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Association of fruit and vegetables with the risk of nasopharyngeal cancer: Evidence from a meta-analysis

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Quantification of the association between the intake of vegetables and fruit and risk of nasopharyngeal cancer (NPC) is controversial. Thus, we conducted a meta-analysis to assess the relationship between vegetables and fruit and NPC risk. Pertinent studies were identified by a search in PubMed, Web of Knowledge and Wan Fang Med Online. Random-effects models were used to calculate summary relative risks (RRs) and the corresponding 95% confidence intervals (CIs). Publication bias was estimated using Egger's regression asymmetry test. Finally, 15 articles comprising 8208 NPC cases were included in this meta-analysis. The combined results showed that there was significant association between vegetables and fruit intake and NPC risk. The pooled RRs were 0.60 (95% CI=0.47–0.76) for vegetables and 0.63 (95% CI=0.56–0.70) for fruit. No publication bias was detected. Our analysis indicated that intake of vegetables and fruit may have a protective effect on NPC. Since the potential biases and confounders could not be ruled out completely in this meta-analysis, further studies are needed.

Nasopharyngeal cancer (NPC) is rare in most parts of the world, where incidences of age standardized rates are generally below 1 per 100,000 person-years[1]. But it is a common malignancy in southern China[2]. The incidence rate for males is more than 20 per 100,000 person-years and is as high as 25 to 40 per 100,000 person-years in some areas bordering the Xijiang River and the Pearl River[2–4]. The distinctive geographic and ethnic distribution of NPC worldwide suggests that genetic predisposition, dietary and environmental factors, and Epstein-Barr virus (EBV) all have been associated with the pathogenesis of this tumor[5].

The intake of fruit and vegetables has long been associated with a decreased risk of various cancers, including NPC. The suggested mechanisms for the major role of vegetables and fruit in the prevention of cancer include: modulation of DNA methylation; protection from and repair of DNA damage; promotion of apoptosis and induction of detoxifying phase-II enzymes[6]. Up to date, a number of epidemiologic studies have been published to explore the relationship between vegetables and fruit intake and NPC risk. However, the results are not consistent. Therefore, we performed a comprehensive meta-analysis to test the hypothesis that vegetables and fruit intake may be a protective effect on NPC risk.

Methods

Search strategy. A comprehensive search was conducted for available articles published in English or Chinese using the databases of PubMed, Web of Knowledge and Wan Fang Med Online (http://www.wanfangdata.com.cn/) up to November 2013 and by hand-searching the reference lists of the computer retrieved articles. The following search terms were used: 'nasopharyngeal' AND (neoplasm OR carcinoma OR cancer) combined with "nutrition OR diet OR lifestyle OR fruit OR vegetable." Two investigators (JJ and ZO) searched articles and reviewed of all retrieved studies independently. Disagreements between the two investigators were resolved by consensus with a third reviewer (ZW).

Inclusion criteria. All relevant studies reporting the association of vegetables and fruit and NPC risk were considered for inclusion. The inclusion criteria were as follows: (1) use a case-control, nested case-control or cohort design; (2) the exposure of interest were vegetables and fruit or total vegetables or total fruit; (3) the outcome of interest was NPC; (4) report associations in the form of RR with the 95% confidence intervals (CI) for total vegetables or total fruit or providing us with sufficient information to calculate them. Accordingly, the following exclusion criteria were also used: (1) reviews and (2) repeated or overlapped publications. In the present meta-analysis, we included the studies evaluating fruit or vegetable groups classified as "all" or "total." Exposures presented as cooked vegetables, raw vegetables, other vegetables, citrus fruit or other fruits were not considered as equivalent to "all" or "total" and thus were not included. Studies that reported "fresh vegetables" or "fresh fruit" were included according to the hypothesis that fresh vegetables or fruit accounts for a very high proportion of the total consumption[7].

Data extraction. Two researchers (JJ and ZO) independently extracted the following information: the name of the first author, study design, publication year, geographic locations, the number of cases and controls or participants, type of controls, the methods used for collection of data on exposure, exposure classification, confounders adjusted for and the RR estimates with corresponding 95% CI for the highest versus lowest level (Every study has one group for the highest versus the lowest amount). From each study, we extracted the risk estimates adjusted for the greatest number of potential confounders. If there was disagreement between the two investigators about eligibility of the data, it was resolved by consensus with a third reviewer (ZW).

