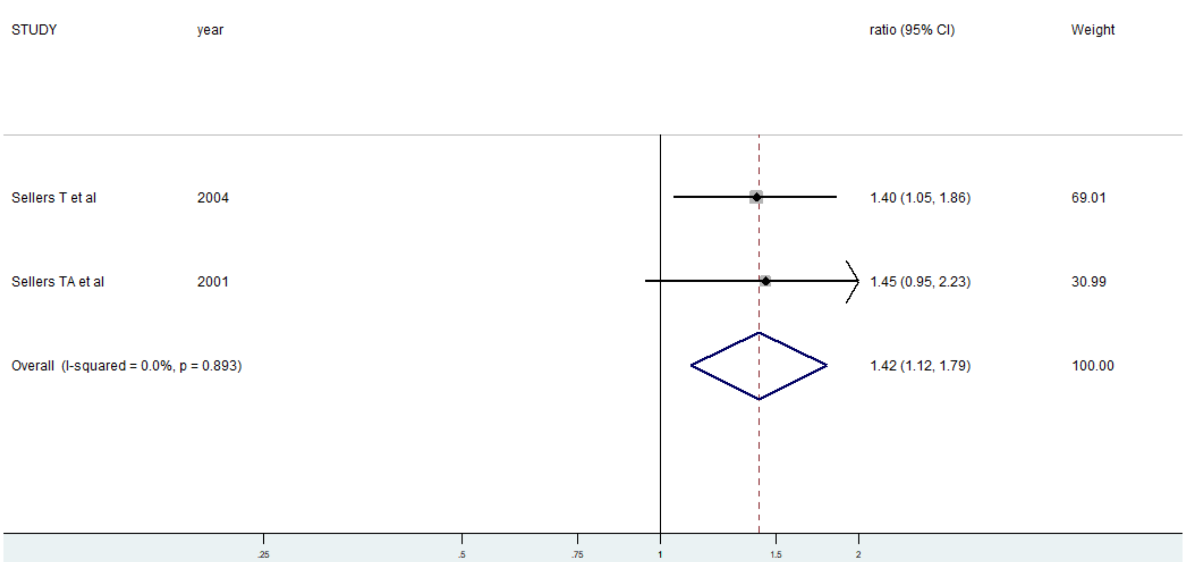


Fig 5b. Forest plot of high alcohol & low folate intake relationship with breast cancer compared with low alcohol & high folate intake in postmenopausal women.



Appendix

Figures are only included when three or more studies were analyzed.

Table 1: Combined exposure analysis stratified by type of folate intake

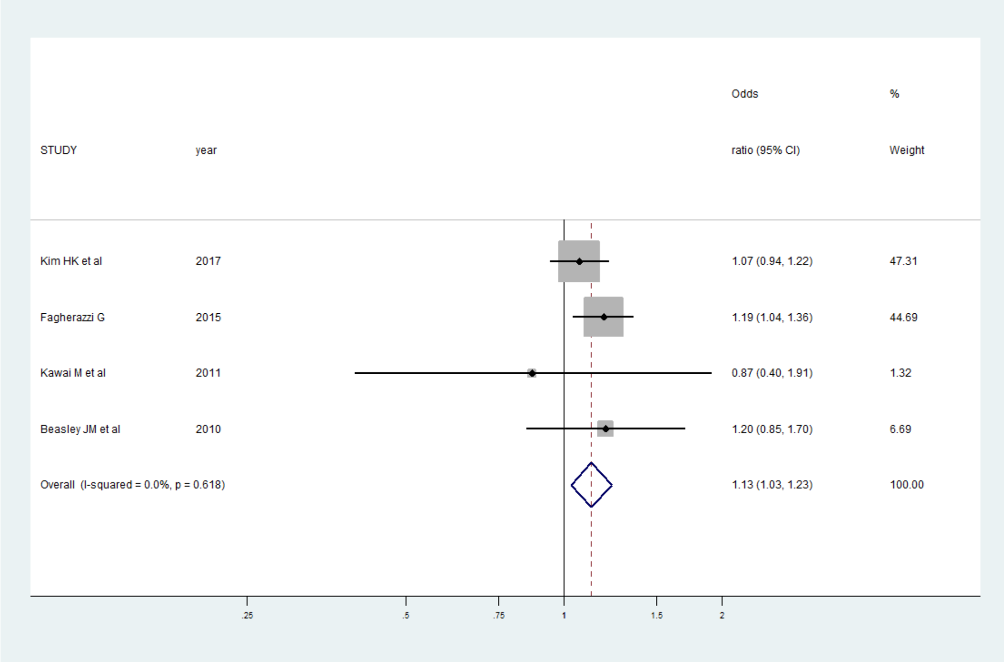
Alcohol exposure	Folate exposure	Group	Any folate intake	Dietary folate	Dietary + supplements folate
High vs low alcohol intake	Low vs high folate intake	All	1.22 (1.09-1.36) N=2	NO STUDIES	NO STUDIES
		Postmenopausal	1.46 (1.52-1.85) N=2	1.46 (1.52-1.85) N=2	NO STUDIES
	Low vs low folate intake	All	1.40 (1.13-1.72) N=4	1.43 (1.08-1.90) N=3	NO STUDIES
		Postmenopausal	1.33 (1.10-1.63) N=5	1.51 (0.88-2.58) N=2	1.33 (1.01-1.76) N=3
	High vs low folate intake	All	0.80 (0.40-1.62) N=3	0.80 (0.40-1.62) N=3	NO STUDIES
		Postmenopausal	1.12 (1.0001-1.26) N=5	1.32 (0.87-2.01) N=2	1.11 (0.98-1.25) N=3

Figures

Alcohol and breast cancer

Figure 1. Forest plot Alcohol intake in all women

a) All studies



b) Prospective studies

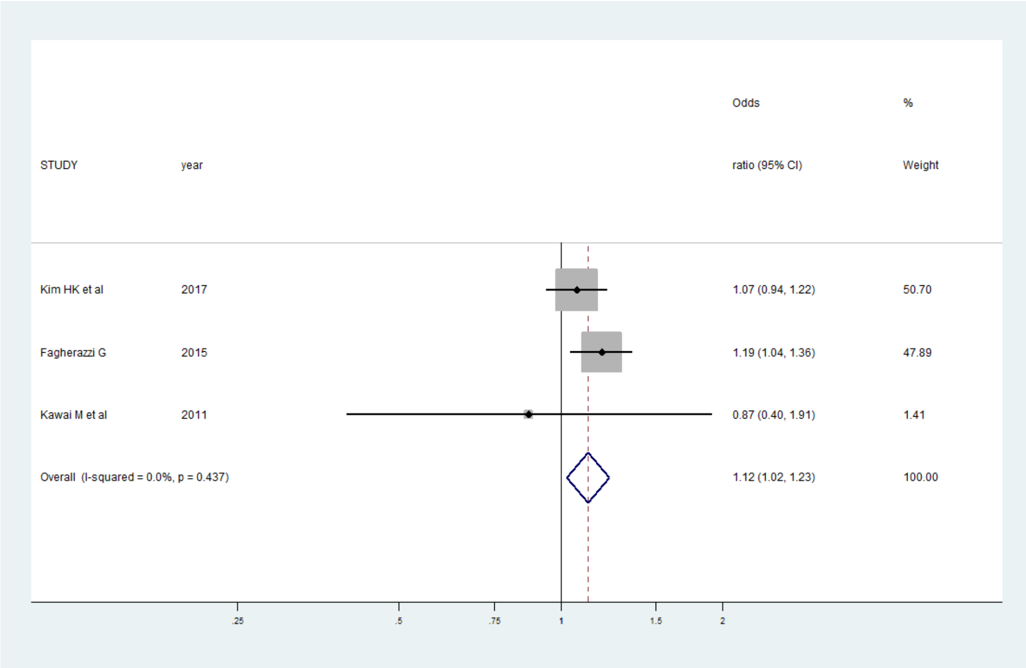
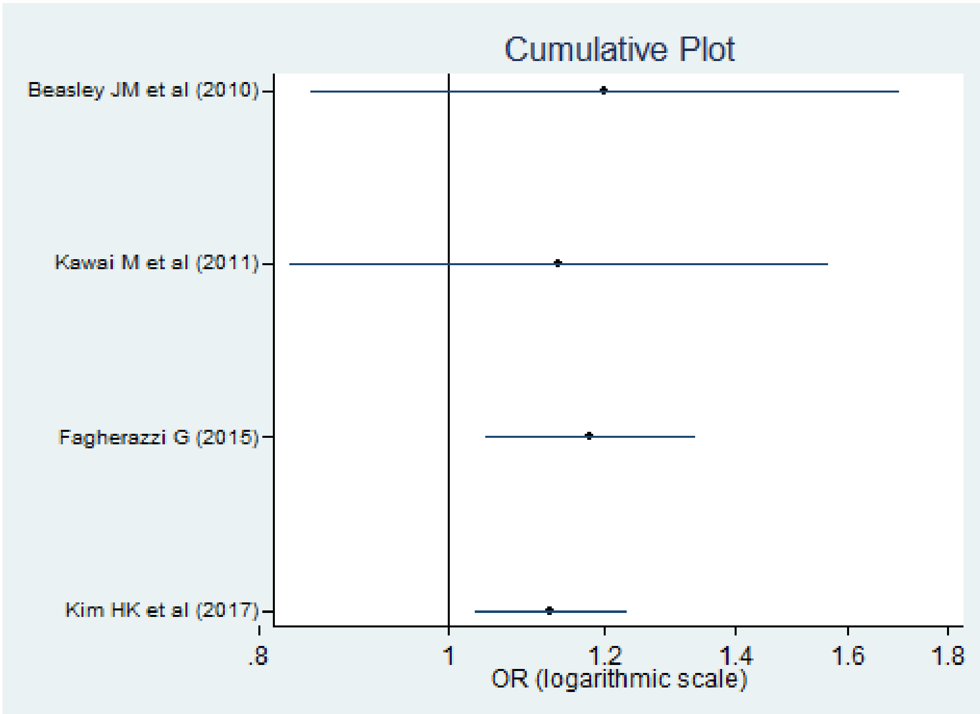


Figure 2. Cumulative plot Alcohol intake in all women

a) All studies



b) Prospective studies

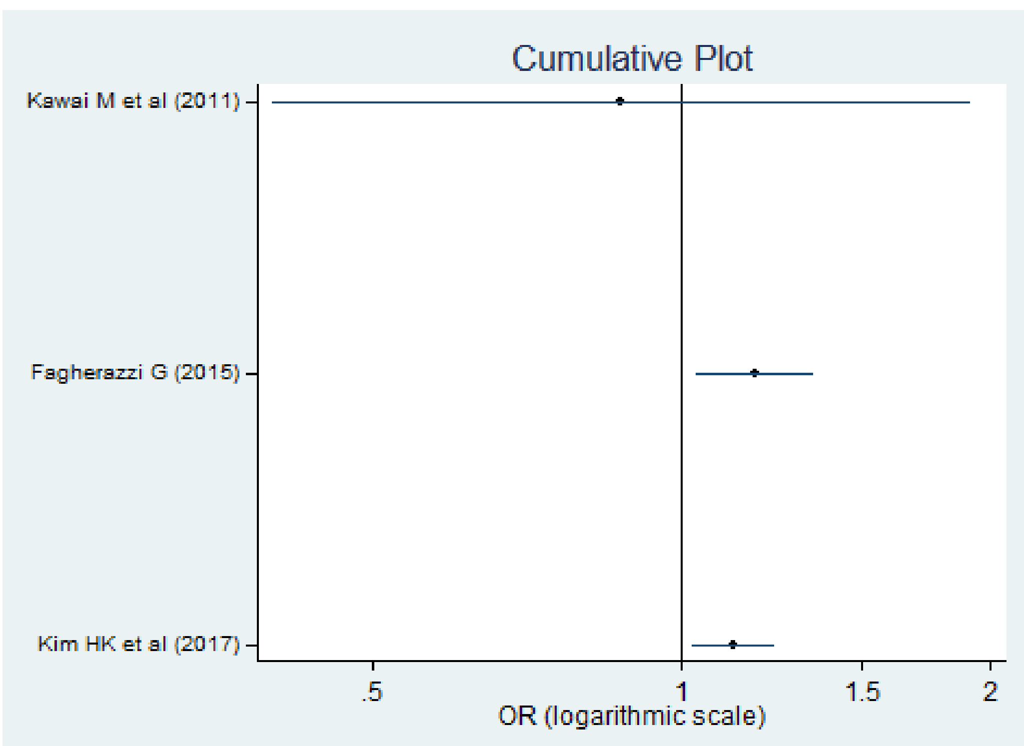
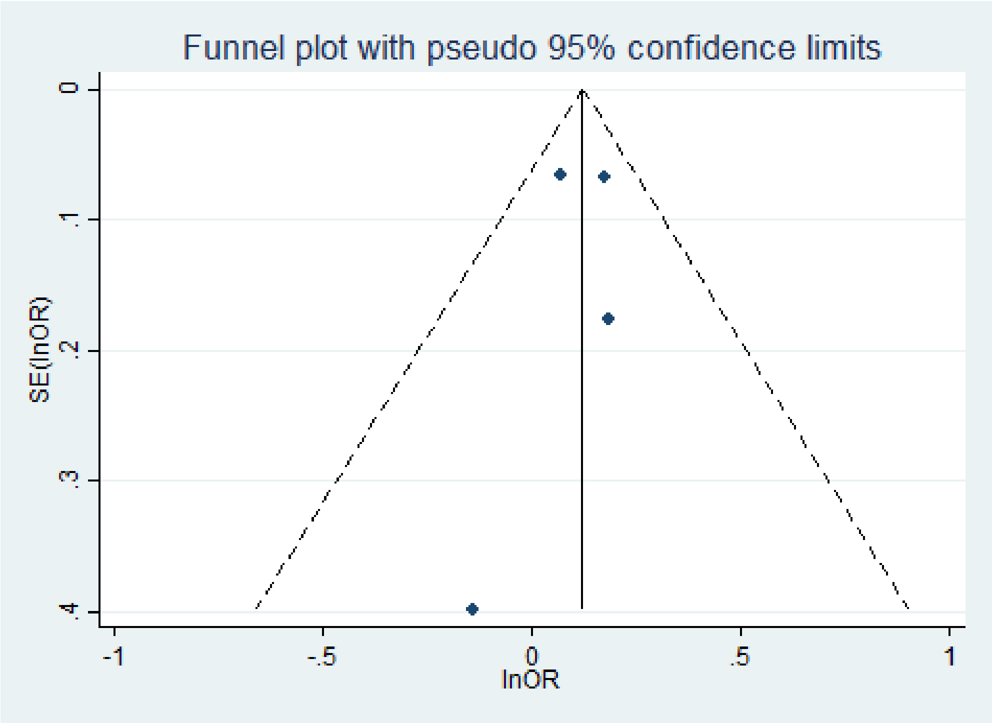


Figure 3. Funnel plot Alcohol intake in all women

a) All studies



b) Prospective studies

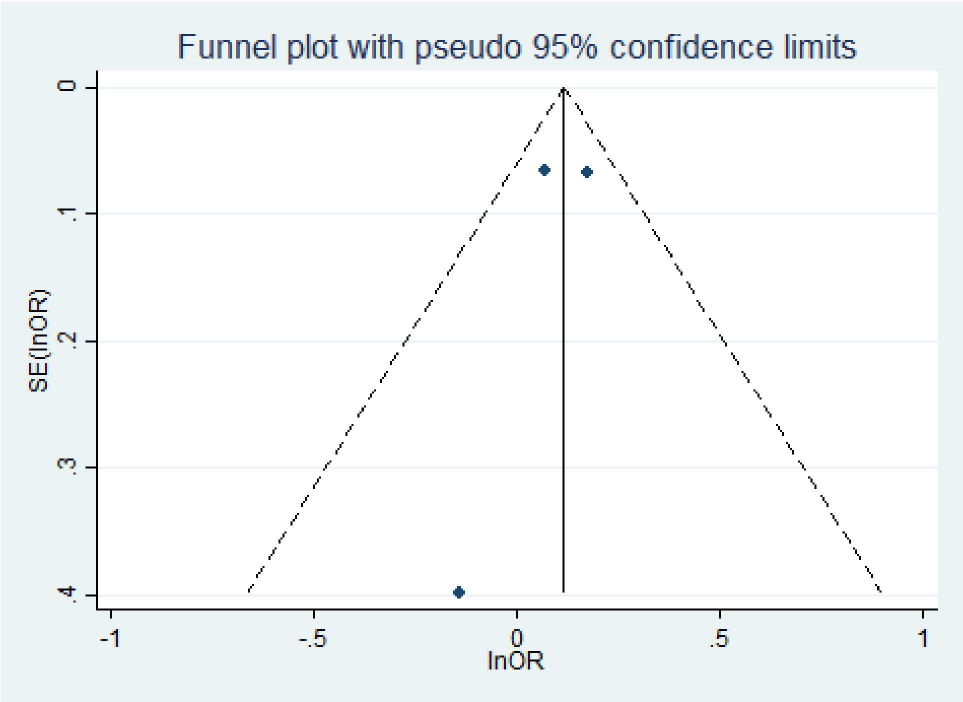
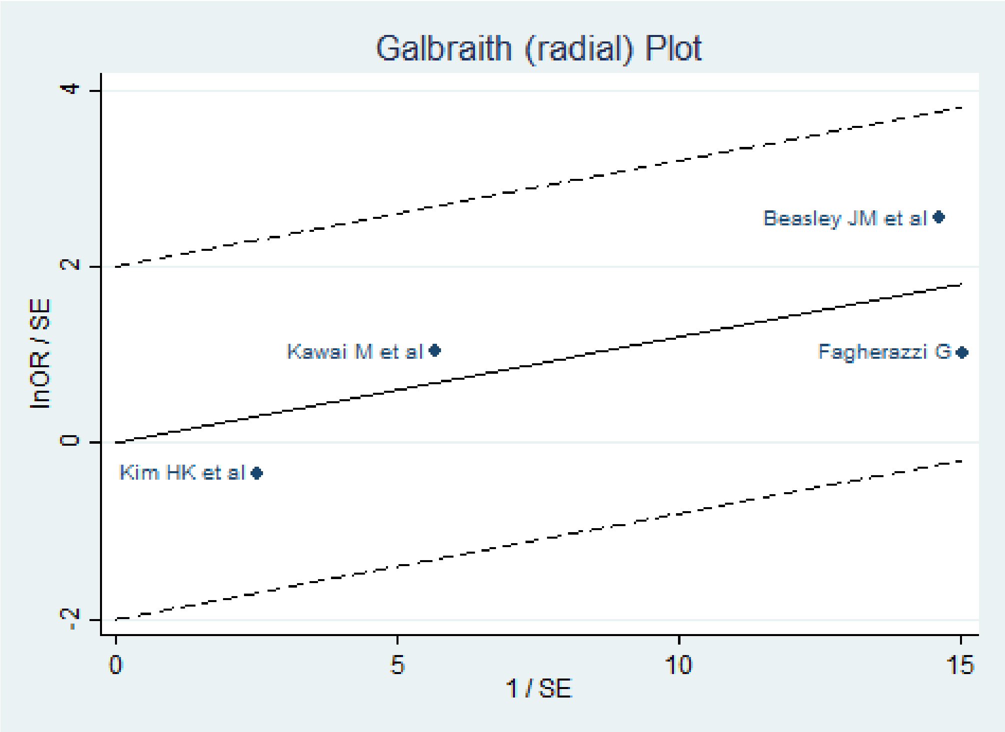


Figure 4. Galbraith plot Alcohol intake in all women

a) All studies



b) Prospective studies

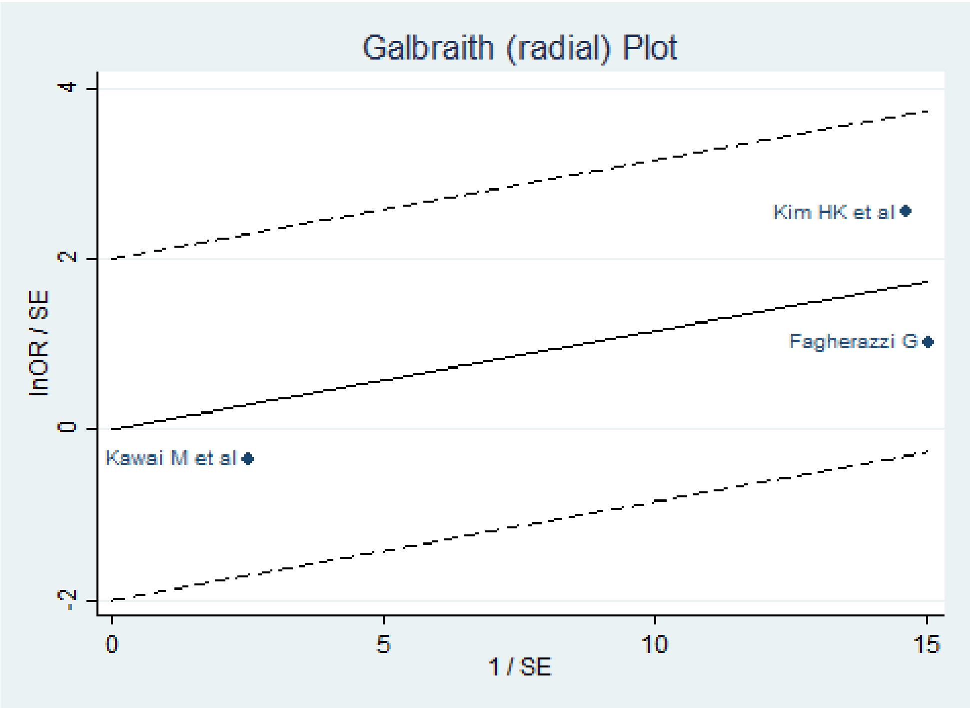


Figure 5. Forest plot Alcohol intake in postmenopausal women. All studies

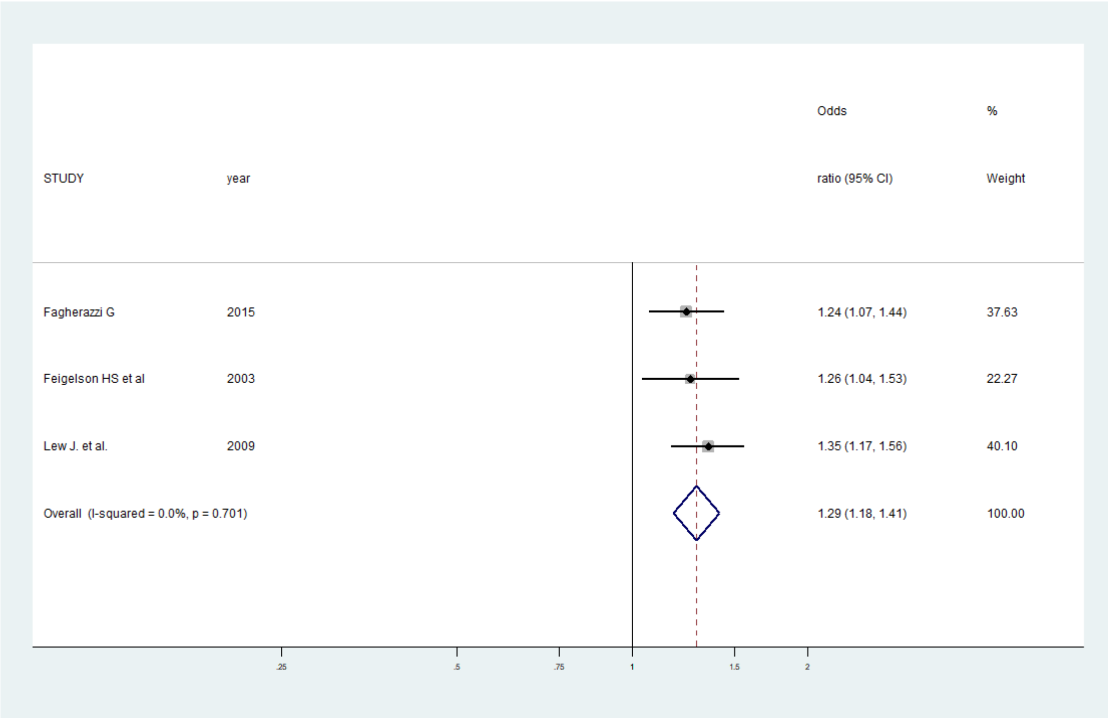


Figure 6. Cumulative plot Alcohol intake in postmenopausal women. All studies

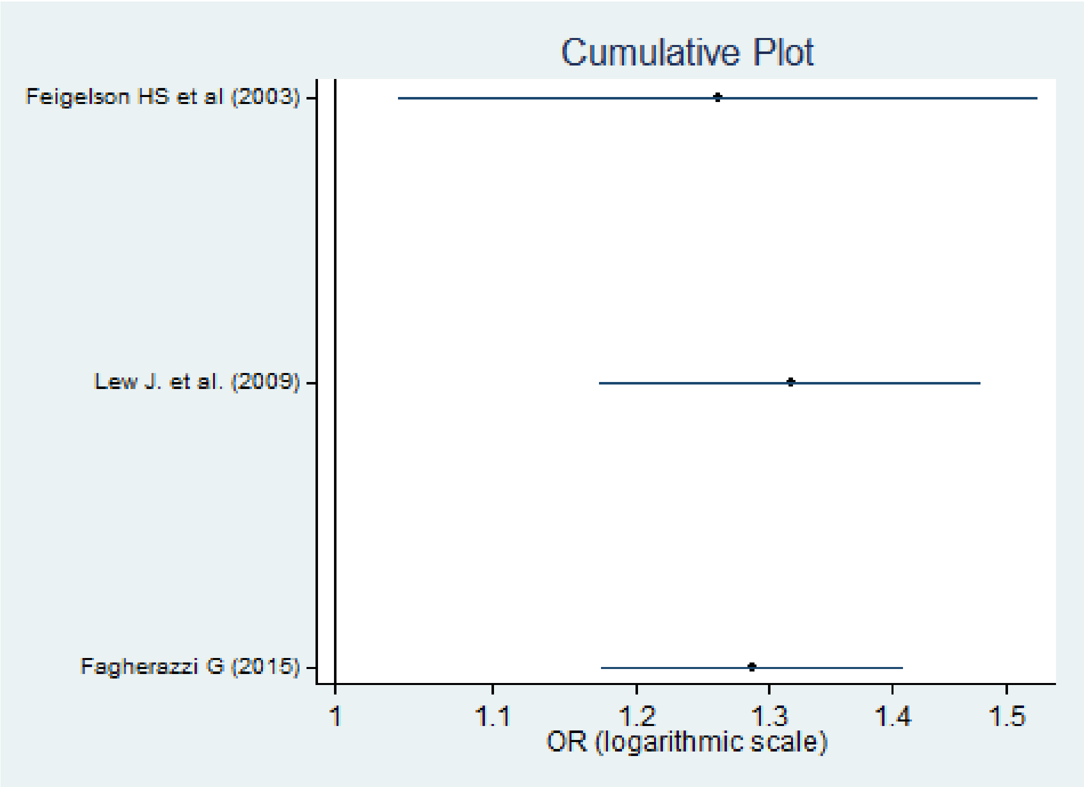


Figure 7. Galbraith plot Alcohol intake in postmenopausal women. All studies

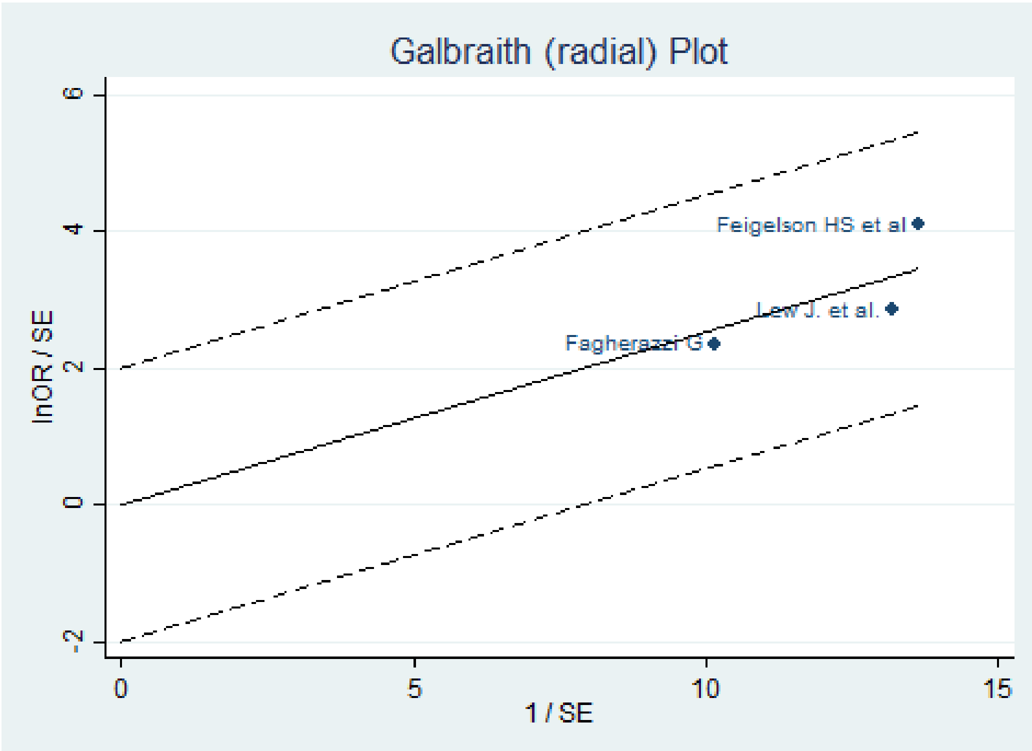


Figure 8. Funnel plot Alcohol intake in postmenopausal women. All studies

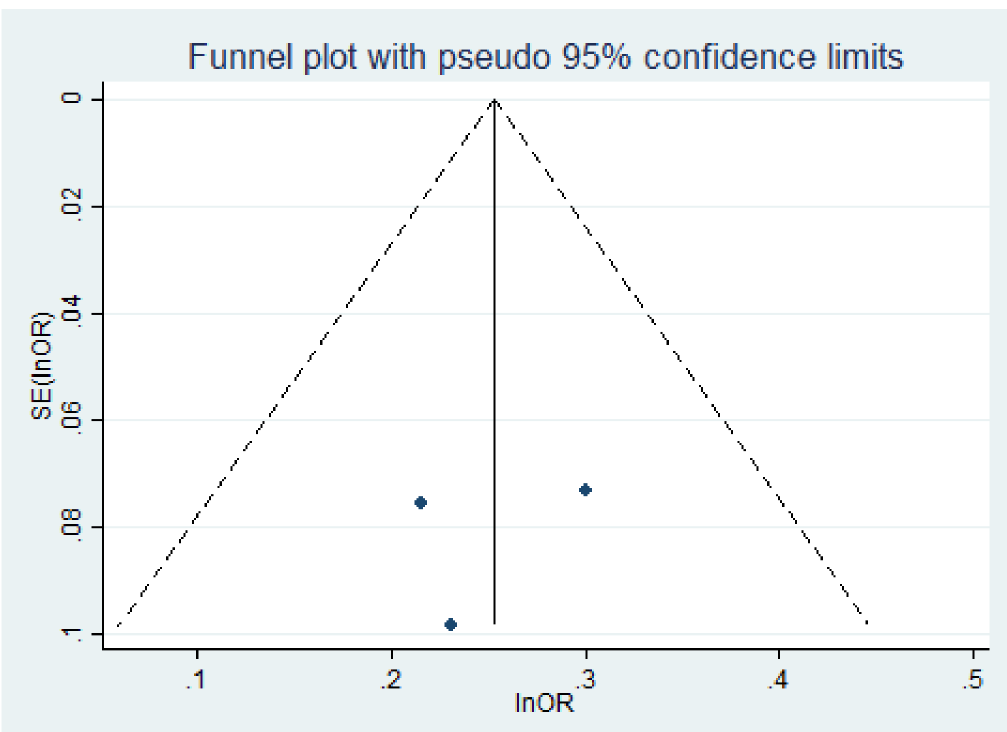
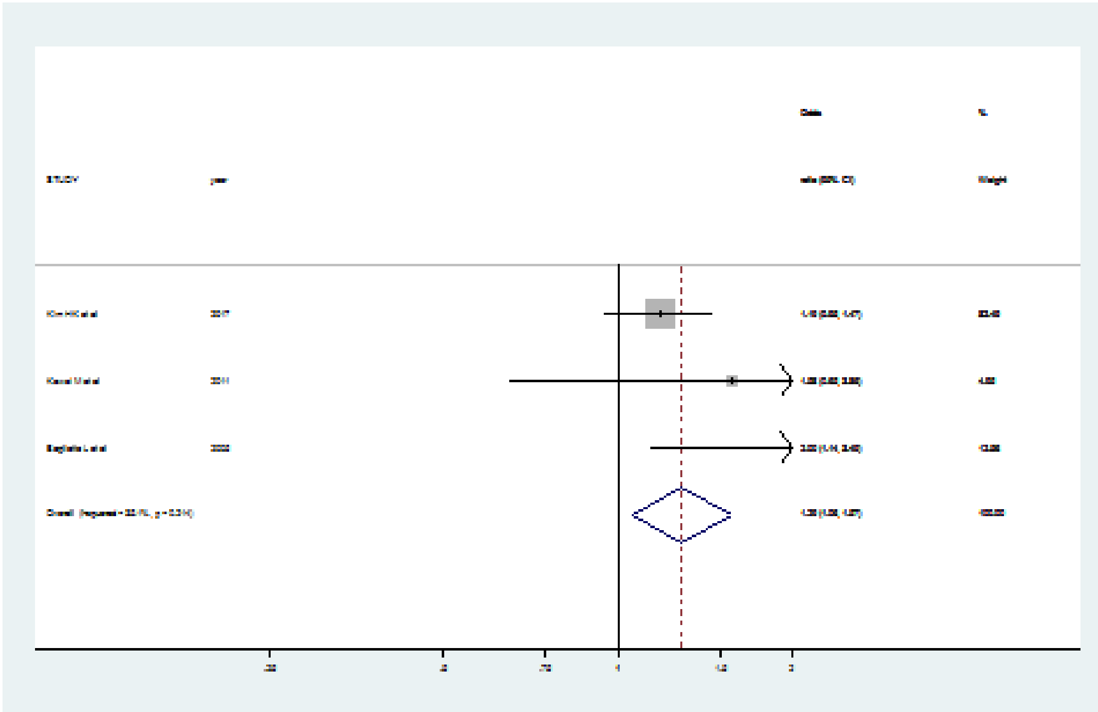


