Effects of β-carotene intake on the risk of fracture: A Bayesian meta-analysis

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Research article

Keywords: Vitamin A, β-carotene, Osteoporosis, Fracture, Bayesian, Meta-analysis

Posted Date: March 26th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-19336/v1

Version of Record: A version of this preprint was published on October 31st, 2020. See the published version at https://doi.org/10.1186/s12891-020-03733-0.

Abstract

Introduction The association between β-carotene intake and risk of fracture has been reported inconsistently. We conducted a meta-analysis to investigate the association between β-carotene intake and risk of fracture using a Bayesian approach.

Methods We systematically searched PubMed, EMBASE and Cochrane library database for relevant articles until December 2019. We also performed a hand search based on reference lists from published articles. The Bayesian random effect model was used to synthesize data from individual studies.

Results Nine studies with a total of 190,545 men and women were included in this meta-analysis. The participants' average age was 59.8 years old. For β-carotene intake, the pooled RR of any fracture was 0.67 (95% Credible Interval (CrI): 0.51-0.82; heterogeneity: P = 0.66, I 2 =0.00%) and 0.63 (95%CrI: 0.44-0. 82) for hip fracture. By study design, the pooled RRs were 0.55 (95% CrI: 0.14-0.96) for case-control studies and 0.82 (95% CrI: 0.58-0.99) for cohort studies. By geographic region, the pooled RRs were 0.58 (95% CrI: 0.28-0.89) for studies conducted in China, 0.86 (95% CrI: 0.35-0.1.37) in America and 0.91(95% CrI: 0.75-1.00) Europe. By gender: the pooled RRs were 0.88 (95% CrI: 0.73-0.99) for males and 0.76 (95% CrI: 0.44-1.07) for females. The probability that β-carotene intakes reduce the risk of any fracture and hip fracture by more than 20% was 95%.

Conclusion The present meta-analysis suggests that β-carotene intake was inversely associated with fracture risk, consistently observed for case-control and cohort studies. Further randomized control trial is warranted to confirm this finding.

Introduction

Osteoporotic fractures are widely recognized as a major public health problem in the elderly [1,2], its consequence is associated with high morbidity, mortality, and huge financial burden of healthcare, especially in the aging population [3,4]. Approximately, in lifetime the incidence of osteoporotic fracture affects 25% of females and 10% of males aged 60 years or above [5–7]. There were an estimated 9.0 million osteoporotic fractures (age ≥ 50 years) worldwide, of which 1.6 million were at the hip, 1.7 million were at the forearm, and 1.4 million were clinical vertebral fractures [8]. This impact is projected to increase over the next decades due to the increasing aging population [9].

Nutrition is an important modifiable factor influencing bone health [10]. Dietary intake of nutrients is a nonpharmacological intervention and prevention strategies for reducing the loss of bone quality or incidence of fracture. Several studies have investigated the effect of nutrition on bone health [10]. Fruit and vegetables are the major sources of beta-carotene antioxidants, which have bone health properties. A meta-analysis based on five prospective and two case-control studies reported that hip fracture risk was decreased by 28% among participants with higher (vs. lower) dietary consumption of total carotenoids and β-carotene [11]. Carotene may reduce fracture risk by counteracting oxidative stress, which also can adversely affect bone mineral density [12–15]. However, epidemiological studies inconsistently reported regarding individual beta-carotene intake and risk of fracture [16–23]. Therefore, this meta-analysis aimed to investigate the association between β-carotene intake and risk of fracture using a Bayesian hierarchical random effect model.

Materials And Methods

The meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24].

Study Selection

We systematically searched PubMed, EMBASE and Cochrane library database for relevant studies until December 2019. The medical subject heading (MeSH) used for the search were “Beta-carotene” OR “Carotenoids” OR “Vitamin A” OR “Carotene” AND “Bone fracture” OR “Fracture” OR “Osteoporosis”. We also performed a hand search based on reference lists from published articles. Studies included in this meta-analysis if they fulfill the following criteria: (1) written in the English language; (2) original

human studies; (3) the exposure of interest was β-carotene; (4) the outcome was fractures; (5) studies provided risk estimates for fractures.