Statistical analysis. The pooled measure was calculated as the inverse variance-weighted mean of the natural logarithm of multivariate adjusted RR with 95% CI for the highest vs. lowest levels to assess the association of vegetables and fruit intake with the risk of NPC. The DerSimo-nian and Laird random effect model was adopted as the pooling method if substantial heterogeneity is present ($I^2 > 50\%$); otherwise, the fixed effect model ($I^2 < 50\%$) was used as the pooling method[8]. The Q test and I^2 of Higgins and Thompson[9] were used to assess heterogeneity among included studies. I^2 describes the proportion of total variation attributable to between-study heterogeneity as opposed to random error or chance. Meta-regression with restricted maximum likelihood estimation was performed to describe the potentially important covariates[10]. If no significant covariates were found to be heterogeneous, the "leave-one-out" sensitive analysis[11] was carried out to evaluate the key studies with substantial impact on between-study heterogeneity. Publication bias was estimated using Begg' funnel plot[12] and Egger's regression asymmetry test[13]. A study of influence analysis[14] was conducted to describe how robust the pooled estimator is to removal of individual studies. An individual study is suspected of excessive influence if the point estimate of its omitted analysis lies outside the 95% CI of the combined analysis. Study quality was assessed using the 9-star NewcastleeOttawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, accessed 10/14/2013). All analyses were conducted using STATA software, version 10.0 (StataCorp LP, College Station, Texas). Two-tailed $P \leq 0.05$ was accepted as statistically significant. For testing the heterogeneity and publication bias, two-tailed $P \leq 0.1$ was accepted as statistically significant.

Results

Search results and study characteristics. The search strategy identified 5252 articles from Pubmed, 23 articles from Wan Fang Med Online and 6144 articles from the Web of Knowledge, and 29 articles were reviewed in full after reviewing the title/abstract. By studying reference lists, we identified 2 additional articles. Sixteen of these 31 articles were subsequently excluded from the meta-analysis for various reasons. Hence, 15 articles[15–29] (one prospective and 14 case–control articles) involving 8208 NPC cases were used in this meta-analysis. The detailed steps of our literature search are shown in Figure 1. The characteristics of these studies are presented in Table 1. Twelve articles were from China, one from America, one from Italy and one from Africa.

Total vegetables. *High versus low analyses*. For vegetable intake and NPC, data from 10 articles[15,18,20,23–29] with 11 case-control studies were used including 3749 NPC cases and 4452 controls. Inverse association of vegetable intake with risk of NPC was reported in 4 studies, and no significant association of vegetable intake with risk of NPC was reported in 7 studies. Pooled results suggested that highest vegetable intake versus lowest level was significantly associated with the risk of NPC [summary RR=0.60, 95% CI=0.47–0.76, I^2=50.0%, $P_{heterogeneity}$=0.03] (Figure 2). The power of effect estimates is 0.86 for vegetables while α=0.05 in this study.

Sources of heterogeneity and subgroup analyses. As seen in Figure 2, evidence of heterogeneity (I^2=50.0%, $P_{heterogeneity}$=0.03) was found in the pooled results. However, univariate meta-regression analysis, with the covariates of study region, number of cases, and sources of controls showed no covariate having a significant impact on between-study heterogeneity, respectively. The key contributor to this high between-study heterogeneity assessed by the leave-one-out analysis was one study conducted by Liu et al (2012). After excluding this study, heterogeneity was reduced to I^2 = 6.9%, and the summary RR for NPC was 0.67 (95% CI=0.56–0.80; $P_{heterogeneity}$ = 0.14).

