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Consumption of fruit and vegetable and risk of coronary heart disease: A meta-analysis of prospective cohort studies

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ABSTRACT

Background: Observational studies suggest that an association between fruit and vegetable consumption and coronary heart disease (CHD). However, the results are inconsistent. We conducted a meta-analysis to evaluate the relationship of fruit and vegetable consumption with CHD risk and quality the dose–response relationship between them.

Methods: Relevant prospective studies were identified by a search of PubMed, Embase and Web of Science databases to July 2014. A random-effects model was used to calculate the pooled relative risk (RR) and 95% confidence intervals (CI).

Results: Twenty-three studies involving 937,665 participants and 18,047 patients with CHD were included. Compared with the lowest consumption levels of total fruit and vegetable, fruit and vegetable, the RR of CHD was 0.84 (95% CI, 0.79–0.90), 0.86 (95% CI, 0.82–0.91), 0.87 (95% CI, 0.81–0.93), respectively. The dose–response analysis indicated that, the RR of CHD was 0.88 (95% CI: 0.85–0.91) per 477 g/day of total fruit and vegetable consumption, 0.84 (95% CI: 0.75–0.93) per 300 g/day of fruit intake and 0.82 (95% CI: 0.73–0.92) per 400 g/day of vegetable consumption. A nonlinear association of CHD risk with fruit or vegetable consumption separately was found (P for nonlinearity <0.001). In the subgroup analysis of location, a significant inverse association was observed in Western populations, but not in Asian populations.

Conclusions: This meta-analysis indicates that total fruit and vegetable, fruit and vegetable consumption, are significantly associated with a lower risk of CHD. The significant inverse association was found in Western populations, but not in Asian populations, which warrants further research.

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1. Introduction

Coronary heart disease (CHD) is a major cause of disease burden in both developed and developing nations. It is the leading cause of death and permanent disability, with heavy economic and social costs owing to functional impairments [1,2]. Therefore the primary prevention of CHD is an important public health and clinical medicine priority.

Foods and nutrients are important, which are one of the main determinants of CHD. Of foods and nutrients, the role of fruit and vegetable has been of increasing interest since they are a good source of micronutrients, macronutrients and fiber requirements without adding substantially to total energy intake [3]. Fruits and vegetables are rich in antioxidant vitamins, minerals (e.g., potassium and magnesium), dietary fiber, and phytochemicals [4]. Controlled trials have shown that fruit and vegetable consumption has beneficial effects on several risk factors of CHD, including lipid levels [5], inflammation [6], and blood pressure [7].

A meta-analysis [8] in 2007 concluded that fruit and vegetable intake >5 servings/day was associated with lower risk of CHD. However, there are some limitations in the review. Firstly, the meta-analysis only included twelve studies. Since then, a number of additional studies have been published. Secondly, it did not assess the potential dose–response relationship. Thirdly, several issues emerging from the inconsistent results of later studies still warranted to be demonstrated, including whether it was total fruit and vegetable consumption that prevent the risk of CHD, fruit or vegetable separately, and whether the associations were consistent in both sexes and different ethnic backgrounds, respectively [9], and what levels of consumption of fruit

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and vegetable that had the greatest protection remained unclear [10]. To investigate these key issues, we conducted a meta-analysis on all published prospective cohort studies to investigate the association between consumption of fruit and vegetable and risk of CHD and quantify the dose–response relationship of fruit and vegetable consumption with CHD risk.

2. Methods

We conducted this systematic review following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [11].

2.1. Search strategy

We performed a comprehensive search of Pubmed, Embase and Web of Science databases from their inception through July 2014 for prospective cohort studies published in peer-reviewed journals describing an association between fruit and vegetable consumption and risk of CHD. Search terms included fruits, vegetables, diet, cardiovascular disease, ischemic heart disease, myocardial infarction, coronary disease, heart disease, sudden cardiac death, cohort studies, prospective studies and follow-up studies. The search was restricted to human studies. No restrictions were imposed on language of publications. We also reviewed references from retrieved articles to identify additional studies. One investigator (YG) screened the titles and abstracts of all identified articles; two investigators (YG and XYT) assessed the eligibility of full-texts of potentially relevant articles.

2.2. Study selection

Studies were included in this meta-analysis if they met the following criteria: (1) the study was a prospective cohort study; (2) the exposure of interest was fruit or vegetable consumption; (3) the outcome of interest was risk of CHD; and (4) the study reported risk estimates with corresponding 95% CI for the association between fruit and vegetables and CHD or provided corresponding data to calculate the variance. If duplicate publications from the same study were identified, we included the result with the largest number of cases from the study.

2.3. Data extraction

Two investigators (YG and XYT) independently extracted the data by using a standardized electronic format, including the name of first author, publication year, study location, sample size, sex, age range or mean age at entry, length of follow-up, number of cases, method of assessment of exposure, outcome measurements, relative risks (RRs) with corresponding 95% CIs for all categories of fruit and vegetable consumption, and covariates included in the adjusted models. We extracted risk estimates with the most adjustment (when available). For dose–response analysis, when studies reported the consumption in servings or times per day or week or month, we standardized all data into g per day, using standard units of 106 g for total fruit and vegetable [12,13], 80 g for fruit and 77 g for vegetable [8]. Differences in data extraction between the two investigators were resolved by discussion with the third investigator (ZXL).