Figure 9. Forest plot Alcohol intake stratified by low folate intake in all women

a) All studies



b) Prospective studies

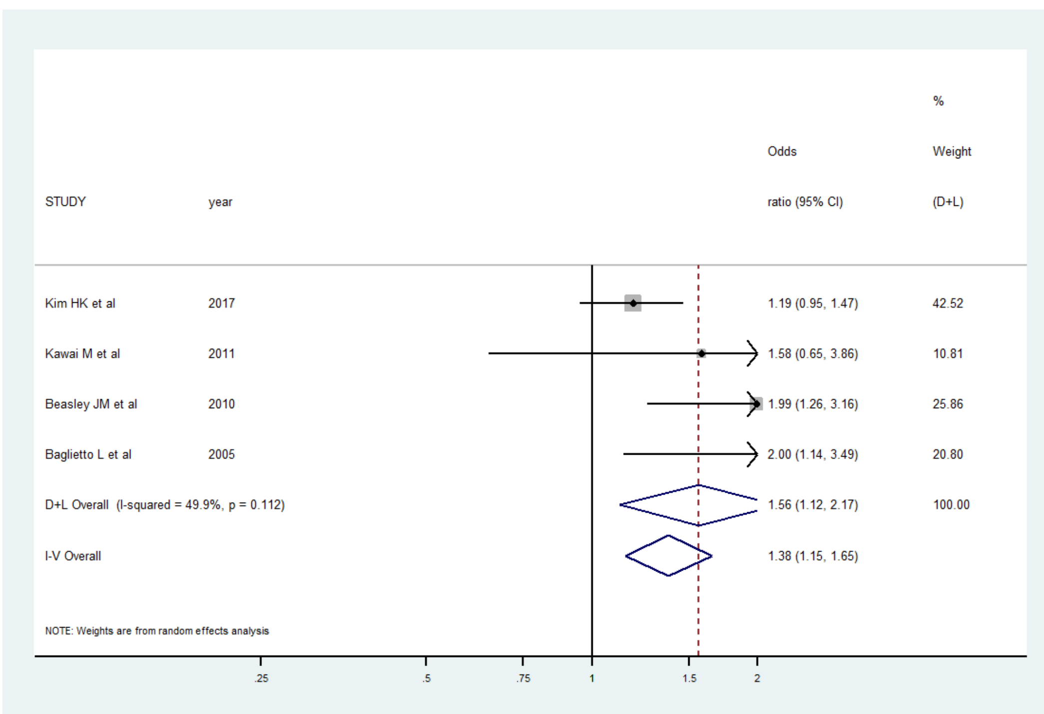
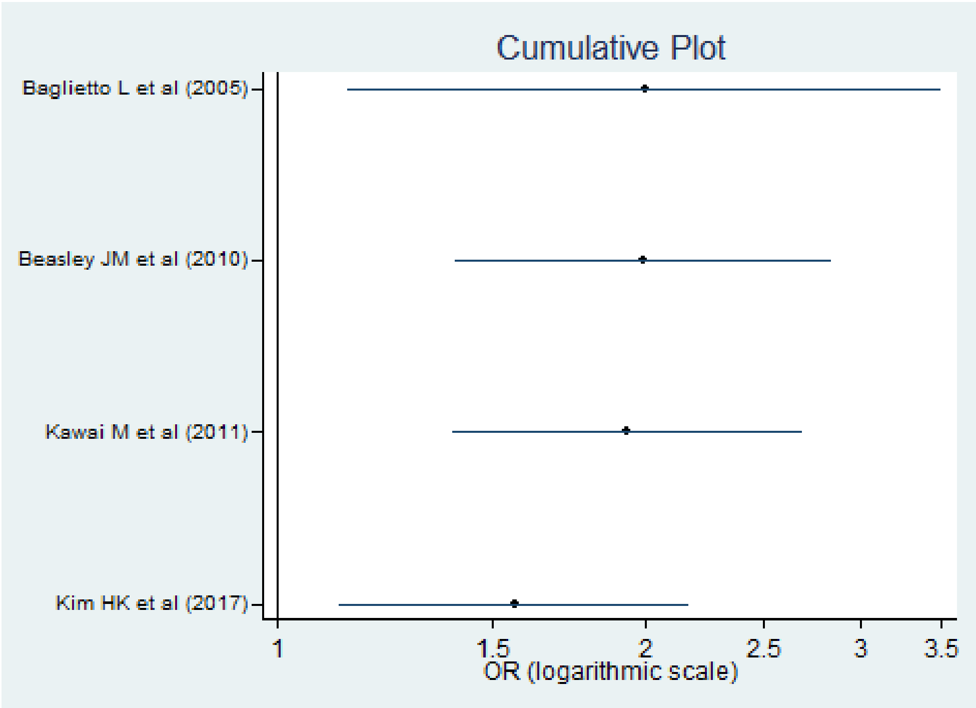


Figure 10. Cumulative plot Alcohol intake stratified by low folate intake in all women

a) All studies



b) Prospective studies

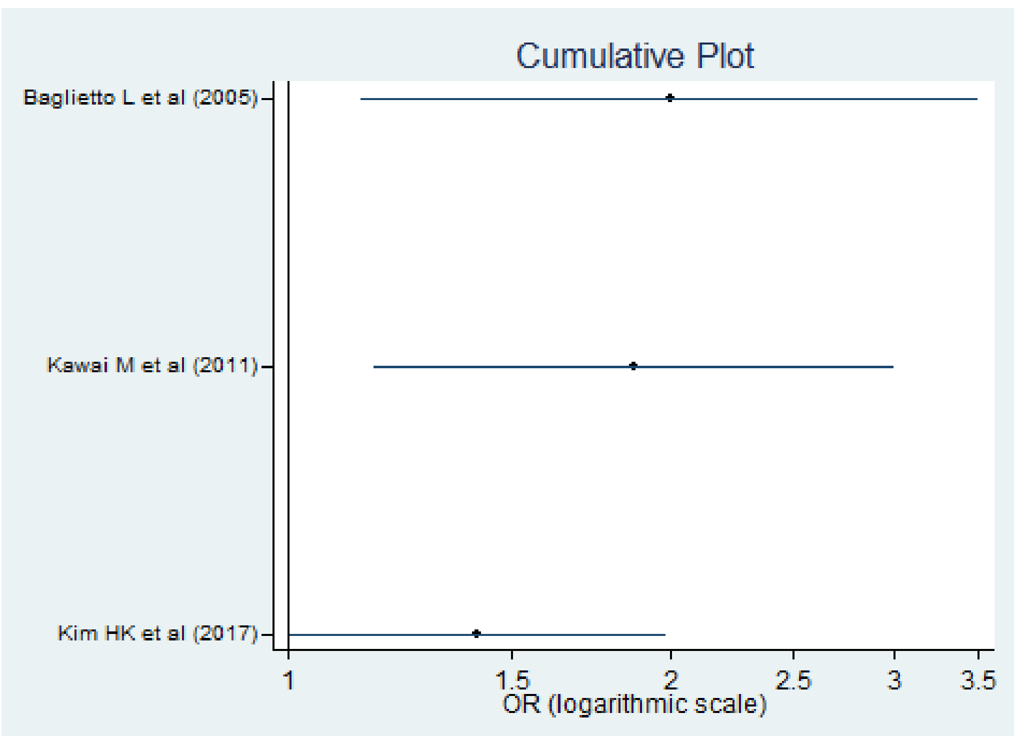
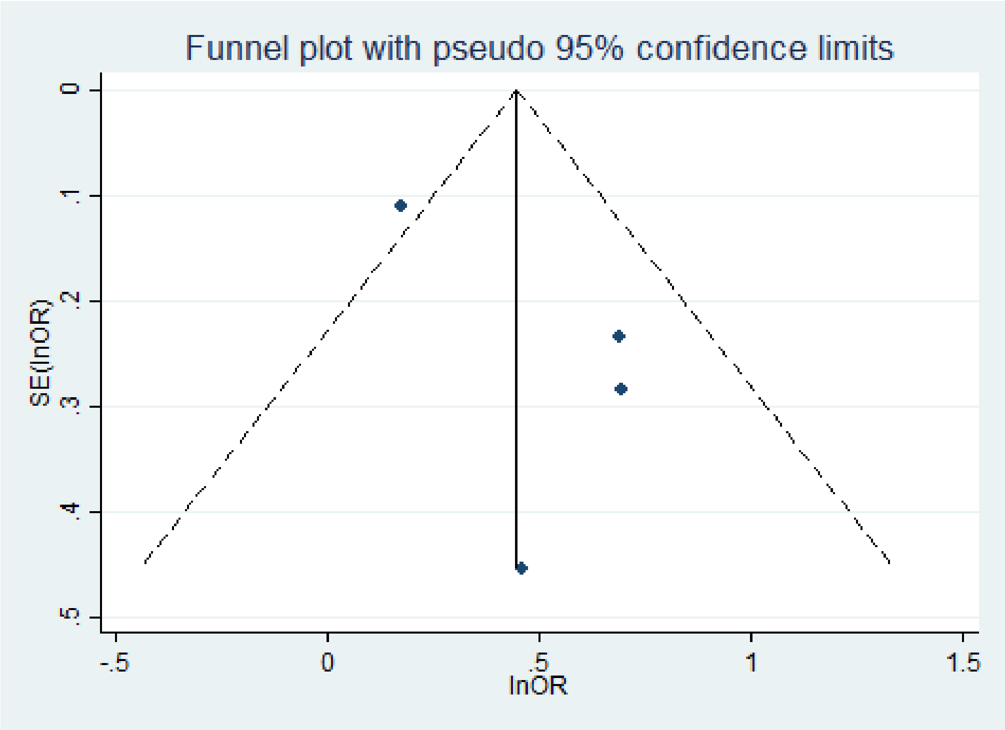


Figure 11. Funnel plot Alcohol intake stratified by low folate intake in all women

a) All studies



b) Prospective studies

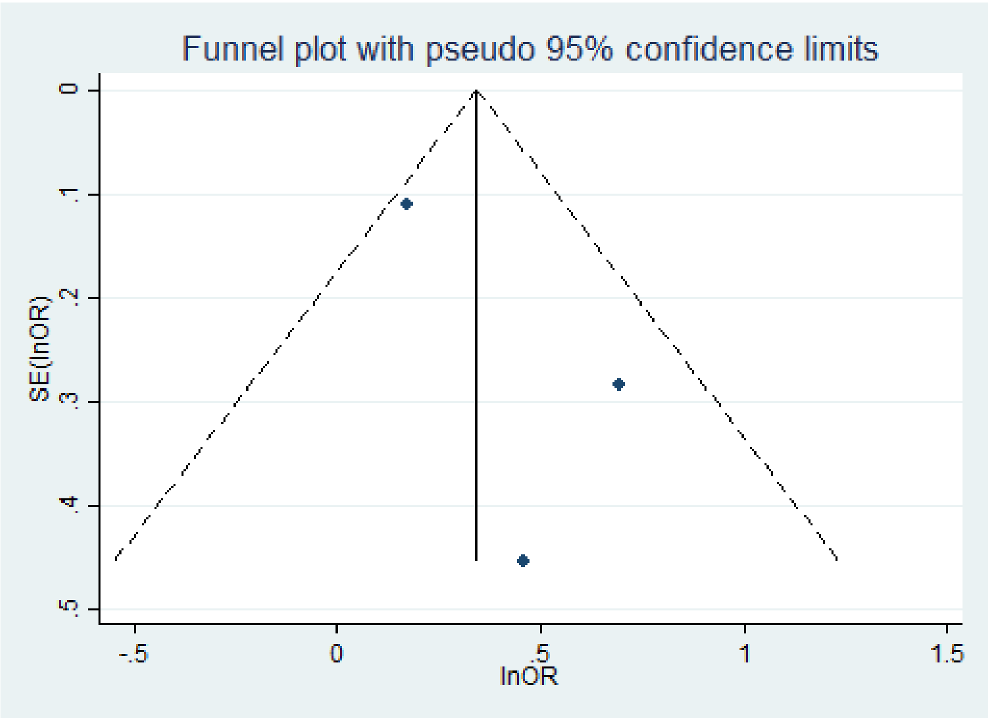
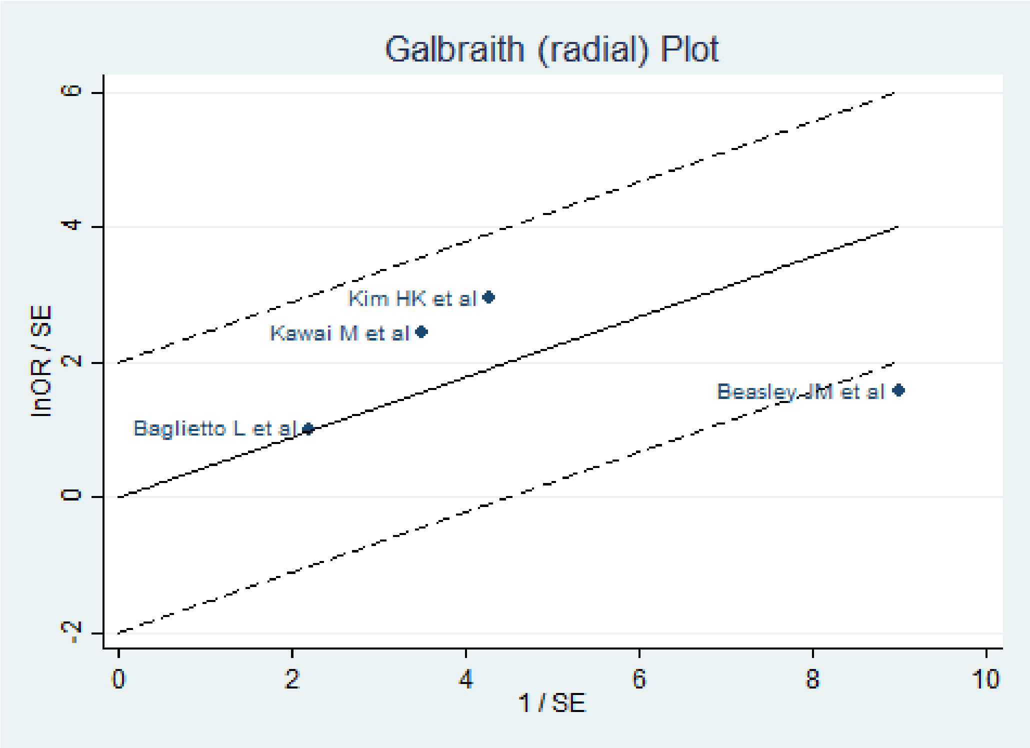


Figure 12. Galbraith plot Alcohol intake stratified by low folate intake in all women

a) All studies



b) Prospective studies

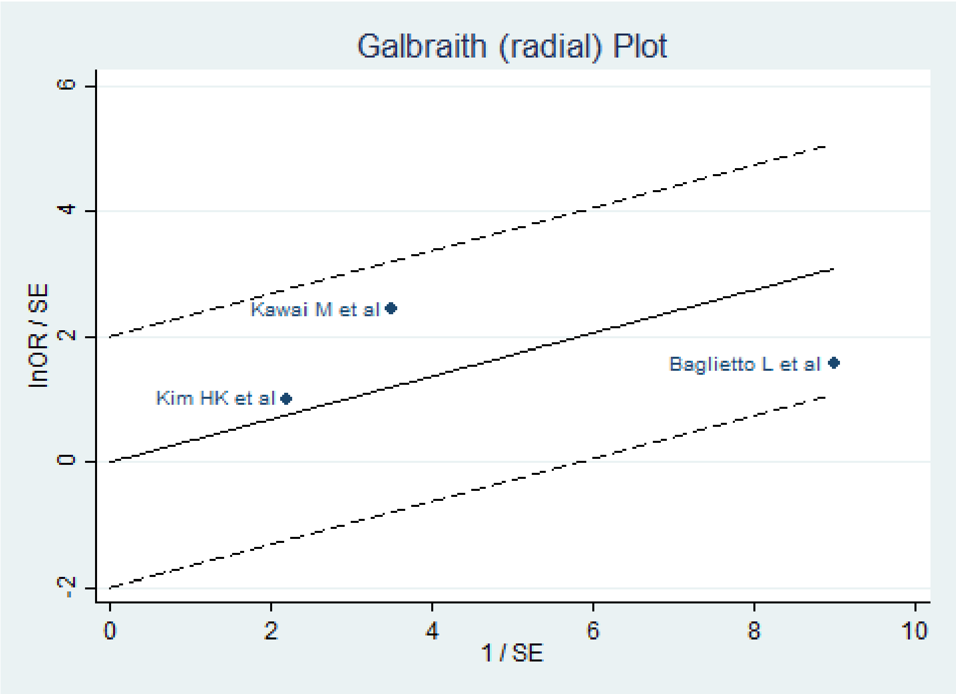


Figure 13. Cumulative plot Alcohol intake stratified by low folate intake in postmenopausal women. All studies.

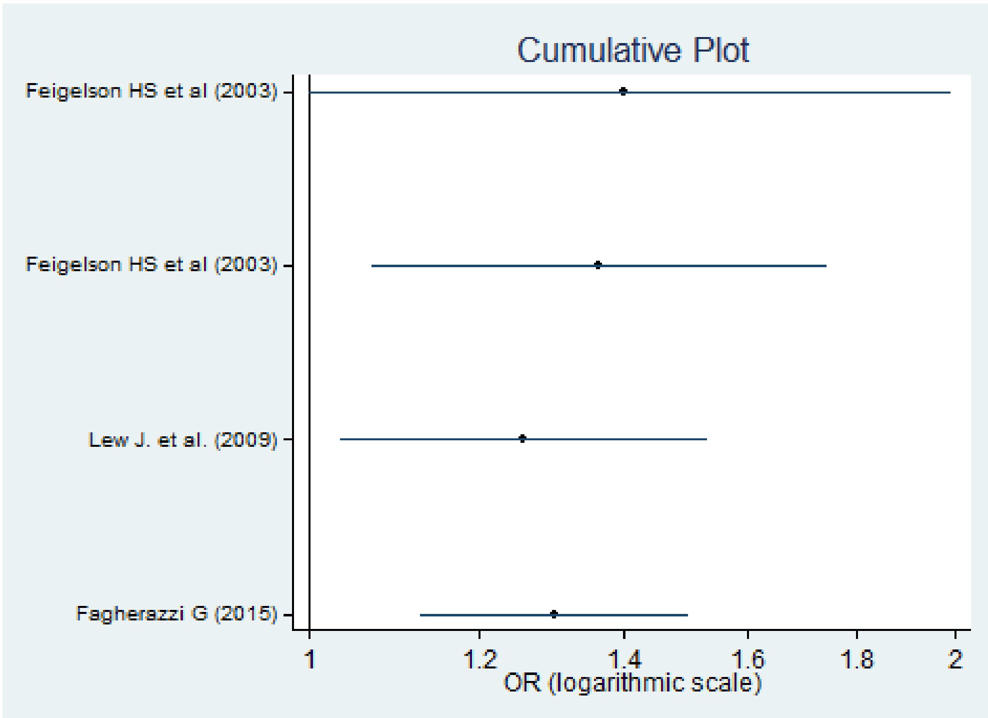


Figure 14. Funnel plot Alcohol intake stratified by low folate intake in postmenopausal women. All studies

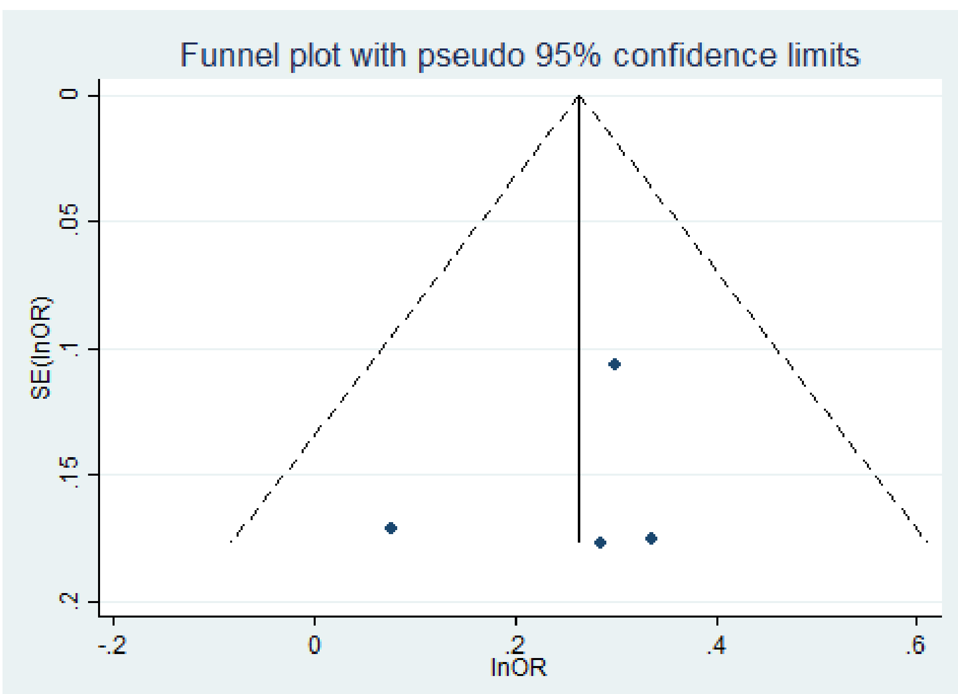


Figure 15. Galbraith plot Alcohol intake stratified by low folate intake in postmenopausal women. All studies

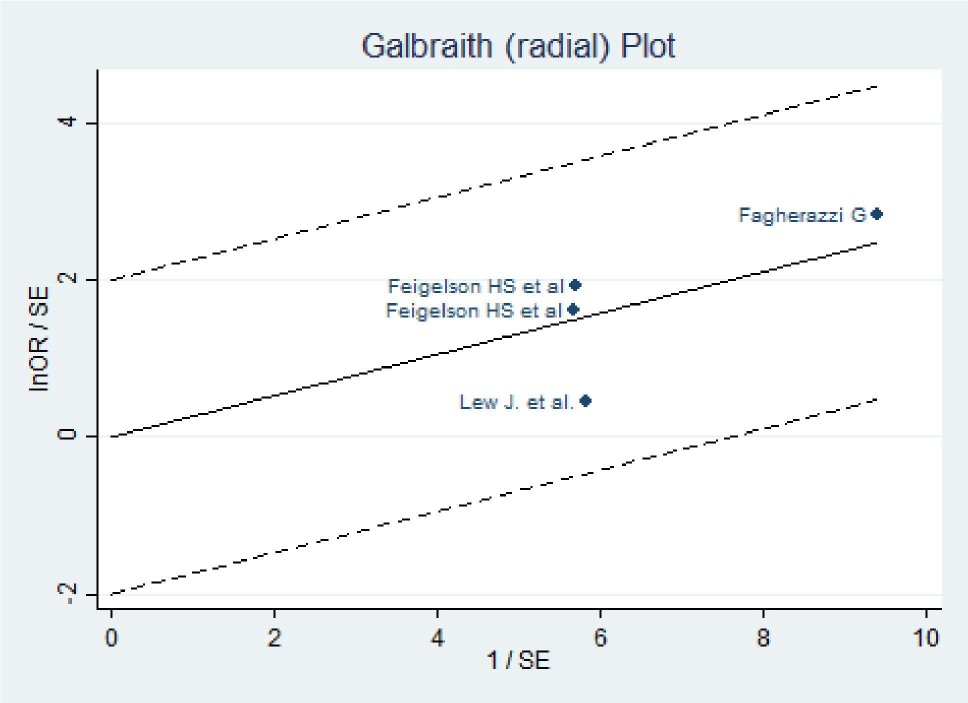
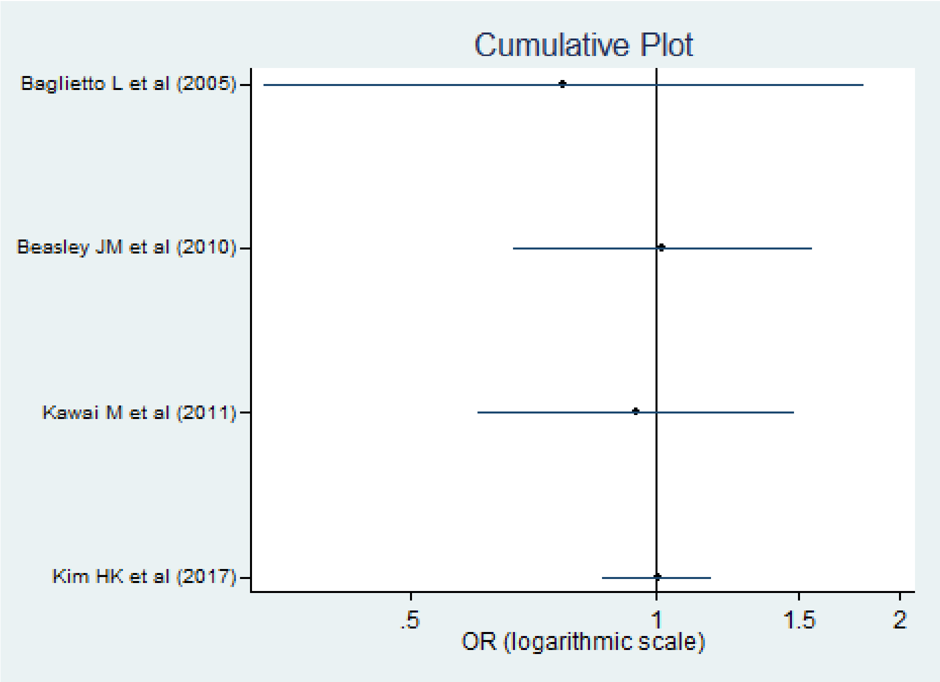


Figure 17. Cumulative plot Alcohol intake stratified by high folate intake in all women.