Data Extraction

Two investigators (TGC and SY) independently extracted all relevant articles and identified eligible studies. During data evaluation, any disagreements were resolved through discussion. The following information was extracted from each included study: first author's, publication year, country of origin, study design, the percent of women, mean age of the participants, RRs and 95% CIs, fracture outcomes, exposure assessment methods and covariate adjustment .

Quality Assessment

Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of individual study [25]. This scale includes a set of items and assigns a maximum of nine stars to the following parameters: selection, comparability, exposure, and outcome. Studies with six star-items or less were considered as low quality, while with seven star-items or more were considered as high quality.

Statistical analysis

Bayesian hierarchical models were used to perform the random-effects meta-analysis. We employed the Bayesian approach for its flexibility and ability to model a small number of studies [26] and account for the uncertainty of the parameters of interest, which is particularly important when data is sparse [27]. The probabilities of exposure effect cannot be calculated with frequentist analyses since parameters of interest (i.e. RR) are treated as fixed. Moreover, Bayesian analyses allow prior information about the exposure effect to incorporate with current data (likelihood) to become the posterior distribution. The natural logarithmic of the RR follows a normal distribution with effect size (θ_i) and within-study variance (δ_i^2). It is a mandatory to specify prior distributions in the Bayesian Model. We applied three different prior distributions to the model: Non-informative prior [28], which assigns equal likelihood on all possible values of the θ_i (i.e. we set relative risk (RR) equals 1.0 with a large variance). In the skeptical prior distribution [29,30], we allowed only a 5% chance to observe a 10% risk change on fracture among β-carotene intake. For enthusiastic prior distribution: we assumed that β-carotene intake decrease the risk of fracture by half was 50%. A uniform distribution with (0, 10) and an inverse gamma distribution (0.1, 0.001) was used for between-study variance (τ^2).

In addition, subgroup analyses were performed based on study design, geographical region, gender and by the site of fracture. Heterogeneity across studies was assessed using Cochran's Q-statistic test and inconsistency was quantified by I^2 statistic[31,32]. The Egger's tests were performed to identify any possible evidence of publication bias [33]. All analyses were performed by the WinBUGS program (Version 1.4.3, MRC Biostatistics Unit, Cambridge, UK) and R program (Version: 3.4.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Study characteristics

A flow chart summarizing the process of study selection was shown in Fig. 1. A total of 343 articles were identified from the electronic database search. Of these, 230 articles were excluded due to duplicates and unrelated titles. After screening, 88 articles were excluded based on reading the title and abstract because of irrelevance to our study aim. Finally, 9 articles with a total of 190,545 men and women were included in the final analysis. Out of these, three studies were performed in the United States of America [14,15,21], one in Australia[34], three in China or Singapore[35 – 37], one in the Netherland[16] and one in United Kingdom of Britain [17] (Table 1). The participants' age was in the range of 25 to 90 years (average age: 59.8 ± 10.2 years). NOS scores of the studies ranged from 5 to 9 star and seven studies were scored 7 or more, which was considered as high-quality. The NOS score of each study was shown in Table 1.

Table 1

Characteristics of included studies on the association between beta-carotene intake and risk of fractures

Author, year	Study design	Sample size	Percent of Women	Fracture outcomes	Mean age	Exposure assessment	Covariate adjustment[]	Country	Quality score
Feskanich, 2002	Cohort	72,337	100	Hip fracture	60	FFQ: Self-reported	1, 7, 8, 14, 15, 16, 17, 18, 19, 20	USA	7
Zhang, 2006	C-C	2564	69.23	Hip fracture	75.2	FFQ: Self-reported	1, 2, 8, 9, 11, 12, 14, 18, 19, 21	USA	9
Sahni, 2009	Cohort	1046	61%	Hip fracture	75	FFQ: Self-reported	1, 2, 8, 9, 12, 14, 19, 21, 22	USA	8
Ambrosini, 2013	Cohort	2322	28.6	Any fracture	55	Medical records	1, 2, 6, 8, 14, 23	Australia	5
Sun, 2014	C-C	1452	NA	Hip fracture	70.5	FFQ: Self-reported	1,2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 13, 14	China	7
Dai, 2014	Cohort	63,154	55.8%	Hip fracture	56.3	FFQ: Self-reported	1, 3, 8, 9, 11, 12, 14, 15, 24, 25, 26, 27, 28	Singapore/ China	7
Jonge, 2015	Cohort	5288	58.9%	Any fracture	67	FFQ: Self-reported	1, 2, 3, 5, 8, 9, 11, 14, 29	Netherland	8
Hayhoe, 2017	Cohort	40,242	55.27	Any/hip/spine fracture	60.8	7-day food diaries	1, 6, 7, 8, 9, 11, 12, 14, 15, 30, 31	UK	9
Cao, 2018	C-C	2140	74.1	Hip fracture	70.6	FFQ: Self-reported	1, 3, 4, 5, 6, 7, 8, 10, 11, 12, 14, 32	China	5

