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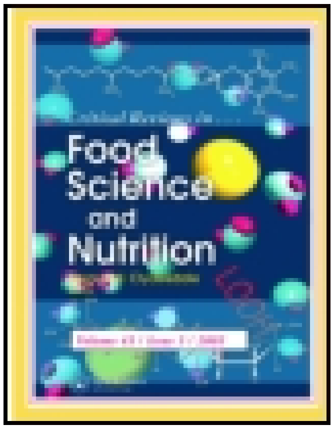

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Fruit and Vegetable Consumption and Risk of Cardiovascular Disease: a Meta-analysis of Prospective Cohort Studies

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Fruit and Vegetable Consumption and Risk of Cardiovascular Disease: a Meta-analysis of Prospective Cohort Studies

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ABSTRACT

A meta-analysis of prospective cohort studies was conducted to examine the relation between fruit and vegetables (FV) consumption and the risk of cardiovascular disease (CVD). We

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searched PubMed and EMBASE up to June 2014 for relevant studies. Pooled relative risks (RRs) were calculated and dose-response relationship was assessed. Thirty-eight studies, consisting of 47 independent cohorts, were eligible in this meta-analysis. There were 1,498,909 participants (44,013 CVD events) with a median follow-up of 10.5 years. The pooled RR (95% confidence interval) of CVD for the highest versus lowest category was 0.83 (0.79-0.86) for FV consumption, 0.84 (0.79-0.88) for fruit consumption, and 0.87 (0.83-0.91) for vegetable consumption, respectively. Dose-response analysis showed that those eating 800 g per day of FV consumption had the lowest risk of CVD. Our results indicate that increased FV intake is inversely associated with the risk of CVD. This meta-analysis provides strong support for the current recommendations to consume a high amount of FV to reduce CVD risk.

KEYWORDS

Fruit, vegetable, cardiovascular disease, meta-analysis

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INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death globally. According to the World Health Organization (WHO) Statistics, 17.3 million people died from CVDs in 2008, which accounted for 30% of total death worldwide. It was estimated that the number will increase to 23.3 million by 2030 (World Health Organization, 2013). Thus, primary prevention of CVD is of tremendous importance.

Over the past few decades, several epidemiological studies have shown that intake of fruit and vegetables (FV) consumption may reduce the CVD risk (Bazzano et al., 2002; Takachi et al., 2008; Bendinelli et al., 2011; Yu et al., 2014). Increasing consumption of FV has been advocated by several dietary and food recommendations to prevent chronic diseases including CVDs and cancer (World Heath Organization, 1990; Krauss et al., 2000). However, there is still much uncertainty about the relation between FV consumption and the risk of CVD. For example, while some studies found an inverse association between FV and CVD among both genders (Sauvaget et al., 2003; Zhang et al., 2011a), Takachi et al. reported that the relation was more apparent among women than among men (Takachi et al., 2008). In the Shanghai Women's Health Study, no significant association with coronary heart disease (CHD) risk was found for FV in men when analyzed either together or separately (Yu et al., 2014). Furthermore, the optimal levels of intake of FV are not entirely consistent.

Although several meta-analyses of prospective cohort studies have been published

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regarding the relation between FV consumption and risk of stroke (He et al., 2006; Hu et al., 2014) and CHD (Dauchet et al., 2005; He et al., 2007), there was no comprehensive study that reviewed CVD events all together. A recent systematic review of randomised controlled trials (RCTs) showed some favorable effects of FV consumptions on cardiovascular risk factors (Hartley et al., 2013). Nevertheless, none of the included studies provided clinical event data. Therefore, we conducted this meta-analysis of prospective cohort studies to quantitatively assess the relation between FV consumption and the risk of CVD.

MATERIALS AND METORDS

Search strategy

To identify the related studies, we conducted a systematic literature search of PubMed and EMBASE up to June 2014 using the following key words: “fruits”, “vegetables”, “heat failure”, “myocardial infarction”, “sudden cardiac arrest”, “acute coronary syndrome”, “cardiovascular disease”, “coronary heart disease”, “stroke”, “ischemic heart disease”, and their variants. Furthermore, we reviewed reference lists of original and review articles for relevant additional studies. The search was restricted to studies on humans and published in English language journals.

Study selection

For inclusion, studies had to meet the following criteria: 1) prospective cohort design; 2) the

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exposure of interest was fruit or vegetable or FV intake; 3) the outcomes of interest were CVD events, the latter including mortality and incidence of CVDs; 4) study participants were generally healthy at baseline; 5) the effect sizes with their corresponding 95% confidence intervals were reported or sufficient data to calculate them. If a study cohort was reported in multiple published papers, the study with the longest follow-up duration was included. We excluded clinical trials, cross-sectional studies, case-control studies, letters, reviews, and meta-analyses.

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Data extraction and quality assessment

Two authors (ZJ and LYJ) independently extracted all data and any disagreements were resolved by consensus. The following information were extracted from each study: first author's name, publication year, cohort name, study location, duration of follow-up, dietary assessment, size of cohort, number of case, outcomes, ascertainment of outcomes, exposure, categories of exposure intake, adjusted size effect and corresponding 95% confidence interval (CI) for each category of exposure intake, and covariates adjusted in the statistical analysis. We also utilized a 9-star system by Newcastle-Ottawa Scale for assessing the quality of studies, the full score was 9 stars, and the high-quality study was defined as a study with ≥7 stars (Stang, 2010).

Statistical analysis

All statistical analyses were conducted using STATA version 11.0 (Stata Corporation, College Station, Texas). We chose the relative risk (RR) estimates from multivariable models with the most complete adjustment for potential confounders. In order to pool the results across included

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studies, hazard ratio (HR) and RR were assumed to be equivalent (Hu et al., 2012; Wang et al., 2013). Forest plots were produced to present the pooled RRs with 95% CI (highest compared to lowest exposure category) to measure the association between fruit, vegetable, and FV and the risk of CVDs.

The potential heterogeneity across studies was assessed using Cochrane Q test and I^2 statistics (Higgins & Thompson, 2002; Higgins et al., 2003). The heterogeneity was considered statistically significant when P≤0.10 or $I^2 > 50\%$. When statistically significant heterogeneity was detected, the random-effect model was presented; otherwise, the fixed-effect model was used to calculate the pooled RR.

The dose-response relationship was examined by using generalized least-squares trend estimation (Orsini et al., 2006). This method requires that the number of case, and person-year or non-case for at least three quantitative exposure categories is available. We assigned the median level of fruit and vegetable intake in each category to the corresponding risk estimate for each study. If the median level was not provided in the papers, we assigned it in each category by calculating the average of the lower and upper bound. When some highest or lowest category ranges were open-ended, we assigned them by multiplying 1.2 and 0.8 respectively (Orsini et al., 2006). In order to estimate the distribution of person-year in studies that did not report, we adopted following strategies: 1) we divided the total person-years by quintile that was used to categorize the exposure; 2) we multiplied the total number of each category by the median or

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average follow-up duration. To take into account the different units of exposure variable across studies, the average serving was calculated as 77 g for vegetables and 80 g for fruit (He et al., 2006).

To flexibly plot the relationship of the natural logarithm of RR with increasing fruit and vegetable without assuming linearity and to test if they were nonlinear, we added a quadratic term of fruit and vegetable; the changes in model fit were tested using the likelihood ratio test. For any nonlinear response, we proceeded to use piecewise regression with an inflection point based on the best goodness-of-fit model (Orsini et al., 2006).

The potential sources of heterogeneity were investigated in subgroup analyses by subtypes of CVD outcomes, gender of participants, study location, publication year and duration of follow-up. In a sensitivity analysis, each study was eliminated in turn from the pooled analysis to assess its effect on pooled results. We also used Begg funnel plots (Begg & Mazumdar, 1994) and Egger's tests (Egger et al., 1997) to examine potential publication bias. If statistically significant publication bias was detected, trim and fill method was applied (Duval & Tweedie, 2000). This method considers the possibility of hypothetical "missing" studies that might exist, then imputes their RRs, and recalculates a pooled RR which incorporates the hypothetical missing studies as though they actually exist.