2.4. Quality assessment

We assessed the methodological quality of study by using an assessment tool with reference to MOOSE [11] and STROBE [14]. The scoring system was a maximum of 5 points (1 point for appropriate inclusion and exclusion criteria; 1 point if the fruit and vegetable consumption assessment was validated; 1 point if the consumption of fruit and vegetable was appropriately categorized; 1 point if the ascertainment of outcome was confirmed according to the accepted clinical criteria and not based on self-report; 1 point for the controlled of confounders). The scores from 0 to 3 were considered as lower study quality, and scores from 4 to 5 were considered as higher study quality. Each study was rated independently by two investigators (YG and XYT).

2.5. Statistical analysis

RRs were considered as the common measure of the association between fruit and vegetable consumption and CHD risk. We preferentially pooled multivariable adjusted RRs' estimates where such estimates were available. When adjusted estimates were unavailable (one study), we pooled the unadjusted estimates. A random effects model was used to calculate summary RRs and 95% CIs for the highest versus the lowest level of consumption of fruit and vegetable and for the dose–response analysis [15]. For two studies [16,17] that included data from multiple cohorts, we considered the analysis for each cohort as an independent report. One study [18] respectively reported the risk estimates of fruit and vegetable intake and CHD by smoking status (never smokers, former smokers and current smokers), and was considered as three independent reports. Any studies that expressed data separately for fatal CHD and nonfatal MI or for men and women, the analysis for each sex or subtype of CHD was also treated as an independent report.

For the dose–response analysis, we used the method described by Greenland and Longnecker [19] to calculate the trend from the correlated estimates for log relative risk across categories of fruit and vegetable consumption. The amount of fruit and vegetable consumption, the distributions of cases and person years, and RRs and 95% CI were extracted according to the method. If the person years were not available for each category of fruit and vegetable intake, but reported the total number of cases/person-years, we estimated the distribution. If consumption of fruit and vegetable was analyzed by quartiles (and could be approximated), e.g., the total number of person years was divided by 4 when the data were analyzed by quartiles in order to derive the number of person-years in each quartile [20].

The median or mean fruit and vegetable consumption in each category was assigned to the corresponding dose of consumption. The midpoint of the upper and lower boundaries was considered the dose of each category if the median or the mean intake per category was not available. When the lower boundary for the lowest category was not provided, the assigned median value was half of the upper boundary of that category. If the highest category was open-ended, we assumed that the median value of the category was the cut-off point plus a 25% increment.

We presented the dose–response results in the forest plots for a 477, 300 and 400 g/day increment for total fruit and vegetable, fruit and vegetable on the basis of intakes associated with the lowest risk in observational studies [21] and the dietary targets set by advocacy organization [22]. Additionally, we used restricted cubic splines with 4 knots at percentiles 5%, 35%, 65%, and 95% to test for nonlinearity in the association between fruit and vegetable consumption and CHD risk.

Statistical heterogeneity across studies was assessed by using the I^2 statistic (ranging from 0% to 100%). I^2 values of 25%, 50%, and 75% represent cut-off points for low, moderate, and high degrees of heterogeneity, respectively [23,24]. Subgroup analyses were conducted to explore the potential sources of heterogeneity among studies, and the differences among groups were tested by using meta-regression. Sensitivity analyses were performed to evaluate the effect of removing a single study from the analysis on pool risk estimates. The Begg's test [25] and Egger's test [26] were used to assess the potential publication bias. All statistical analyses were conducted with STATA version 12.0 (StataCorp, College Station, Texas, USA). *P* values were two tailed with a significance level of 0.05.

3. Results

3.1. Literature search

The results of literature research and selection were shown in Fig. 1. We identified 408 articles from the PubMed, 564 articles from the Embase and 332 articles from the Web of Science. After the initial screening, based on titles and abstracts, 452 articles remained for further full-text assessment. After retrieving the full-text review of the remaining 26 articles for detailed evaluation, three articles were excluded because they were duplicate publications. Finally, 23 prospective cohort studies [16–18,27–46] comprising 25 independent cohorts were included in this meta-analysis.

3.2. Study characteristics

Characteristics of the included studies are presented in Supplemental Table 1. These studies involving 937,665 participants and 18,047 patients with CHD were published between 1992 and 2014 during follow-up periods ranging from 5 to 37 years. Nine studies [16,33,34,36,37,39,40,44,46] were from the United States, 9 studies [18,27,29–31,35,38,41,42] were from Europe, and 5 studies [17,28,32,43,45] were from Asia (China and Japan). 14 studies [16,17,27–29,32,35–37,41–44,46] included both men and women, 5 studies [18,30,34,38,40] men only and 4 studies [31,33,39,45] women only. The dietary intake was assessed by food frequency questionnaires (FFQ) in all studies, except for 5 studies (3-day food record [46], dietary history interview [42], 7-day diet record [34], 7-day household inventory [35], 24-hour recall [29]). The scores from our assessment of study quality ranged from 3 to 5 scores. The average score was 4.6.