a) All studies



b) Prospective studies

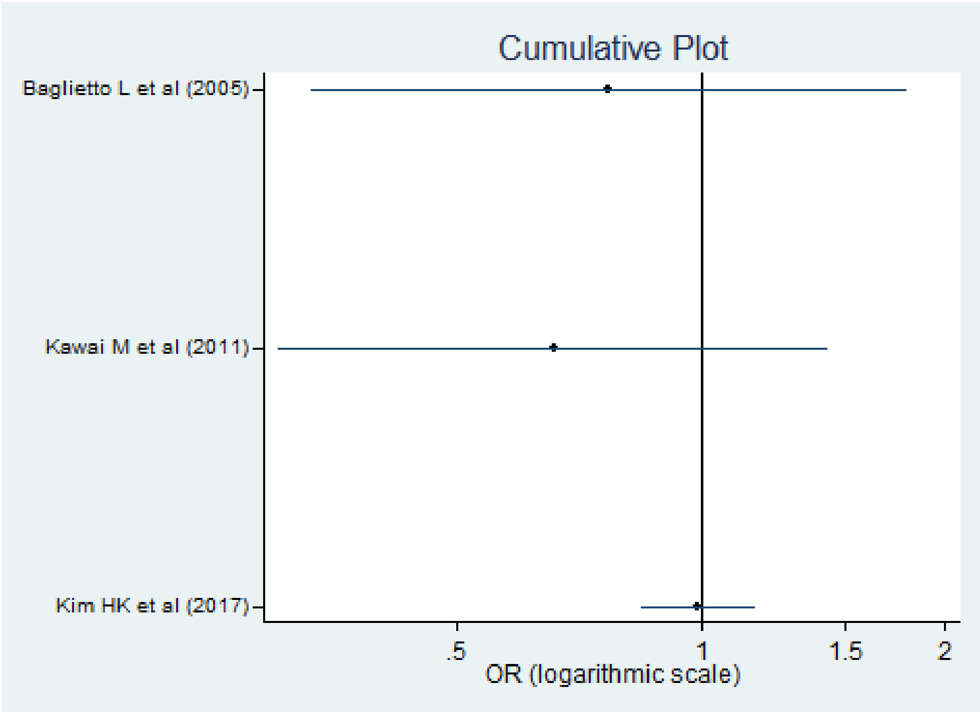
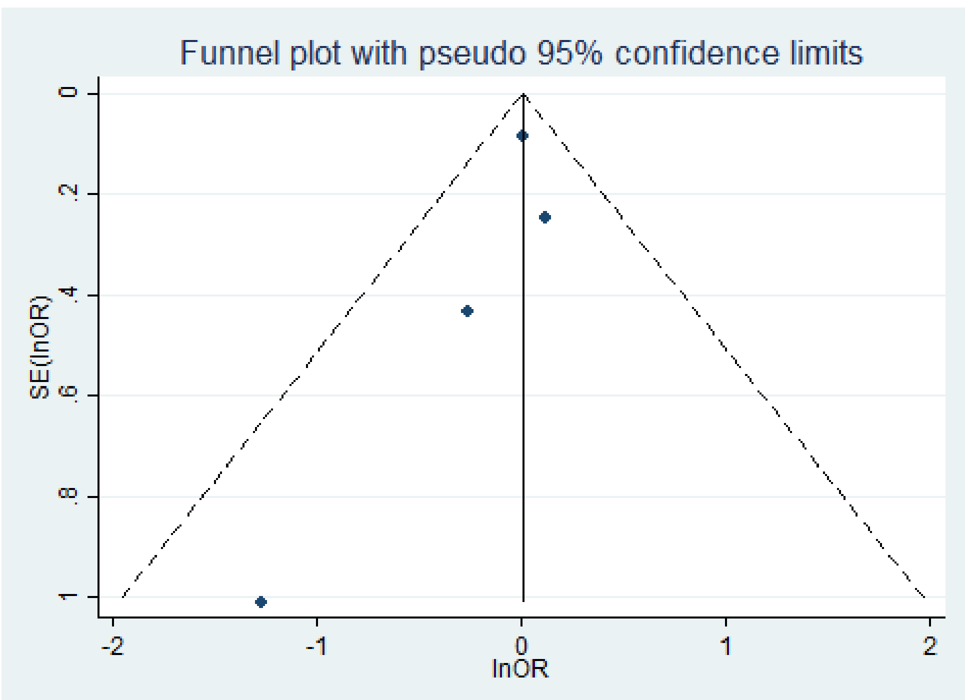


Figure 18. Funnel plot Alcohol intake stratified by high folate intake in all women.

a) All studies



b) Prospective studies

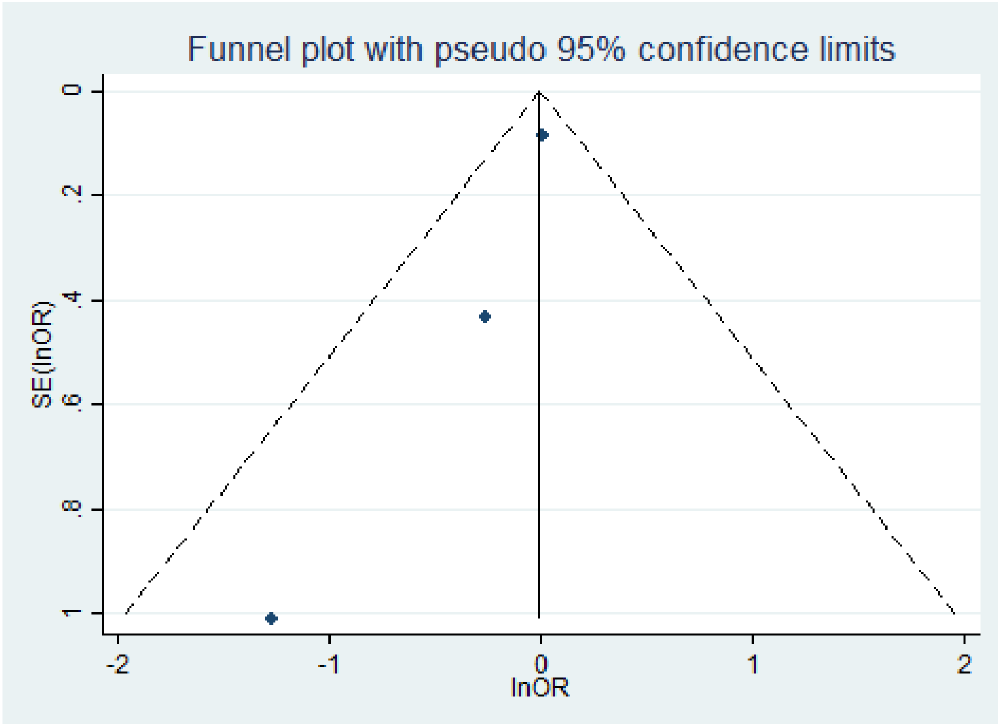
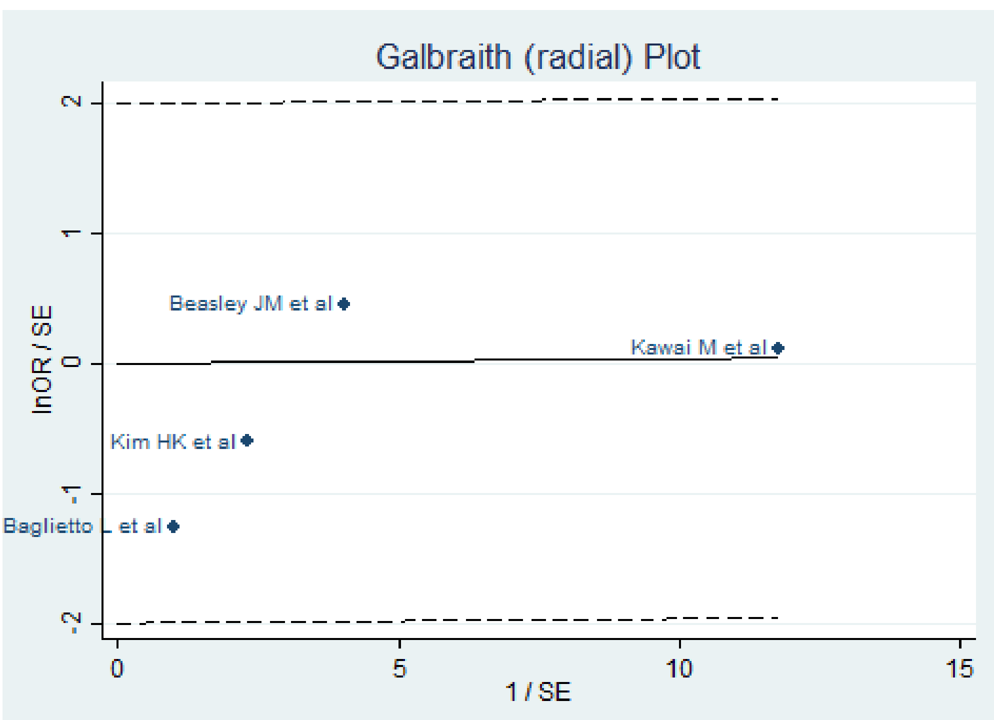


Figure 19. Galbraith plot Alcohol intake stratified by high folate intake in all women

a) All studies



b) Prospective studies

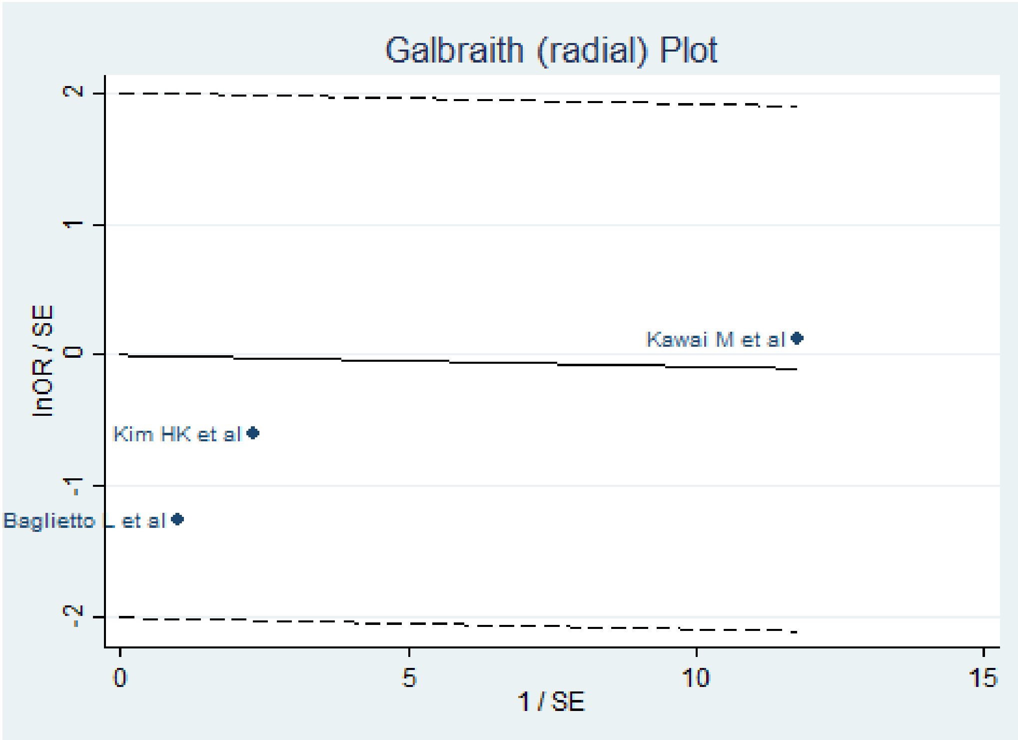


Figure 20. Forest plot Alcohol intake stratified by high dietary folate intake in all women. All studies

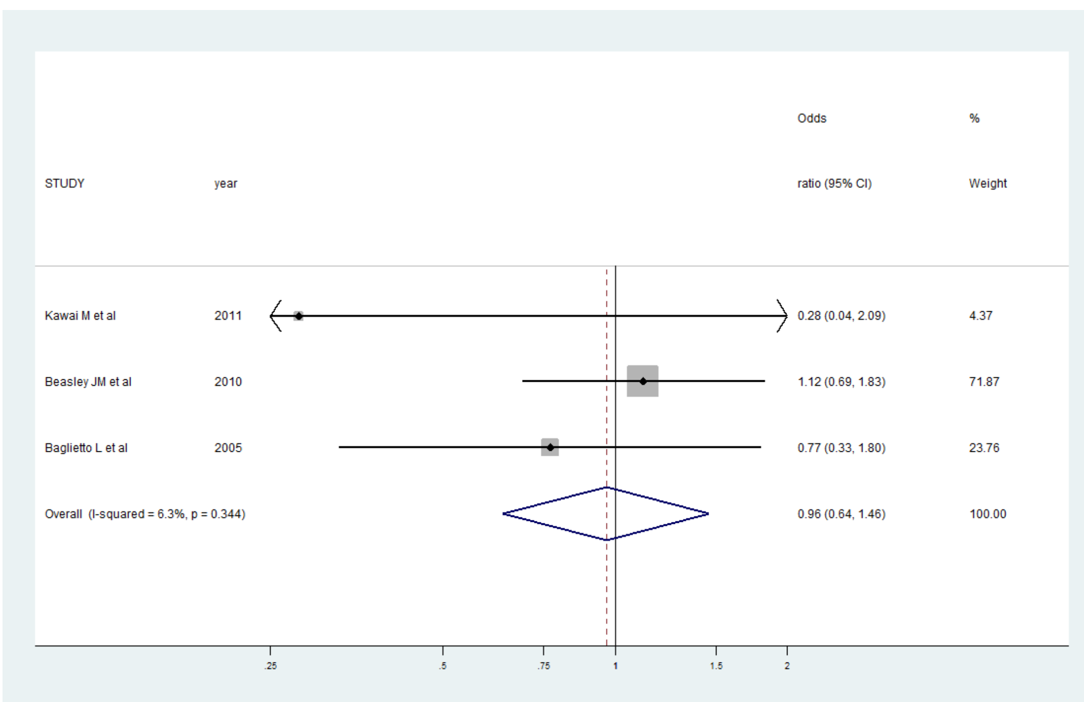


Figure 21. Cumulative plot Alcohol intake stratified by high dietary folate intake in all women. All studies

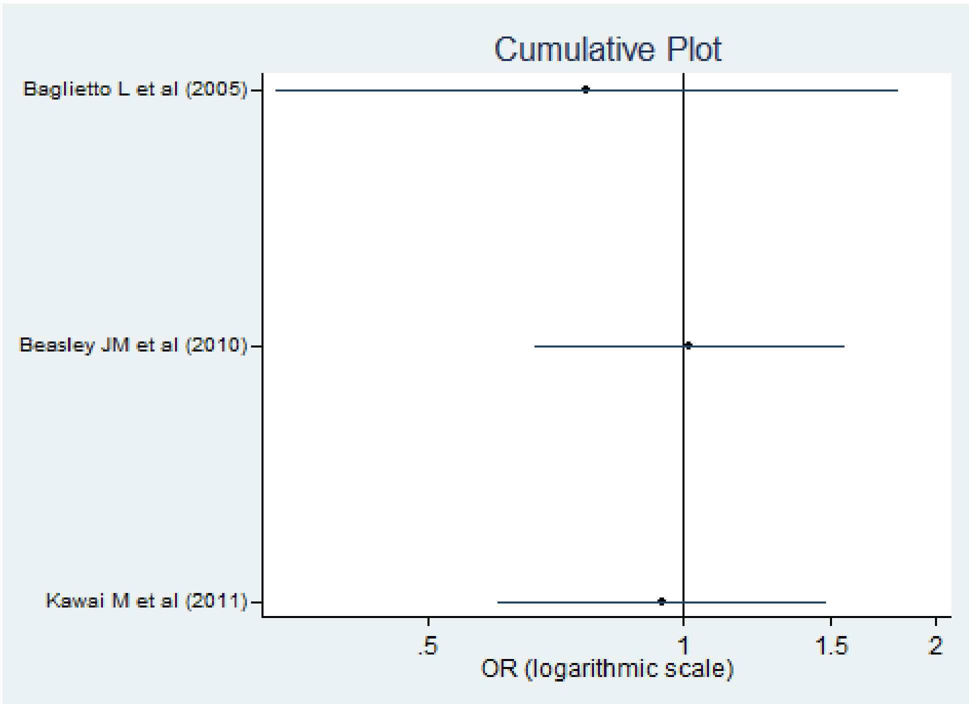


Figure 22. Funnel plot Alcohol intake stratified by high dietary folate intake in all women. All studies

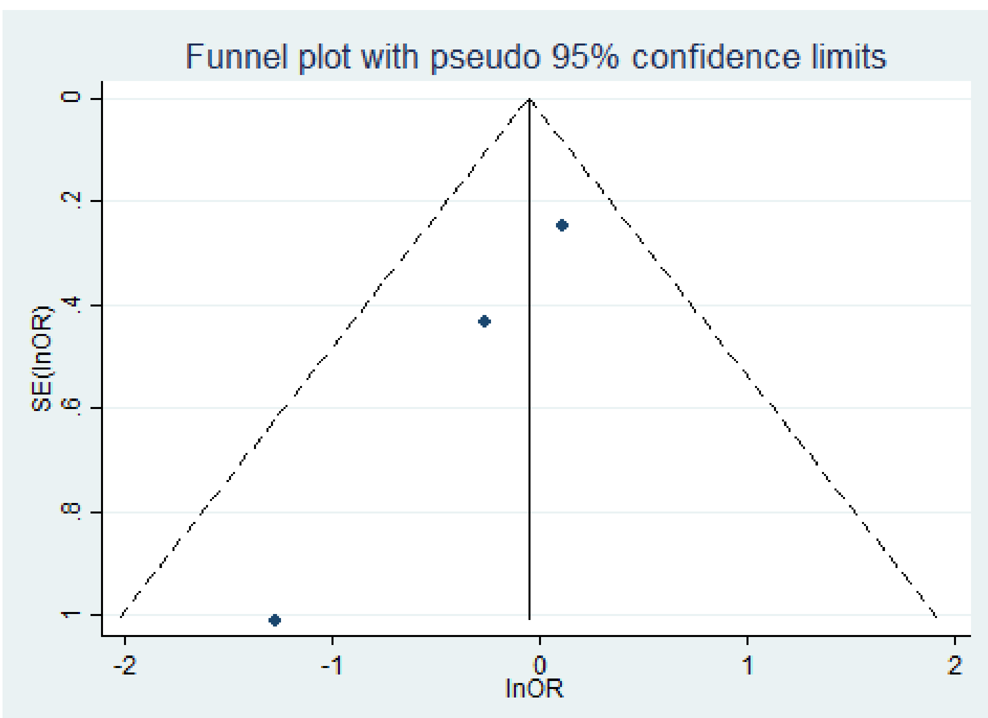


Figure 23. Galbraith plot Alcohol intake stratified by high dietary folate intake in all women. All studies

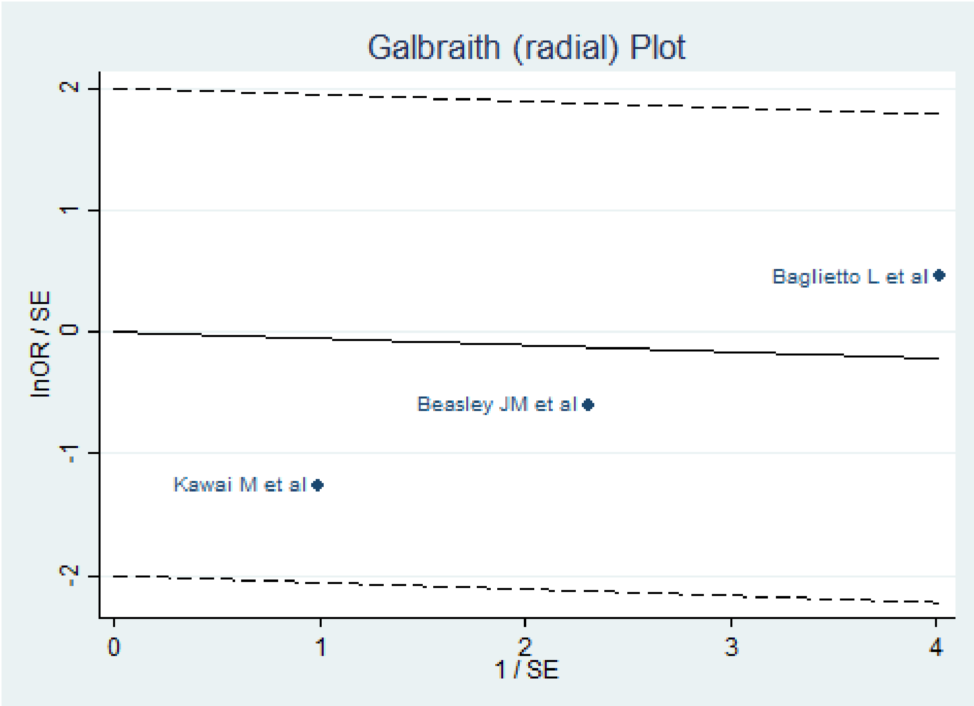


Figure 24. Cumulative plot Alcohol intake stratified by high folate intake in postmenopausal women. All studies

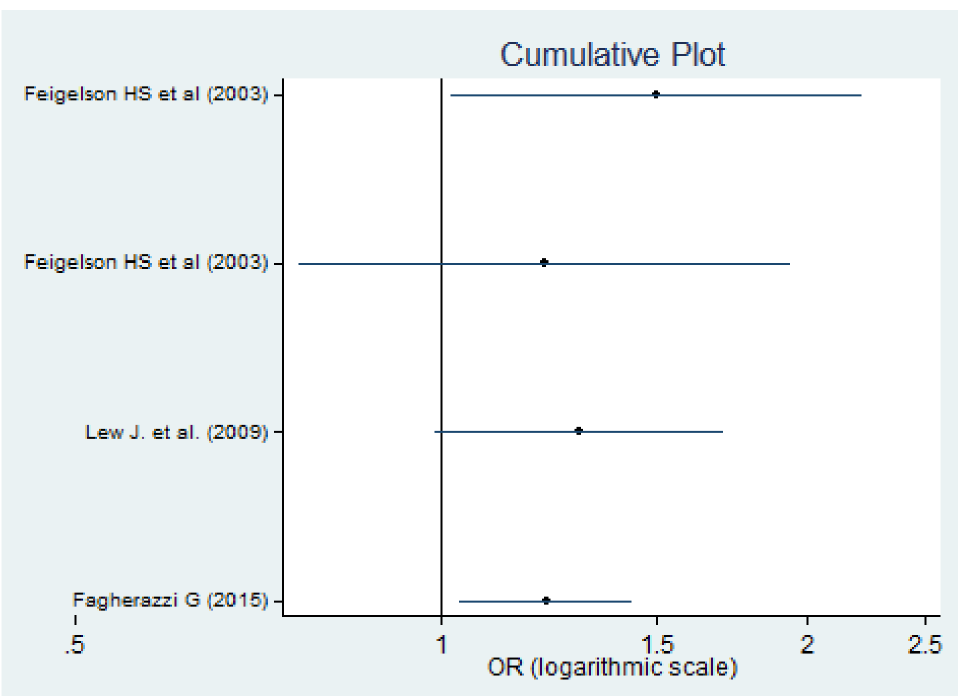


Figure 25. Funnel plot Alcohol intake stratified by high folate intake in postmenopausal women. All studies

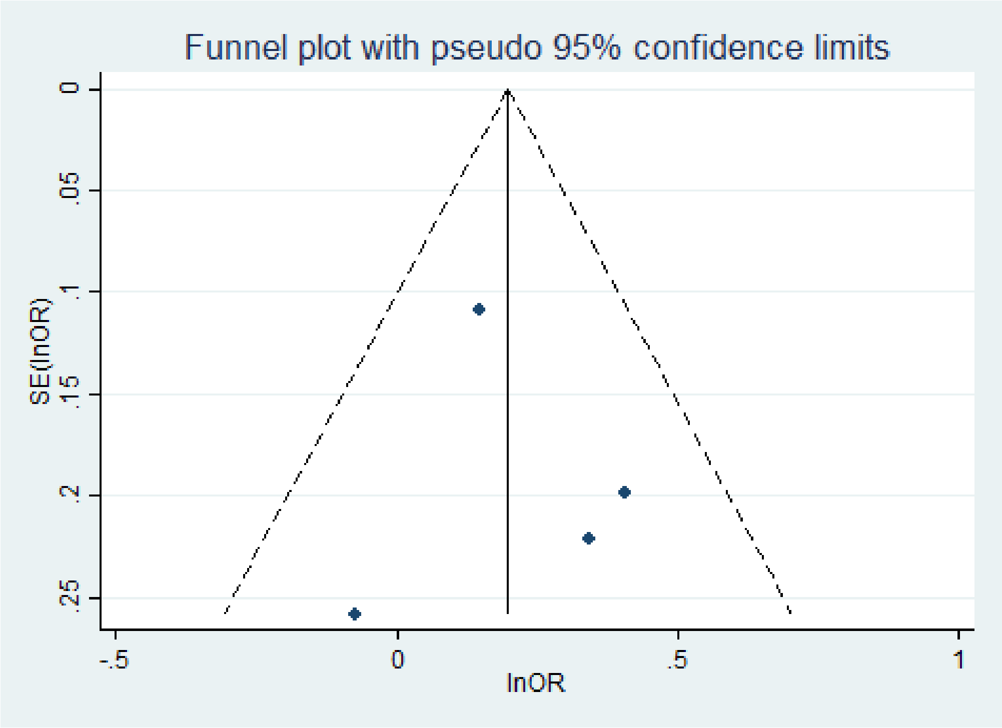


Figure 26. Galbraith plot Alcohol intake stratified by high folate intake in postmenopausal women. All studies

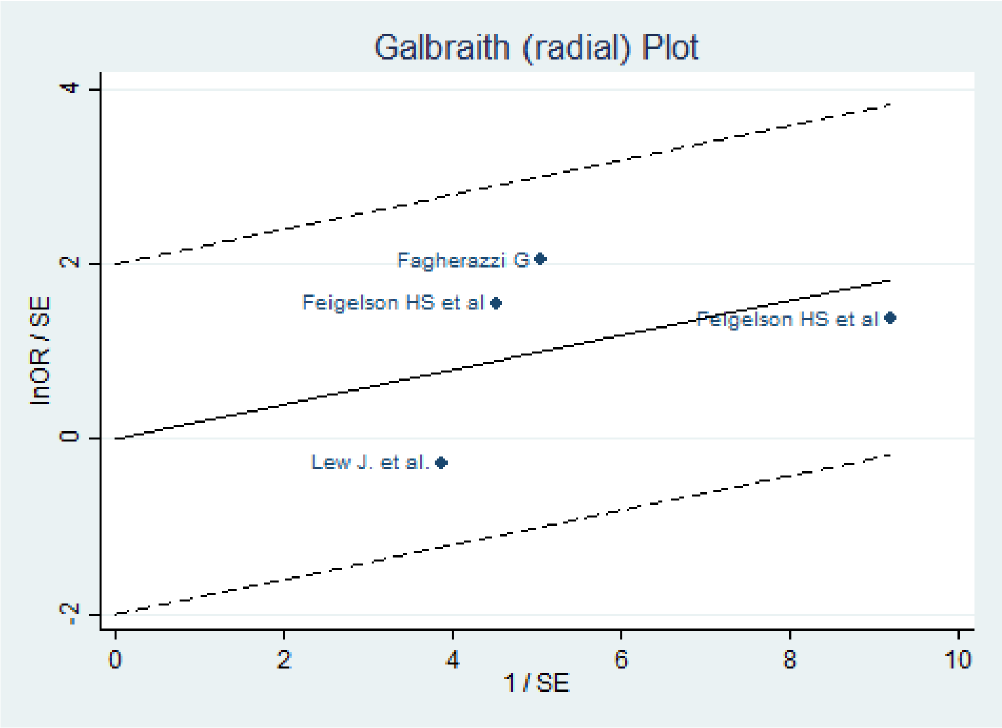


Figure 27. Forest plot Alcohol intake stratified by high total folate intake in postmenopausal women. All studies

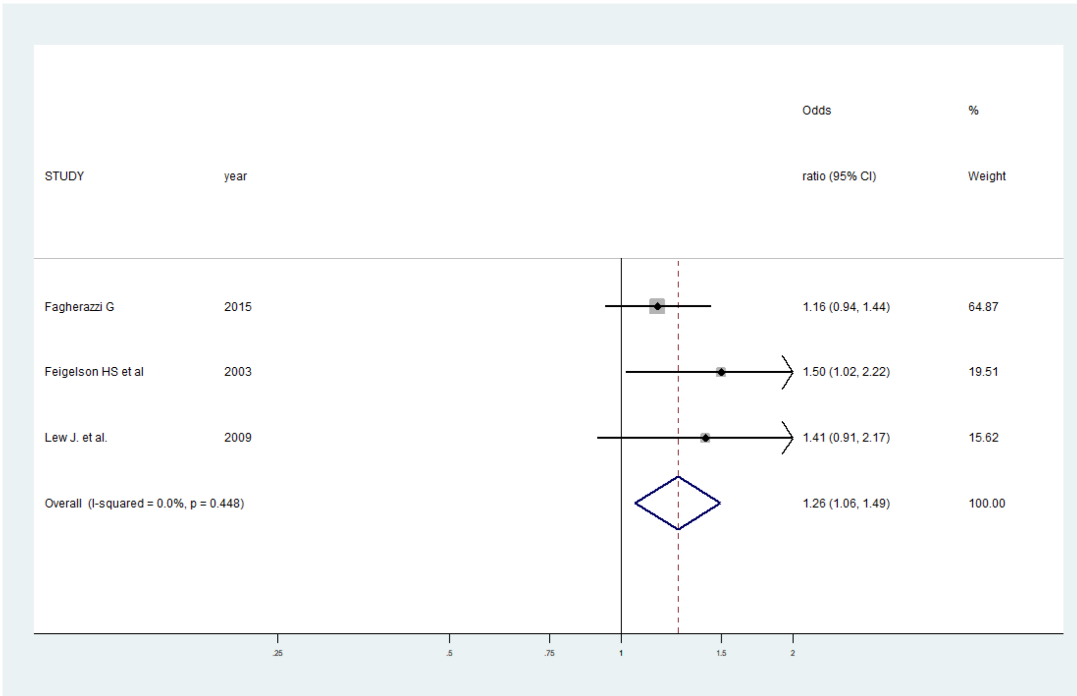


Figure 28. Cumulative plot Alcohol intake stratified by high total folate intake in postmenopausal women. All studies