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RESULTS

Literature search and study characteristics

Figure 1 displays the study selection process. We finally identified 38 publications, consisting of 47 independent cohorts (Gillman et al., 1995; Key et al., 1996; Knekt et al., 1996; Mann et al., 1997; Joshipura et al., 1999; Whiteman et al., 1999; Liu et al., 2000; Strandhagen et al., 2000; Liu et al., 2001; Bazzano et al., 2002b; Johnsen et al., 2003; Rissanen et al., 2003; Sauvaget et al., 2003; Steffen et al., 2003; Dauchet et al., 2004; Genkinger et al., 2004; Ness et al., 2005; Iso & Kubota, 2007; Nakamura et al., 2008; Takachi et al., 2008; Holmberg et al., 2009; Nagura et al., 2009; Dauchet et al., 2010; Kvaavik et al., 2010; Nechuta et al., 2010; Oude Griep et al., 2010; Bendinelli et al., 2011; Crowe et al., 2011; Oude Griep et al., 2011; Zhang et al., 2011a; Zhang et al., 2011b; Bhupathiraju et al., 2013; Larsson et al., 2013; Leenders et al., 2013; Sharma et al., 2013; Oyebode et al., 2014; Sharma et al., 2014; Yu et al., 2014) that met the inclusion criteria, with a total number of 1,498,909 participants (44,013 CVD events). Characteristics of the included studies are present in Table 1. The duration of follow-up ranged from 3.09 years to 26 years (median: 10.5 years). Six studies included only men, 3 studies included only women, and 29 studies included both men and women. Twenty studies were from Europe, 10 from America, 3 from China and 5 from Japan. Results from the quality assessments show that all studies achieved a moderate to high quality with a score from 6-9 stars.

Total FV and risk of CVD

Thirty-four cohorts from 23 publications (Gillman et al., 1995; Joshipura et al., 1999; Liu et al.,

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2000; Bazzano et al., 2002b; Johnsen et al., 2003; Rissanen et al., 2003; Steffen et al., 2003; Dauchet et al., 2004; Genkinger et al., 2004; Takachi et al., 2008; Holmberg et al., 2009; Dauchet et al., 2010; Kvaavik et al., 2010; Nechuta et al., 2010; Oude Griep et al., 2010; Bendinelli et al., 2011; Crowe et al., 2011; Oude Griep et al., 2011; Bhupathiraju et al., 2013; Larsson et al., 2013; Leenders et al., 2013; Yu et al., 2014; Oyebode et al., 2014) investigated the association between total FV consumption and the risk of CVD, comprising 1,102,228 participants and 29,831 (Figure 2). The fixed-effect model showed that the highest versus the lowest intake of total FV was inversely associated with the risk of CVD (pooled RR: 0.83; 95% CI: 0.79-0.86; P for heterogeneity=0.161, I^2=19.4%). Data from 30 cohorts (Gillman et al., 1995; Liu et al., 2000; Bazzano et al., 2002b; Johnsen et al., 2003; Rissanen et al., 2003; Steffen et al., 2003; Genkinger et al., 2004; Takachi et al., 2008; Dauchet et al., 2010; Nechuta et al., 2010; Oude Griep et al., 2010; Bendinelli et al., 2011; Crowe et al., 2011; Oude Griep et al., 2011; Bhupathiraju et al., 2013; Larsson et al., 2013; Leenders et al., 2013; Oyebode et al., 2014; Yu et al., 2014) were used in the dose-response analysis. A nonlinear dose-response relationship was observed between total FV and risk of CVD (P=0.043 for non-linearity). RR (95% CI) of CVD was 0.96 (0.94-0.98), 0.92 (0.88-0.96), 0.88 (0.85-0.91), 0.85 (0.82-0.88), 0.83 (0.80-0.86), 0.82 (0.79-0.85), 0.81 (0.77-0.85), and 0.80 (0.75-0.86) for 100, 200, 300, 400, 500, 600, 700, and 800 g per day of FV consumption.

Fruits and risk of CVD

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Forty-one cohorts from 25 publications (Key et al., 1996; Knekt et al., 1996; Mann et al., 1997; Joshipura et al., 1999; Whiteman et al., 1999; Liu et al., 2000; Strandhagen et al., 2000; Johnsen et al., 2003; Sauvaget et al., 2003; Dauchet et al., 2004; Ness et al., 2005; Nakamura et al., 2008; Takachi et al., 2008; Nagura et al., 2009; Dauchet et al., 2010; Bendinelli et al., 2011; Crowe et al., 2011; Zhang et al., 2011a; Zhang et al., 2011b; Bhupathiraju et al., 2013; Larsson et al., 2013; Leenders et al., 2013; Sharma et al., 2013; Sharma et al., 2014; Yu et al., 2014) reported fruit intake and the risk of CVDs, including 1,340,460 participants and 34,026 cases (Figure 3). The pooled RR for the highest versus the lowest intake of fruits was 0.84 (95% CI: 0.79-0.88), with significant heterogeneity (P for heterogeneity=0.003, I^2=41.6%). Data from 34 cohorts (Mann et al., 1997; Whiteman et al., 1999; Liu et al., 2000; Strandhagen et al., 2000; Johnsen et al., 2003; Sauvaget et al., 2003; Dauchet et al., 2004; Ness et al., 2005; Nakamura et al., 2008; Nagura et al., 2009; Dauchet et al., 2010; Bendinelli et al., 2011; Crowe et al., 2011; Zhang et al., 2011a; Zhang et al., 2011b; Bhupathiraju et al., 2013; Leenders et al., 2013; Yu et al., 2014) were used in the dose-response analysis. A nonlinear dose-response relationship was observed between fruits and risk of CVDs (P<0.001 for non-linearity). RR (95% CI) of CVD was 0.88 (0.86-0.91), 0.86 (0.83-0.90), 0.85 (0.82-0.89), 0.85 (0.80-0.90), and 0.84 (0.76-0.92) for 100, 200, 300, 400, and 500 g per day of fruit consumption.

Vegetables and risk of CVD

Forty-five cohorts from 26 publications (Knekt et al., 1996; Mann et al., 1997; Joshipura et al.,

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1999; Whiteman et al., 1999; Liu et al., 2000; Strandhagen et al., 2000; Liu et al., 2001; Johnsen et al., 2003; Sauvaget et al., 2003; Dauchet et al., 2004; Ness et al., 2005; Iso & Kubota 2007; Nakamura et al., 2008; Takachi et al., 2008; Nagura et al., 2009; Dauchet et al., 2010; Bendinelli et al., 2011; Crowe et al., 2011; Zhang et al., 2011a; Zhang et al., 2011b; Bhupathiraju et al., 2013; Larsson et al., 2013; Leenders et al., 2013; Sharma et al., 2013; Sharma et al., 2014; Yu et al., 2014) reported vegetable intake and risk of CVD, including 1,344,909 participants and 35,416 cases (Figure 4). The pooled RR for the highest versus the lowest intake of vegetables was 0.87 (95% CI: 0.83-0.91), with significant heterogeneity (P for heterogeneity =0.027, I^2=31.1%). Data from 36 cohorts (Mann et al., 1997; Liu et al., 2000; Strandhagen et al., 2000; Liu et al., 2001; Johnsen et al., 2003; Sauvaget et al., 2003; Dauchet et al., 2004; Ness et al., 2005; Iso & Kubota, 2007; Nakamura et al., 2008; Nagura et al., 2009; Dauchet et al., 2010; Bendinelli et al., 2011; Crowe et al., 2011; Zhang et al., 2011a; Zhang et al., 2011b; Bhupathiraju et al., 2013; Larsson et al., 2013; Leenders et al., 2013; Yu et al., 2014) were used in the dose-response analysis, and the results also showed a nonlinear relationship between vegetables and risk of CVDs (P=0.024 for nonlinearity). RR (95% CI) of CVD was 0.90 (0.87-0.93), 0.89 (0.85-0.93), 0.86 (0.82-0.90), 0.80 (0.75-0.85), 0.76 (0.70-0.82), and 0.72 (0.64-0.80) for 100, 200, 300, 400, 500, and 600 g per day of vegetable consumption.

Subgroup and sensitivity analyses

Results of stratified analyses are shown in Table 2. The relationships between fruit, vegetable,

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and FV consumption and the risk of CVD did not vary by gender, locations, follow-up periods, and publication time.

Sensitivity analysis was conducted by omitting one study each time and re-calculating the pooled results. The overall risk estimates did not vary materially, indicating that the pooled RR was not substantially influenced by any of the individual study (data not shown).

Publication bias

Begg's tests indicated no evidence of publication bias with regard to fruit, vegetable and FV intake in relation to risk of CVD. Nevertheless, Egger's tests suggested possible publication bias for the association between FV and CVDs (P=0.020). However, the trim-and-fill approach suggested no missing study to the funnel plot and made no change in the risk estimate.

DISCUSSION

The results of this meta-analysis indicate that FV consumption is significantly associated with a reduced risk of CVD, and the inverse associations are consistent between genders and locations. Compared with individuals who had the lowest FV intake, those with the highest FV intake had a 17% reduction in the risk of CVD. The dose-response relationship shows that the lowest risk for CVD was observed among those who consumed FV 800 g or more per day.