% present of women in the individual study, [a] Mean age is the average age of the participant, C-C case-control, C-S cross-sectional, FFQ food frequency questionnaire, NA not available, USA United State of America, UK United Kingdom, and NOS Newcastle Ottawa Scale

[]Age (1), sex (2), educational level (3), occupation (4), household income (5), family history of fracture (6), smoking status (7), alcohol intake (8), Calcium use (9), multivitamin supplement use (10), physical activity (11), daily energy intake (12), dietary intake of selected nutrients (13), body mass index (14), use of postmenopausal hormones (15), hours of leisure-time activity (16), use of thiazide diuretics (17), protein use (18), vitamin D (19) and K (20), caffeine use (21), height (22), medication use (23), dialect group (24), vitamin B6 (25), soy isoflavones (26), history of diabetes and stroke (27), use of HRT (28), disability index (29), hormone replacement therapy (30), corticosteroid use (31), and Ca supplement use (32).

Association Between β-carotene Intake And Fracture Risk

The observed risk ratio [RR] and 95% confidence interval [CI] of fracture risk and overall RR was shown in Fig. 2. In the classical meta-analysis, the overall risk ratio of fracture risk was 0. 63 (95%CI: 0.52–0.77) for high (vs low) β-carotene intake. Statistically significant heterogeneity was found for fracture risk across included studies ($P < 0.001$, $I^2 = 94.1\%$).

Under the skeptical prior, β-carotene intake was associated with a 12% decrease in the risk of fracture (RR 0.88; 95% credible interval [CrI] 0.76–0.98) among high (vs low) intake. The posterior probability that β-carotene intake reduces the risk of any fracture by at least 20% was almost 95% (Table 2). We have noted a significant association between β-carotene intake and risk of hip fracture (RR 0.63; 95% CrI: 0.44–0.82), with heterogeneity across studies ($p < 001$, $I^2 = 91.8\%$; Fig.S1).

Table 2
Association between β-carotene intake and risk of fracture under the Bayesian meta-analysis

Subgroup	No. of studies	RR (95% CrI)	Probability (%) that risk ratio
			≤ 1.0 ≤ 0.9 ≤ 0.8
Overall studies	12	0.67 (0.51, 0.82)	1.00 0.99 0.95
Hip fracture	6	0.63 (0.44, 0.82)	0.99 0.99 0.95
By study design			
Case-control studies	3	0.55 (0.14, 0.96)	0.95 0.92 0.88
Cohort studies	6	0.82 (0.58, 0.99)	0.92 0.77 0.45
By Country			
USA	3	0.86 (0.35, 1.37)	0.75 0.62 0.46
Europe	3	0.91 (0.75, 1.00)	0.91 0.44 0.10
China/ Singapore	3	0.58 (0.28, 0.89)	0.97 0.95 0.91
By Gender			
Women	8	0.76 (0.44, 1.07)	0.92 0.83 0.66
Men	6	0.88 (0.73, 099)	0.91 0.85 0.75
Abreviation: RR: risk ratio; 95% CrI: 95% credible interval			