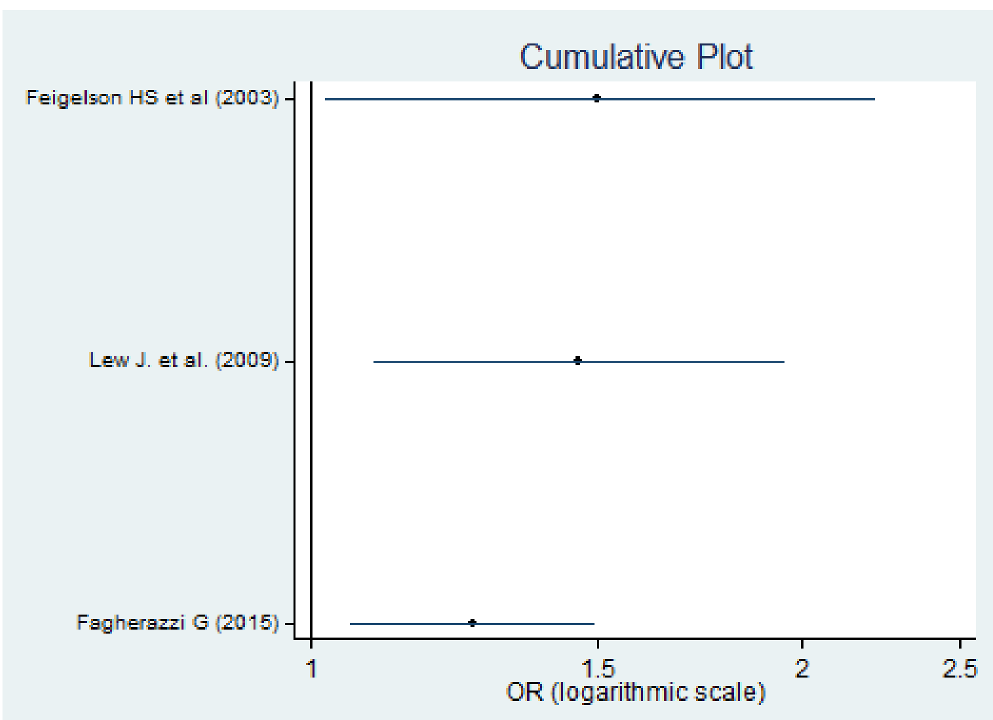


Figure 29. Funnel plot Alcohol intake stratified by high total folate intake in postmenopausal women. All studies

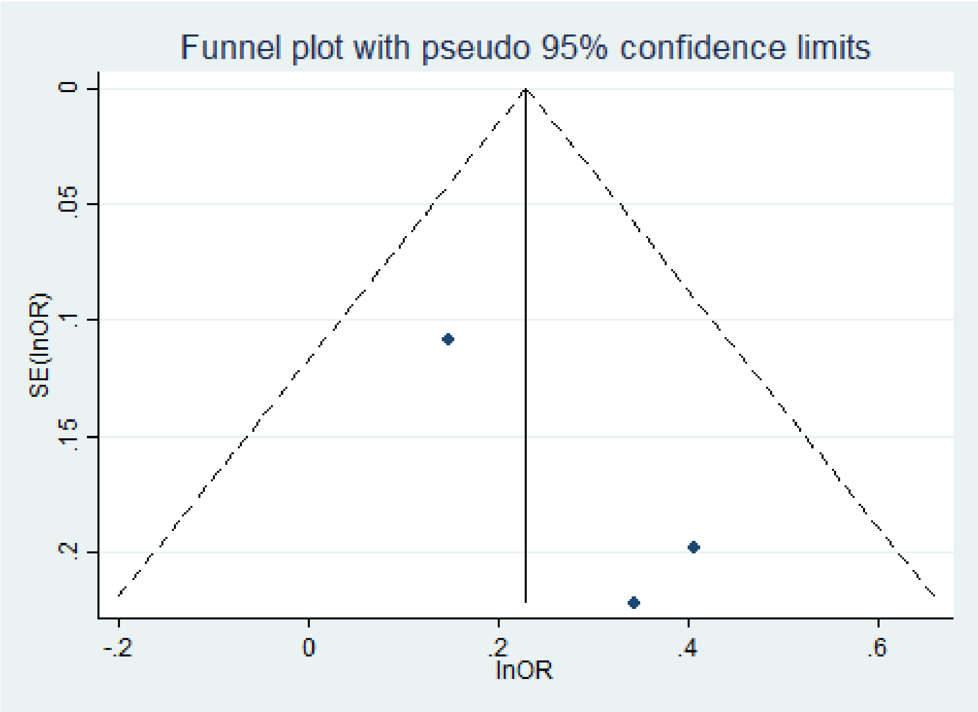
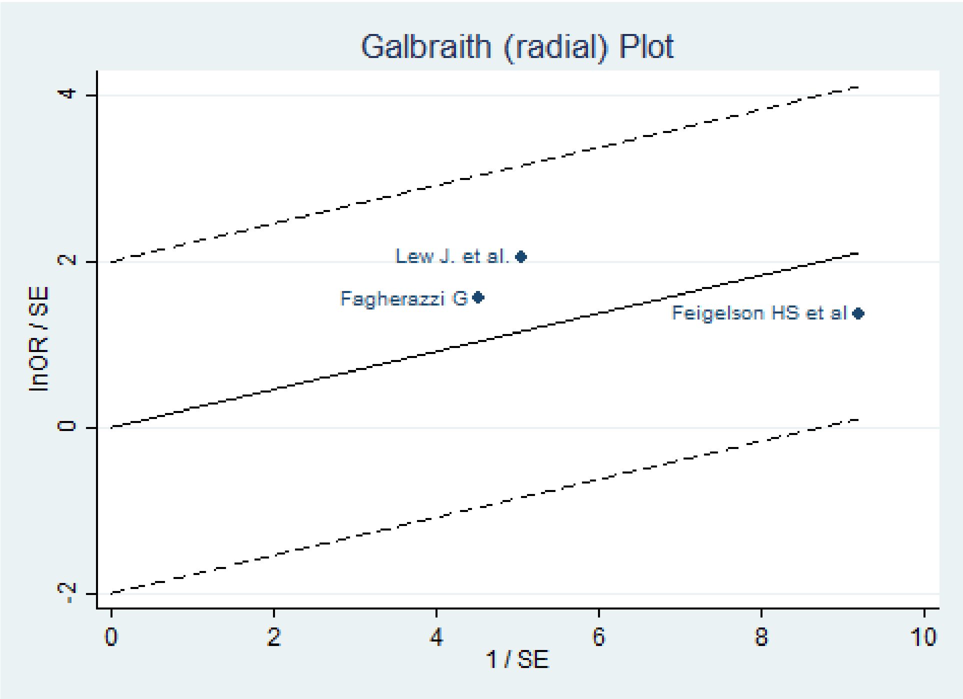


Figure 30. Galbraith plot Alcohol intake stratified by high total folate intake in postmenopausal women. All studies



Folate intake and breast cancer

Figure 31. Forest plot folate intake in all women.

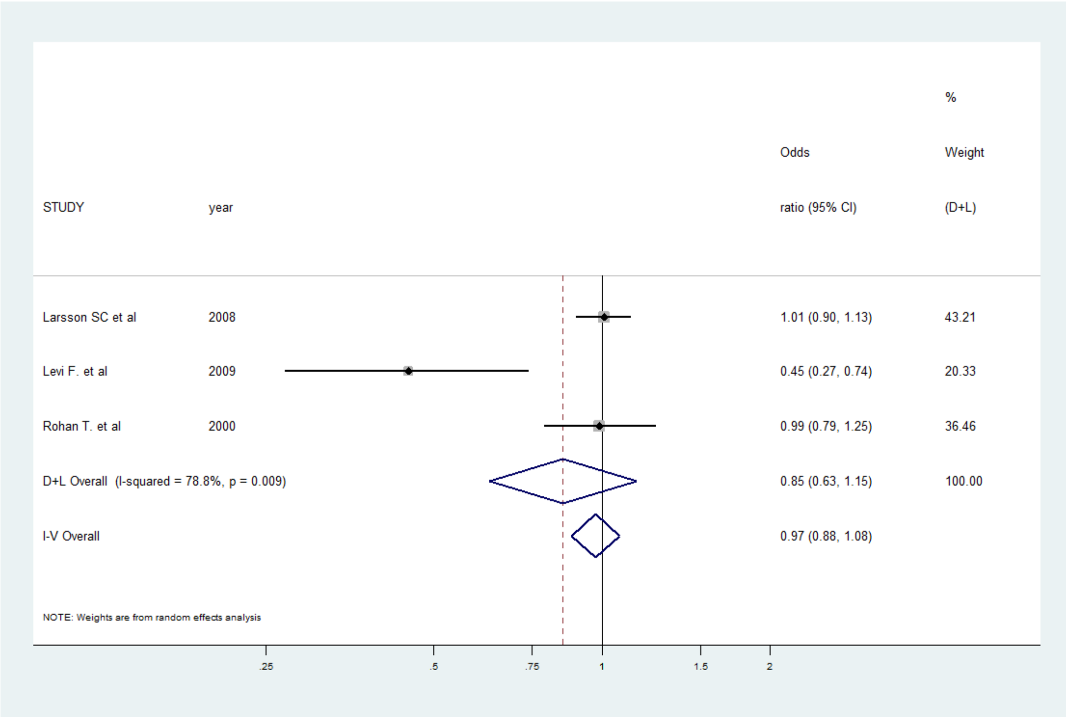


Figure 32. Cumulative plot folate intake in all women. All studies

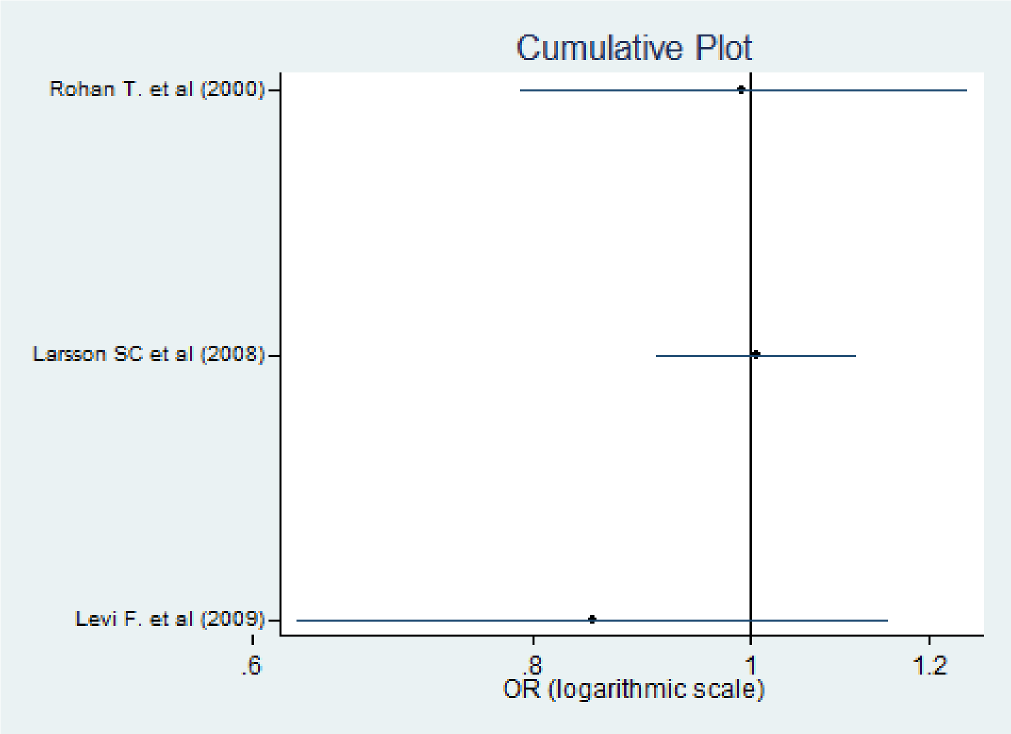


Figure 33. Funnel plot folate intake in all women. All studies

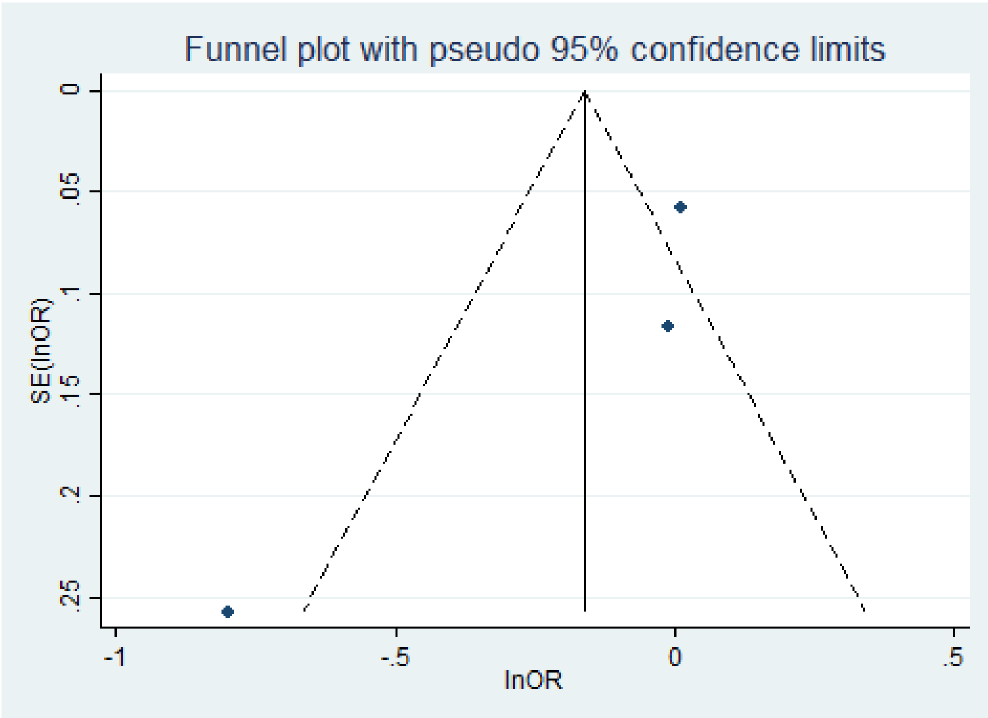


Figure 34. Galbraith plot folate intake in all women. All studies

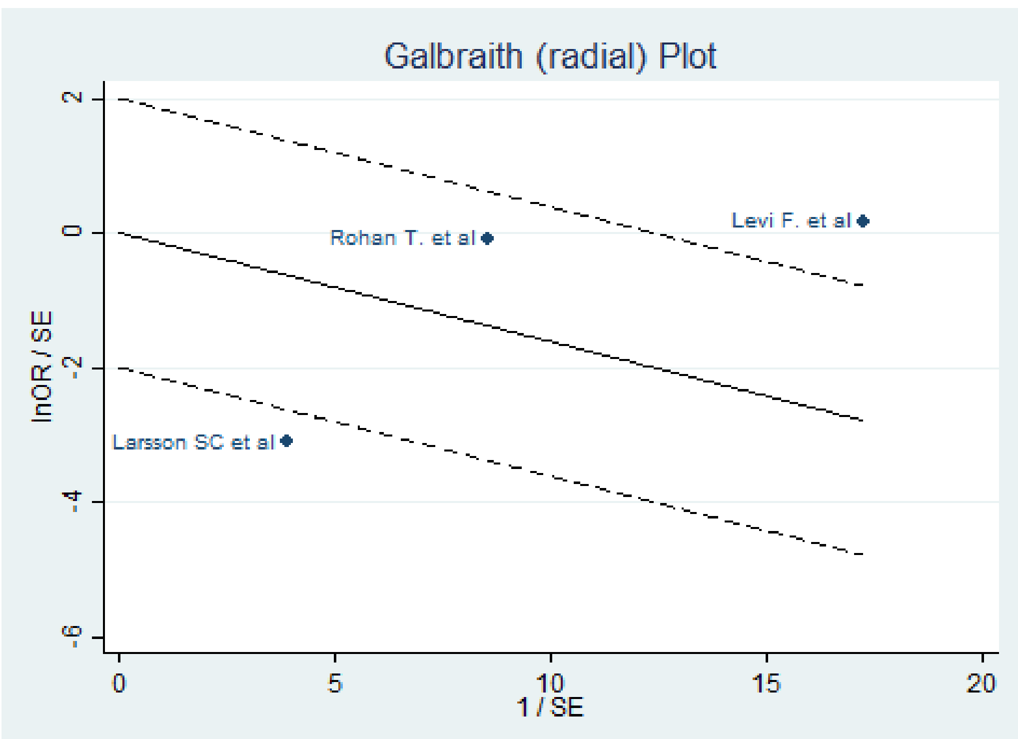


Figure 35. Forest plot folate intake in postmenopausal women. All studies

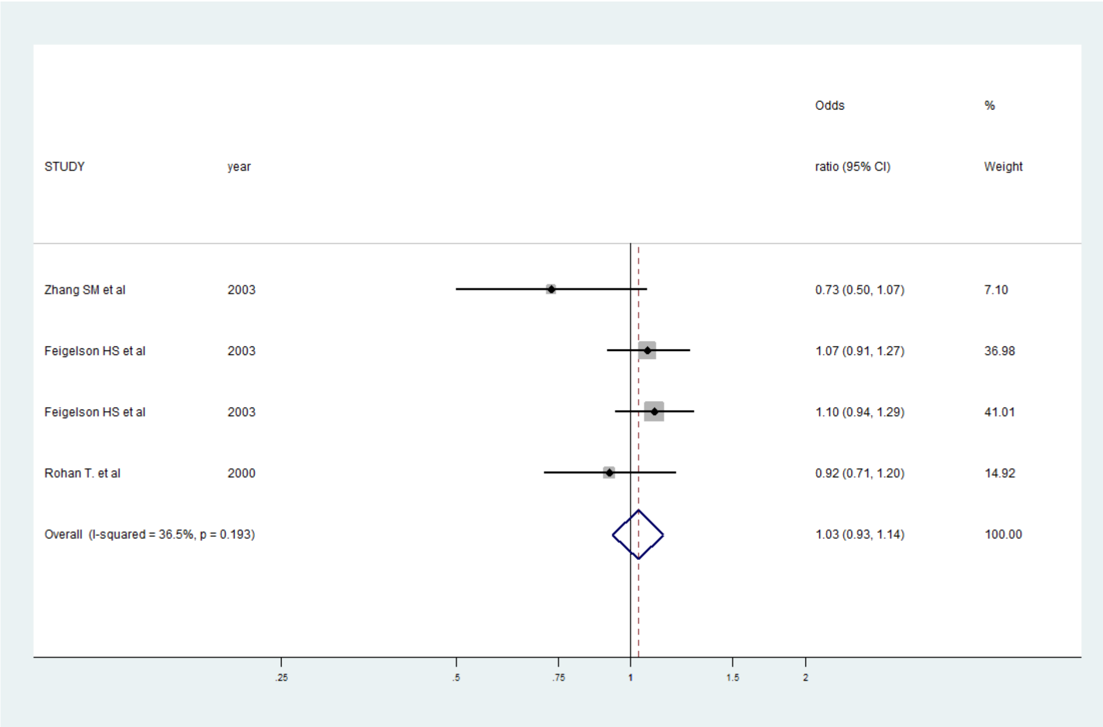


Figure 36. Cumulative plot folate intake in postmenopausal women. All studies

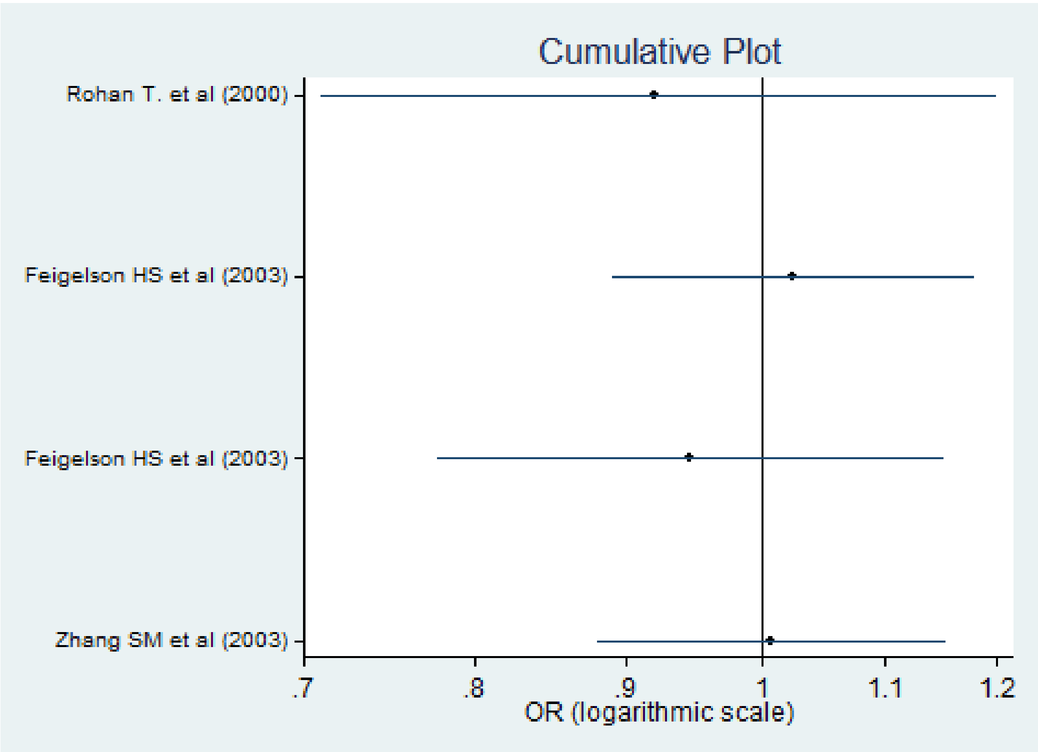


Figure 37. Funnel plot folate intake in postmenopausal women. All studies

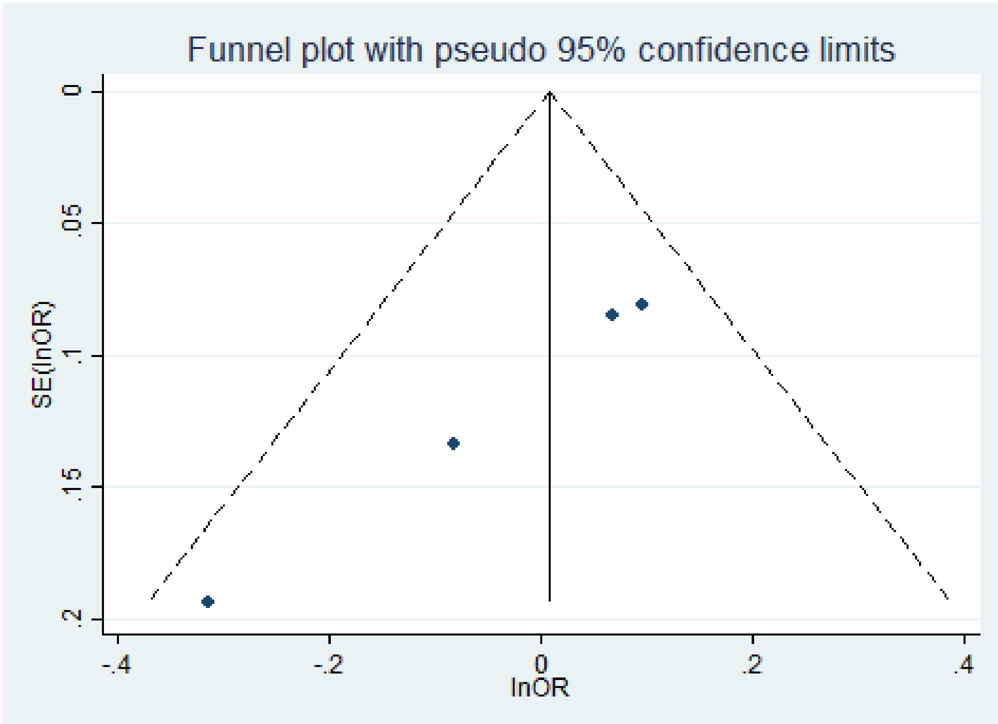


Figure 38. Galbraith plot folate intake in postmenopausal women. All studies

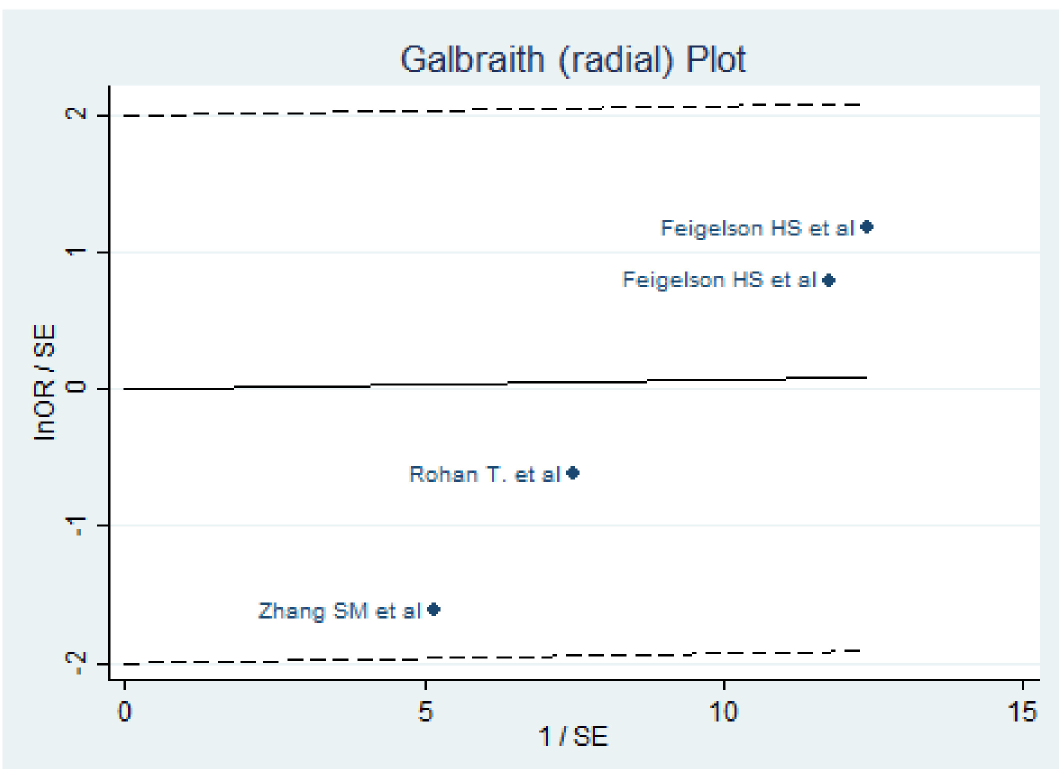


Figure 39. Forest plot folate intake stratified by low alcohol intake in all women. All studies

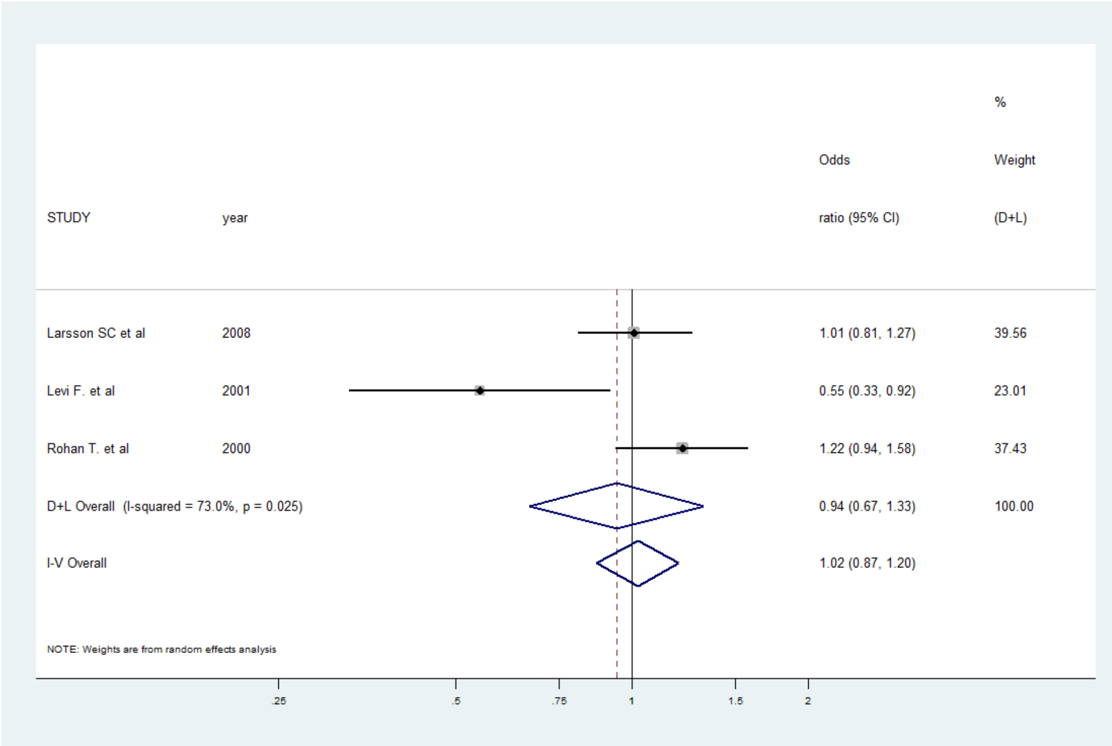


Figure 40. Cumulative plot folate intake stratified by low alcohol intake in all women. All studies