Ideally, a long-term randomized trial would offer the strongest level of evidence for clinical guidelines. However, such trials can be challenging and costly to conduct, especially for an

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exposure such as fruits and vegetables consumption. A recent review of 10 RCTs concluded that no strong evidence was found for effects of individual trials of provision of FV on cardiovascular risk factors (Hartley et al., 2013). Nevertheless, the included studies were all relatively short term (from 3 months to one year), and five trials only provided one fruit or vegetable. Since there is a lack of RCTs that examine the effects of increasing FV consumption over a long period of time on CVD outcomes, findings derived from long-term prospective cohort studies should reflect the best available evidence.

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The findings of inverse associations between FV consumption and CVD are broadly consistent, despite the magnitudes of the effects differ, with several previous meta-analyses on stoke and CHD (Dauchet et al., 2005; He et al., 2006; Dauchet et al., 2006; He et al., 2007; Hu et al., 2014). Two meta-analyses (comprising 9 or 12 studies) showed a reduction in CHD risk of 17% (He et al., 2007) with more than 5 servings/day or 4% (Dauchet et al., 2006) with each additional portion/day of FV intake, respectively. Another two pool analyses, based on studies conducted prior to 2005, indicated that the risk of stoke was decreased by 5% (Dauchet et al., 2005) for each increment of one portion/day of FV intake or 26% (He et al., 2006) with more than 5 servings/day. In a recent meta-analysis, the risk of stroke was 21% lower for the highest versus lowest category of FV consumption (Hu et al., 2014). However, none attempt has been made to include a broad range of relevant cardiovascular outcomes. To our best knowledge, our extensive search identifying 47 cohorts is the most comprehensive study that quantitatively

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evaluated the effects of FV intake on the risk of CVD.

Although according to a report by the WHO, increasing consumption of fruit and vegetable ≥ 600 g daily could reduce the total burden of disease by 1.8% worldwide, and reduce the burden of IHD and stroke by 31% and 19% respectively (Lock et al., 2005), there is still a debate regarding the recommendation for FV consumption. The present dose-response analysis demonstrates that intake ≥ 800 g per day offered further reduction in the risk of CVD compared with intake of 500 g per day. WHO recommends a minimum of 400 g of FV per day (World Health Organization, 1990) and the American Heart Association dietary guideline advised consuming FV ≥ 5 servings/d (Krauss et al., 2000). A latest prospective study by Oyebode et al. (2014) suggest that there may be further health benefits to be obtained from increasing consumption to more than seven portions a day. Similarly, Joshipura et al. (2001) found the lowest CHD mortality in persons who consumed 8 or more servings daily. However, Joshipura et al. (1999) reported that there was no apparent further reduction in the risk of ischemic stroke beyond 6 servings/d FV intakes. Therefore, further investigations are warranted to determine the threshold at which the protective effects of FV are maximized.

Several plausible mechanisms might explain the inverse association between FV intake and the risk of CVD. Both fruits and vegetables are rich sources of micronutrients which may act synergistically or antagonistically to exert a holistic beneficial effect (Van Duyn & Pivonka, 2000); Antioxidant compounds and polyphenols, including vitamin C, E, flavonoids and

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carotenoids, might increase the antioxidant capacity of serum, enhance the formation of endothelial prostacyclin, protect against in vivo lipid peroxidation, and inhibit platelet aggregation (Gaziano, 1999); Folate, which is plentiful in green leafy vegetables, may lower plasma homocysteine levels, a proposed risk factor for arterial endothelial dysfunction (Bazzano et al., 2002a); soluble fibers have cardioprotective properties that act to lower cholesterol (Fernandez, 2001); several minerals, such as potassium, magnesium, and calcium, have been shown to increase natriuresis and vasomotricity, thus lowering blood pressure (Savige, 2001). Nevertheless, it should be noted that the protective role of individual nutrient could not be isolated from the complex biochemical content of fruits and vegetables, and their effects in combination with other constituents in whole foods may have the greatest effect.

Strengths of the present meta-analysis include the considerable number of included studies from various populations, increasing the generalizability. The prospective cohort study design minimized the possibility of recall bias. Furthermore, a large number of participants and cases were identified, thus providing sufficient statistical power to evaluate reduction in the risks. However, several limitations should be considered. First, our meta-analysis was based on observational studies. Although most studies have adjusted for lifestyle factors, residual confounding factors may still affect the favorable association between FV intake and risk of CVD. Second, FV consumption was assessed only at baseline by food frequency questionnaires (FFQs) in most included studies. Misclassification of FV consumption will be a major concern,

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and some subjects might have changed their dietary habits during the follow-up period. However, FFQ has been shown to be a reasonable tool to assess FV intakes (Sauvageot et al., 2013) and nondifferential misclassification at baseline would tend to attenuate the actual association. Third, there was significant heterogeneity among the included studies, which might be partly caused by the differences in various populations, multiple endpoints, or dietary assessment methods. However, our subgroup analyses and sensitivity analysis clearly indicated that the relations were largely consistent. Finally, significant publication bias was detected by the Egger's tests but not the Begg method, which might because small studies with null results were less likely to be published. Although the fill and trim analysis showed no significant change of the general result, the possibility of publication bias could not be fully excluded.

In summary, findings from the present meta-analysis of prospective cohort studies suggest a significant inverse association between higher FV consumption and risk of CVD. Our study provides strong support for the recommendations to increase FV consumption to promote cardiovascular health.

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REFERENCES

Bazzano, L.A., He, J., Ogden, L.G., Loria, C., Vupputuri, S., Myers, L., and Whelton, P.K. (2002a). Dietary intake of folate and risk of stroke in US men and women: NHANES I Epidemiologic Follow-up Study. National Health and Nutrition Examination Survey. *Stroke.* **33**:1183-8.

Bazzano, L.A., He, J., Ogden, L.G., Loria, C.M., Vupputuri, S., Myers, L., and Whelton. P.K. (2002b). Fruit and vegetable intake and risk of cardiovascular disease in US adults: the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. *Am J Clin Nutr.* **76**:93-9.

Begg, C.B.,and Mazumdar, M. (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics* .**50**:1088-101.

Bendinelli, B., Masala, G., Saieva, C., Salvini, S., Calonico, C., Sacerdote, C., Agnoli, C., Grioni, S., Frasca, G., and Mattiello, A. (2011). Fruit, vegetables, and olive oil and risk of coronary heart disease in Italian women: the EPICOR Study. *Am J Clin Nutr* .**93**:275-83.

Bhupathiraju, S.N., Wedick, N.M., Pan, A., Manson, J.E., Rexrode, K.M., Willett, W.C., Rimm, E.B., and Hu, F.B. (2013). Quantity and variety in fruit and vegetable intake and risk of coronary heart disease. *Am J Clin Nutr.* **98**:1514-23.

Crowe, F.L., Roddam, A.W., Key, T.J., Appleby, P.N., Overvad, K., Jakobsen, M.U., Tjonneland, A., Hansen, L.,Boeing, H., and Weikert, C., (2011). Fruit and vegetable intake and mortality

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from ischaemic heart disease: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Heart study. *Eur Heart J*. **32**:1235-43.

Dauchet, L., Amouyel, P., and Dallongeville, J. (2005). Fruit and vegetable consumption and risk of stroke: a meta-analysis of cohort studies. *Neurology*. **65**:1193-7.

Dauchet, L., Amouyel, P., Hercberg, S., and Dallongeville J. (2006). Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. *J Nutr*. **136**:2588-93.

Dauchet, L., Ferrieres, J., Arveiler, D., Yarnell, J.W., Gey, F., Ducimetiere, P., Ruidavets, J.B., Haas, B., Evans, A., and Bingham, A. (2004). Frequency of fruit and vegetable consumption and coronary heart disease in France and Northern Ireland: the PRIME study. *Br J Nutr*. **92**:963-72.

Dauchet, L., Montaye, M., Ruidavets, J.B., Arveiler, D., Kee, F., Bingham, A., Ferrieres, J., Haas, B., Evans, A., and Ducimetiere, P. (2010). Association between the frequency of fruit and vegetable consumption and cardiovascular disease in male smokers and non-smokers. *Eur J Clin Nutr*. **64**:578-86.

Duval, S., and Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. **56**:455-63.

Egger, M., Davey, Smith, G., Schneider, M., and Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*. **315**:629-34.

Fernandez, M.L. (2001). Soluble fiber and nondigestible carbohydrate effects on plasma lipids

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and cardiovascular risk. *Curr Opin Lipidol.* **12**:35-40.

Gaziano, J.M. (1999). Antioxidant vitamins and cardiovascular disease. *Proc Assoc Am Physicians.* **111**:2-9.