3.3. Association between total fruit and vegetable consumption and risk of CHD

Twelve studies [16–18,27–31,34,36,37,39] with 16 reports investigated the relationship between the highest versus the lowest categories of total fruit and vegetable consumption levels and CHD risk. The RRs of CHD for the highest versus the lowest total fruit and vegetable consumption categories were shown in Fig. 2. Of the 16 reports, 5 showed

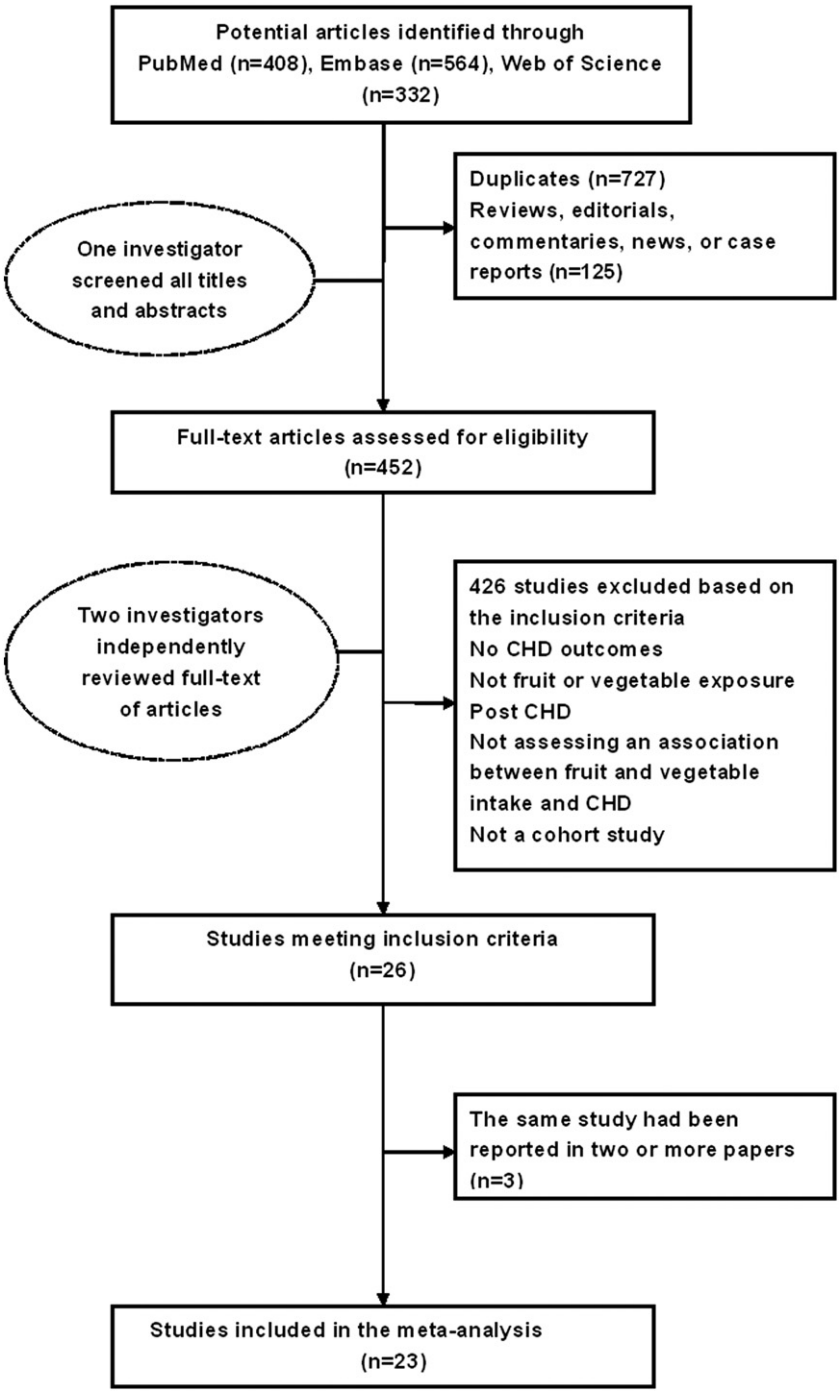

Fig. 1. Screening and selection process of studies investigating effect of fruit and vegetable consumption on coronary heart disease.

a significantly inverse relationship between total fruit and vegetable intake and risk of CHD, while the other reports did not. The pooled RR was 0.84 (95% CI, 0.79–0.90), and there was a low heterogeneity ($I^2 = 9.0\%$; $P = 0.350$).

Ten studies [16–18,27–29,31,36,37,39] with 14 reports were included in the dose–response analysis of total fruit and vegetable consumption and CHD risk. Pooling these studies, an increment of 477 g/day of total fruit and vegetable consumption was associated with 12% lower risk of CHD (RR: 0.88; 95% CI: 0.85, 0.91), and there was no heterogeneity ($I^2 = 0\%$, $P = 0.643$) (Fig. 3). In the cubic spline model that included all studies, we did not find evidence suggesting any nonlinear association between total fruit and vegetable consumption and risk of CHD (Fig. 4; P for nonlinearity = 0.205).

3.4. Association between fruit consumption and risk of CHD

Eighteen studies [16–18,27,29,31–35,38,39,41–46] with 26 reports investigated the relationship between comparing high with low fruit consumption levels and CHD risk. The RRs of CHD for the highest versus the lowest fruit consumption categories were shown in Fig. 5. Of the 26 reports, 6 showed a significantly inverse relationship between fruit intake and risk of CHD, while the other reports did not. The pooled RR was 0.86 (95% CI, 0.82–0.91), and there was no heterogeneity ($I^2 = 0\%$; $P = 0.762$).