Subgroup Analysis

In subgroup analysis, the pooled RR of fracture risk was 0.82 (95% CrI: 0.58–0.99) in cohort studies and 0.55 (95% CrI: 0.14–0.96) in case-control studies (Table 2). Statistically significant evidence of heterogeneity was found in cohort studies ($p < 001$, $I^2 = 81.2\%$) but not in case-control studies ($p = 0.45$, $I^2 = 0.0\%$; Fig. 3). By geographic region, the pooled RR of fracture risk was 0.58 (95% CrI: 0.28–0.89) for studies conducted in China/Singapore, 0.86 (95% CrI: 0.35 – 0.1.37) in America and 0.91 (95% CrI: 0.75-1.00) in Europe. Evidence of heterogeneity was found across studies conducted in America ($p < 001$, $I^2 = 92.2\%$) and in China/Singapore ($p < 001$, $I^2 = 97.3\%$), but not in Europe ($p = 0.09$, $I^2 = 47.7\%$; Fig.S2). Subgroup analysis by gender, the pooled RR of fracture risk for males was 0.88 (95% CrI: 0.73–0.99) and 0.76 (95% CrI: 0.44–1.07) for females. Heterogeneity was found in males ($p < 001$, $I^2 = 79.4\%$) and females ($p < 001$, $I^2 = 95.0\%$; Fig.S3).

Publication Bias

The visualization of the funnel plot shows that there was no asymmetry across the studies (Fig. 3). Although, there was no statistically significant evidence of publication bias was found using Egger's test (P = 0.09) and Begg's test (P = 0.19).

Discussion

In this meta-analysis, we investigated the association between β-carotene intake and the risk of fractures. A total of 9 studies with 190,545 men and women were included. We found that β-carotene was associated with a 12% reduction in the risk of fracture. There also, a higher intake of β-carotene was associated with a lower risk of hip fracture. The findings of our meta-analysis suggested that higher dietary intake of β-carotene may have a favorable role in the protection of fracture risk.

To our knowledge, this is the first meta-analysis that synthesized the relationship between beta-carotene intakes from only dietary sources with the risk of fracture. Our findings were consistent with the results of a previous meta-analysis published by Xu et al. [11], who found that a high intake of dietary β-carotene was significantly decreased the risk of hip fracture by 28% (OR 0.72; 95% CI: 0.54–0.95). However, our findings were contradicted with recent meta-analysis [38], which revealed that higher β-carotene intake was weakly associated with the increased risk of total fracture (RR 1.07; 95% CI: 0.97, 1.17). The difference can be explained by a limited number of studies included for both total fracture and hip fracture risk by Zhang et al.[38], in their studies all sources of beta-carotene such as serum, plasma, and dietary intake were analyzed together.

In the current meta-analysis, we also found that an inverse association between beta-carotene intake and risk of fracture in cohort and case-control study; this may strength the robustness of our results. Regarding gender, we found that a lower risk of fracture for males compared to females among high (vs low) beta-carotene intakes. This may be a plausible result because due to hormone differences across gender, while this extends the results of the previous two meta-analyses [11,38] that reported a null association between beta-carotene intakes and fracture risk in females rather than in males. In a meta-analysis, the individual studies were performed in different geographical regions and the population also shared different genetic backgrounds, different dietary habits, and lifestyles, thus why it is no surprise to found inconsistent results across the continents.

The underlying mechanism for the association between beta-carotene intakes with lower incidence of fracture risk remains unclear. However, some probable biological mechanisms have been proposed: a sufficient intake of vitamin A including beta-carotene is essential for normal physiological activities [39] by affecting the growth hormone axis [40,41]. Although, some evidence from animal studies suggest that antioxidant β-carotene contributes as a body's defense against reactive oxygen species [42]. Thus, oxidative stress is thought to play an important role in the development of several chronic diseases including osteoporotic fracture. Therefore, antioxidant beta-carotene may have a beneficial effect against oxidative stress related to chronic diseases or osteoporosis. Indeed, β-carotene antioxidant seems a reactive oxygen species that enhance osteoclastogenesis and reduce osteoblast apoptosis by stabilizing the β-catenin signaling pathway, this leads to a decrease in bone resorption [43–45]. In addition, carotenoids may interfere with growth factor receptor signaling by regulating IGF-1/IGFBP3, which are associated with cognitive function [46], and impaired cognitive function is a known risk factor for falls and hip fracture [47].