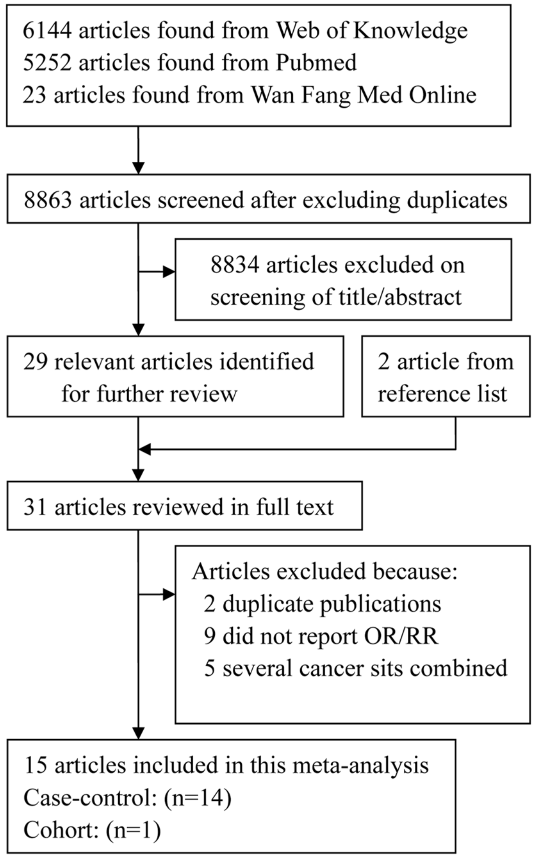

Figure 1 | The flow diagram of screened, excluded, and analyzed publications.

In subgroup analyses for ethnicity, when we restricted the analysis to Asia and Caucasian, the pooled RR of NPC for the highest category of vegetable intake versus the lowest category were 0.58 (95% CI=0.39–0.85) and 0.65(0.45–0.94), respectively. When we conducted the subgroup analysis by sources of control, number of cases (<200 or ≥200)[7], adjustment for smoking or alcohol, the significant associations were found between vegetable intake and NPC in all strata. The main results are summarized in Table 2.

Influence analysis and publication bias. Influence analysis showed that no individual study had excessive influence on the association of vegetable intake and NPC. Begg's funnel plot (Figure 3) and Egger's test showed no evidence of significant publication bias between vegetable intake and NPC (Table 2).

Total fruit. *High versus low analyses*. Data from 10 articles[15,17–22,25,27,29] (1 prospective study and 9 case-control studies) for fruit intake and NPC risk were used including 6155 NPC cases 6654 controls. Four studies reported that fruit intake can reduce the NPC risk, while 6 studies didn't showed the significant association between fruit intake and NPC risk. The meta-analysis showed an inverse association between total fruit intake and NPC risk (summary RR=0.63, 95% CI=0.56–0.70) (Figure 4). There was no evidence of heterogeneity was found (I^2=0.0%, $P_{heterogeneity}$=0.78). The power of effect estimates is 0.91 for vegetables while α=0.05 in this study.

Subgroup analyses. Nine case-control studies were included in this meta-analysis, and the pooled RR was 0.61 (95% CI=0.54–0.69) for the highest category of fruit intake versus the lowest category and NPC risk. For the subgroup of ethnicity, the associations were significant in the Asia (RR=0.62, 95% CI=0.55–0.70) and Caucasian (RR=0.66, 95% CI=0.49–0.91). Inverse associations of fruit intake