Fifteen studies [16–18,27,29,31–33,35,38,39,41,43,44,46] with 22 reports were included in the dose–response analysis of total fruit and vegetable consumption and CHD risk. Pooling these studies, an

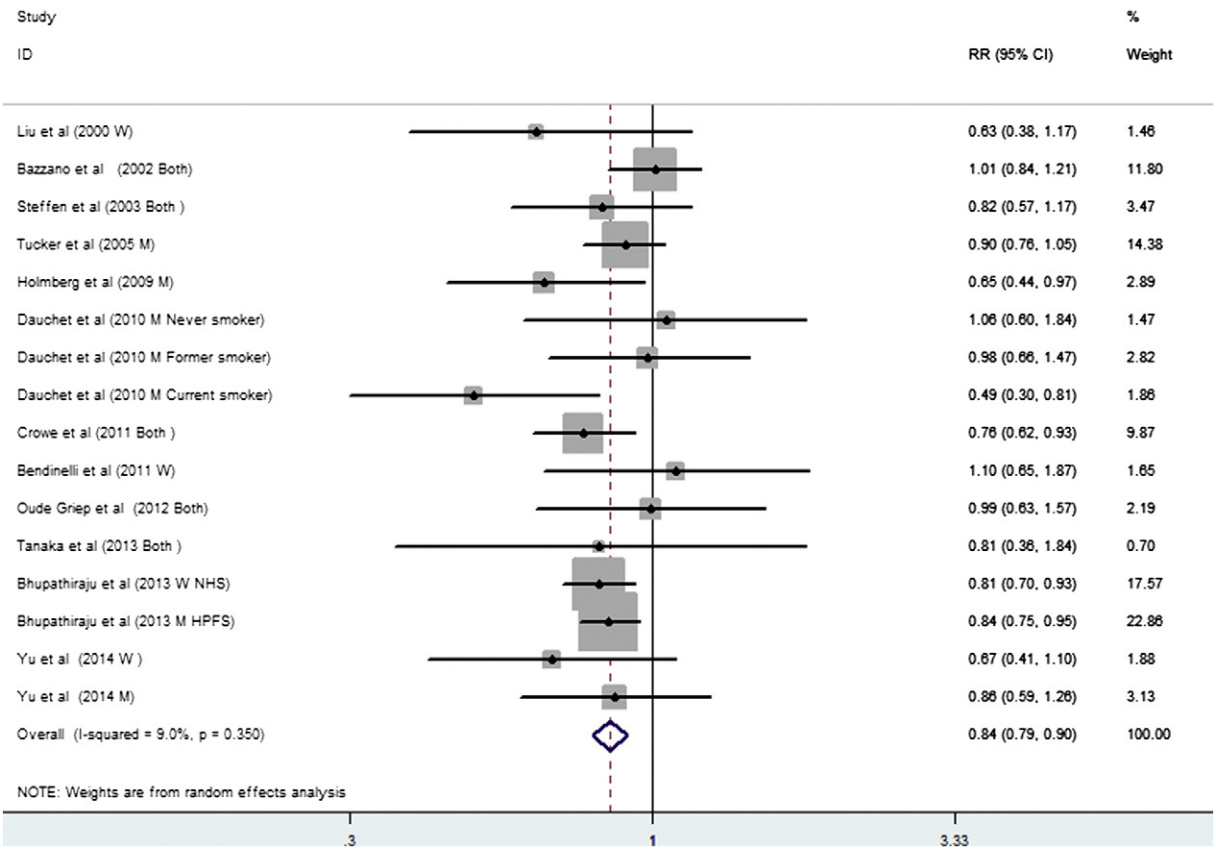

Fig. 2. Pooled random effects relative risk (95% CI) of coronary heart disease comparing the highest with the lowest fruit and vegetable consumption levels.