There are some limitations in our meta-analysis. First, the beta-carotene intake consumption level is not consistent in most of the individual studies. In addition, the fruit and vegetable consumption patterns among countries are quite different; this might influence the reliability of our results. Second, the methods of beta-carotene intake assessment across studies are quite different, some of them used the standard form of food frequency questionnaire and the other not, and this also plays a great role in diverging our results. Third, the extracted relative risk was adjusted for multiple variables, and all included studies made an attempt to control for the confounding variables. However, some of the potential confounding factors (i.e., age, physical activity, supplementary carotenoid intake, smoking, and vitamins) have not been taken into account, which contributes to heterogeneity and sparse finding within individual's studies. Lastly, our analysis was based on observational studies, in which randomized control trials might be needed to confirm our findings.

Conclusions

The present meta-analysis summarized the association between beta-carotene intake and risk of fracture based on nine observational studies. We found that β-carotene intake was inversely associated with fracture risk, consistently observed for case-control and cohort studies. We suggest that a high intake of fruit and vegetable in rich β-carotene antioxidants might have a beneficial effect on bone health and reducing the risk of fractures.

Declarations

Author contributions

TGC and SY contributed to study conception and design. Literature search and analysis was performed by TGC. The first draft of the manuscript was written by TGC and all authors commented on the previous version of the manuscript. All authors read and

approved the final manuscript.

Funding: This study was partly supported by a research start-up and a grant from the Education Department of Jilin, China (Grant number: JJKH20190090KJ to Y.S.) from Shuman Yang.

Compliance with ethical standards

Competing Interests: All other authors have no conflicts of interest.

Ethical Approval

This article does not contain any studies with human participants performed by any of the authors.