Table 1 | Characteristics of studies on vegetables and fruit and NPC risk

First author, year	Country	Study design	Cases, age	Quality score	RR (95% CI) for highest versus lowest category	Adjustment or matched for
Polesel et al. 2013	Italy	Case-control (HCC)	198, Cases: 52 Controls: 52	8	0.51(0.29–0.90) for vegetable 0.68(0.40–1.16) for fruit	Age, sex, place of living, year of interview, education, tobacco, smoking, alcohol drinking, and non-alcohol energy
Li et al. 2012	China	Case-control (HCC)	100, Cases: 48.2 Controls: 48.6	7	0.19(0.05–0.68) for vegetable and fruit combined	Age, sex
Shen et al. 2012	China	Prospective	1533, 46.1	7	0.78(0.53–1.14) for fruit	Age, BMI, spouse, education, clinical stage, smoking status, alcohol intake
Liu et al. 2012	China	Case-control (HCC)	600, Cases: 47.39 Controls: 47.34	7	0.37(0.25–0.55) for vegetable and fruit combined 0.33(0.22–0.50) for vegetable 0.70(0.47–1.04) for fruit	BMI, educational level, marital status, occupation, household income, occupational and domestic exposure to potential toxic substances, chronic rhinitis history, smoking status, passive smoking, daily energy intake (log-transformed), and energy-adjusted intakes of other food groups (including preserved vegetables, cereals, soybeans, fresh meats, preserved meats, roasted meats, dairy products, nuts and vegetables or fruits) by stepwise forward method
Turkoz et al. 2011	Turkey	Case-control (HCC)	183, Cases: 44.9 Controls: 43.9	8	0.59(0.38–0.94) for fruit	Age and sex
Xu et al. 2010	China	Case-control (HCC)	184, Cases: 45.9 Controls: 47.7	7	0.30(0.18–0.50) for vegetable and fruit combined 0.44(0.27–0.72) for vegetable 0.56(0.34–0.92) for fruit	Age, sex, place of living, occupation, educational level, income, smoking status, daily energy intake
Jia et al. 2010	China	Case-control (HCC)	1387, Cases: 46.92 Controls: 47.34	6	0.63(0.51–0.77) for fruit	Age, sex, education, dialect and household type
Luo et al. 2009	China	Case-control (PCC)	1256, Cases: 47 Controls: 47.23	7	0.56(0.45–0.70) for fruit	Age, sex, place of living
Feng et al. 2007	Africa	Case-control (HCC)	636, 15–81	7	0.6(0.4–0.8) for vegetable	Age, sex, socio-economic status variables and exposure to toxic substances
Yuan et al. 2000	China	Case-control (PCC)	935, 15–74	8	0.85(0.65–1.10) for vegetable	Age, gender, level of education, cigarette smoking, exposure to smoke from heated rapeseed oil and burning coal during cooking, occupational exposure to chemical fumes and history of chronic ear and nose condition (see text for more detailed description of confounding variables)
Ward et al. 2000	China	Case-control (PCC)	375, ≤75	7	0.9(0.3–2.6) for vegetable 0.9(0.3–2.3) for fruit	Age, gender and ethnicity
Armstrong et al. 1998	China	Case-control (PCC)	282, Cases: 45.29 Controls: 44.82	7	0.50(0.23–1.07) for vegetable	Age, sex, residence and marital status
Farrow et al. 1998	United States	Case-control (PCC)	133, 18–74	8	0.99(0.51–1.94) for green vegetable 0.59(0.29–1.22) for yellow vegetable 0.87(0.41–1.83) for fruit	Age, alcohol consumption (0–6, 7–13, 14–20, or 21+ drinks per week), cigarette smoking (never, former, current with history of 1–34 pack years, current with history of 35–59 pack years or current with history of 60+ pack years), total caloric intake, broccoli, cauliflower, spinach, mustard or turnip greens, coleslaw, winter squash, carrots, yams
Ning et al. 1990	China	Case-control (PCC)	100, Cases: 44.9 Controls: 45.2	7	0.8(0.3–1.9) for vegetable	Age (yr of birth within 5 yr), sex, and race (Han)
Yu et al. 1989	China	Case-control (PCC)	306, ≤50	6	0.77(0.20–3.33) for vegetable 0.3(0.1–1.1) for fruit	Age, sex

Abbreviations: PCC= population-based case–control study; HCC: hospital-based case–control study; BMI: Body Mass Index.