Genkinger, J.M., Platz, E.A., Hoffman, S.C., Comstock, G.W., and Helzlsouer, K.J. (2004). Fruit, vegetable, and antioxidant intake and all-cause, cancer, and cardiovascular disease mortality in a community-dwelling population in Washington County, Maryland. *Am J Epidemiol.* **160**:1223-33.

Gillman, M.W., Cupples, L.A., Gagnon, D., Posner, B.M., Ellison, R.C., Castelli, W.P., and Wolf, P.A. (1995). Protective effect of fruits and vegetables on development of stroke in men. *JAMA.* **273**:1113-7.

Hartley, L., Igbinedion, E., Holmes, J., Flowers, N., Thorogood, M., Clarke, A., Stranges, S., Hooper, L., and Rees, K. (2013). Increased consumption of fruit and vegetables for the primary prevention of cardiovascular diseases. *Cochrane Database Syst Rev.* **6**:CD009874.

He, F.J., Nowson, C.A., Lucas, M., and MacGregor, G.A. (2007). Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: meta-analysis of cohort studies. *J Hum Hypertens.* **21**:717-28.

He, F.J., Nowson, C.A., and MacGregor, G.A. (2006). Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet.* **367**:320-6.

Higgins, J.P., and Thompson, S.G. (2002). Quantifying heterogeneity in a meta-analysis. *Stat*

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Med. **21**:1539-58.

Higgins, J.P., Thompson, S.G., Deeks, J.J., and Altman, D.G. (2003). Measuring inconsistency in meta-analyses. *BMJ.* **327**:557-60.

Holmberg, S., Thelin, A., and Stiernstrom, E.L. (2009). Food choices and coronary heart disease: a population based cohort study of rural Swedish men with 12 years of follow-up. *Int J Environ Res Public Health.* **6**:2626-38.

Hu, D., Huang, J., Wang, Y., Zhang, D., and Qu, Y. (2014). Fruits and vegetables consumption and risk of stroke: a meta-analysis of prospective cohort studies. *Stroke.* **45**:1613-9.

Hu, E.A., Pan, A., Malik, V., and Sun, Q. (2012). White rice consumption and risk of type 2 diabetes: meta-analysis and systematic review. *BMJ.* **344**:e1454.

Iso, H., and Kubota, Y. (2007). Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). *Asian Pac J Cancer Prev.* **8 Suppl**:35-80.

Johnsen, S.P., Overvad, K., Stripp, C., Tjonneland, A., Husted, S.E., and Sorensen, H.T. (2003). Intake of fruit and vegetables and the risk of ischemic stroke in a cohort of Danish men and women. *Am J Clin Nutr.* **78**:57-64.

Joshipura, K.J., Ascherio, A., Manson, J.E., Stampfer, M.J., Rimm, E.B., Speizer, F.E., Hennekens, C.H., Spiegelman, D., and Willett, W.C. (1999). Fruit and vegetable intake in relation to risk of ischemic stroke. *JAMA.* **282**:1233-9.

Joshipura, K.J., Hu, F.B., Manson, J.E., Stampfer, M.J., Rimm, E.B., Speizer, F.E., Colditz, G.,

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Ascherio, A., Rosner, B., and Spiegelman, D. (2001). The effect of fruit and vegetable intake on risk for coronary heart disease. *Ann Intern Med.* **134**:1106-14.

Key, T.J., Thorogood, M., Appleby, P.N., and Burr, M.L. (1996). Dietary habits and mortality in 11,000 vegetarians and health conscious people: results of a 17 year follow up. *BMJ.* **313**:775-9.

Knekt, P., Jarvinen, R., Reunanen, A., and Maatela, J. (1996). Flavonoid intake and coronary mortality in Finland: a cohort study. *BMJ.* **312**:478-81.

Krauss, R.M., Eckel, R.H., Howard, B., Appel, L.J., Daniels, S.R., Deckelbaum, R.J., Erdman, J.W., Kris-Etherton, P., Goldberg, I.J., and Kotchen, T.A. (2000). AHA Dietary Guidelines: revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Circulation.* **102**:2284-99.

Kvaavik, E., Batty, G.D., Ursin, G., Huxley, R., and Gale, C.R. (2010). Influence of individual and combined health behaviors on total and cause-specific mortality in men and women: the United Kingdom health and lifestyle survey. *Arch Intern Med.* **170**:711-8.

Larsson, S.C., Virtamo, J., and Wolk, A. (2013). Total and specific fruit and vegetable consumption and risk of stroke: a prospective study. *Atherosclerosis.* **227**:147-52.

Leenders, M., Sluijs, I., Ros, M.M., Boshuizen, H.C., Siersema, P.D., Ferrari, P., Weikert, C., Tjonneland, A., Olsen, A., and Boutron-Ruault, M.C. (2013). Fruit and vegetable consumption and mortality: European prospective investigation into cancer and nutrition. *Am J Epidemiol.* **178**:590-602.

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Liu, S., Lee, I.M., Ajani, U., Cole, S.R., Buring, J.E., and Manson, J.E. (2001). Intake of vegetables rich in carotenoids and risk of coronary heart disease in men: The Physicians' Health Study. *Int J Epidemiol.* **30**:130-5.

Liu, S., Manson, J.E., Lee, I.M., Cole, S.R., Hennekens, C.H., Willett, W.C., and Buring, J.E. (2000). Fruit and vegetable intake and risk of cardiovascular disease: the Women's Health Study. *Am J Clin Nutr.* **72**:922-8.

Lock, K., Pomerleau, J., Causer, L., Altmann, D.R., and McKee, M. (2005). The global burden of disease attributable to low consumption of fruit and vegetables: implications for the global strategy on diet. *Bull World Health Organ.* **83**:100-8.

Mann, J.I., Appleby, P.N., Key, T.J., and Thorogood, M. (1997). Dietary determinants of ischaemic heart disease in health conscious individuals. *Heart.* **78**:450-5.

Nagura, J., Iso, H., Watanabe, Y., Maruyama, K., Date, C., Toyoshima, H., Yamamoto, A., Kikuchi, S., Koizumi, A., and Kondo, T. (2009). Fruit, vegetable and bean intake and mortality from cardiovascular disease among Japanese men and women: the JACC Study. *Br J Nutr.* **102**:285-92.

Nakamura, K., Nagata, C., Oba, S., Takatsuka, N., and Shimizu, H. (2008). Fruit and vegetable intake and mortality from cardiovascular disease are inversely associated in Japanese women but not in men. *J Nutr.* **138**:1129-34.

Nechuta, S.J., Shu, X.O., Li, H.L., Yang, G., Xiang, Y.B., Cai, H., Chow, W.H., Ji, B.T., Zhang,

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X.L., and Wen, W.Q. (2010). Combined impact of lifestyle-related factors on total and cause-specific mortality among Chinese women: prospective cohort study. *PLoS Med.* **7**.

Ness, A.R., Maynard, M., Frankel, S., Smith, G.D., Frobisher, C., Leary, S.D., Emmett, P.M., and Gunnell, D. (2005). Diet in childhood and adult cardiovascular and all cause mortality: the Boyd Orr cohort. *Heart.* **91**:894-8.

Orsini, N., Bellocco, R., and Greenland, S. (2006). Generalized least squares for trend estimation of summarized dose-response data. *Stata J.* **6**:40-57.

Oude, Griep, L.M., Geleijnse, J.M., Kromhout, D., Ocke, M.C., and Verschuren, W.M. (2010). Raw and processed fruit and vegetable consumption and 10-year coronary heart disease incidence in a population-based cohort study in the Netherlands. *PLoS One.* **5**:e13609.

Oude, Griep, L.M., Verschuren, W.M., Kromhout, D., Ocke, M.C., and Geleijnse, J.M. (2011). Raw and processed fruit and vegetable consumption and 10-year stroke incidence in a population-based cohort study in the Netherlands. *Eur J Clin Nutr.* **65**:791-9.

Oyebode, O., Gordon-Dseagu, V., Walker, A., and Mindell, J.S. (2014). Fruit and vegetable consumption and all-cause, cancer and CVD mortality: analysis of Health Survey for England data. *J Epidemiol Community Health.* **68**:856-62.

Rissanen, T.H., Voutilainen, S., Virtanen, J.K., Venho, B., Vanharanta, M., Mursu, J., and Salonen, J.T. (2003). Low intake of fruits, berries and vegetables is associated with excess mortality in men: the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study. *J Nutr.*

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133:199-204.

Sauvageot, N., Alkerwi, A., Albert, A., and Guillaume, M. (2013). Use of food frequency questionnaire to assess relationships between dietary habits and cardiovascular risk factors in NESCAV study: validation with biomarkers. *Nutr J*. **12**:143.