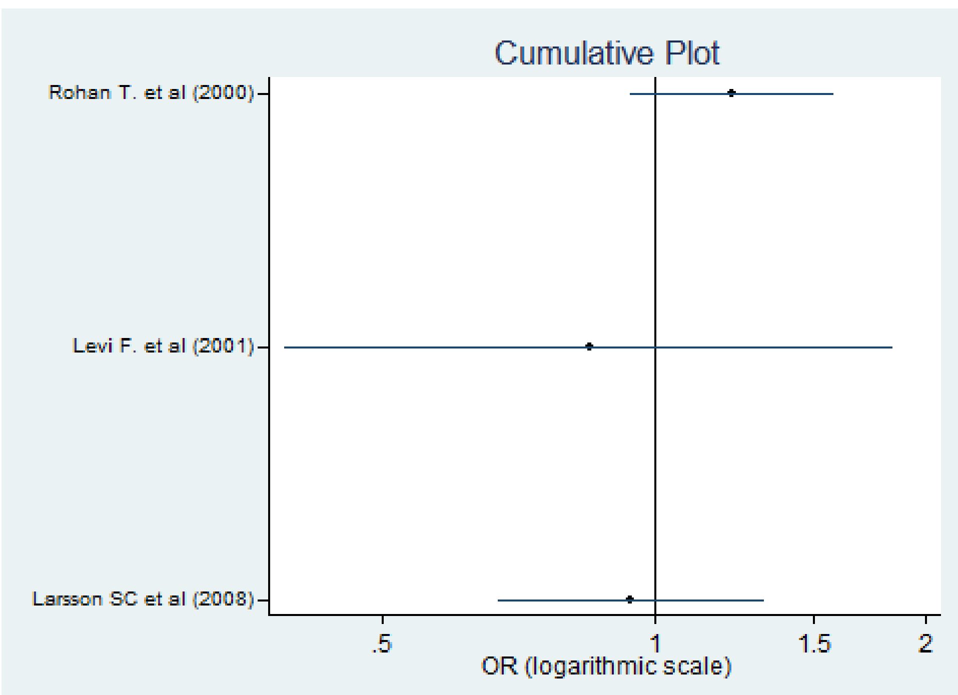


Figure 41. Funnel plot folate intake stratified by low alcohol intake in all women. All studies

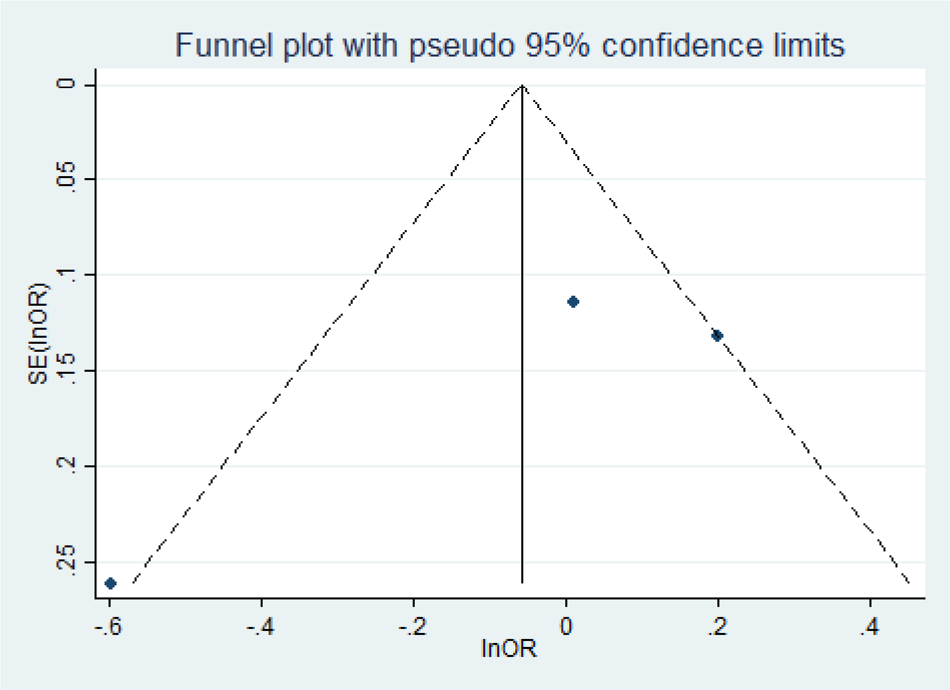


Figure 42. Galbraith plot folate intake stratified by low alcohol intake in all women. All studies

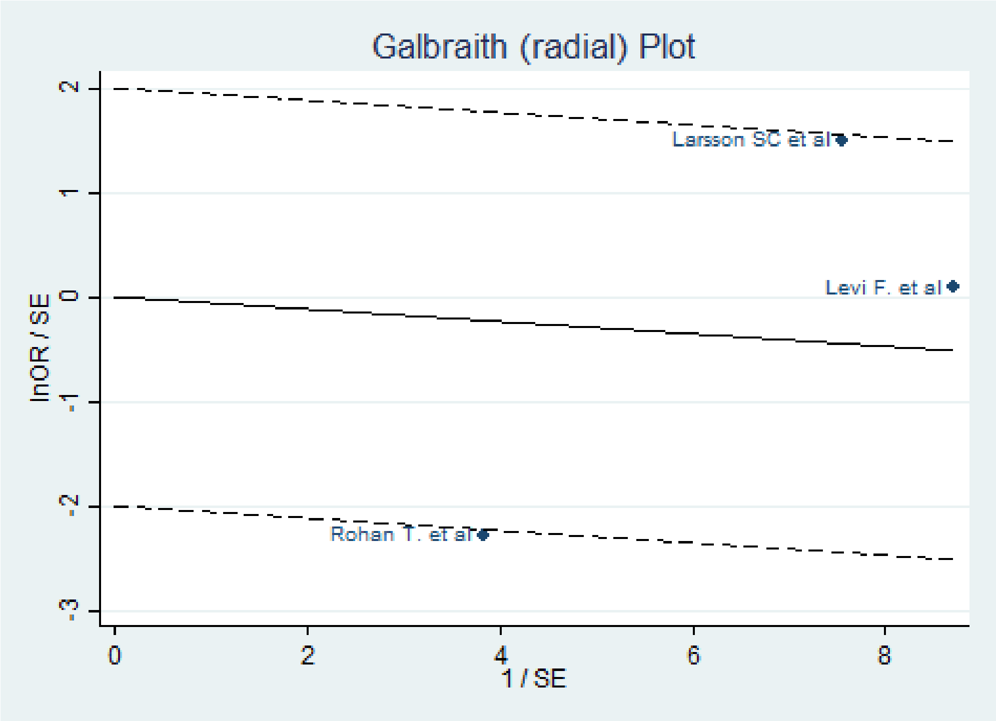


Figure 43. Forest plot folate intake stratified by high alcohol intake in all women. All studies

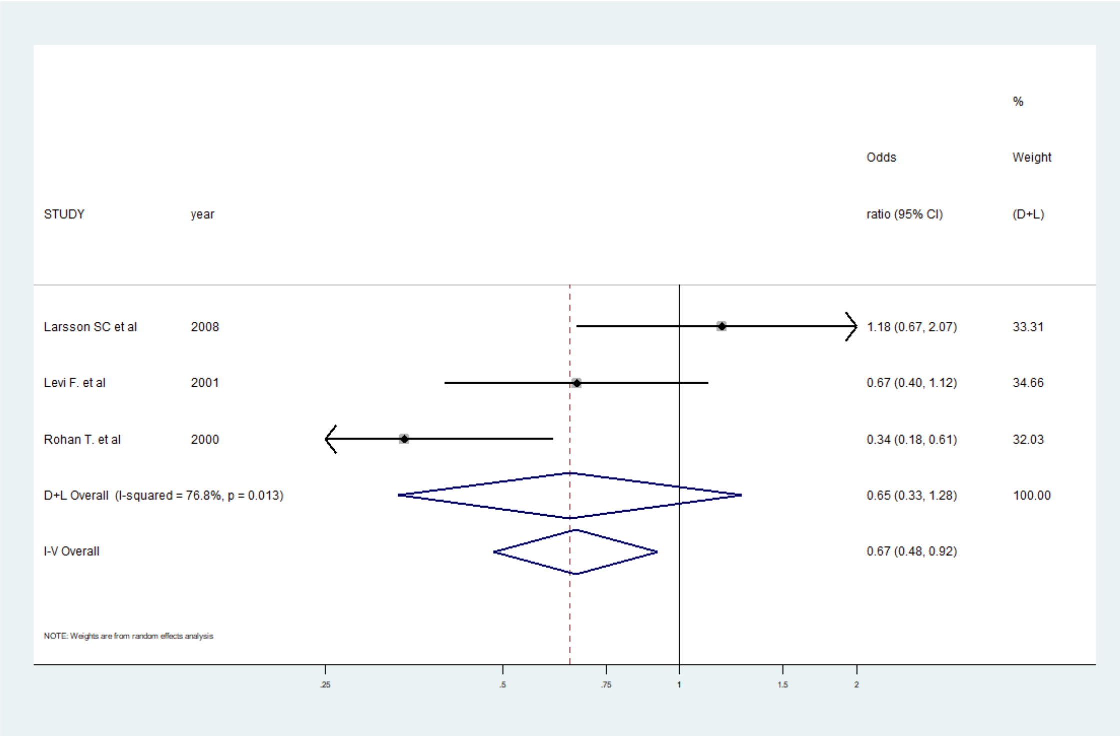


Figure 44. Cumulative plot folate intake stratified by high alcohol intake in all women. All studies

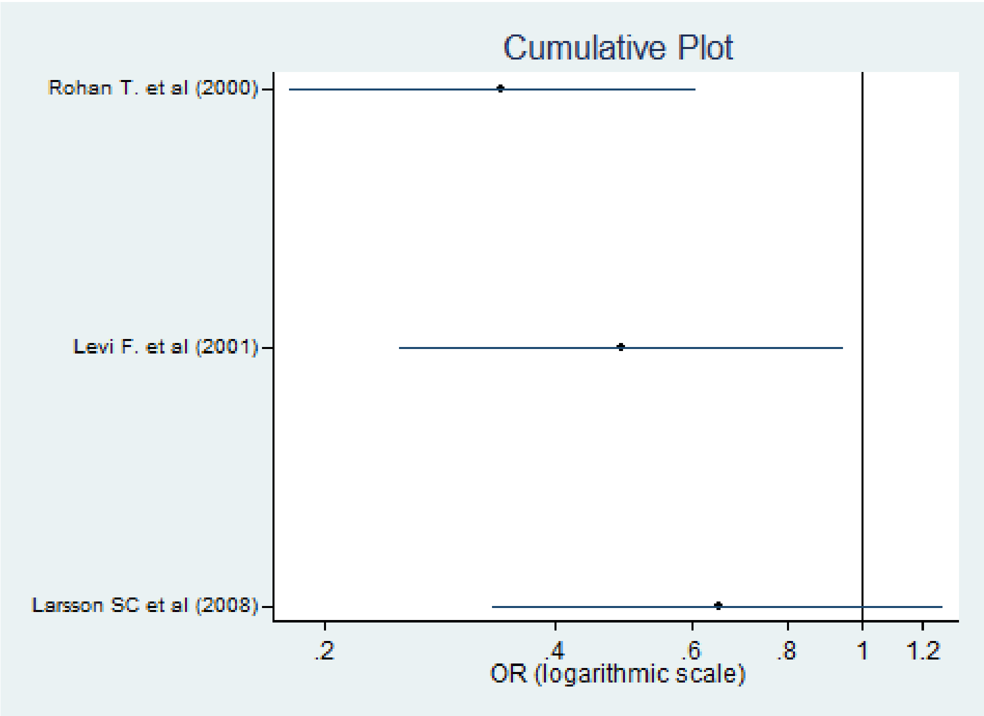


Figure 45. Funnel plot folate intake stratified by high alcohol intake in all women. All studies

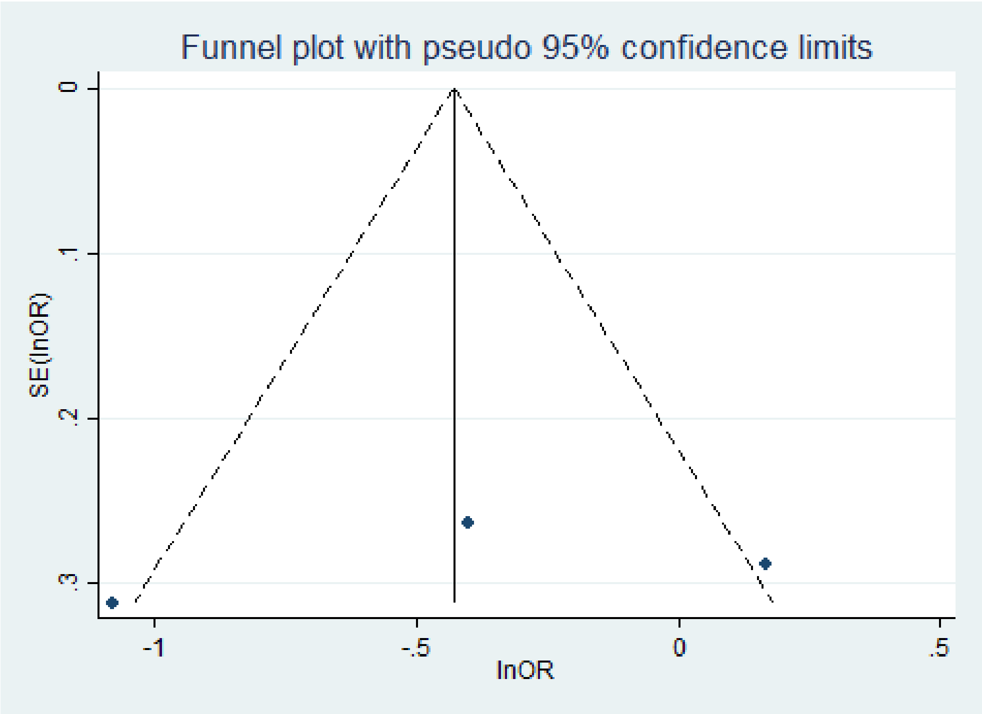
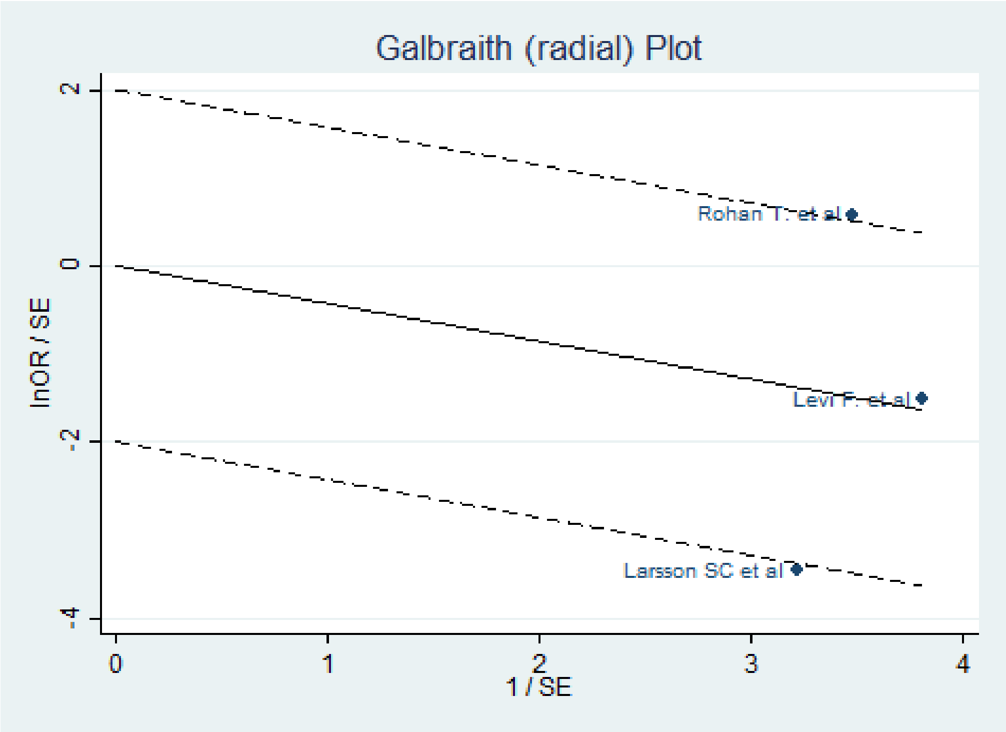


Figure 46. Galbraith plot folate intake stratified by high alcohol intake in all women. All studies



Combined effect of folate and alcohol and breast cancer

Figure 47. Forest plot low alcohol and high folate intake vs low alcohol and low folate intake in all women

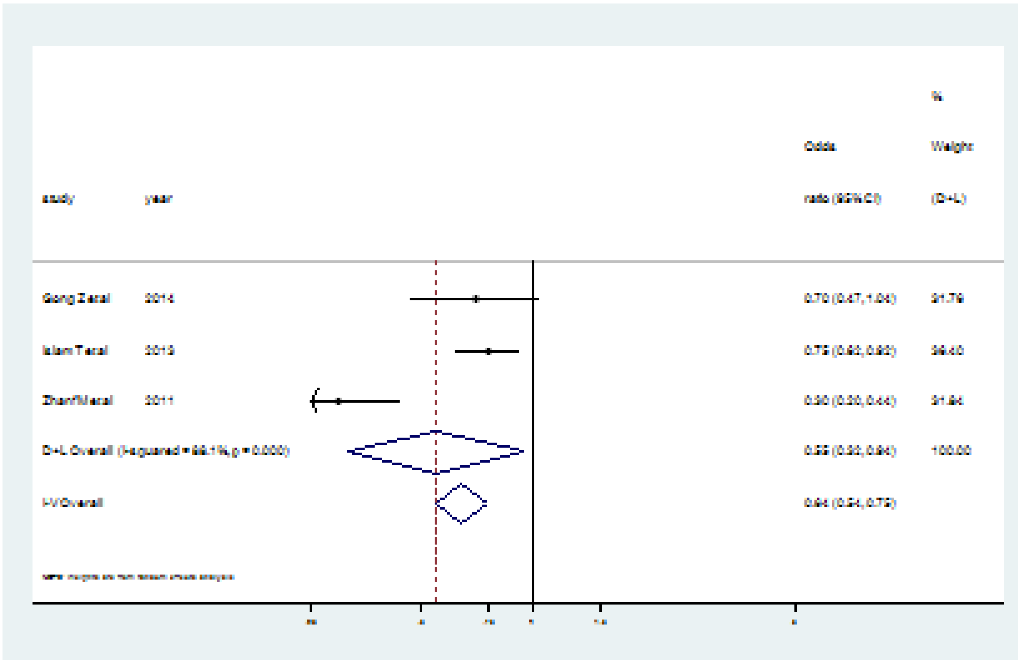


Figure 48. Cumulative plot low alcohol and high folate intake vs low alcohol and low folate intake in all women

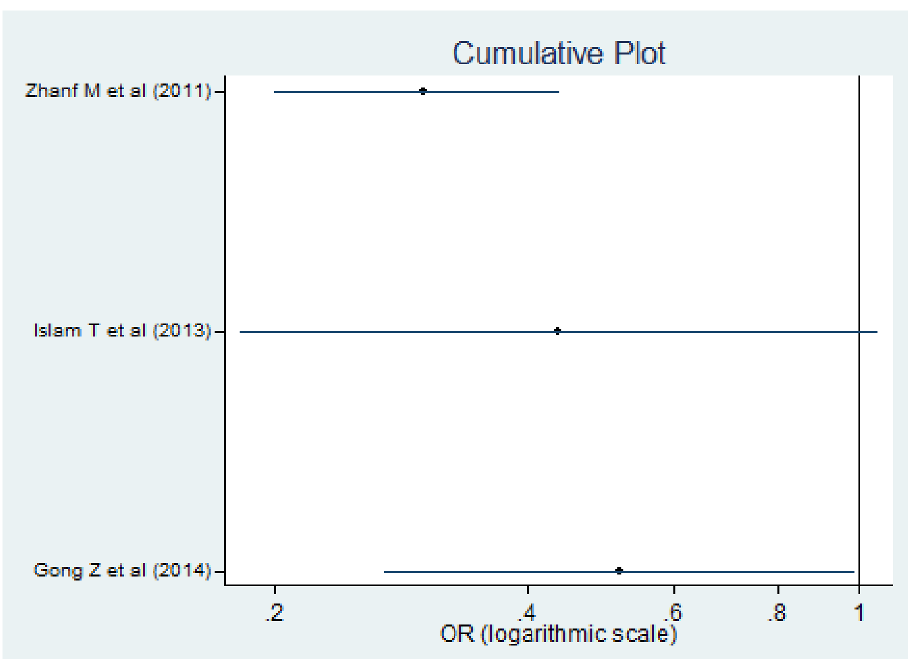


Figure 49. Funnel plot low alcohol and high folate intake vs low alcohol and low folate intake in all women

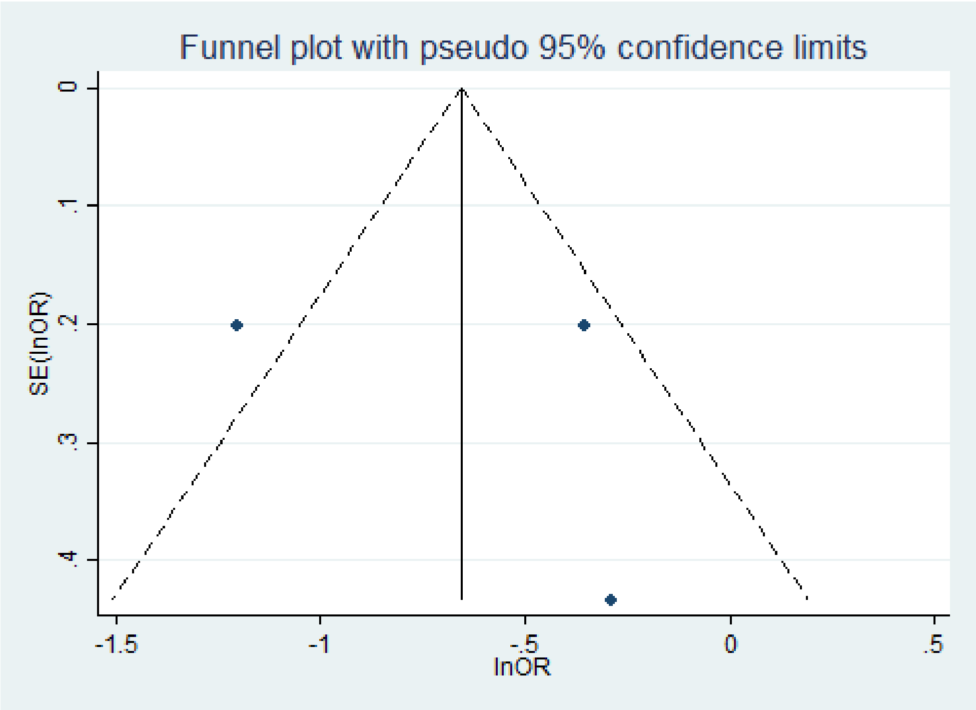


Figure 50. Galbraith plot low alcohol and high folate intake vs low alcohol and low folate intake in all women

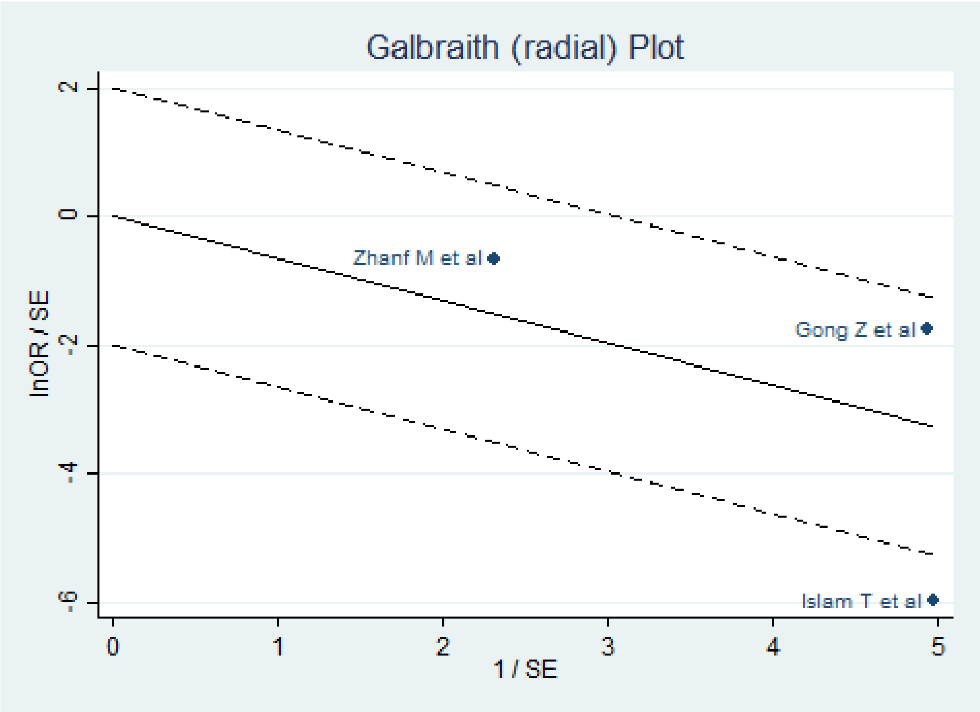


Figure 51. Forest plot low alcohol and high folate intake vs low alcohol and low folate intake in postmenopausal women. All studies

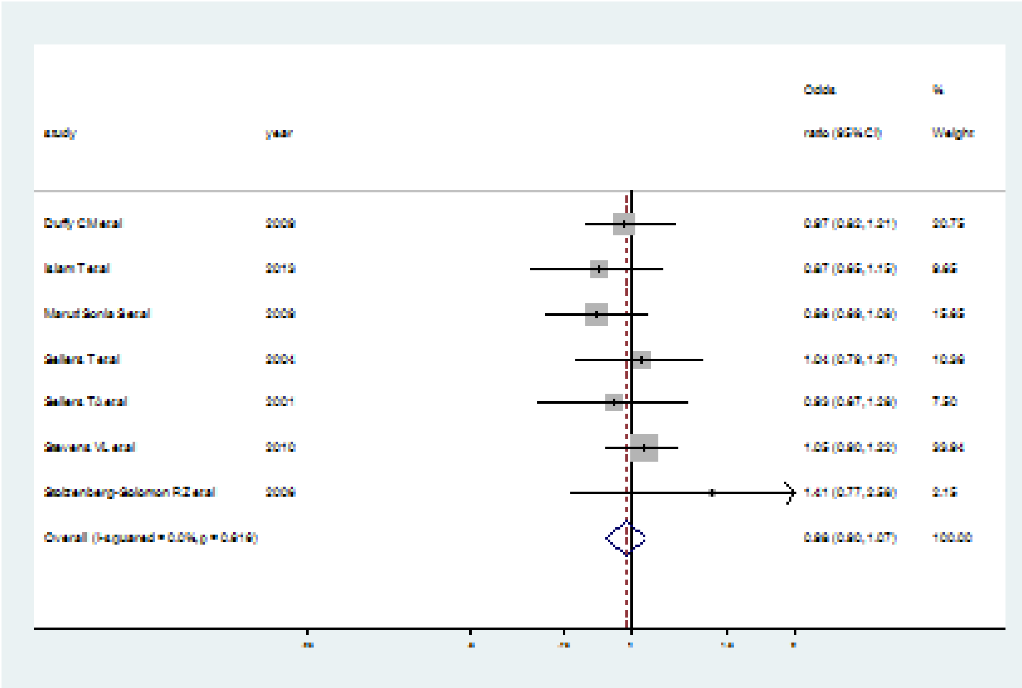


Figure 52. Cumulative plot low alcohol and high folate intake vs low alcohol and low folate intake in postmenopausal women. All studies