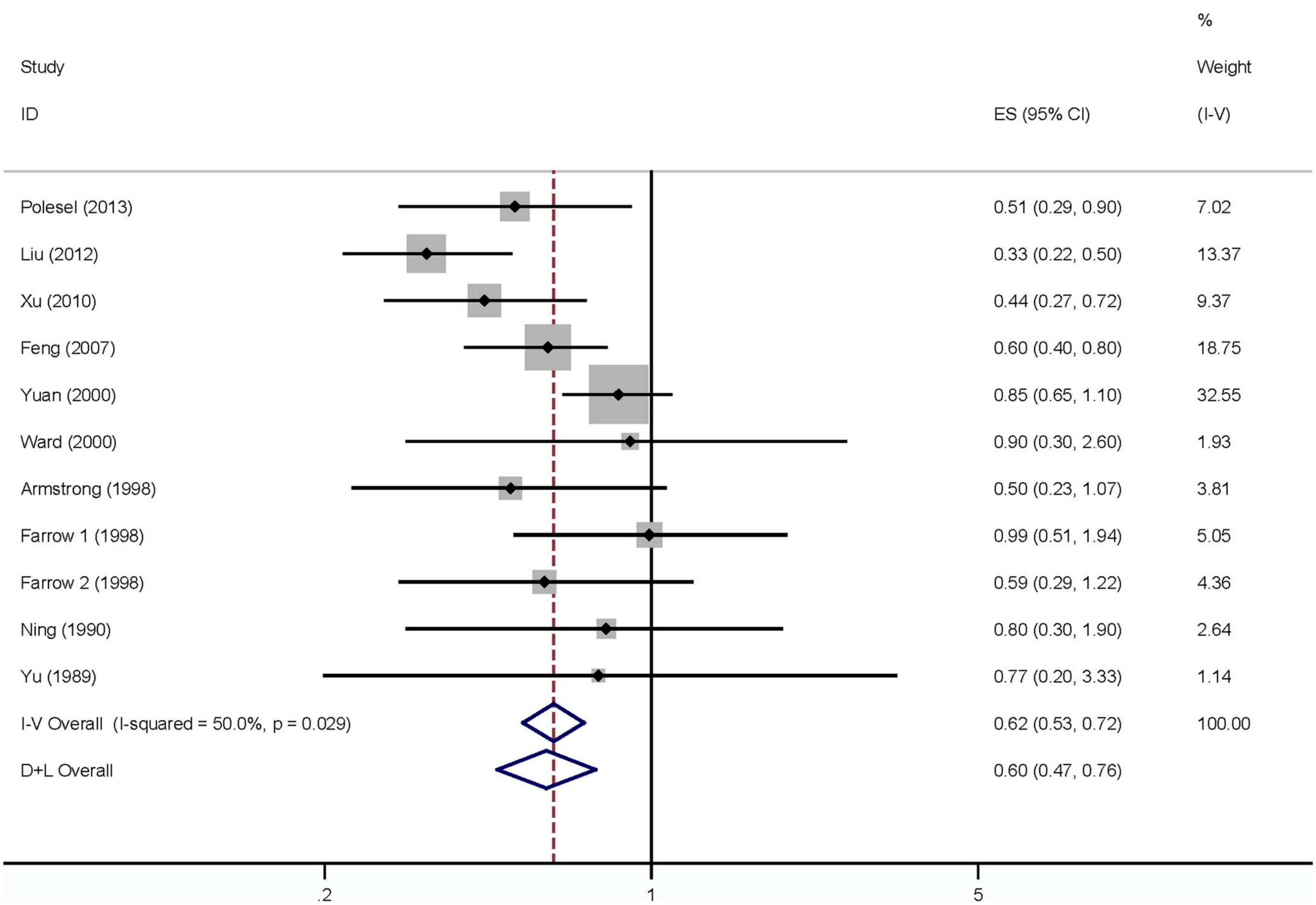

Figure 2 | The forest plot between highest versus lowest categories of vegetables intake and NPC risk.

with risk of NPC were found in all strata for the subgroups of sources of control, number of cases, adjustment for smoking or alcohol, respectively. The main results are summarized in Table 2.

Influence analysis and publication bias. No individual study had excessive influence on the association of fruit intake and NPC in the influence analysis. Begg's funnel plot (Figure 5) and Egger's test

Table 2 | Summary risk estimates of the association between vegetables and fruit and NPC risk

	Vegetables							Fruit						
Sub-groups	Studies, n	RR(95%CI)[a]	P^b	Q value	I^2 (%)	P^c	P^d	Studies, n	RR(95%CI)[a]	P^b	Q value	I^2 (%)	P^c	P^d
All	11	0.60(0.47–0.76)	0.00	20.0	50.0	0.03	0.81	10	0.67(0.58–0.70)	0.00	9.0	0.0	0.78	0.60
Case-control	11	0.60(0.47–0.76)	0.00	20.0	50.0	0.03	0.81	9	0.61(0.54–0.69)	0.00	8.0	0.0	0.84	0.68
Sources of control														
Population-based	7	0.80(0.65–0.99)	0.04	6.0	0.0	0.84	0.43	4	0.58(0.47–0.71)	0.00	3.1	3.3	0.38	0.75
Hospital-based	4	0.47(0.380.58)	0.00	4.9	38.9	0.18	0.51	5	0.63(0.54–0.74)	0.00	4.0	0.0	0.96	0.47
Ethnicity														
Asia	7	0.58(0.39–0.85)	0.00	17.6	65.9	0.01	0.67	7	0.62(0.55–0.70)	0.00	6.1	0.0	0.59	0.69
Caucasian	3	0.65(0.45–0.94)	0.03	2.9	13.0	0.32	0.24	3	0.66(0.49–0.91)	0.01	2.0	0.0	0.68	0.42
Publication language														
Chinese	1	0.44(0.27–0.72)	--	--	--	--	--	2	0.63(0.56–0.70)	0.00	1.1	0.0	1.00	0.52
English	10	0.64(0.55–0.75)	0.00	17.9	49.9	0.04	0.73	8	0.66(0.57–0.77)	0.00	7.0	0.0	0.80	0.79
Number of cases														
<200	5	0.58(0.44–0.77)	0.00	4.3	8.0	0.36	0.46	4	0.63(0.49–0.82)	0.00	3.0	0.0	0.78	0.51
≥200	6	0.59(0.41–0.86)	0.01	15.4	67.6	0.01	0.52	6	0.63(0.55–0.71)	0.00	4.9	0.0	0.48	0.69
Adjustments														
Smoking, yes	6	0.57(0.39–0.84)	0.00	18.8	73.4	0.00	0.63	4	0.69(0.56–0.86)	0.00	3.0	0.0	0.78	0.40
no	5	0.63(0.47–0.83)	0.00	4.0	0.0	0.88	0.49	6	0.60(0.53–0.69)	0.00	5.0	0.0	0.63	0.58
Alcohol, yes	3	0.65(0.45–0.94)	0.03	2.9	13.0	0.32	0.16	2	0.74(0.55–1.02)	0.06	1.1	0.0	0.68	0.73
no	8	0.58(0.43–0.79)	0.00	17.6	60.3	0.01	0.65	8	0.61(0.54–0.69)	0.00	7.1	0.0	0.78	0.49