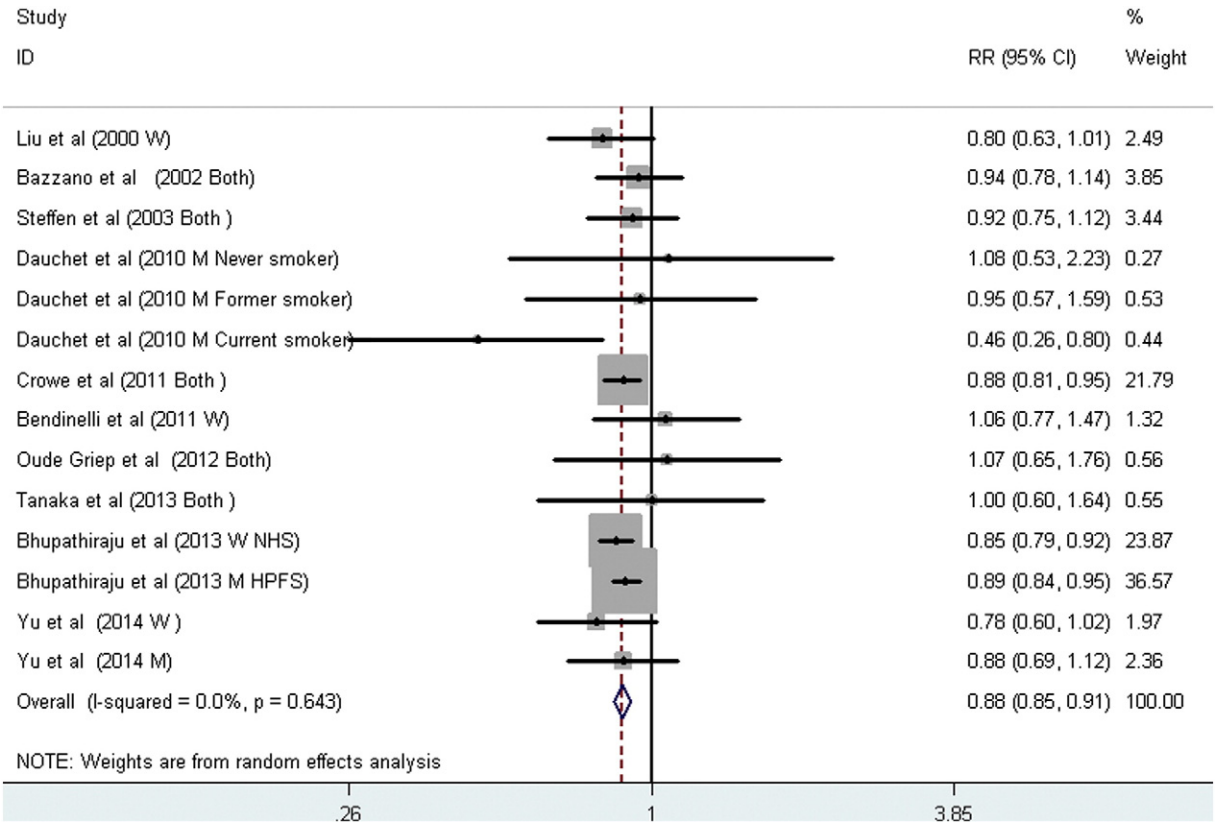

Fig. 3. Risk of coronary heart disease associated with per 477 g/day in total fruit and vegetable consumption.

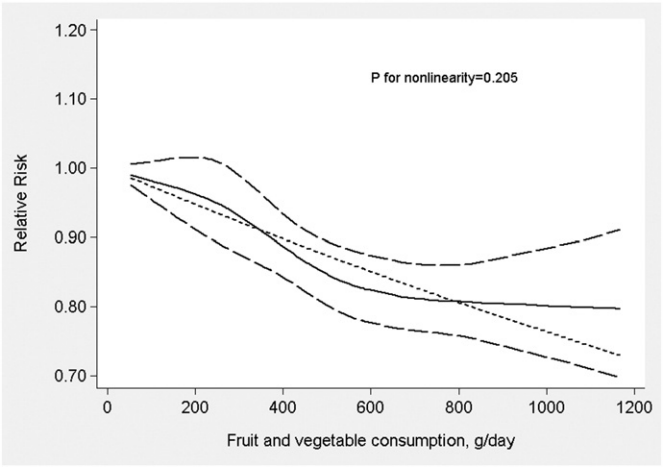

Fig. 4. Dose–response relation plots between fruit and vegetable consumption (g/day) and the risk of coronary heart disease.

increment of 300 g/day of fruit consumption was associated with 16% lower risk of CHD (RR: 0.84, 95% CI: 0.75, 0.93), and there was a medium heterogeneity (I^2 = 31.7%, P = 0.078) (Fig. 6). In the cubic spline model that included all studies, nonlinear association between fruit consumption and risk of CHD was found (Fig. 7; P for nonlinearity <0.001).

3.5. Association between vegetable consumption and risk of CHD

Sixteen studies [16–18,27,29,31,32,34,35,38–42,45,46] with 22 reports investigated the relationship between comparing high with low vegetable consumption levels and CHD risk. The RRs of CHD for the highest versus the lowest vegetable consumption categories were shown in Supplemental Fig. 1. Of the 22 reports, 6 showed a significantly inverse relationship between vegetable intake and risk of CHD, while the other reports did not. The pooled RR was 0.87 (95% CI, 0.81–0.93), and there was a low heterogeneity (I^2 = 13.3%; P = 0.282).

Thirteen studies [16–18,27,29,31,32,35,38–41,46] with 18 reports were included in the dose–response analysis of vegetable consumption and CHD risk. Pooling these studies, an increment of 400 g/day of vegetable consumption was associated with 18% lower risk of CHD (RR: 0.82, 95% CI: 0.73, 0.92), and there was a medium heterogeneity (I^2 = 35.6%, P = 0.068) (Supplemental Fig. 2). In the cubic spline model that included all studies, nonlinear association between vegetable consumption and risk of CHD was found (Supplemental Fig. 3; P for nonlinearity <0.001).

3.6. Subgroup analyses

The results from subgroup analyses examining the robustness of the primary results and exploring the resource of potential heterogeneity were shown in Supplemental Table 2. For the relations between fruit and vegetable consumption and CHD risk, a low statistical heterogeneity was found. However, no statistically significant source of