Informed consent: NA

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Figures

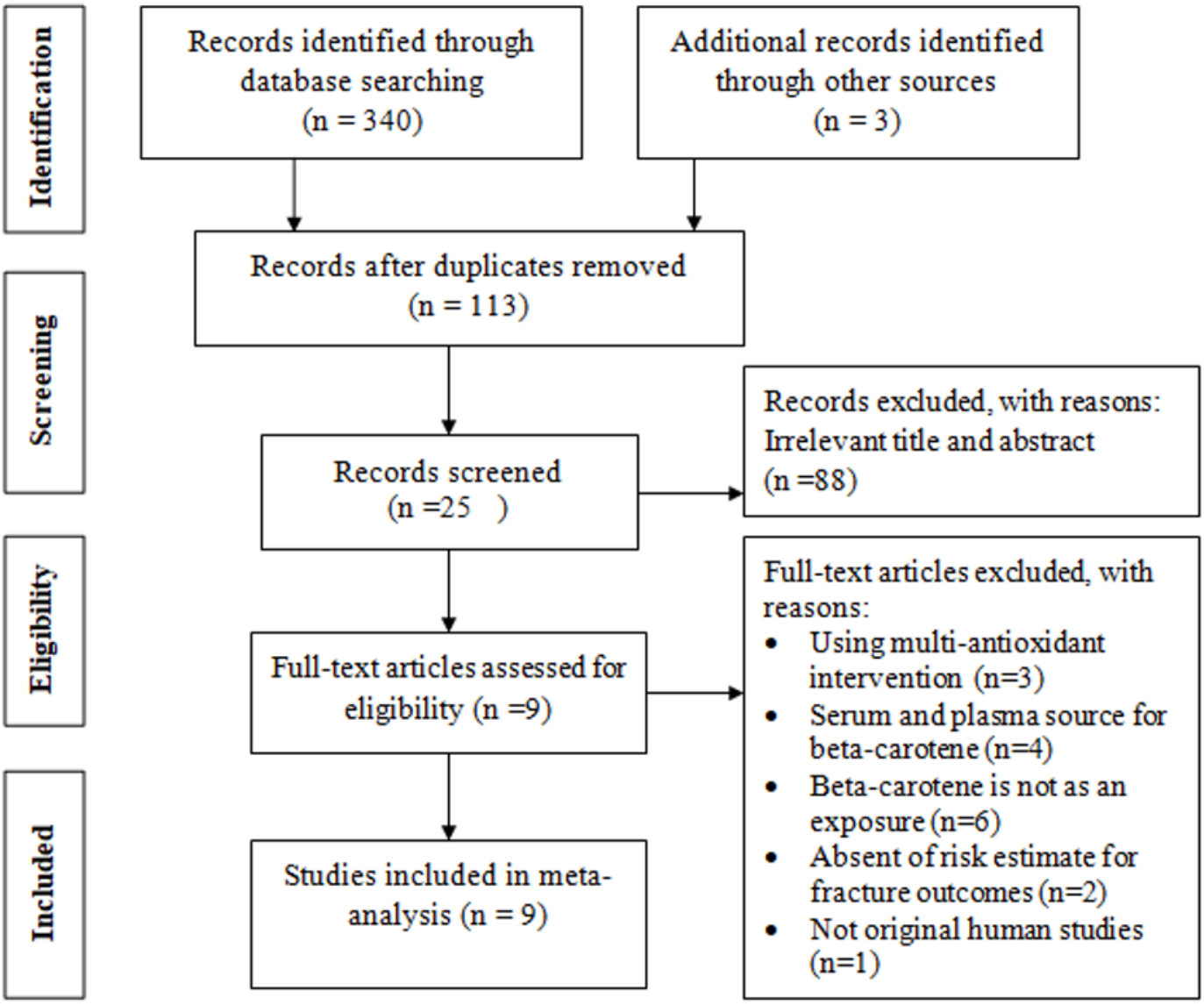

Figure 1

Flow chart for study inclusion and exclusions