[a]The random effect model was adopted the pooling method if I2>50%; otherwise, the fixed effect model (I^2<50%) was used as the pooling method.
[b]the P value for RR; [c]the p value for heterogeneity; [d]the p value for publication bias.

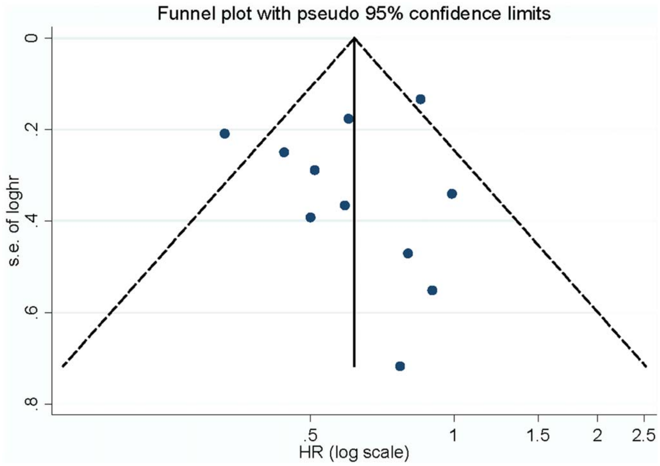

Figure 3 | Begg's funnel plot for publication bias of vegetables intake and NPC risk.

($P=0.60$) showed no evidence of significant publication bias between fruit intake and NPC risk (Table 2).

Total vegetables and fruit. Three studies[16,18,20] were conducted to assess the association between total vegetables and fruit and NPC risk, and the summary RR for the highest versus the lowest intake was 0.33 (95% CI=0.25–0.45, $I^2=0.0\%$, $P_{heterogeneity}=0.56$) for fruits and vegetables combined.

Discussion

Finding from this meta-analysis suggested that the intake of fruit and vegetables is associated with significant reductions in the risk of NPC. The associations were also found in subgroups of Asia and Caucasian for vegetables or fruit intake and NPC risk.

One previous meta-analysis has suggested that a favorable effect was found between the intake of fruit and vegetables and risk of esophageal squamous cell carcinoma[7]. Although no association was found between vegetables and breast cancer risk, inverse associations of fruits intake and fruits and vegetables combined with risk of breast cancer were found[30]. In the lung cancer study, cruciferous vegetables intake was showed a favorable effect for female in a meta-analysis[31]. Furthermore, cruciferous vegetables intake has a significantly decreased risk with renal cell carcinoma[32], colorectal neoplasms[33] and gastric cancer[34]. Our meta-analysis result is consisted with most of the published studies.