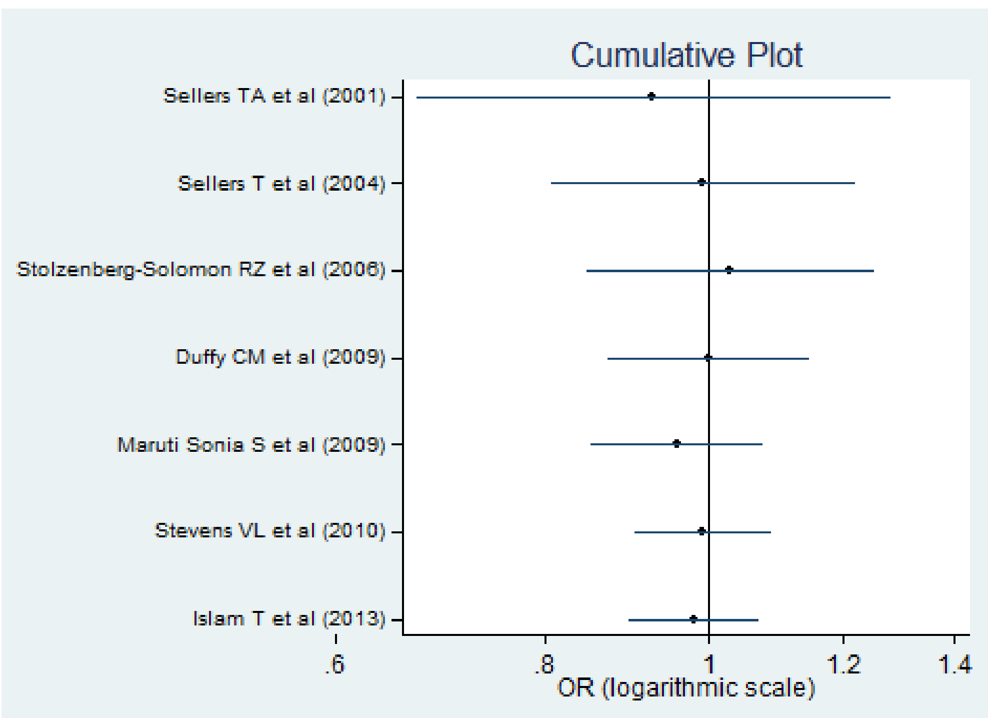


Figure 53. Funnel plot low alcohol and high folate intake vs low alcohol and low

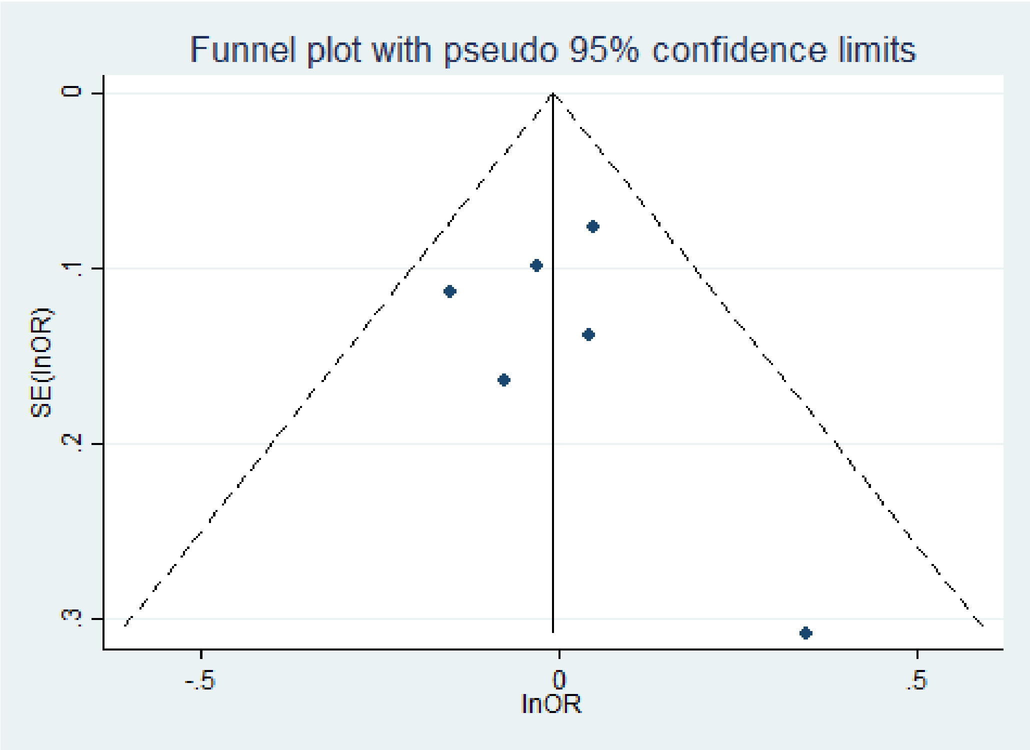


Figure 54. Galbraith plot low alcohol and high folate intake vs low alcohol and low folate intake in postmenopausal women. All studies

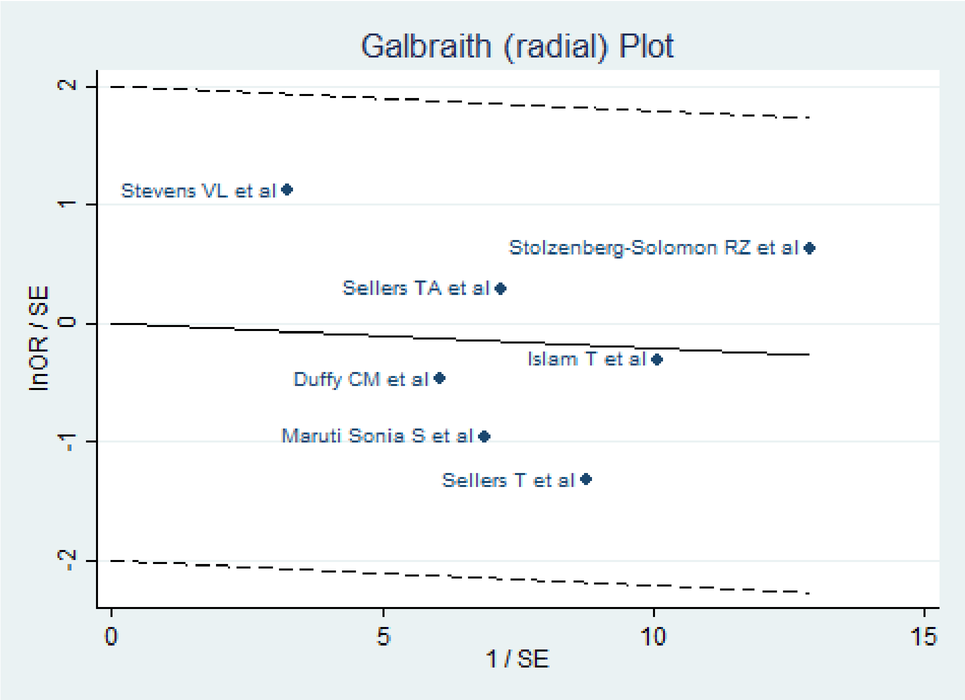


Figure 55. Forest plot High alcohol and low folate intake vs low alcohol and low folate intake in all women

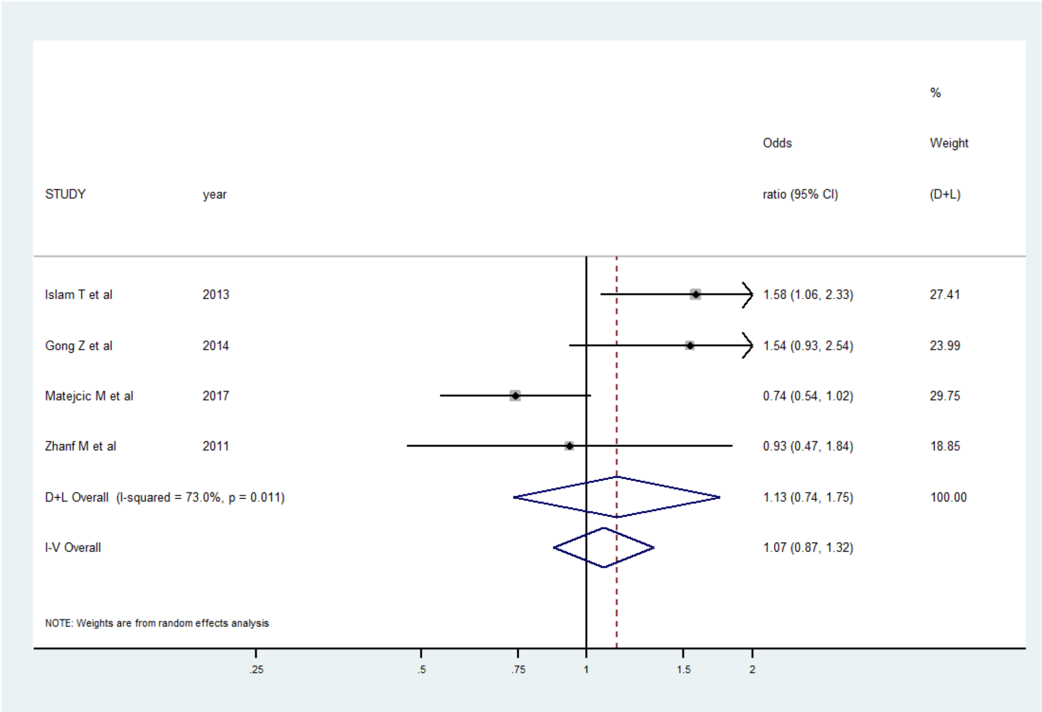


Figure 56. Cumulative plot High alcohol and low folate intake vs low alcohol and low folate intake in all women

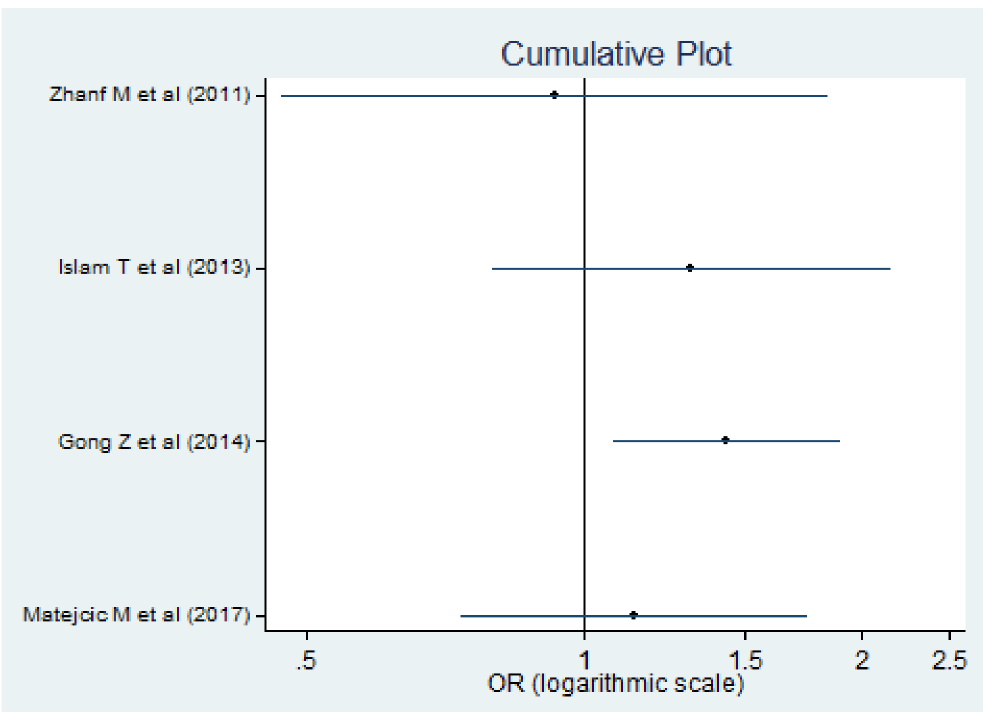


Figure 57. Funnel plot High alcohol and low folate intake vs low alcohol and low folate intake in all women

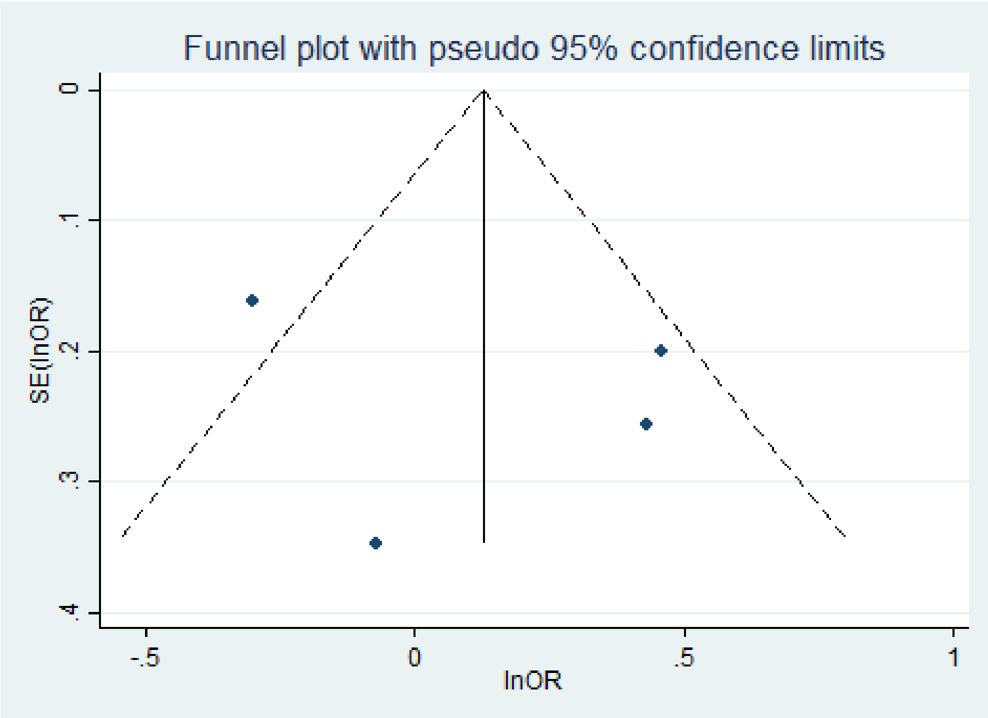


Figure 58. Galbraith plot High alcohol and low folate intake vs low alcohol and low folate intake in all women

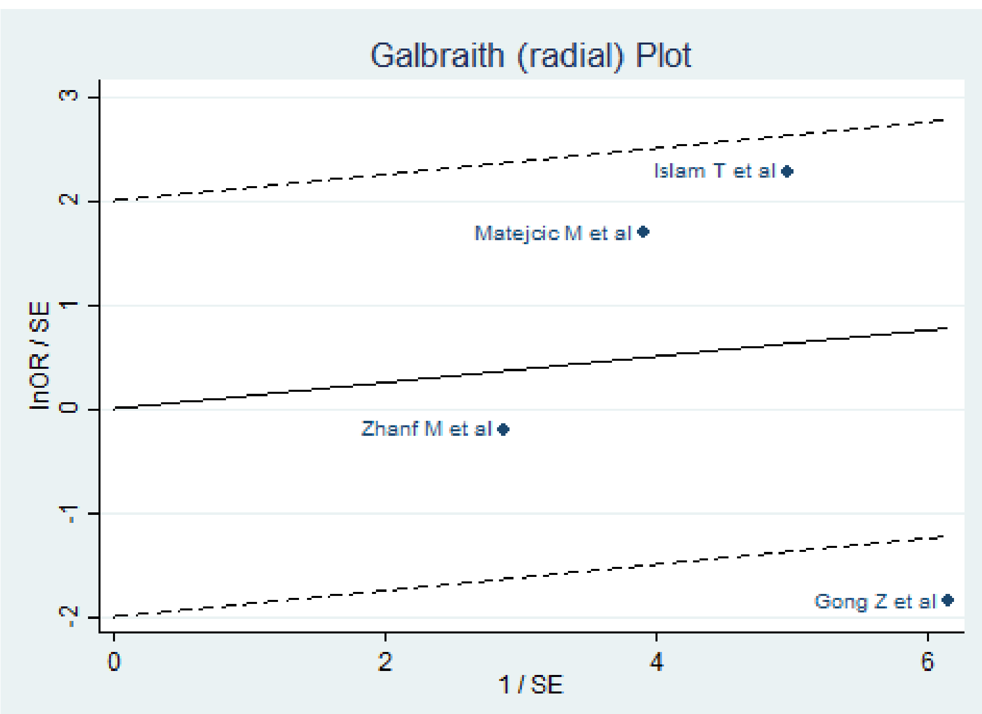
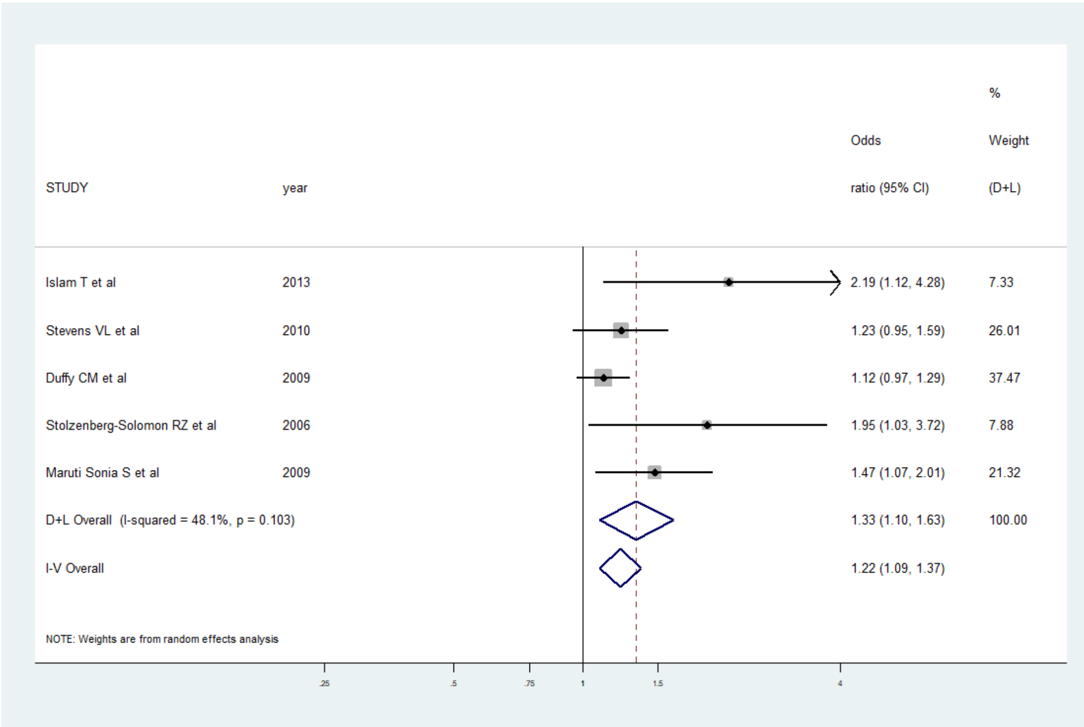


Figure 59. Forest plot High alcohol and low folate intake vs low alcohol and low folate intake in postmenopausal women

a) All studies



b) Prospective studies

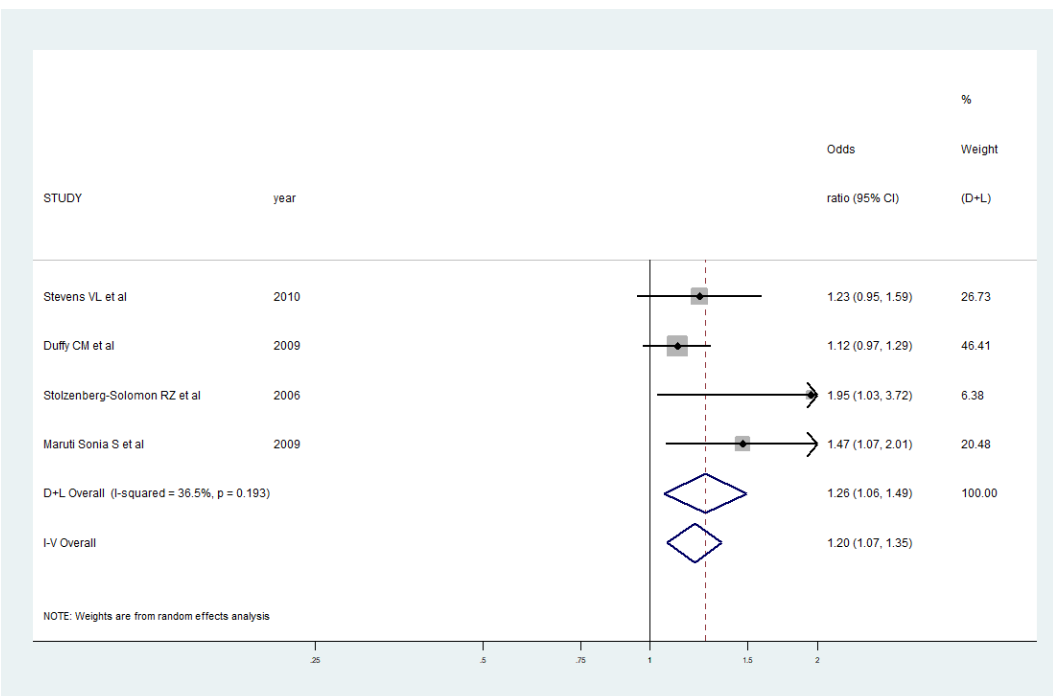
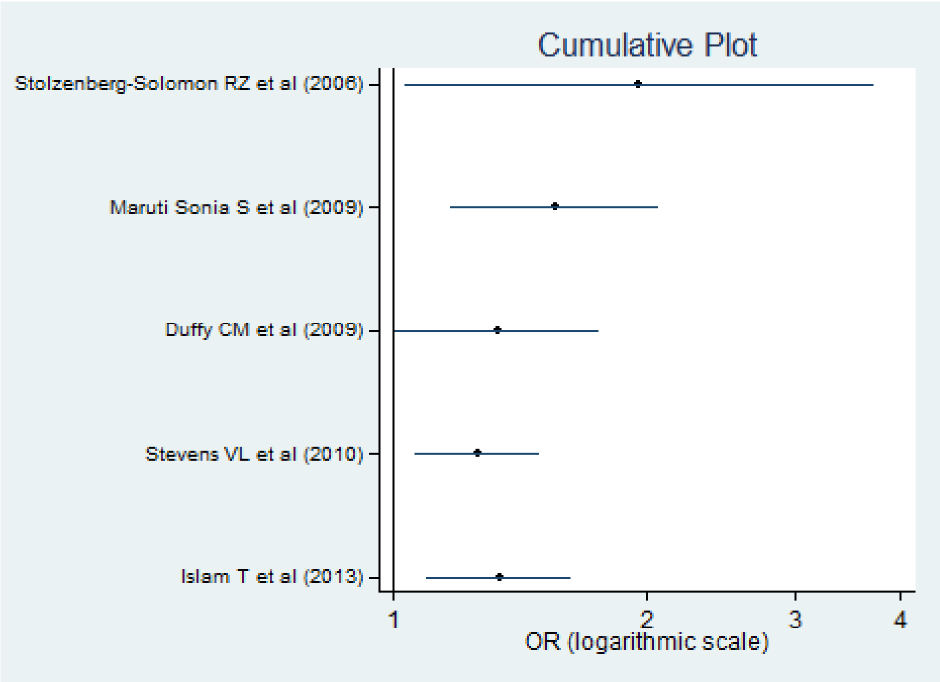


Figure 60. Cumulative plot High alcohol and low folate intake vs low alcohol and low folate intake in postmenopausal women

a) All studies



b) Prospective studies

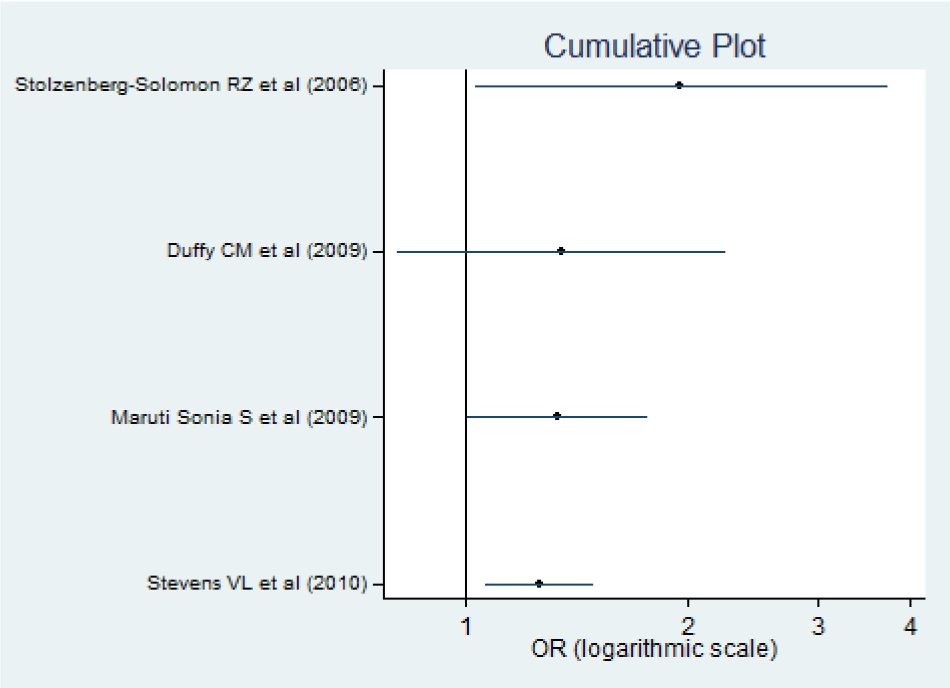
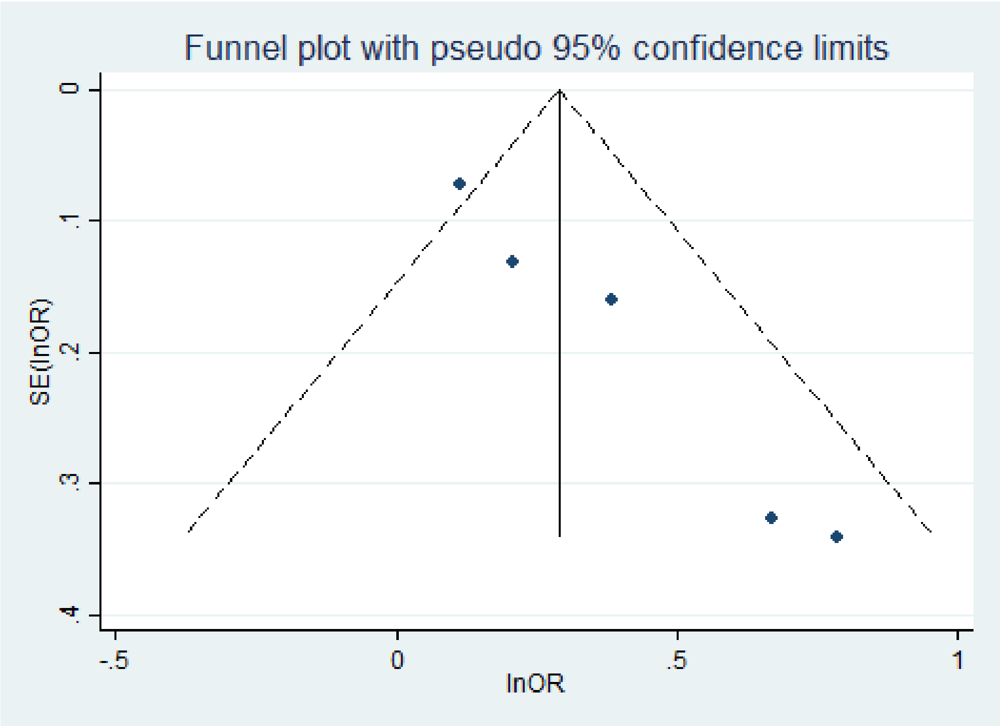


Figure 61. Funnel plot High alcohol and low folate intake vs low alcohol and low folate intake in postmenopausal women

a) All studies



b) Prospective studies

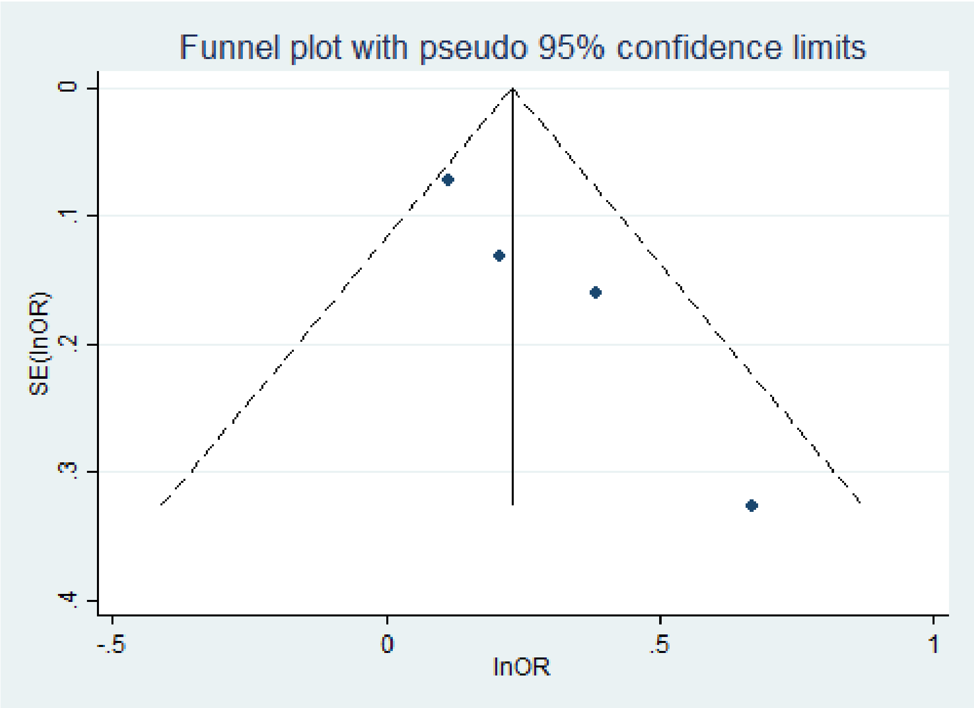
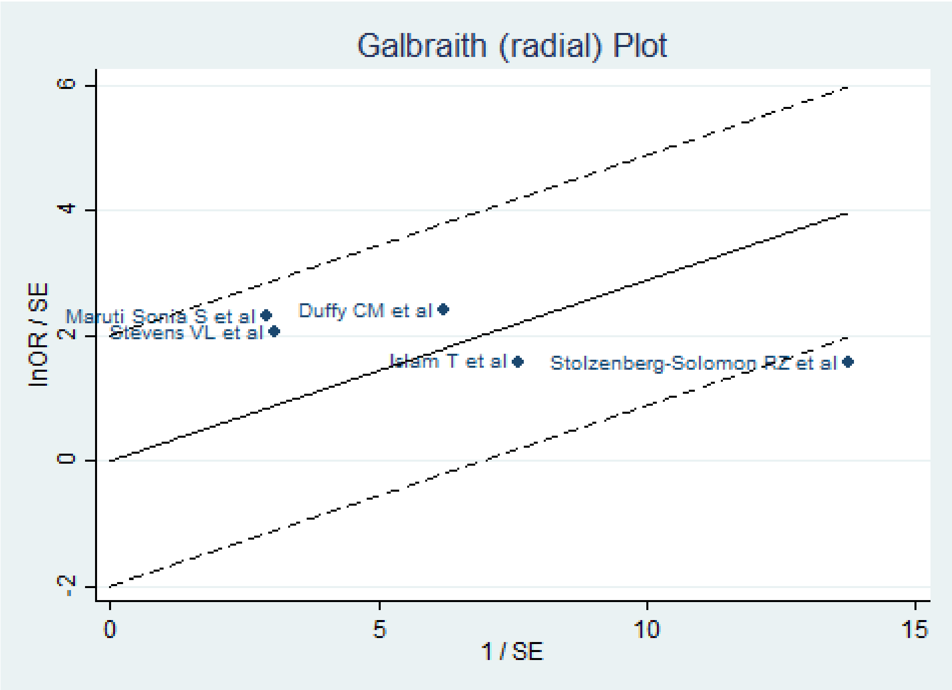