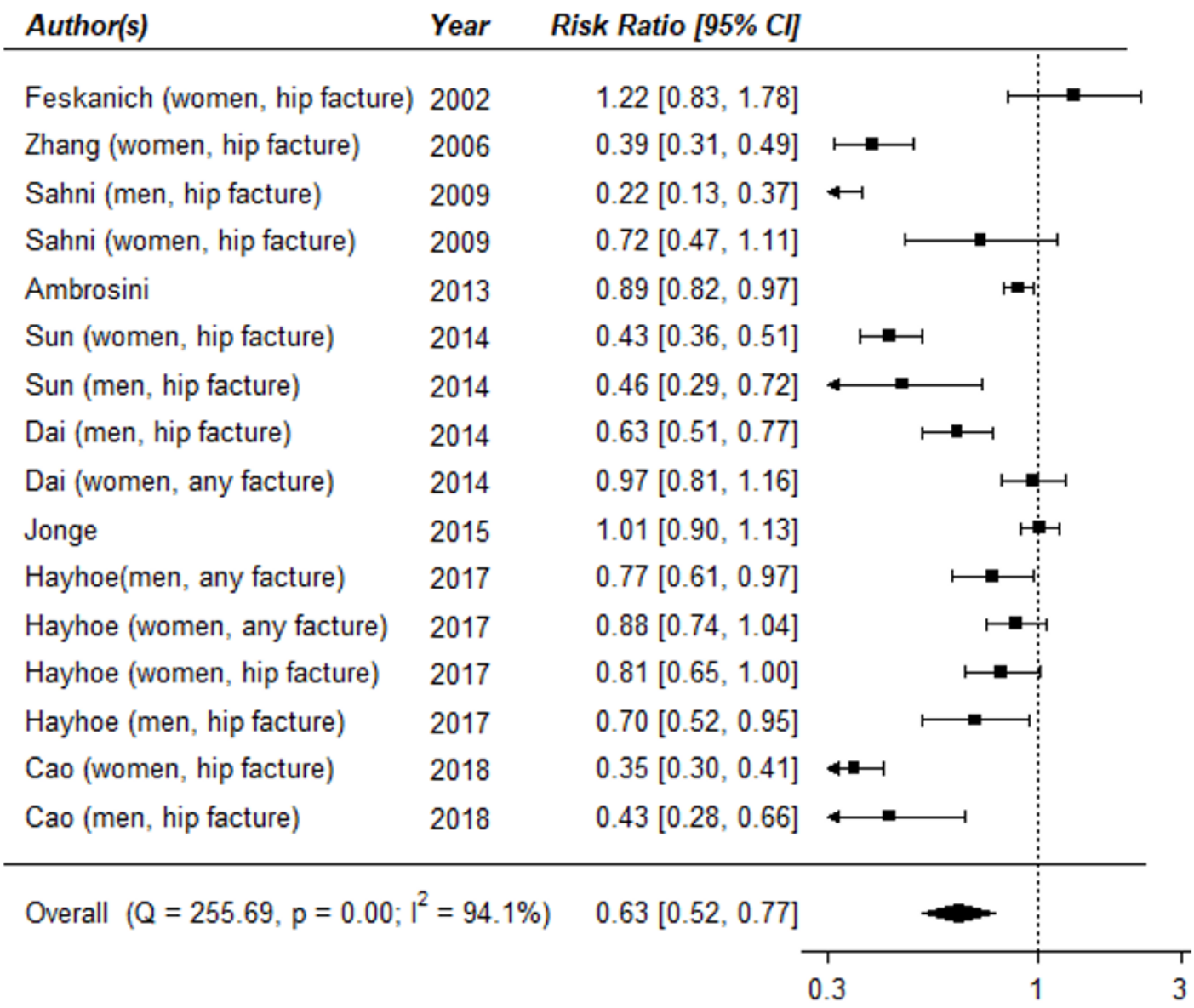

Figure 2

Forest plot of beta-carotene and risk of fracture for all studies under a classical meta-analysis