Sauvaget, C., Nagano, J., Allen, N., and Kodama, K. (2003). Vegetable and fruit intake and stroke mortality in the Hiroshima/Nagasaki Life Span Study. *Stroke*. **34**:2355-60.

Savige, G.S. (2001). Candidate foods in the Asia-Pacific region for cardiovascular protection: fish, fruit and vegetables. *Asia Pac J Clin Nutr*. **10**:134-7.

Sharma, S., Cruickshank, J.K., Green, D.M., Vik, S., Tome, A., and Kolonel, L.N. (2013). Impact of diet on mortality from stroke: results from the U.S. multiethnic cohort study. *J Am Coll Nutr*. **32**:151-9.

Sharma, S., Vik, S., and Kolonel, L.N. (2014). Fruit and vegetable consumption, ethnicity and risk of fatal ischemic heart disease. *J Nutr Health Aging*. **18**:573-8.

Stang, A. (2010). Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. **25**:603-5.

Steffen, L.M., Jacobs, D.R., Jr., Stevens, J., Shahar, E., Carithers, T., and Folsom, A.R. (2003). Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr*. **78**:383-90.

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Strandhagen, E., Hansson, P.O., Bosaeus, I., Isaksson, B., and Eriksson, H. (2000). High fruit intake may reduce mortality among middle-aged and elderly men. The Study of Men Born in 1913. *Eur J Clin Nutr.* **54**:337-41.

Takachi, R., Inoue, M., Ishihara, J., Kurahashi, N., Iwasaki, M., Sasazuki, S., Iso, H., Tsubono, Y., and Tsugane, S. (2008). Fruit and vegetable intake and risk of total cancer and cardiovascular disease: Japan Public Health Center-Based Prospective Study. *Am J Epidemiol.* **167**:59-70.

Van, Duyn, M.A., and Pivonka, E. (2000). Overview of the health benefits of fruit and vegetable consumption for the dietetics professional: selected literature. *J Am Diet Assoc.* **100**:1511-21.

Wang, F., Yeung, K.L., Chan, W.C., Kwok, C.C., Leung, S.L., Wu, C., Chan, E.Y.Y., Yu, I.T.S., Yang, X.R., and Tse, L.A. (2013). A meta-analysis on dose-response relationship between night shift work and the risk of breast cancer. *Ann Oncol.* **24**:2724-32.

Whiteman, D., Muir, J., Jones, L., Murphy, M., and Key, T. (1999). Dietary questions as determinants of mortality: the OXCHECK experience. Public Health Nutr. 2:477-87.

World Health Organization. (1990). Diet, Nutrition, and the Prevention of Chronic Diseases. Geneva: World Health Organization,. http://www.who.int/nutrition/

World Health Organization. (2013). Cardiovascular diseases (CVDs). http://www.who.int/mediacentre/factsheets/fs317/en/

Yu, D., Zhang, X., Gao, Y.T., Li, H., Yang, G., Huang, J., Zheng, W., Xiang, Y.B., and Shu, X.O. (2014). Fruit and vegetable intake and risk of CHD: results from prospective cohort studies of

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Chinese adults in Shanghai. *Br J Nutr.* **111**:353-62.

Zhang, X., Shu, X.O., Xiang, Y.B., Yang, G., Li, H., Gao, J., Cai, H., Gao, Y.T., and Zheng, W. (2011a). Cruciferous vegetable consumption is associated with a reduced risk of total and cardiovascular disease mortality. *Am J Clin Nutr.* **94**:240-6.

Zhang, Y., Tuomilehto, J., Jousilahti, P., Wang, Y., Antikainen, R., and Hu, G. (2011b). Lifestyle factors on the risks of ischemic and hemorrhagic stroke. *Arch Intern Med*..**171**:1811-8.

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Table 1 Basic characteristics of included studies

Author, publication year, region	**Study name, duration of follow-up, population**	**Dietary assessment, Ascertainment of outcomes**	**Cohort /case**	**Outcome**	**Exposure and estimate effects**	**Adjustment**	**Quality score**
Ness et al., 2005, England and Scotland	Boyd Orr's survey (1937-2000), 37 years; men & women, 7.5years old.	A seven-day dietary record, NA	4028/83	Stroke mortality	Fruit(90.0 Vs. 0.7g/d): 0.48(0.21, 1.10); Vegetable(116.1 Vs. 23.8g/d): 0.40(0.19, 0.83).	Within-family clustering of diet with the “irr” cluster option, childhood family food expenditure, father’s social class, district of	7
			4028/298	CHD mortality	Fruit(90.0 Vs. 0.7g/d): 0.19(0.76, 1.87);		

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					Vegetable(116.1 Vs. 23.8g/d): 1.01(0.70, 1.63).	residence as a child, period of birth, season when studied as a child, and Townsend score for current address or place of death.	
Strandhagen et al., 2000, Sweden	The Study of Men Born in 1913(1963-1993), 26 years; men, 54 years old.	FFQ; hospital discharge diagnosis, Swedish Register	730/209	CVD disease	Fruit (6-7 Vs. 0-1times/d): 0.74(0.47, 1.18); vegetable (6-7 Vs.		7

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		of the National Bureau of Statistic.			0-1times/d): 0.39(0.23, 0.66).		
			730/226	CVD mortality	Fruit (6-7 Vs. 0-1times/d): 0.66(0.43, 1.04); vegetable (6-7 Vs. 0-1times/d): 0.67(0.39, 1.14).		
Steffen et al., 2003, America	Atherosclerosis Risk in Communities Study (1987-1999), 11 years; men	66-items FFQ; Events were validated by	11940/214	Incident ischemic stroke	F&V (7.5 Vs. 1.5serving/day): 0.94(0.54, 1.63).	Age at baseline, race, sex, time-dependent energy intake,	8

	& women (men, 53.4years old, women 54.1years old).	hospital records, deaths were validated by physician records and next-of-kin interviews.				education, smoking status, pack-years of smoking, physical activity, alcohol intake, hormone replacement in women, BMI, waist-to-hip ratio, systolic blood pressure, and use of	

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						antihypertensive medications; HDL, LDL.	
Key et al., 1996, Britain	Prospective population-based cohort study (1973-1995), 16.8 years.	NA; copies of all the death certificates.	10771/ NA	IHD	Fruit (daily Vs. non-daily): 0.76(0.60, 0.97).	Age, sex, and smoking.	7
Whiteman et al., 1999, Britain	The OXCHECK Study (1989-1997), 9 years; men & women, 35–64 years old.	A list of foods; the Office for National Statistics National Health Service Central	10522/ 95	IHD mortality	Fruit (4-7 Vs. <1day/week): 0.84(0.50, 1.43); vegetable (4-7 Vs. <3day/week): 0.63(0.42, 0.95).	Gender, smoking and age group.	6

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		Register.					
Holmberg et al., 2009, Sweden	Prospective population-based cohort study, 12 years; men, 50.2years old.	15-item FFQ; NA	1752/138	CHD	F&V(Daily Vs. Less than daily): 0.65(0.44, 0.97)	None	7
Nakamura et al., 2008, Japan	Takayama Study (1992-1999), 7.3 years; men & women).	169-items FFQ; the office of National Vital Statistics.	29079/200	CVD mortality	Fruit (211.7 Vs.24.1g/day, men): 1.27(0.81, 2.01); vegetable (553.6 Vs.176.4g/day, men): 1.02(0.57, 1.82).	Age, total energy, marital status, years of education, BMI, smoking status, alcohol intake, exercise,	7

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				CVD mortality	Fruit (213.6 Vs.35.7g/day, women): 0.83(0.51, 1.34); vegetable (573.9 Vs.195.5g/day, women): 0.77(0.41, 1.46).	history of hypertension or diabetes mellitus, and Menopausal status, dietary confounders.	
Bazzano et al., 2002, America	National Health and Nutrition Examination Survey Epidemiologic Follow-up Study	FFQ; interview, death certificates	9608/888	Stroke incidence	F&V(≥3times Vs. <1time/day): 0.73(0.57, 0.95);	Age, sex, race, history of diabetes, physical activity (3 categories), education level	8

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	(1971-1992), 19 years; men & women, 25-74 years old.					(completed or did not complete high school), regular alcohol consumption (4 categories), current cigarette smoking at baseline (yes or no), vitamin supplement use (yes or no), and total energy	
			9608/1786	IHD incidence	F&V(≥3times Vs. <1 time/day): 1.01(0.84, 1.21);		
			9608/1145	CVD mortality	F&V(≥3times Vs. <1 time/day): 0.73(0.58, 0.92);		
			9608/218	Stroke mortality	F&V(≥3times Vs. <1 time/day): 0.58(0.33,		