The mechanisms of the anti-NPC properties of fruit and vegetables have not been thoroughly investigated. As we know, the epidemiology of NPC varies greatly between Asia (predominantly WHO type 3) and the rest of the world (predominantly WHO Type 1). Although they are difference in histology because of traditionally, the natural history and risk factors for WHO type 1 and 3 nasopharyngeal carcinoma, the association of fruits and vegetables with NPC remains consistent. A few in vitro and epidemiological studies have discovered mechanisms that allow fruit and vegetables to protect against other cancers[35–37]. Antioxidants and dietary fibers might play a key role in the prevention of NPC development. The protective effects of vegetables and fruit are thought to be mediated by multiple components, including beta-carotene, fiber, vitamins, alpha-tocopherol, retinoids, phytoestrogens and folate[5]. These components are involved in numerous biological processes that may alter cancer risk, including the inhibition of cell growth, the normal synthesis and methylation of DNA, and protection against oxidative stress and DNA damage.

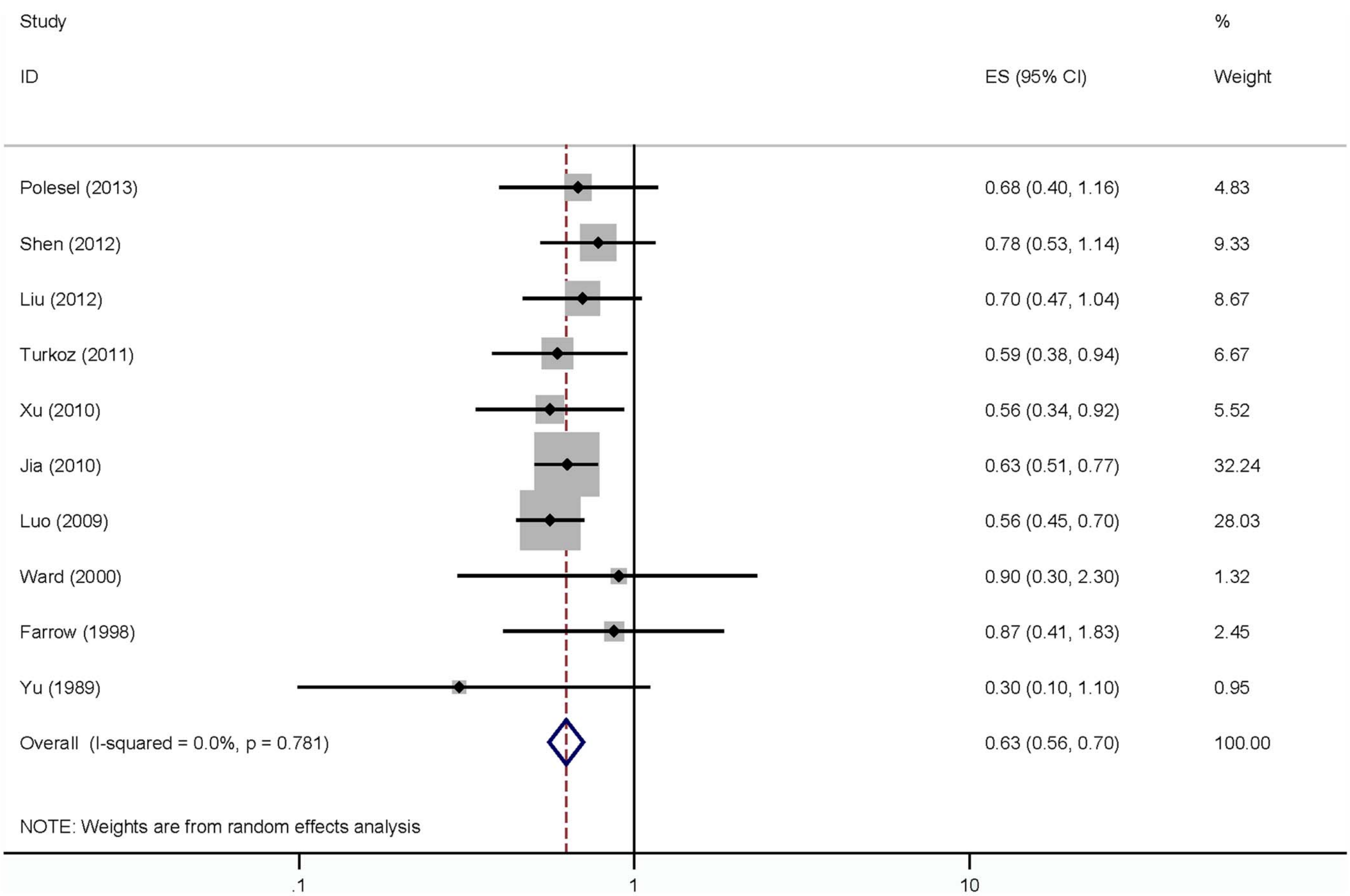

Figure 4 | The forest plot between highest versus lowest categories of fruit intake and NPC risk.