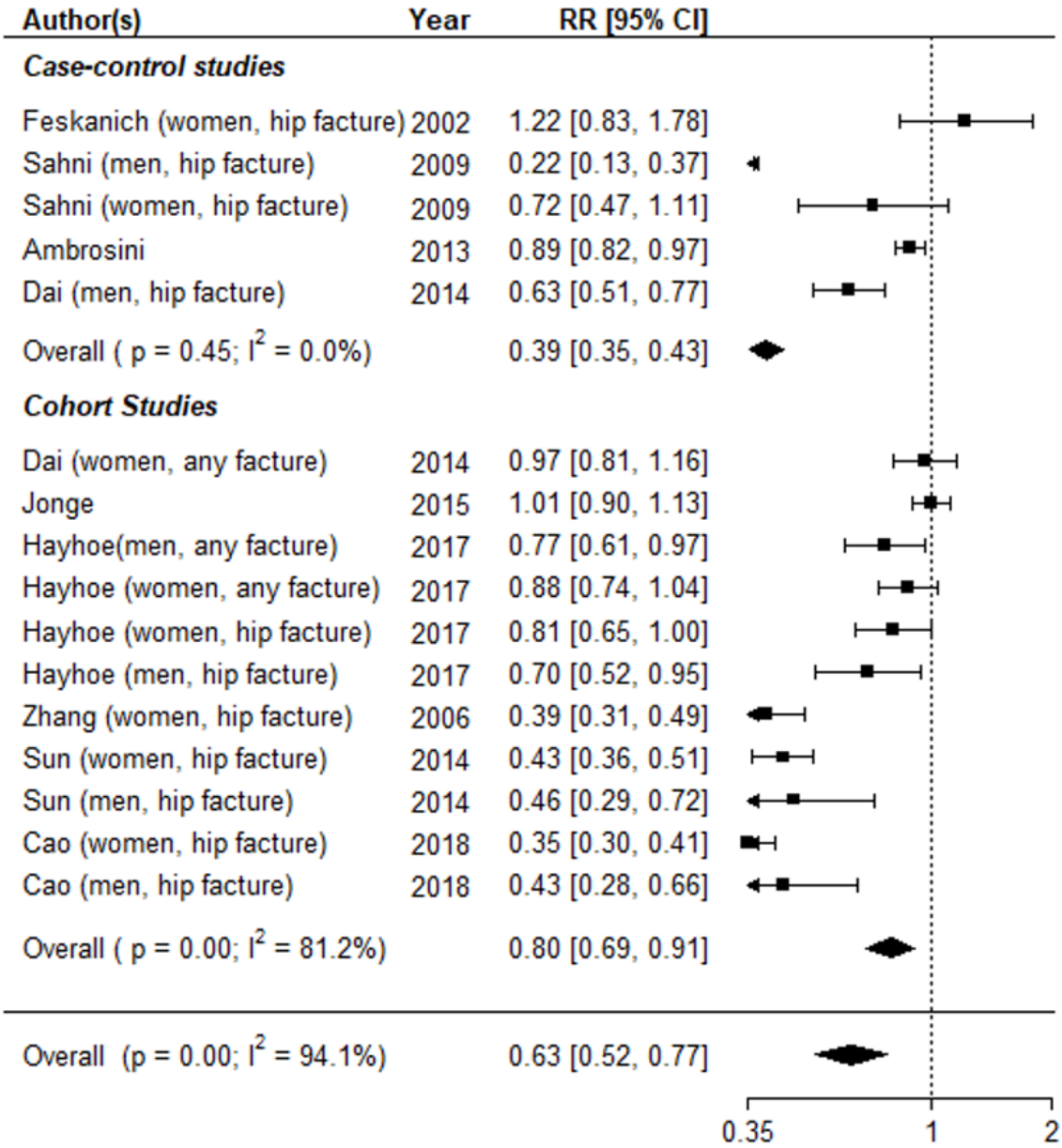

Figure 3

Forest plot of case-control and cohort studies of the association between β-carotene intake and risk of fracture under classical meta-analysis

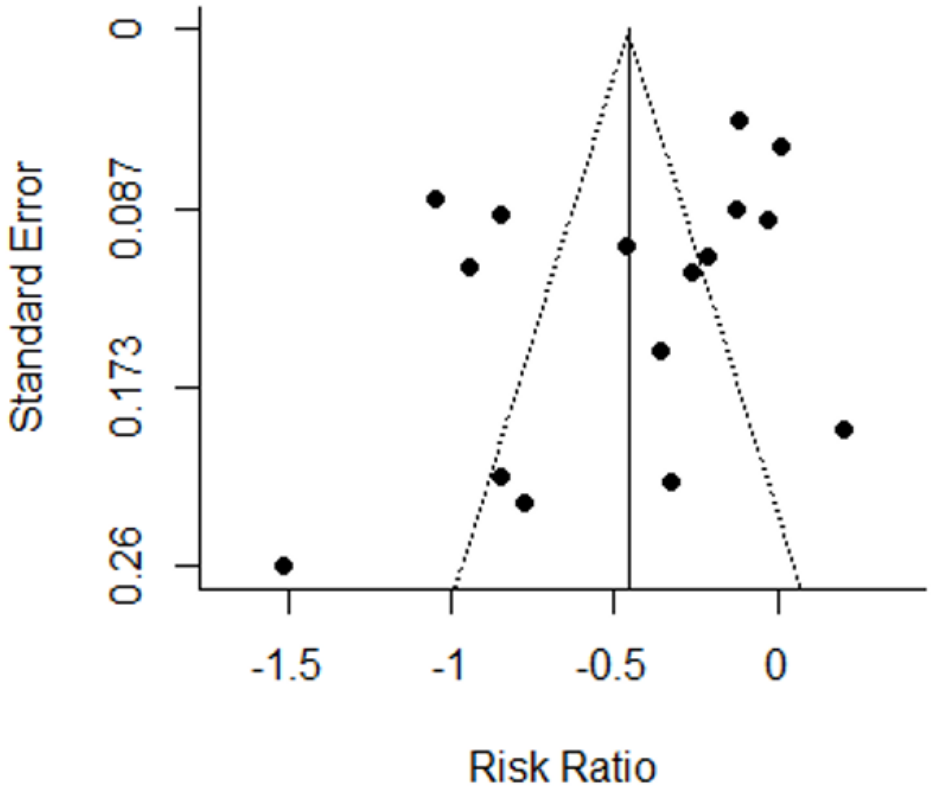

Figure 4

Funnel plot of publication bias, risk ratio versus standard error

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfigure.docx