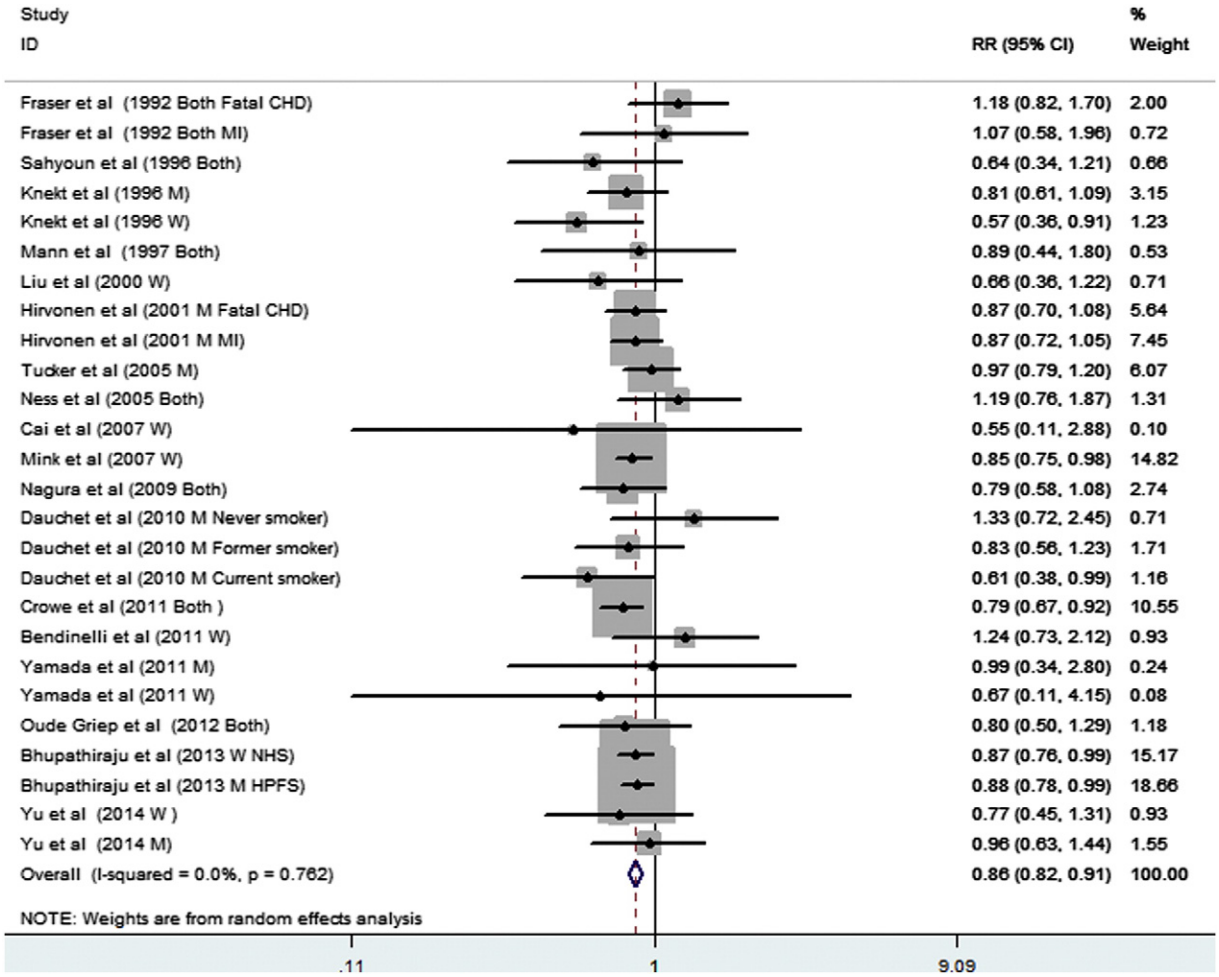

Fig. 5. Pooled random effects relative risk (95% CI) of coronary heart disease comparing the highest with the lowest fruit consumption levels.

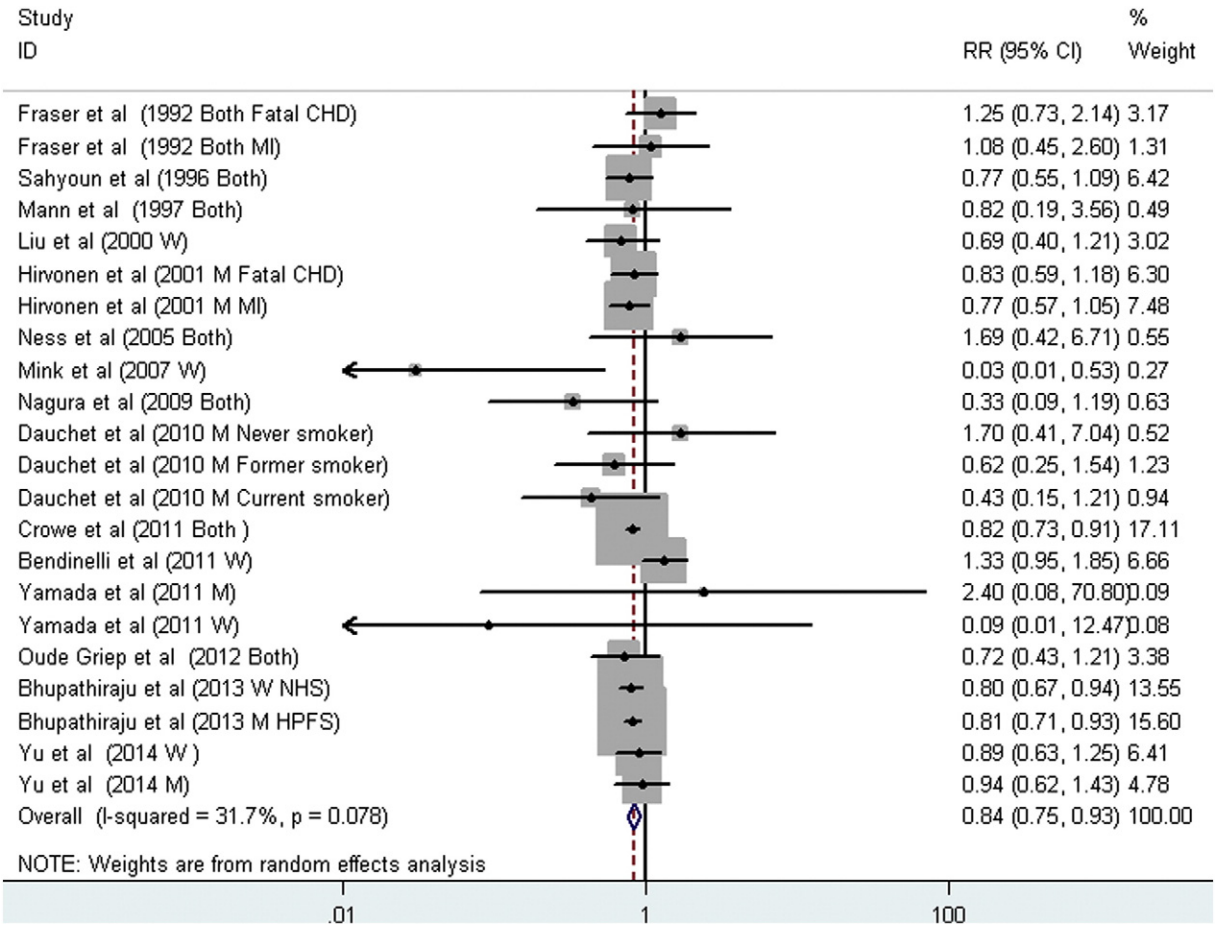

Fig. 6. Risk of coronary heart disease associated with per 300 g/day in fruit consumption.