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					1.02);	intake.	
			9608/639	IHD mortality	F&V (≥3times Vs. < 1time/day): 0.76(0.56, 1.03).		
Takachi et al., 2008, Japan	The Japan Public Health Center-based Prospective Study (1995-2002), 5 years; men & women, 56.9 years old.	138-items FFQ; medical records, death certificate or self-report.	77891/1386	CVD	Fruit (Highest Vs. Lowest): 0.81(0.67, 0.97); vegetable (Highest Vs. Lowest): 0.97(0.82, 1.15); F&V (733 Vs.186g/day): 0.90(0.75, 1.07).	Sex, age, public health center area, BMI, physical activity in metabolic equivalent task-hours/day, smoking status, alcohol consumption	7

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						, quartile of energy intake, screening examination, medication , and daily vitamin supplement use.	
Genkinger et al., 2004, America	Odyssey Cohort (1974-2002), 13 years; men&women,55.7 years old.	61-items, modified Block FFQ; Maryland State death certificates.	6151/378	CVD mortality	F&V (4.89 Vs. 0.87servings/day): 0.76(0.54, 1.06).	Age, smoking status, BMI, cholesterol concentration, and energy.	8

Kvaavik et al., 2010, Britain	The Health and Lifestyle Survey (1984-2005), 20 years; men & women, 43.7 years old.	FFQ; death certificates	4889/266	CVD mortality	F&V (≥3 times/day Vs. <3 times/day): 0.78(0.60, 1.03).	Age, sex, occupational social class, BMI, blood pressure, and the other 3 health behaviors.	8
Johnsen et al, 2003, Denmark	The Danish Diet, Cancer, and Health study (1993-1999), 3.09 years; men & women, 56.1 years old.	192-item FFQ; Medical records and hospital discharge letters.	54506/266	Ischemic stroke	Fruit (249 Vs. 41g/d): 0.60(0.38, 0.95); vegetable (312 Vs 66g/d): 1.00(0.66, 1.53); F&V (673 Vs. 147g/d): 0.72(0.47,	Sex, total energy intake, smoking status, systolic blood pressure, diastolic blood pressure,	7

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					1.12).	total serum cholesterol, history of diabetes, BMI, alcohol intake, intake of red meat, intake of n3 polyunsaturated fatty acids, physical activity, and education.	

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Zhang et al., 2011, Finland	Surveys were performed in 6 geographic areas of Finland (1982-2007), 13.7 years; men & women, 45.4 years old.	A self-administered questionnaire; Mortality data were obtained from Statistics Finland and data on nonfatal events from the National Hospital Discharge	36686 /1478	Stroke	Fruit (≥7times/week Vs. <1times/week) :0.99(0.82, 1.20); vegetable (≥7times/week Vs. <1times/week) : 0.82(0.67, 1.00).	Age, study year, sex, smoking, physical activity, vegetable consumption, fruit consumption, education, alcohol consumption, family history of stroke, history of diabetes mellitus, BMI,	7

		Register.				systolic blood pressure, and total cholesterol level, other than the variable in the analytic model.	
Rissanen et al., 2003, Finland	Kuopio Ischemic Heart Disease Risk Factor Study (1984-2000), 12.8 years.	4-day food intake records; the national death registry	2641/115	CVD mortality	F&V (>408 Vs.<133g/d): 0.66(0.28, 1.55)	Age, examination years, urinary excretion of nicotine metabolites, alcohol consumption	8

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						, BMI, systolic and diastolic blood pressure, diabetes, serum LDL, HDL, triglycerides, maximal oxygen uptake, dietary factors.	
Gillman et al., 1995, America	The Framingham Study (1966-1986), 20 years; men,	The Framingham composite Table and	832/75	Stroke	F&V (9.6 Vs. 1.3servings/d): 0.33(0.15, 0.73).	Age	6

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	55.9 years old.	interview; surveillance of hospital admissions records and communication with family physicians and relatives.					
Sauvag et et al., 2003, Japan	The Life Span Study (1980-1998), 16 years; men & women.	22-items FFQ; death certificates	39337/ 692	Total stroke mortality	Fruit (≥7serving Vs.0-1serving/ week, men): 0.65(0.53, 0.80);	Age-stratified, and adjusted for radiation dose, city, BMI,	8

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					vegetable (≥7serving Vs.0-1serving/ week, men): 0.77(0.62, 0.95);	smoking status, alcohol habits, education level, medical history of hypertension, myocardial infarction, diabetes, and Consumption of animal products.	
			39337/ 1234	Total stroke mortality	Fruit (≥7serving Vs.0-1serving/ week, women): 0.75(0.64, 0.88); vegetable(≥7serving Vs.0-1serving/ week, women): 0.81(0.68, 0.96).		

Larsson et al., 2013, Sweden	Prospective population-based cohort study(1998-2008), 10.2 years; men & women, 60.2 years old.	96-item FFQ; the Swedish Hospital Discharge Registry	74961/ 4089	Stroke	Fruit(3.1 Vs.0.1servings /d): 0.87(0.78, 0.97); vegetable(5.1 Vs. 0.9servings/d): 0.90(0.80, 1.01); F&V(7.6 Vs. 1.6servings/d): 0.87(0.78, 0.97	Age, sex, smoking status and pack-years of smoking, education, BMI, total physical activity, aspirin use, history of hypertension, diabetes, family history of myocardial infarction, and intakes of total	8

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						energy, alcohol, coffee, fresh red meat, processed meat, and fish. Total fruit and total vegetable consumption was mutually adjusted by including both variables in the same multivariabl	

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						e model.	
Mann et al., 1997, Britain	Prospective population-based cohort study(1980-1995), 13.3 years; men & women, 33.4 years old;	SFFQ; death certificates	10802/63	IHD mortality	Fruit (≥10 Vs. <5times/week): 0.89(0.44, 1.80); vegetable (≥5times Vs. ＜once/week): 1.34(0.47, 3.84);	Age, sex, smoking and social class for subjects with no evidence of pre-existing disease at the time of recruitment.	
Knekt et al., 1996, Finland	Finnish mobile clinic health examination. Survey (1967-1992),	Interview on dietary history; death certificate	5133/NA	CHD mortality	Vegetable (≥458 Vs. <262g/d, men):0.89(0.65, 1.21);	Age, smoking, serum cholesterol, hypertension	7

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	26 years; men, 44.6 years old; women, 45.4 years old.	s			vegetable (≥369 Vs. <216g/d, women):0.77(0 .49, 1.21).	, and BMI.	
Griep et al., 2011, Netherl ands	Prospective population-bas ed cohort study (1993-2006), 10.3 years; men & women, 41.5 years old.	178-item FFQ; The hospital discharge register, Statistics Netherlan ds	20069/ 233	Strok e incid ence	F&V(589 Vs. 185g/day): 0.97(0.66, 1.44)	Age, gender, energy intake, alcohol intake, smoking status, educational level, dietary supplement use, use of hormone replacement therapy,	8

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						family history of acute myocardial infarction, BMI, intake of fish, whole grain foods and processed meat.	
Griep et al., 2010, Netherlands	Prospective population-based cohort study(1993-2006), 10.5 years; men & women, 41.5 years old.	178-item FFQ; The hospital discharge register, Statistics Netherlands	20069/ 245	CHD incidence	F&V(589 Vs. 185g/day): 0.66(0.45, 0.99)	Age, gender, energy intake, alcohol intake, smoking status, educational	8

						level, dietary supplement use, use of hormone replacement therapy, family history of MI before 60, BMI, intake of fish, whole grain foods and processed meat.	
Iso et al., 2007,	Japan Collaborative Cohort Study	39 items food questionn	102392 /601	IHD	Vegetable (≥3-4 Vs.<1time/w,	Age and area of study.	7

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Japan	for Evaluation of Cancer (1988-2003), 12 years; men & women.	aire; NA			men): 0.91(0.71, 1.16)		
			102392 /402	IHD	Vegetable (≥3-4 Vs.<1time/w, women): 0.88(0.64, 1.20)		
Nagura et al., 2009, Japan	The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (1988-2003), 12.7 years; men & women,	33-items FFQ; death certificate s	59485/ 2243	CVD morta lity	Fruit(5.9 Vs. 0.9servings/we ek): 0.77(0.67, 0.88); vegetable(5.2 Vs. 1.2servings/we ek): 0.96(0.84,	Sex, age, BMI, smoking status, alcohol intake, hours of walking, hours of	8