Figure 62. Galbraith plot High alcohol and low folate intake vs low alcohol and low folate intake in postmenopausal women

a) All studies



b) Prospective studies

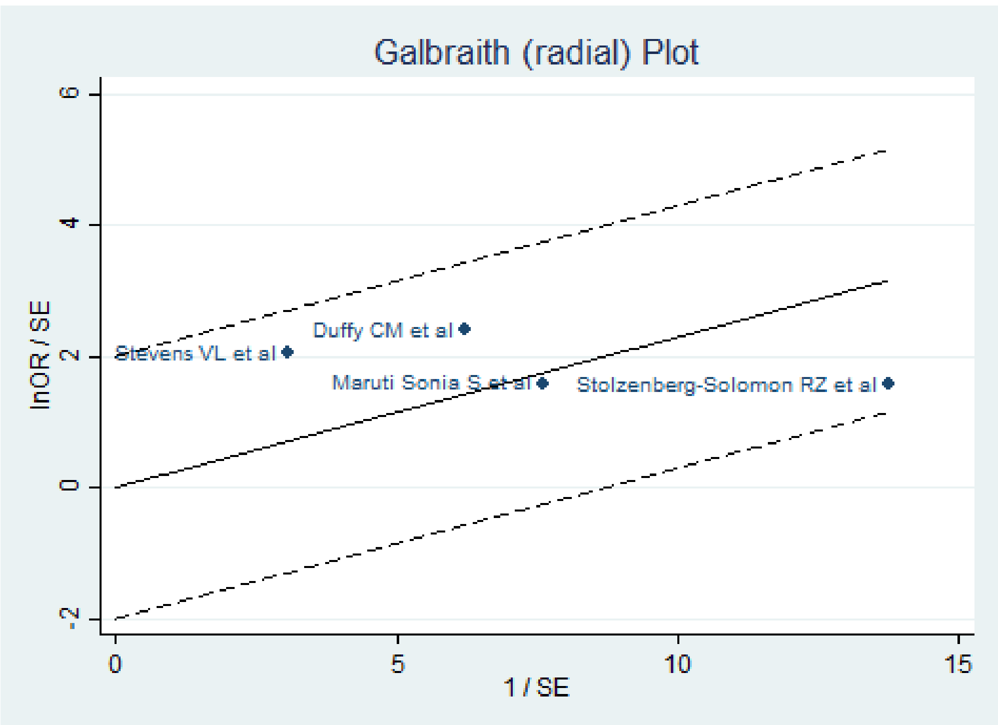


Figure 63. Cumulative plot High alcohol and high folate intake vs low alcohol and low folate intake in all women

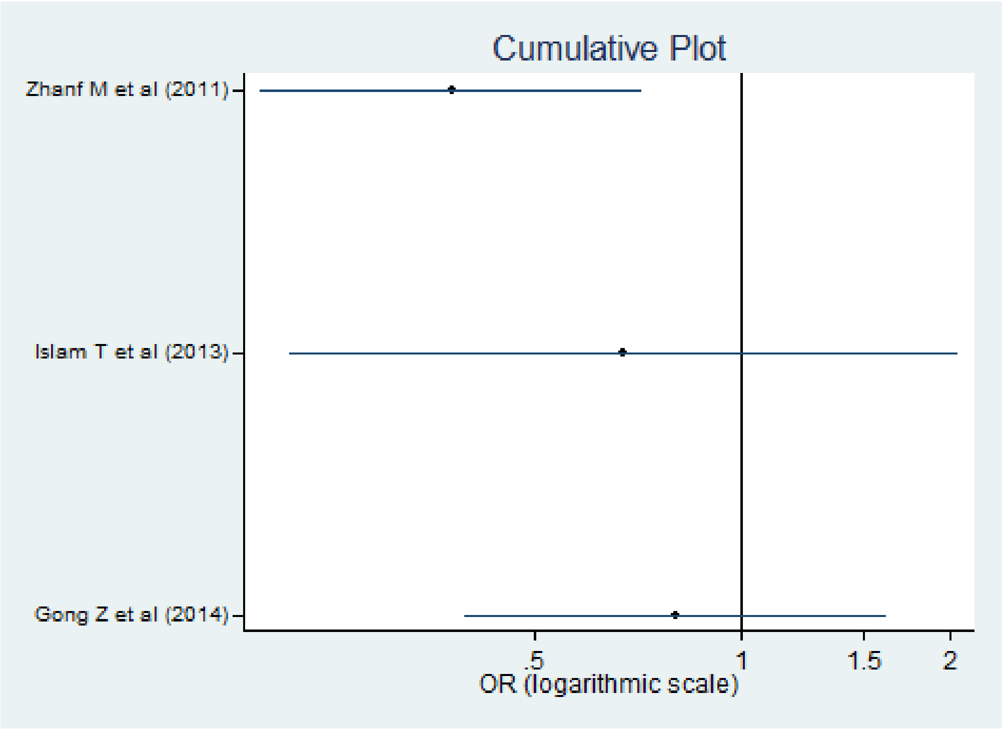


Figure 64. Funnel plot High alcohol and high folate intake vs low alcohol and low folate intake in all women

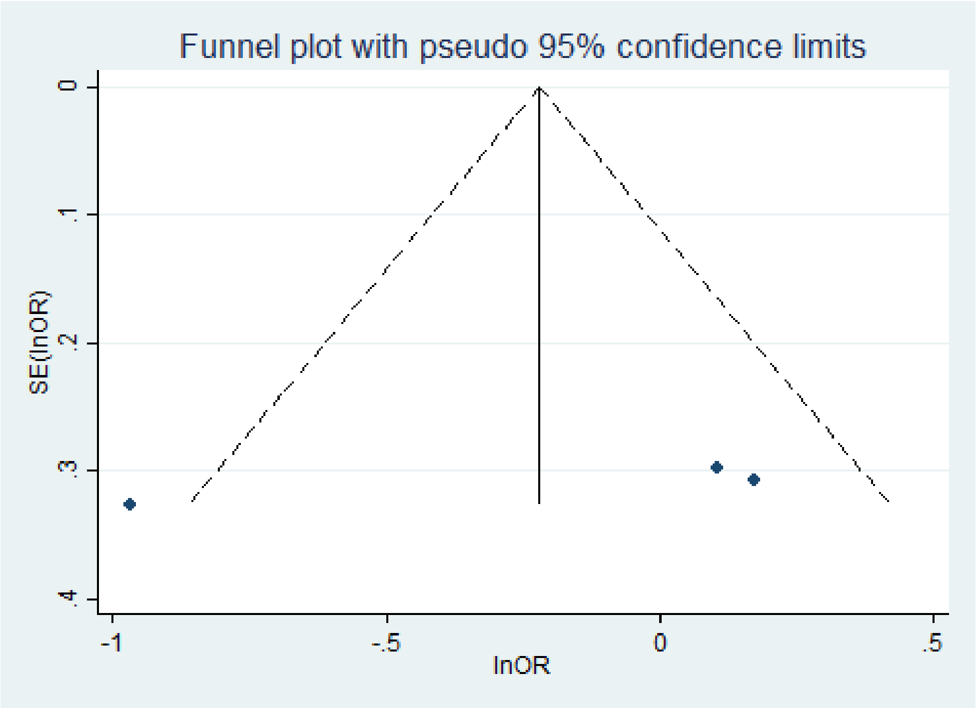


Figure 65. Galbraith plot High alcohol and high folate intake vs low alcohol and low folate intake in all women

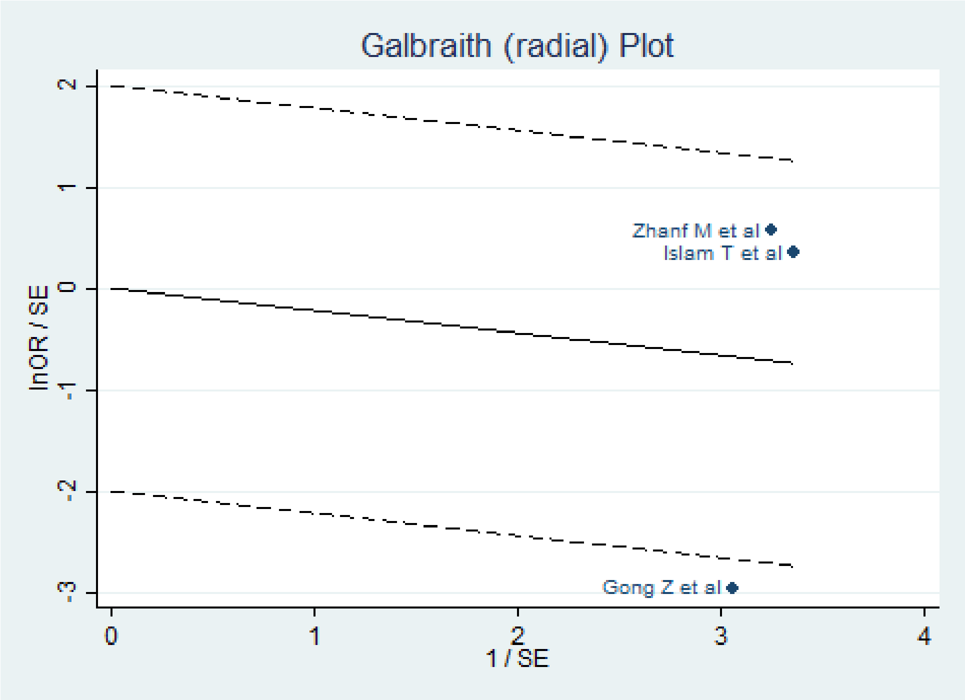


Figure 66. Forest plot High alcohol and high folate intake vs low alcohol and low folate intake in postmenopausal women. Prospective studies

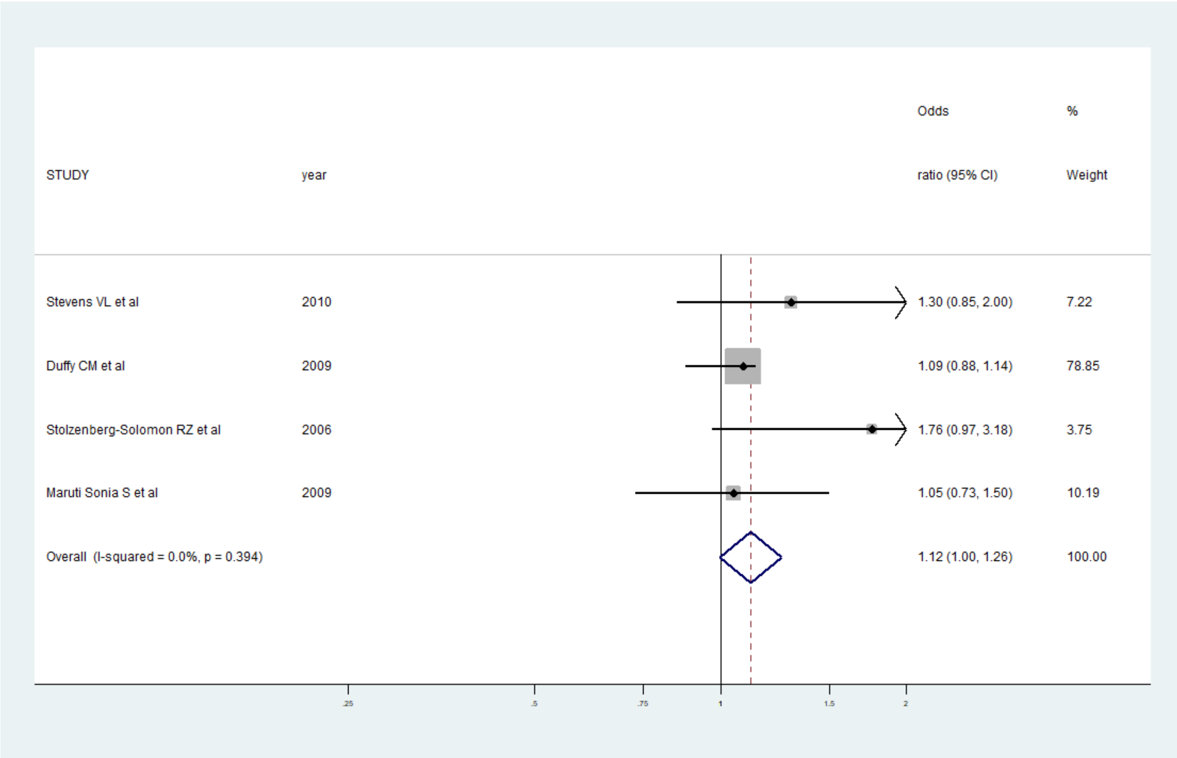
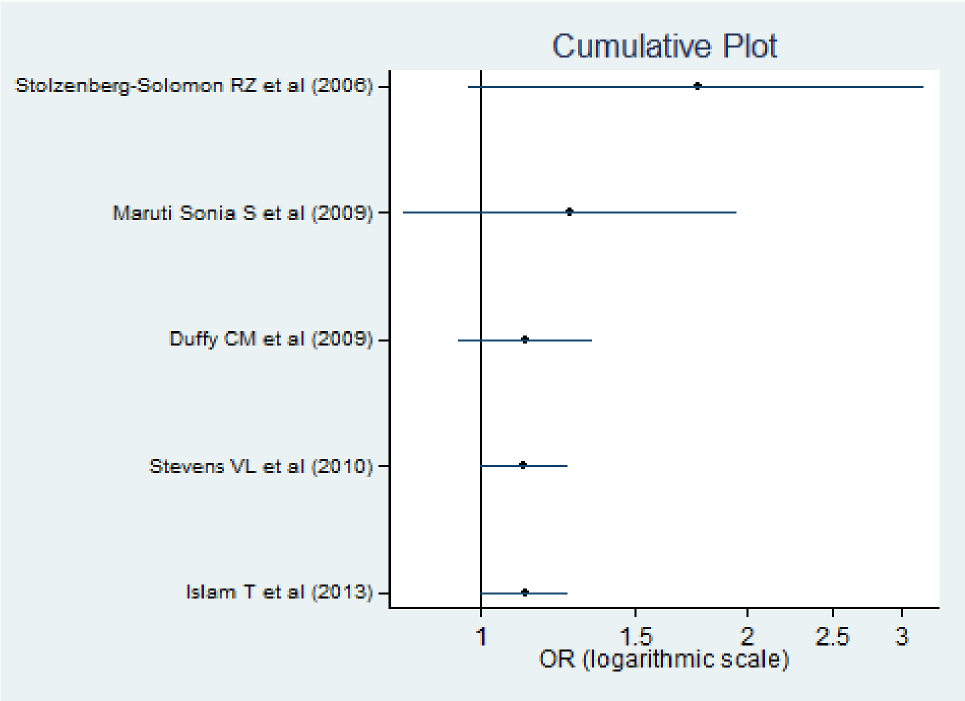


Figure 67. Cumulative plot High alcohol and high folate intake vs low alcohol and low folate intake in all women

a) All studies



b) Prospective studies

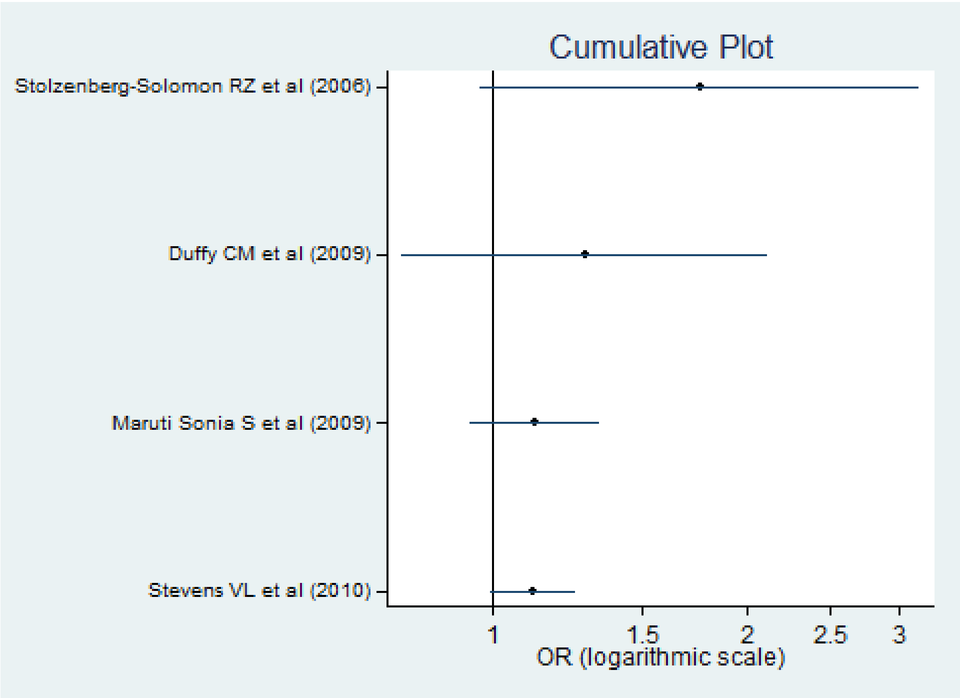
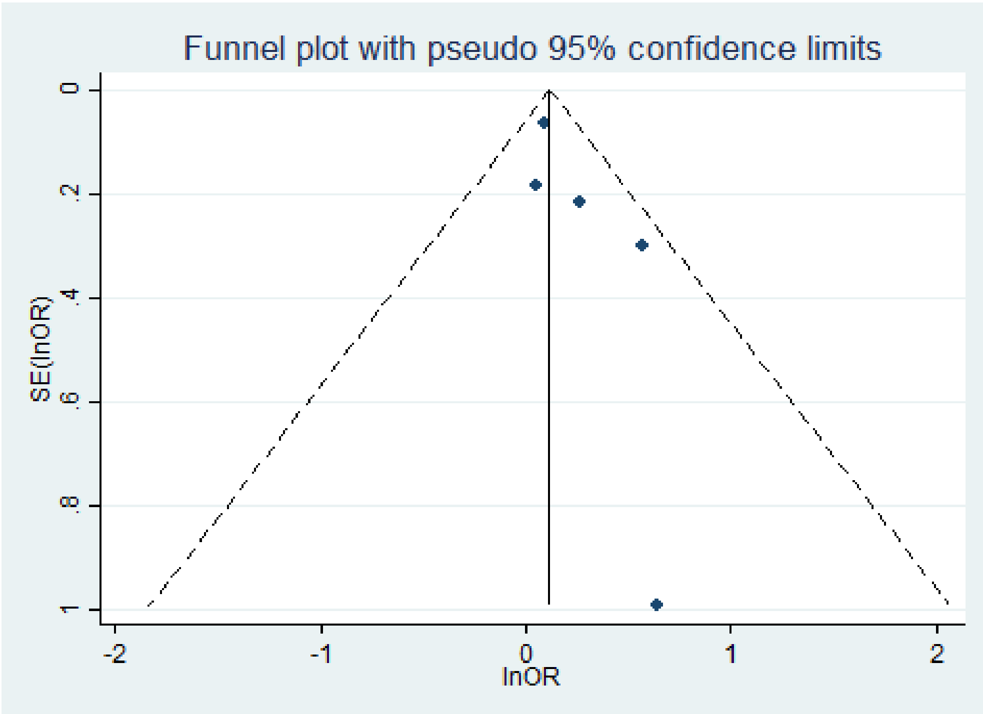


Figure 68. Funnel plot High alcohol and high folate intake vs low alcohol and low folate intake in postmenopausal women

a) All studies



b) Prospective studies

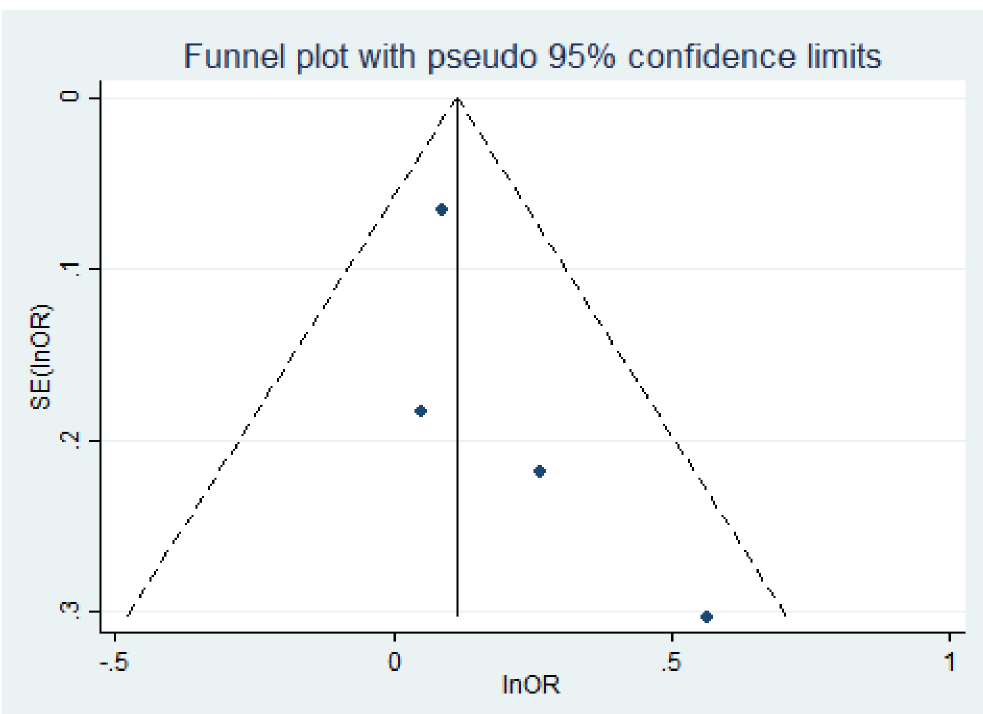
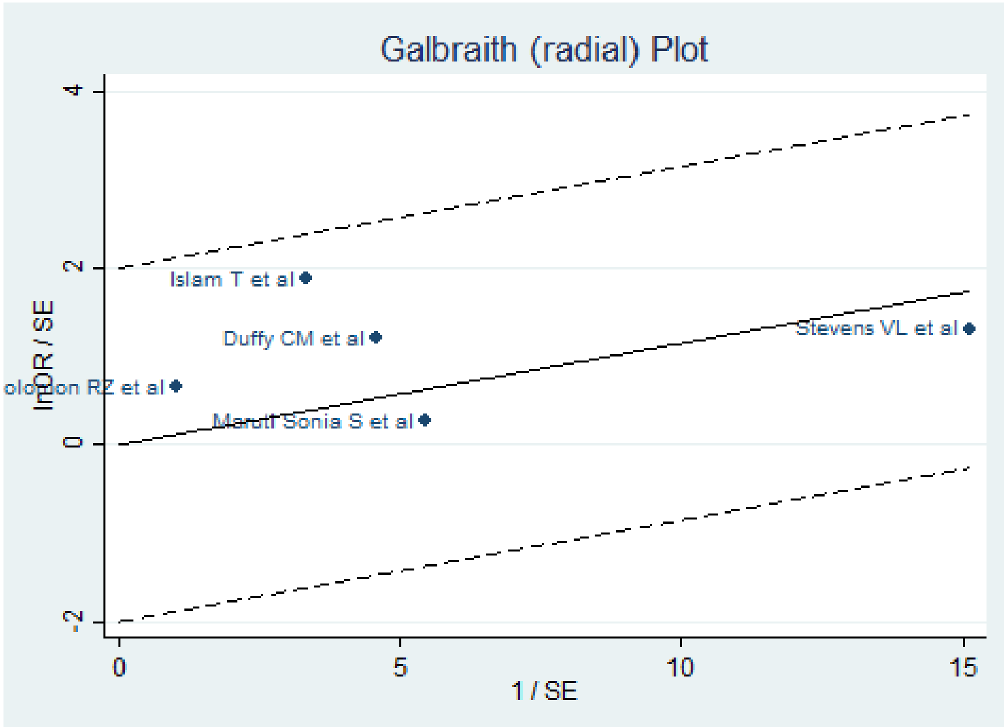
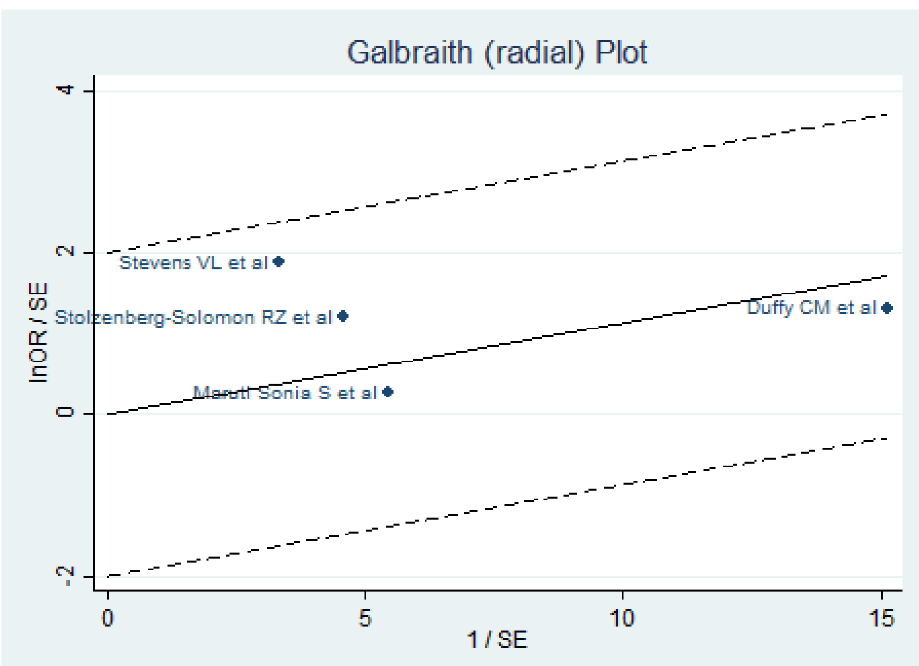


Figure 69. Galbraith plot High alcohol and high folate intake vs low alcohol and low folate intake in postmenopausal women

a) All studies



b) Prospective studies



Combined effect of folate and alcohol and breast cancer stratified by type of folate intake

Figure 70. Forest plot high alcohol and low folate intake vs low alcohol and folate intake in all women. Only dietary folate. All studies

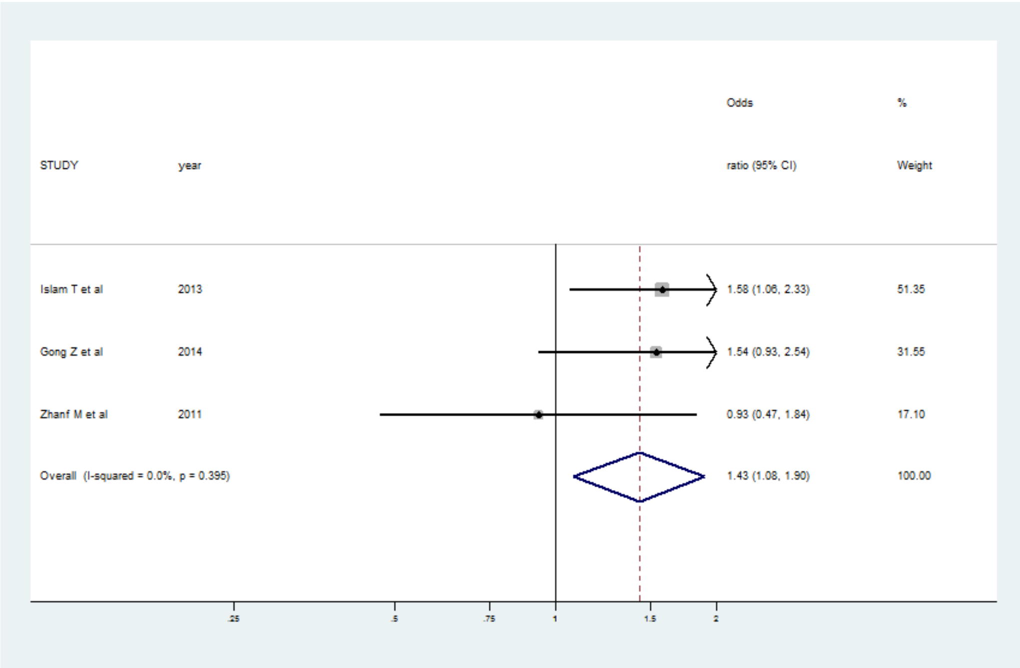


Figure 71. Cumulative plot high alcohol and low folate intake vs low alcohol and folate intake in all women. Only dietary folate. All studies

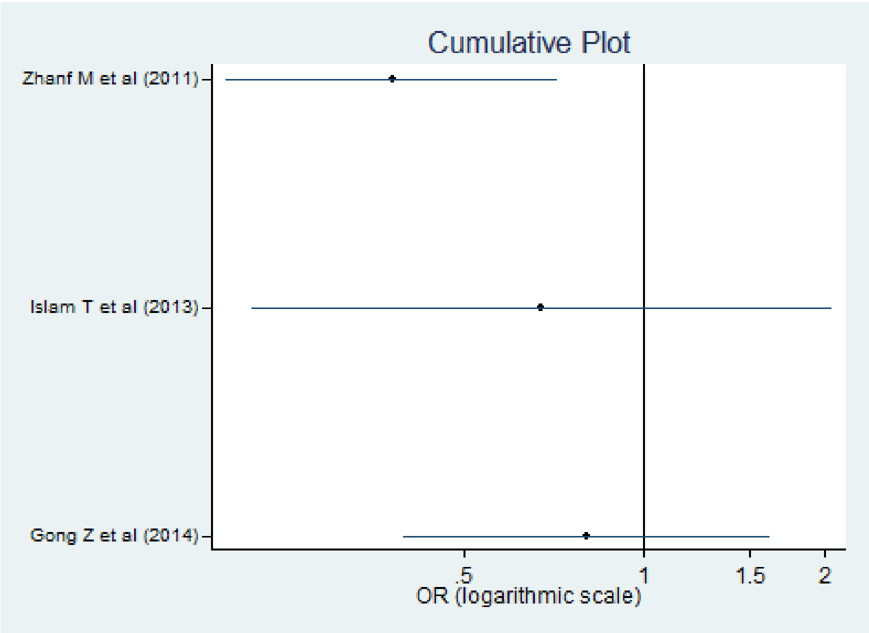


Figure 72. Funnel plot high alcohol and low folate intake vs low alcohol and folate intake in all women. Only dietary folate. All studies

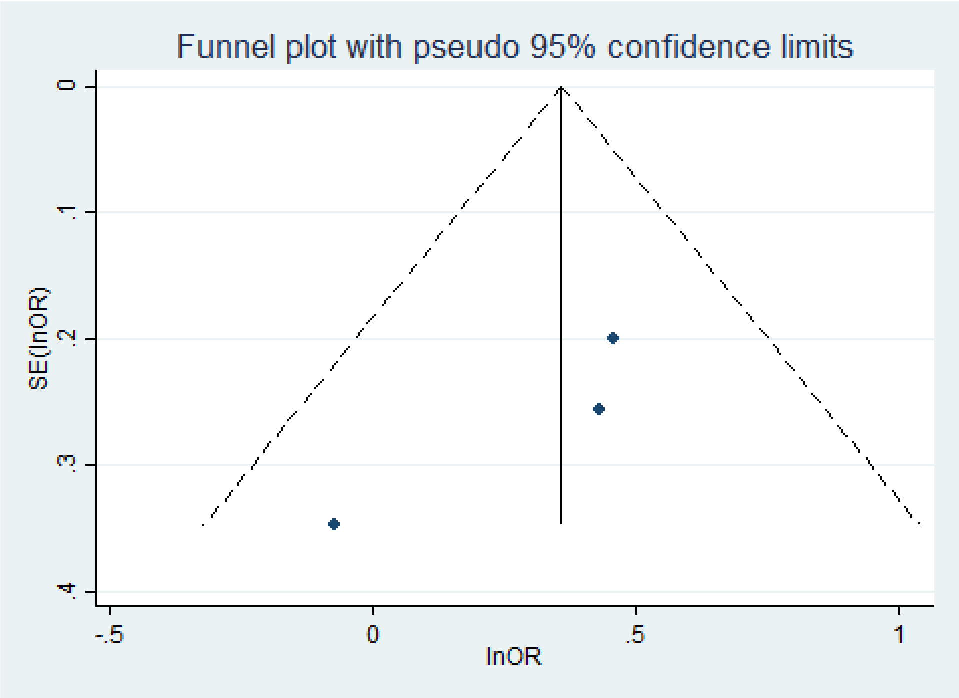


Figure 73. Gallbraith plot high alcohol and low folate intake vs low alcohol and folate intake in all women. Only dietary folate. All studies.