heterogeneity was identified for the association between the total fruit and vegetable consumption and risk of CHD in the meta-regression analysis of sex, study location, follow-up duration, dietary assessment, publication year, smoking status, physical activity, body mass index, energy intake, and other diet variables ($P > 0.05$ for each). A statistically significant source of heterogeneity was identified for the association between vegetable consumption and risk of CHD in the meta-regression analysis of publication year ($P = 0.01$). The decreased risk of CHD was more evident in these studies published before 2006 (RR: 0.77, 95% CI, 0.69, 0.85) than after 2006 (RR: 0.92, 95% CI, 0.85, 0.98). Notably, we found that in studies published before 2006, total fruit and vegetable consumption was not significantly associated with risk of CHD (RR: 0.92, 95% CI, 0.81, 1.03), but in later studies, total fruit and vegetable consumption was associated with CHD risk (RR: 0.82, 95% CI, 0.76, 0.88). For total fruit and vegetable, fruit or vegetable consumption, the significant inverse associations were identified in western countries, but not in Asian countries.

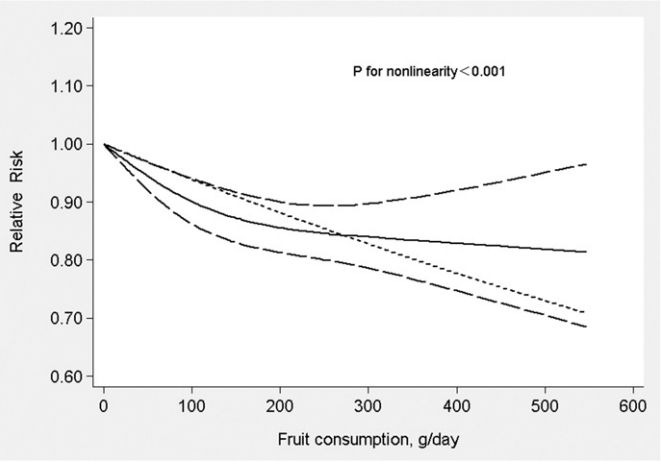

Fig. 7. Dose–response relation plots between fruit consumption (g/day) and the risk of coronary heart disease.

3.7. Sensitive analysis

The inverse association was not materially changed in the leave-one-out analyses by omitting one study in turn, with a pooled RR of CHD range from 0.85 (95% CI, 0.79–0.91; $I^2 = 9.3\%$, $P = 0.350$) to 0.83 (95% CI 0.77–0.88; $I^2 = 0\%$, $P = 0.577$), from 0.87 (95% CI, 0.83–0.92; $I^2 = 0\%$, $P = 0.786$) to 0.86 (95% CI 0.81–0.91; $I^2 = 0\%$, $P = 0.719$), from 0.87 (95% CI, 0.82–0.93; $I^2 = 6.8\%$, $P = 0.371$) to 0.85 (95% CI 0.79–0.92; $I^2 = 12.8\%$, $P = 0.291$) for the highest versus the lowest consumption of total fruit and vegetable, fruit and vegetable, respectively. Similarity, in dose–response analysis, the inverse association was not still changed by removing one study at a time, with a pooled RR range from 0.89 (95% CI, 0.85–0.93; $I^2 = 0\%$, $P = 0.641$) to 0.87 (95% CI 0.83–0.91; $I^2 = 0\%$, $P = 0.589$), from 0.84 (95% CI, 0.74–0.95; $I^2 = 34.8\%$, $P = 0.059$) to 0.81 (95% CI 0.75–0.88; $I^2 = 11.7\%$, $P = 0.306$), from 0.84 (95% CI, 0.76–0.93; $I^2 = 27.5\%$, $P = 0.141$) to 0.80 (95% CI 0.70–0.91; $I^2 = 32.6\%$, $P = 0.095$) for the consumption of total fruit and vegetable, fruit and vegetable, respectively.

3.8. Publication bias

In the analyses of the highest compared with the lowest category, the Begg's and the Egger's tests did not provide any significant evidence of the publication bias for studies that investigate the relation of CHD risk with total fruit and vegetable consumption (Begg's $P = 0.822$, Egger's $P = 0.529$), fruit consumption (Begg's $P = 0.597$, Egger's $P = 0.947$) and vegetable consumption (Begg's $P = 0.910$, Egger's $P = 0.889$). Additionally, no significant evidence of substantial publication bias was observed for dose–response analyses (Begg's $P = 0.367$, Egger's $P = 0.591$ for fruit consumption, Begg's $P = 0.880$, Egger's $P = 0.381$ for vegetable consumption and Begg's $P = 0.880$, Egger's $P = 0.381$ for total fruit and vegetable consumption).

4. Discussion

This meta-analysis indicated that higher fruit and vegetable consumption is inversely associated with CHD. In the dose–response analysis, we found that the risk of CHD decreased by 12%, 16% and 18% for daily 477 g of total fruit and vegetable, daily 300 g of fruit and daily 400 g of vegetable, respectively. There was evidence of a nonlinear association for both fruit and vegetable consumption.