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	56.2 years old.				1.10);	sleep, education years, perceived mental stress, cholesterol intake, SFA intake, n-3 fatty acids intake, sodium intake and histories of hypertension and diabetes, vegetable, fruit and bean intakes.	
			59485/ 1053	Total stroke mortality	Fruit (5.9 Vs. 0.9servings/week): 0.65(0.53, 0.80); vegetable(5.2 Vs. 1.2servings/week): 1.09(0.90, 1.33);		
			59485/ 452	CHD mortality	Fruit (5.9 Vs. 0.9servings/week): 0.79(0.58, 1.08); vegetable (5.2 Vs. 1.2servings/we		

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					ek): 0.85(0.64, 1.14).		
Dauchet et al., 2010, France and Northern Ireland	The PRIME study, 10 years; men, 50-59 years old.	Face-to-face interview; self-report and confirmed by hospital or family doctor	8060/79	Acute coronary syndrome	Fruit (≥1.29 Vs. ≤0.57 times/day, never smokers): 1.33(0.72, 2.45); vegetable (≥1.5 Vs. ≤0.79 times/day, never smokers): 1.25(0.74, 2.13); F&V(≥2.6 Vs. ≤1.57	Centre, age, alcohol consumption, physical activity, education level, employment status, supplement vitamin intake, systolic blood pressure, total cholesterol,	8

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					times/day, never smokers): 1.06(0.60, 1.84);	HDL-cholesterol, BMI, treatment for hypertension, diabetes and dyslipidaemia.	
			8060/140	Acute coronary syndrome	Fruit (≥1.29 Vs. ≤0.57 times/day, former smokers): 0.83(0.56, 1.23); vegetable (≥1.5 Vs. ≤0.79 times/day, former smokers): 1.29(0.85,		

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					1.95); F&V(≥2.6 Vs. ≤1.57 times/day, former smokers): 0.98(0.66, 1.47);		
			8060/148	Acute coronary syndrome	Fruit (≥1.29 Vs. ≤0.57 times/day, current smokers): 0.61(0.38, 0.99); vegetable (≥1.5 Vs. ≤0.79 times/day,		

					current smokers): 0.72(0.45, 1.14); F&V(≥2.6 Vs. ≤1.57 times/day, current smokers): 0.49(0.30, 0.81);		
			8060/145	CVD	Fruit (≥1.29 Vs. ≤0.57 times/day, never smokers): 1.45(0.94, 2.23); vegetable		

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					(≥1.5 Vs. ≤0.79 times/day, never smokers): 1.14(0.77, 1.71); F&V(≥2.6 Vs. ≤1.57 times/day, never smokers): 1.27(0.84, 1.93);		
			8060/237	CVD	Fruit (≥1.29 Vs. ≤0.57 times/day, former smokers):		

					1.06(0.77, 1.45); vegetable (≥1.5 Vs. ≤0.79 times/day, former smokers): 1.04(0.76, 1.44); F&V(≥2.6 Vs. ≤1.57 times/day, former smokers): 0.93(0.68, 1.27);		

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			8060/230	CVD	Fruit (≥1.29 Vs. ≤0.57 times/day, current smokers): 0.82(0.57, 1.16); vegetable (≥1.5 Vs. ≤0.79 times/day, current smokers): 0.74(0.51, 1.07); F&V(≥2.6 Vs. ≤1.57 times/day, current		

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					smokers): 0.64(0.44, 0.93);		
Dauchet et al., 2004, France and Northern Ireland	The PRIME study, 5 years; men, 54.7years old.	Face-to-face interview; self-report and confirmed by hospital or family doctor	8087/249	CHD	Fruit (≥1.29 Vs. ≤0.57times/day): 0.90(0.66, 1.24); vegetable (≥1.5 Vs. ≤0.79times/day): 1.01(0.88, 1.15); F&V(≥2.6 Vs.≤ .57times/day): 0.78(0.56, 1.07).	Centre, age, smoking, alcohol consumption, physical activity, education level, employment status, systolic blood pressure, total cholesterol, HDL-cholest	8

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						erol, BMI, treatment for hypertension , diabetes or dyslipidaemi a.	
Nechut a et al., 2010, China	Shanghai Women's Health Study (1996-2007), 9.1 years; women, 40-70 years old.	77-items FFQ; death certificate s	71243/ 775	CVD morta lity	F&V(≥626.5 Vs. <404.3g/d): 0.84(0.70, 1.00)	Education, occupation， income，and other lifestyle factors.	8
Yu et al., 2013, China	The Shanghai Women’s Health Study(1996-20 09), 9.8 years; the Shanghai	Semi-qua ntitative FFQ; medical record, death	67211/ 148	CHD incid ence	Fruit (449 Vs. 83g/d, women): 0.77(0.45, 1.31); vegetable (429	Baseline age, BMI, income, education, smoking, alcohol	7

	Men's Health Study (2002-2009), 5.4 years; women, 51.7 years old; men, 54.5 years old.	certificates			Vs. 137g/d, women): 0.83(0.52, 1.33); F&V(814 Vs. 274g/d, women): 0.67(0.41, 1.10)	consumption, physical activity, use of aspirin and vitamin E and multivitamin supplements, total energy, red meat and fish/shellfish intake and history of diabetes, hypertension or dyslipidaemia.	
			55474/217	CHD incidence	Fruit (285 Vs. 23g/d, men): 0.96(0.63, 1.44); vegetable (502 Vs. 160g/d, men): 1.02(0.71, 1.48); F&V(722 Vs.		

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					242g/d, men): 0.86(0.59, 1.26);		
Zhang et al., 2011, China	Shanghai Women's Health Study (1996-2009), 10.2 years; Shanghai Men's Health Study(2002-2009), 4.6 years; women, 53 years old; men, 55 years old.	77-items FFQ; the Shanghai Cancer Registry and the Shanghai Vital Statistics Registry	134796 /1023	CVD mortality	Fruit (489 Vs. 62g/d, women): 0.78(0.62, 0.98); vegetable (506 Vs. 124g/d, women): 0.84(0.67, 1.04);	Age, education, occupation, family income, cigarette smoking, alcohol consumption, BMI, amount of regular exercise, multivitamin supplement use, intakes	8
			134796 /635	CVD mortality	Fruit (308 Vs. 14g/d, men): 0.63(0.48, 0.85);		

					vegetable(583 Vs. 144g/d, men): 0.64(0.49, 0.83);	of total energy and saturated fat, menopausal status and hormone therapy use and history of coronary heart disease, stroke, hypertension, or diabetes.	
Liu et al., 2000, America	Female health professionals(1993-1999), 5 years; women;	131-items FFQ; medical records, autopsy	39876/126	MI	Fruit (3.9 Vs. 0.6 servings/day): 0.66(0.36, 1.22);	Age, smoking, exercise, alcohol use, postmenopa	6

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		reports, and death certificates,			vegetable(6.9 Vs. 1.5servings/day): 0.88(0.50, 1.58); F&V(10.2 Vs. 2.6 servings/day): 0.63(0.38, 1.17);	usal, postmenopausal hormone use, BMI, multivitamin use, vitamin C supplement, history of hypertension or high cholesterol and parental history of MI.	
			39876/110	CVD	Fruit (3.8 Vs. 0.6servings/day): 0.57(0.30, 1.09); vegetable (6.8 Vs. 1.5servings/day): 0.45(0.24, 0.89); F&V		

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					(10.0 Vs. 2.2 servings/day): 0.45(0.22, 0.91).		
Sharma et al., 2013, America	The Multiethnic Cohort (1993-2001), 7.5 years; men & women (men, 65.7 years old; women, 59.3 years old).	QFFQ; state death files	174888 /860	Stroke mortality	Fruit (≥3.8 Vs. 0-1.7servings/d): 1.01(0.84, 1.21); vegetable (≥5.2 Vs. 0-3servings/d): 0.85(0.70, 1.05).	Adjusted for time on study, years of education, energy intake, smoking, BMI, physical activity, history of diabetes, alcohol intake, and history of	7

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						hormone replacement therapy	
Leenders et al., 2013, Europe	European Prospective Investigation Into Cancer and Nutrition (1992-2010), 13 years; men & women, 25-70 years old.	FFQ; health insurance records, cancer and pathology registries, and active follow-up of study subjects and their next of kin	451151 /5125	CVD mortality	Fruit (403.0 Vs. 74.6g/day): 0.96(0.87, 1.05); vegetable (339.4 Vs. 91g/day): 0.79(0.71, 0.87); F&V(725.3 Vs.178.8g/day): 0.85(0.77, 0.93);	Smoking status, smoking duration, time since stopped smoking, number of cigarettes smoked per day, alcohol consumption, BMI, physical activity, education,	8