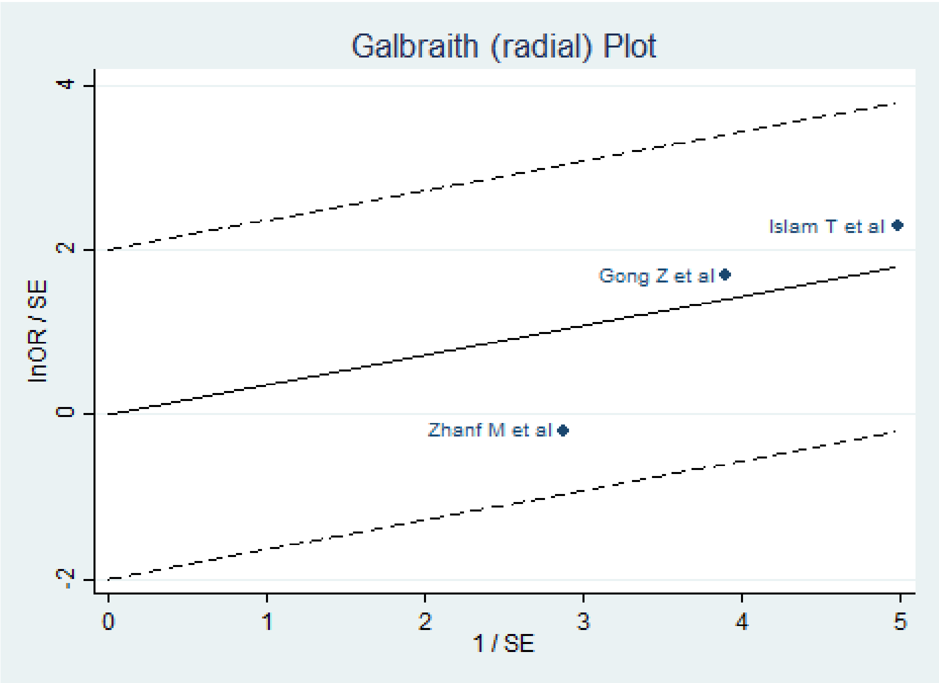


Figure 74. Forest plot high alcohol and low folate intake vs low alcohol and folate intake in postmenopausal women. Total folate (including supplements). All studies

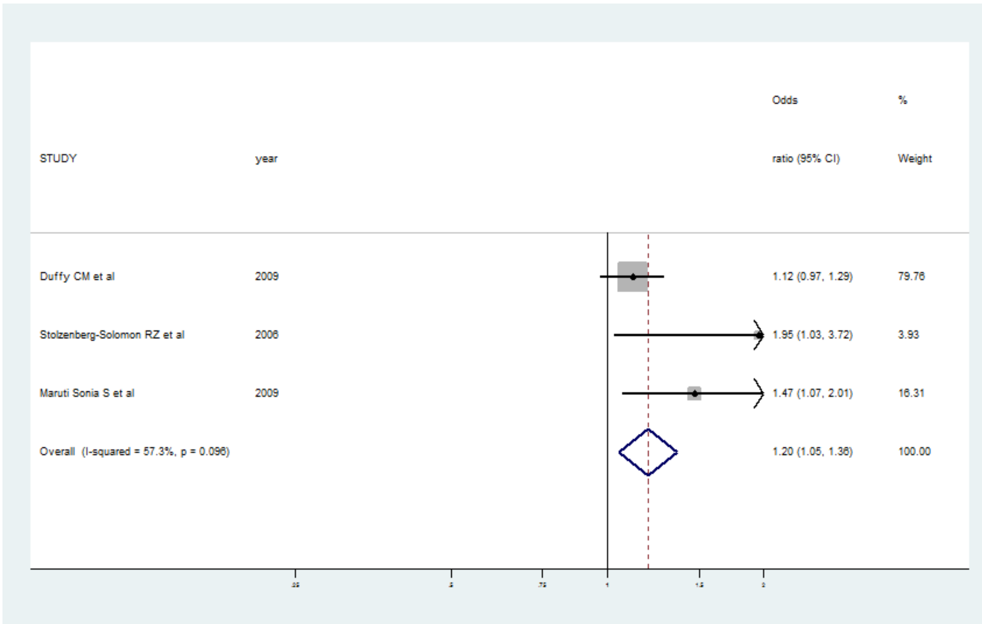


Figure 75. Cumulative plot high alcohol and low folate intake vs low alcohol and folate intake in postmenopausal women. Total folate (including supplements). All studies

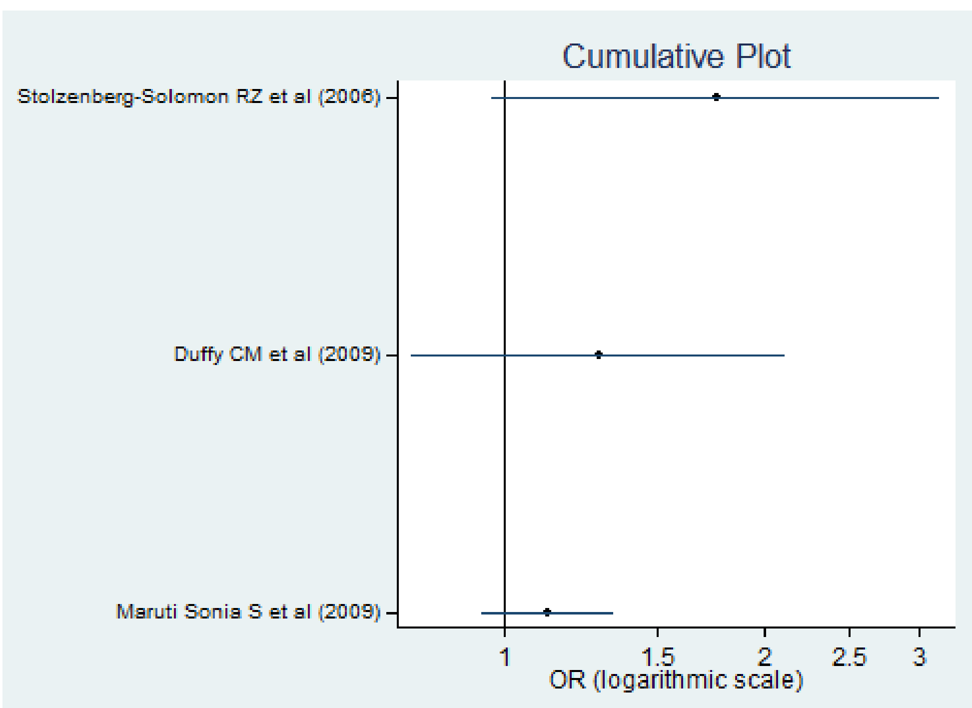


Figure 76. Funnel plot high alcohol and low folate intake vs low alcohol and folate intake in postmenopausal women. Total folate (including supplements). All studies.

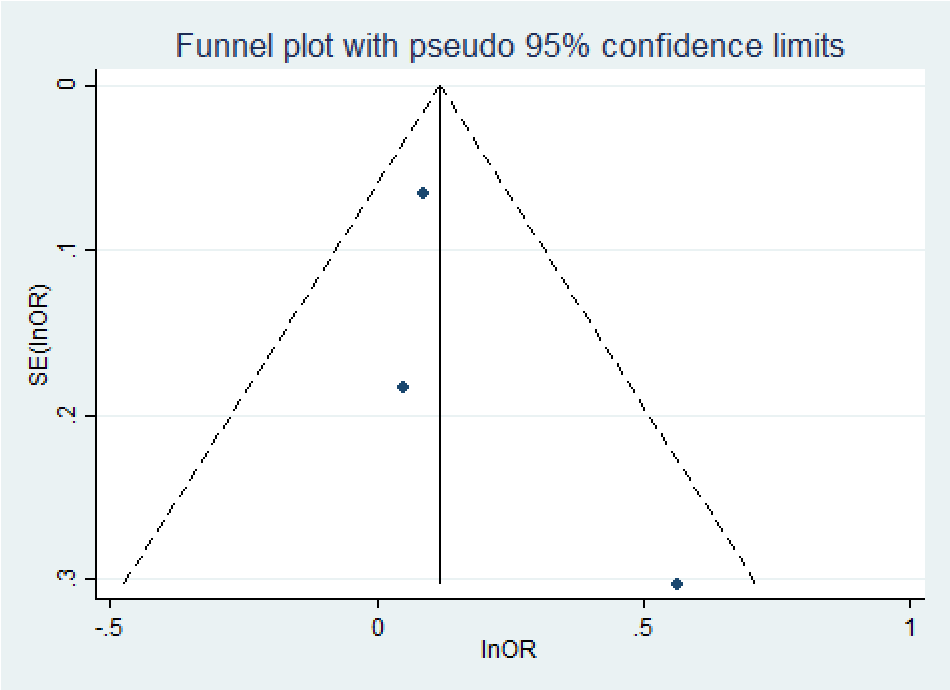


Figure 77. Gallbraith plot high alcohol and low folate intake vs low alcohol and folate intake in postmenopausal women. Total folate (including supplements). All studies.

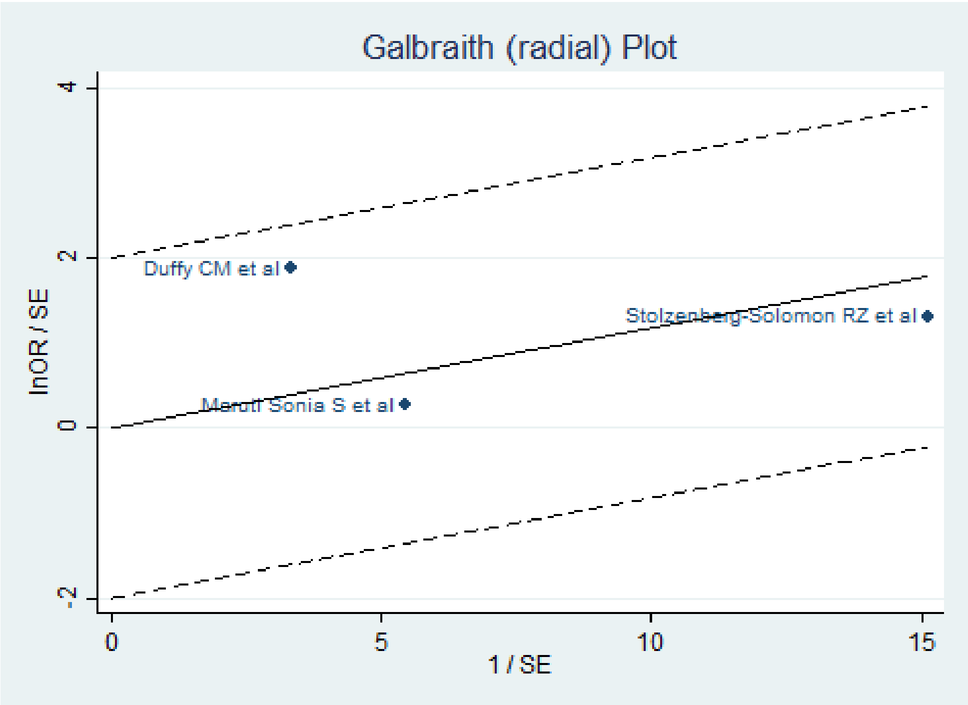


Figure 78. Forest plot high alcohol and folate intake vs low alcohol and folate intake in all women. Only dietary folate. All studies

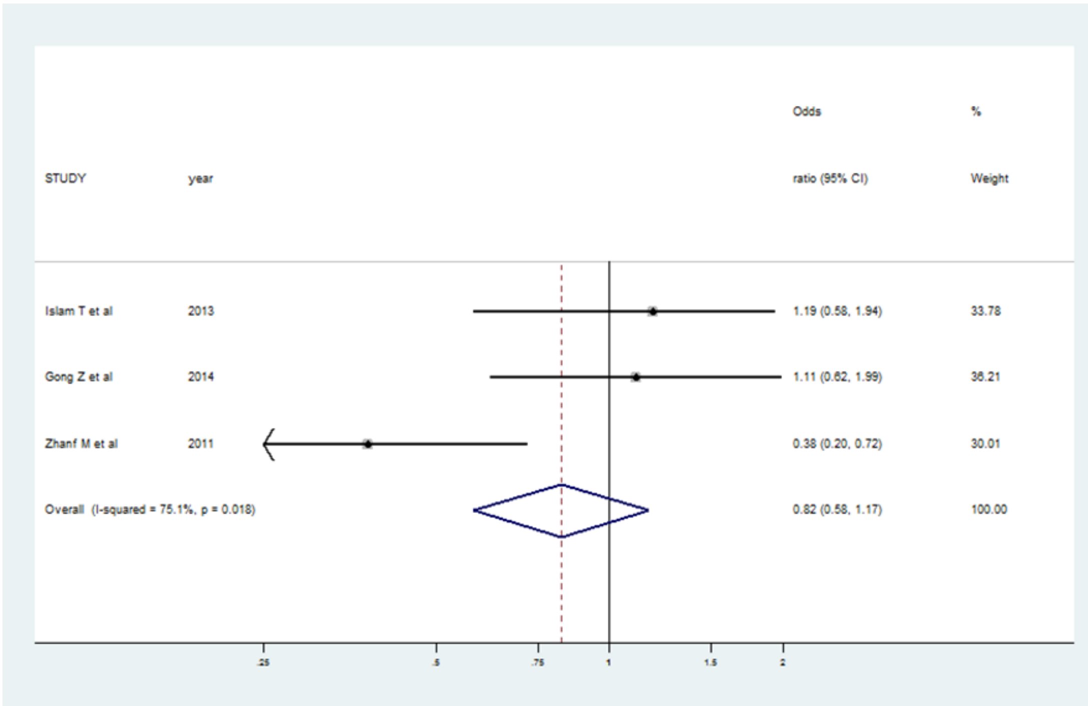


Figure 79. Cumulative plot high alcohol and folate intake vs low alcohol and folate intake in all women. Only dietary folate. All studies

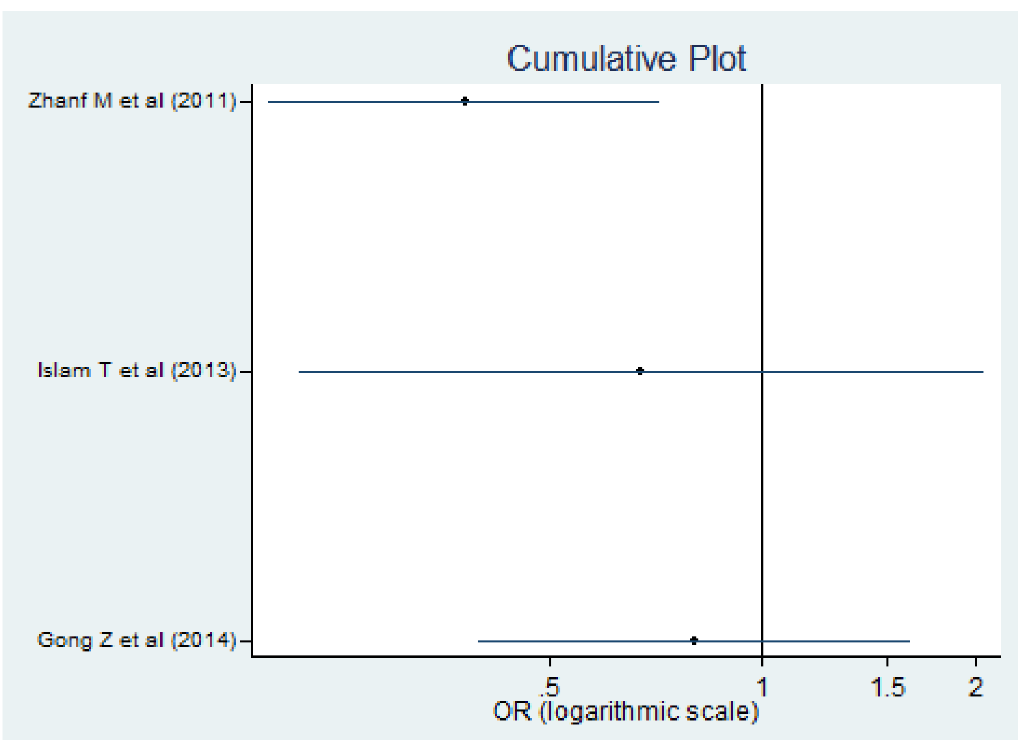


Figure 80. Funnel plot high alcohol and folate intake vs low alcohol and folate intake in all women. Only dietary folate. All studies.

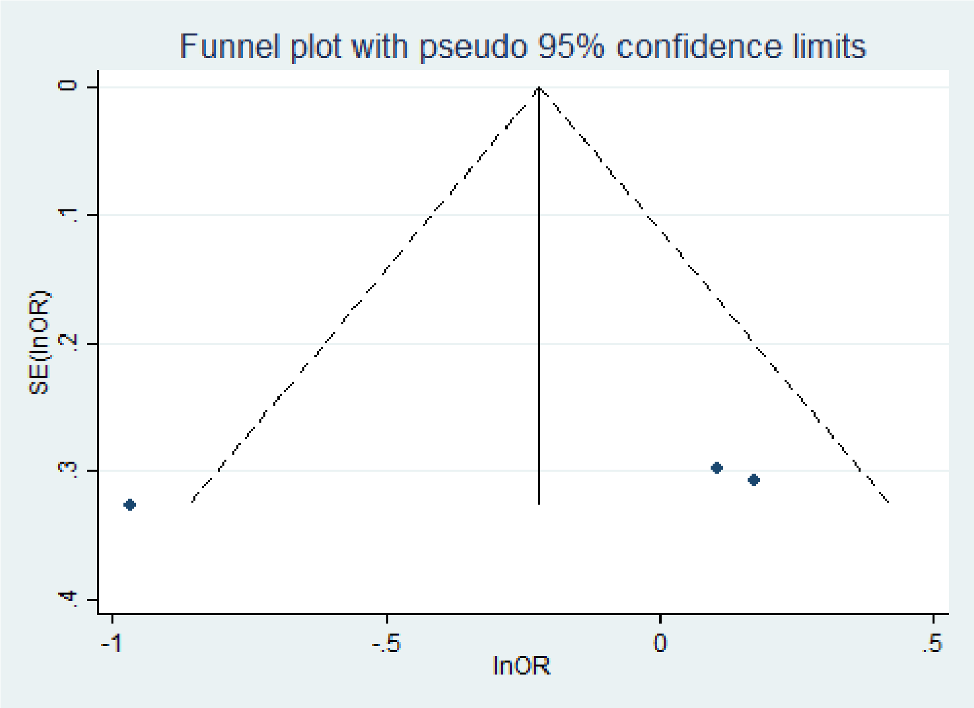


Figure 81. Gallbraith plot high alcohol and folate intake vs low alcohol and folate intake in all women. Only dietary folate. All studies.

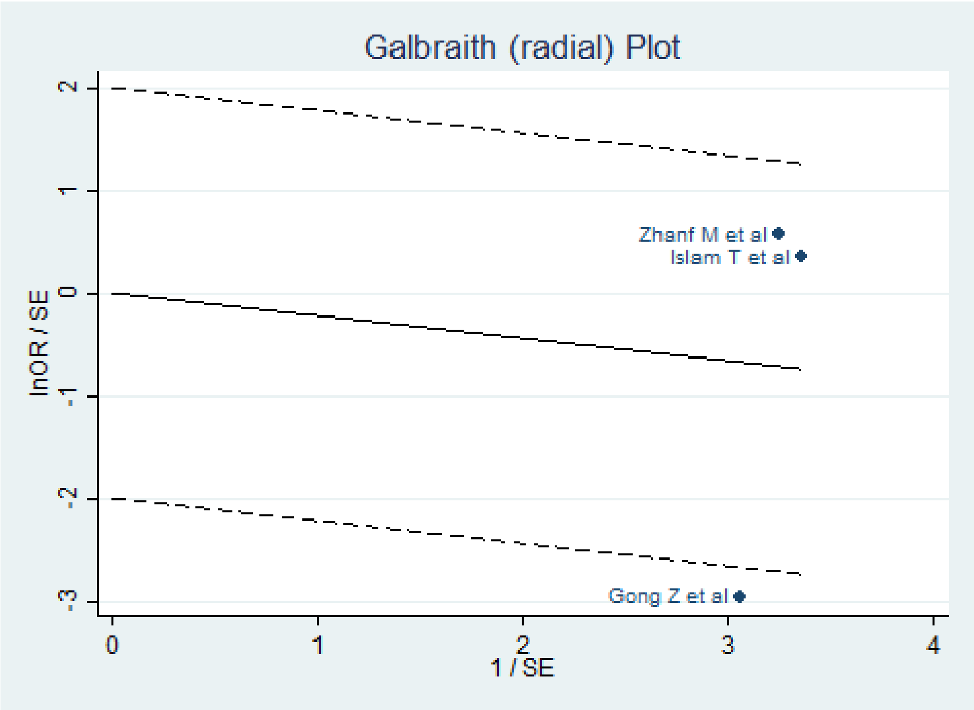


Figure 82. Forest plot high alcohol and folate intake vs low alcohol and folate intake in postmenopausal women. Total folate (including supplements). All studies

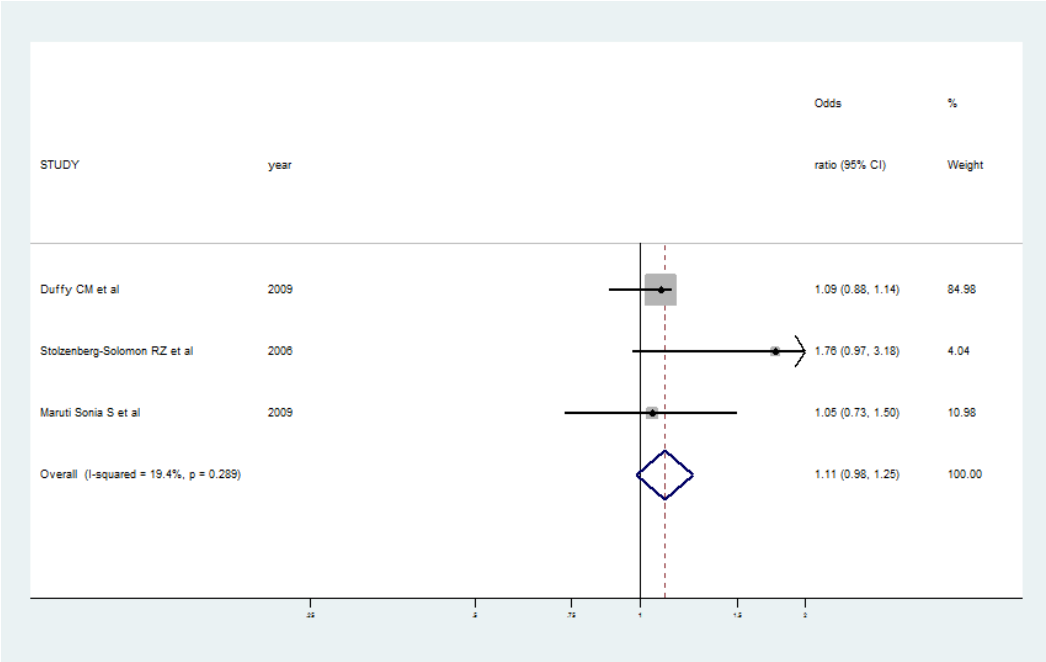


Figure 83. Cumulative plot high alcohol and folate intake vs low alcohol and folate intake in postmenopausal women. Total folate (including supplements). All studies

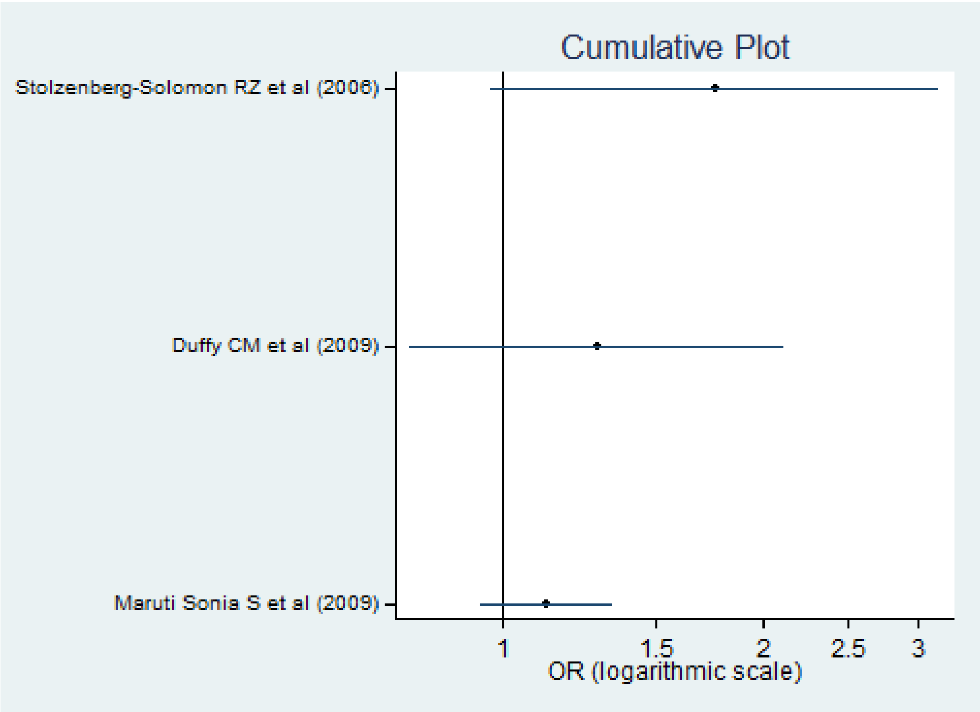


Figure 84. Funnel plot high alcohol and folate intake vs low alcohol and folate intake in postmenopausal women. Total folate (including supplements). All studies.

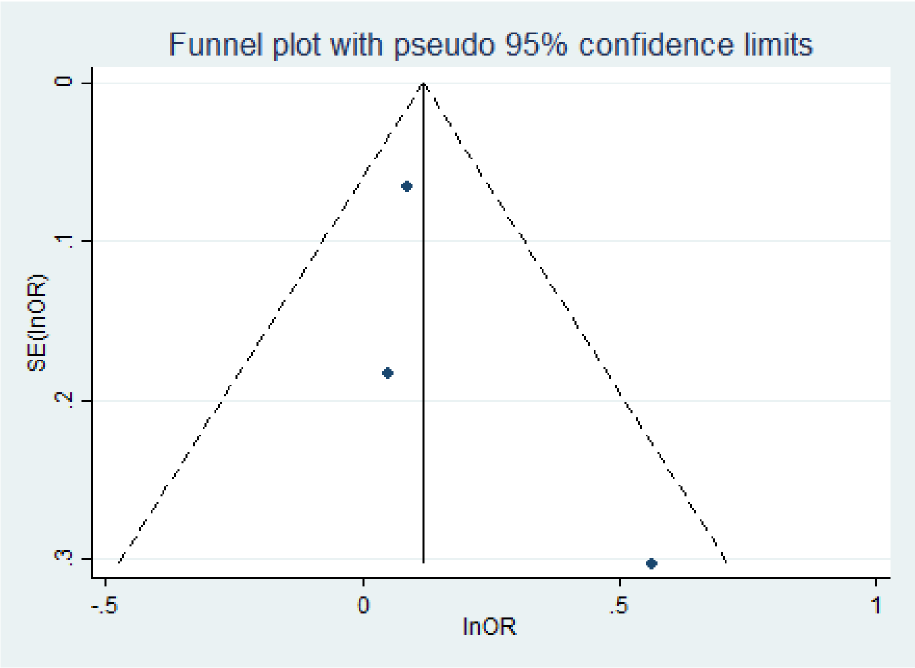


Figure 85. Gallbraith plot high alcohol and folate intake vs low alcohol and folate intake in postmenopausal women. Total folate (including supplements). All studies.