Results of this updated meta-analysis generally concur and further complement the findings of previous review in several important aspects. Our meta-analysis strengthens previous results by including 11 additionally published large scale prospective cohort studies. Our analyses on prospective studies investigating the association between fruit and vegetable intake and CHD risk involved about twice as many CHD events as the previous review. The present review also further quantifies the dose–response relationship of fruit and vegetable consumption with the risk of CHD. Additionally, we performed the more detailed subgroup analyses (such as adjustment for physical activity and energy intake) to test the robustness of results and explore the potential heterogeneity.

In subgroup analyses, we obtained a valuable and important finding. We found that there was a statistically significant inverse association between fruit and/or vegetable consumption and CHD risk in Western populations, but not in Asian populations, which was an interesting phenomenon. Food preparation methods may partially explain the differences. Cooked, boiled, and steamed vegetable are major preparation methods in Eastern cuisine. Such methods of processing vegetables may lead to loss of water-soluble, heat-sensitive and oxygen-labile nutrients. In addition, more salt was generally added during home cooking and this may decrease the benefits of vegetables, [47] which could contribute to the lower CHD risk in Western populations than in Asian populations. More importantly, we noted that the amounts of fruit and vegetable consumption in studies conducted in Western countries were much higher than the amounts of fruit and vegetable consumption in Asian countries. In other words, the finding confirmed that the fruit and vegetable consumption was associated with CHD risk. Notably, the null inverse association in Asian participants might also result from the limited number of included studies (five studies including 194,207 participants and 989 patients with CHD). More studies are warranted to investigate the potential difference between the different ethnic backgrounds.

Some potential biological mechanisms may preliminarily explain the inverse association between fruit and vegetable consumption and CHD. Investigating the effects of fruit and vegetable consumption on established cardiovascular disease risk factors is proposed as an important step in determining the biological plausibility of the causal relationship between consumption of fruit and vegetable and the risk of CHD [48]. Evidence from epidemiological studies and clinical trials has shown that fruit and vegetable consumption is inversely associated with blood pressure [49–52], cholesterol [53] and lipid [54], which are main risk factors for cardiovascular disease. Additionally, the specific constituents of fruits and vegetables have been proposed as for the mechanisms for the inverse association between consumption of fruit and vegetable and CHD risk. Antioxidant compounds and polyphenols in fruit and vegetables, such as vitamin C, vitamin E, carotenoids, and flavonoids, have been shown to increase the antioxidant capacity of serum [55], protect against the oxidation of cholesterol and other lipids [56], decrease in cellular oxidative stress [57], inhibition of inflammation [58], and increase the formation of endothelial prostacyclin that prevents platelet aggregation and reduces vascular tone [59,60].

4.1. Strengths and limitations

Although our review is an updated meta-analysis, the strengths and importance are obvious. Firstly, we added more than twice as many participants as the previous review, which provided stronger and more sufficient evidence. Secondly, we obtained an important finding that a significantly inverse association between fruit and vegetable consumption and CHD risk was observed in Western populations, but not in Asian populations. Thirdly, we not only analyzed the association of higher fruit and vegetable consumption with CHD risk, but also conducted the dose–response analysis to evaluate the linear and non-linear relations by using all the categories of data, which could help to quantify the associations and examine the shape of these possible associations. A significant nonlinear association of CHD risk with fruit and vegetable consumption was found.

Several limitations should be acknowledged. Most original studies included used FFQ to assess levels of fruit and vegetable consumption. Although validation studies showed that FFQ was a reasonable tool to assess the intakes of fruit and vegetable [61], measurement error was inevitable. Secondly, although the original studies included in our analysis adjusted for multiple major risk factors except for one study, the possibility of residual confounding by imprecisely or unmeasured factors should be considered, because fruit and vegetable consumers tended to follow other healthy diet behaviors. Thus, it was difficult to identify the independent effects of fruit and vegetable consumption from other healthy diet and lifestyle in observational analyses. Thirdly, the differences in classifications of fruit and vegetable and in the types consumed among original studies, which could have attenuated our results.

For future research, based on our findings, we suggest that initially, the investigators need to improve the standardization of different dietary assessment methods, which may make observed effects more accurate and conceivable. Then, the use of biological and genetic markers as surrogate end points in future research should help to clarify the cause and effect relationship that link fruit and vegetable consumption and CHD.

5. Conclusion

In summary, this meta-analysis indicates significant inverse associations between higher consumption of fruit and vegetable and CHD. The risk of CHD was reduced by 12% for per 477 g/day in total fruit and vegetable, by 16% for per 300 g/day in fruit, and by 18% for per 400 g/day in vegetable. This nonlinear association of CHD risk with fruit or vegetable consumption separately was observed. Our results support current recommendations to increase fruit and vegetable consumption to promote health and prevent chronic disease.

Contributors

YG and ZXL conceived the study. YG and XYT searched and checked the databases according to the inclusion and exclusion criteria. ZJ and ZXL helped to develop search strategies. YG and XYT extracted the data and assessed their quality. YG, LQL, SYC, XXY and CG analyzed the data. SYC gave advice on meta-analysis methodology. YG wrote the draft of the paper. All authors contributed to reviewing or revising the paper and read and approved the final manuscript. ZXL is the

guarantor of this work and had full access to all the data in the study and takes responsibility for its integrity and the accuracy of the data analysis.

Funding source

No funding was received for this systematic review.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.01.077.

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