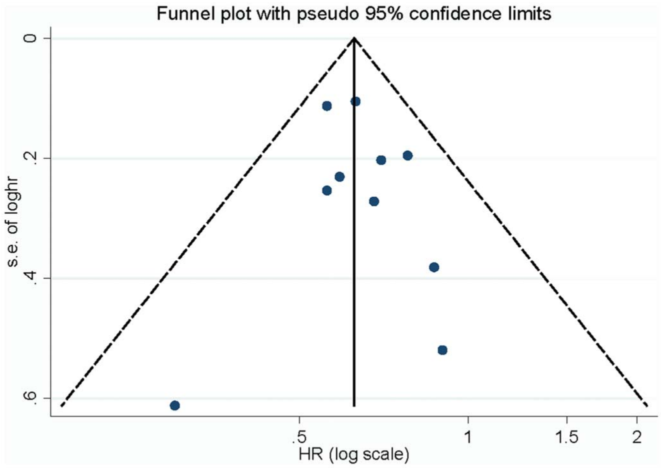

Figure 5 | Begg's funnel plot for publication bias of fruit intake and NPC risk.

Between-study heterogeneity is common in meta-analysis[38], and exploring the potential sources of between-study heterogeneity is the essential component of meta-analysis. For vegetable intake and NPC, evidence of heterogeneity ($I^2=50.0\%$, $P_{heterogeneity}=0.03$) was found in the pooled results. The between-study heterogeneity might arise from study region, number of cases and sources of controls. Thus, we used meta-regression to explore the causes of heterogeneity for covariates. No covariate having a significant impact on between-study heterogeneity for the above mentioned covariates. Then, we used "leave-one-out" sensitive analysis, which aims to reduce between-study heterogeneity and explore the potential important causes of between-study heterogeneity for both covariates and studies. The key contributor to this high between-study heterogeneity was one study conducted by Liu et al[16]. After excluding this study, heterogeneity was reduced to $I^2 = 6.9\%$ and the association was also significant between vegetable and NPC risk. For the larger studies (≥200), high heterogeneity was found ($I^2=67.6\%$, $P_{heterogeneity}=0.01$). The key contributor to this high between-study heterogeneity assessed by the leave-one-out analysis was one study conducted by Liu et al (2012). The study conducted by Liu et al. has large participants (600 cases and 600 controls), and the RR was 0.33 (95% CI=0.22–0.50). After excluding this study, heterogeneity was reduced to $I^2 = 0.0\%$, and the summary RR for NPC was 0.73 (95% CI=0.60–0.89).

As a meta-analysis of published studies, our findings showed some advantages. First, a major strength of this study was the large number of participants included in this analysis and this may derive a more precise estimation of the relationship between vegetables and fruit and NPC risk. Second, no significant publication bias was found. However, there were some limitations in this meta-analysis. First, a meta-analysis of observational studies is susceptible to potential bias inherent in the original studies, especially for case-control studies. Overstated association may be expected from the case-control studies because of recall or selection bias, and early symptoms in patients may have resulted in a change in dietary habits. Second, measurement errors are important in the assessment of dietary intake, which can lead to overestimation of the range of intake and underestimation of the magnitude of the relationship between dietary intake and cancer risk[39,40]. Third, incomparability of results between studies may also occur because definitions and categories of vegetables and fruit as well as analytical comparisons vary across studies. Studies from different regions, ethnicities and periods probably address very different exposures. However, we only decided to consider the studies that evaluated all types of fruit or vegetables to assess exposure that was as broad as possible. Finally, small sample sizes in subgroup analysis were present, more studies need to confirm the result.

In summary, results from this meta-analysis suggested that intake of fruit and vegetables may have a protective effect on NPC. Since the potential biases and confounders could not be ruled out completely in this meta-analysis, further studies are warranted to confirm this result.

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Author contributions

J.J. and Z.W. designed of the experiments; J.J., Z.O. and Z.W. collected the date; J.J. and Z.W. wrote the main manuscript text and all authors reviewed the manuscript.

Additional information

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