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						and processed meat consumption. The model for vegetables was additionally adjusted for fruit consumption and vice versa.	
Crowe et al., 2011, Europe	EPIC (1992-2000); 8.4 years, men & women, 53.8 years old.	Country-specific food questionnaires;	313074 /1636	IHD mortality	Fruit (≥4 Vs.<1.5portions/day): 0.79(0.67, 0.92):	Sex, centre, smoking, alcohol intake, BMI, physical	7

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		active follow-up of study participants and next-of-kin			vegetable (≥4 Vs.<1.5portions/day): 0.92(0.76, 1.12); F&V(11.0 Vs. 2.1 portions/day): 0.76(0.62, 0.93);	activity, marital status, highest education level, current employment, hypertension, angina pectoris, diabetes mellitus, and total energy intake.	
Bendinelli et al., 2011, Italia	The Italian cohort of the European Prospective Investigation	188-items FFQ; the hospital discharge files, all	29689/ 144	CHD events	Fruit (>441.3 Vs. ≤219.3g/d): 1.24(0.73, 2.12);	Educational level, smoking status, alcohol	7

	into Cancer and Nutrition study (1993-2004), 7.85 years; women, 50 years old.	records reporting and death certificates			vegetable (>241.7 Vs. ≤117.5g/d): 0.62(0.37, 1.04); F&V(>441.3 Vs. ≤219.3g/d): 1.10(0.65, 1.87)	consumption, body height(cm), body weight(kg), waist circumference, daily nonalcoholic caloric intake(log kcal), hypertension, menopausal status, total physical activity index, total meat	

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						consumption , vegetable consumption in analysis for fruit and fruit consumption in analyses for vegetables.	
Joshipura et al., 1999, America	The Nurses' Health Study(1980-1994), 14 years; the Health Professionals' Follow-up study(1986-1994), 8 years;	126-item FFQ; medical records	75596/366	Ischemic stroke	Fruit (Q5 Vs. Q1, women): 0.69(0.49, 0.98); vegetable (Q5 Vs. Q1, women): 0.89(0.63, 1.26);	Age, smoking, alcohol, family history of myocardial infarction, BMI, vitamin	7

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	women, 46.1 years old; men, 53.7 years old;				F&V(Q5 Vs. Q1, women): 0.74(0.52, 1.05);	supplement use, vitamin E use, physical activity, aspirin use, 7 time periods for women, 4 time periods for men, hypertension and hypercholesterolemia, total energy intake, and among women,	
			38683/ 204	ischemic stroke	Fruit (Q5 Vs. Q1, men): 0.68(0.42, 1.10); vegetable (Q5 Vs. Q1, women): 0.90(0.58 1.41); F&V(Q5 Vs. Q1, women): 0.61(0.37, 1.00);		

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						postmenopausal hormone use.	
Bhupathiraju et al, 2013, America	The Nurses' Health Study(1984-2008), 24 years; the Health Professionals Follow-Up Study(1986-2008), 22 years; women, 50.1 years old; men, 53.1 years old;	126-item SFFQ; medical records	71141/ 2582	CHD	Fruit(2.84 Vs. 0.44servings/d, women): 0.87(0.76, 0.99); vegetable(5.14 Vs. 1.49servings/d, women): 0.85(0.74, 0.97); F&V(7.59 Vs. 2.26servings/d, women): 0.81(0.70,	Age, calendar year, BMI, total energy intake, smoking status, physical activity, menopausal status and postmenopausal hormone use, alcohol	7

					0.93);	intake, parental history of early myocardial infarction, multivitamin use, aspirin use, intakes of trans fatty acids. Cereal fiber, red meat, and fish.	
			42135/ 3607	CHD	Fruit (3.07 Vs. 0.42servings/d, men): 0.88(0.78, 0.99); vegetable (5.22 Vs. 1.38servings/d, men): 0.92(0.82, 1.03); F&V(7.83 Vs. 2.14servings/d, men): 0.84(0.75, 0.95);		

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Liu et al., 2001, America	The Physician's Health Study (1982-1995), 12 years; men, 52.1 years old.	SFFQ; NA	15220/ 387	MI	Vegetable (≥2.5 Vs.<1serving/day): 0.81(0.59, 1.31);	Age, treatment, cigarette smoking, alcohol intake, physical activity, BMI, history of diabetes mellitus, history of high cholesterol, history of hypertension and use of multivitamins.	7

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Oyebode et al.,2014, Britain	The 2001–2008 Health Surveys for England, 7.7 years.	24-hour recall, link to UK mortality data	85347/1482	CVD mortality	F&V(7+ Vs. <1 portions/day): 0.69(0.53, 0.88);	Age-group, sex, social class, cigarette smoking, BMI and additionally adjusted for physical activity, education and alcohol intake.	7
Sharma et al., 2014, America	The Multiethnic Cohort Study (1993-2001), 6.5 years, 45 to 75 years old.	QFFQ; state death files	164617/1140	Fatal IHD	Fruit (>4.8 Vs. <1.0 servings/day, men): 0.96(0.77, 1.19);	Age, ethnicity, time on study, maximum years of	7

					vegetable (>6.6 Vs. <2.3 servings/day, men): 0.73(0.58, 0.92);	education, energy intake, smoking behavior, BMI, physical activity, history of diabetes, alcohol intake.	
			164617 /811	Fatal IHD	Fruit (>4.8 Vs. <1.0 servings/day, women); 0.96(0.73, 1.26); vegetable (>6.6 Vs. <2.3 servings/day, women): 0.95(0.72, 1.26).		

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BMI= body mass index; CVD=cardiovascular disease; CHD=coronary heart disease;

IHD=ischemic heart disease; FFQ=food frequency questionnaire; MI=myocardial infarction.

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Table 2 Sub-group analyses of FV with risk of CVD

	Vegetable only				Fruit only				Fruit and vegetables			
	n	**RR (95% CI)**	**I^2 (%)**	***P***	**n**	**RR (95% CI)**	**I^2 (%)**	***P***	**n**	**RR (95% CI)**	**I^2 (%)**	***P***
All studies	45	0.87(0.83, 0.91)	31.1	0.027	41	0.84(0.79, 0.88)	41.6	0.003	34	0.83(0.79, 0.86)	19.4	0.161
Subtypes of CVD events												
CVD	13	0.82(0.73, 0.93)	59.0	0.004	13	0.85(0.76, 0.95)	55.3	0.008	12	0.83(0.78, 0.88)	22.8	0.219
CHD	10	0.91(0.86, 0.97)	0.0	0.641	8	0.88(0.78, 0.99)	0.0	0.756	8	0.81(0.75, 0.88)	0.0	0.709
IHD	7	0.85(0.77, 0.95)	1.00	0.417	6	0.85(0.76, 0.94)	0.0	0.605	2	0.88(0.67, 1.16)	76.1	0.041
Stroke	10	0.87(0.82, 0.93)	27.8	0.189	10	0.77(0.68, 0.88)	65.0	0.002	8	0.82(0.75, 0.90)	29.9	0.190
Other	5	0.96(0.78, 1.18)	22.5	0.271	4	0.81(0.76, 0.86)	30.1	0.232	4	0.77(0.61, 0.99)	52.5	0.097

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Gender												
Women	12	0.83(0.77, 0.90)	0.0	0.859	12	0.82(0.75, 0.89)	0.0	0.488	8	0.81(0.73, 0.89)	0.0	0.561
Men	19	0.88(0.84, 0.94)	48.1	0.010	18	0.85(0.76, 0.96)	49.6	0.013	14	0.83(0.77, 0.90)	41.7	0.051
Mix	14	0.79(0.71, 0.87)	38.5	0.070	13	0.83(0.76, 0.90)	53.2	0.012	14	0.84(0.80, 0.88)	7.2	0.374
Location												
Europe	21	0.86(0.79, 0.95)	48.5	0.007	20	0.90(0.85, 0.94)	33.3	0.075	18	0.83(0.78, 0.88)	20.3	0.212
America	10	0.87(0.81, 0.93)	0.0	0.561	9	0.89(0.83, 0.95)	8.8	0.362	12	0.81(0.76, 0.87)	37.7	0.090
Asia	14	0.89(0.84, 0.95)	22.1	0.213	12	0.75(0.70, 0.80)	14.6	0.302	4	0.86(0.76, 0.96)	0.0	0.730
Follow-up years												
≤10	23	0.88(0.85, 0.91)	32.6	0.067	23	0.87(0.82, 0.93)	32.5	0.068	18	0.81(0.75, 0.87)	25.5	0.155

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>10	22	0.86(0.83, 0.90)	30.2	0.090	18	0.81(0.76, 0.87)	51.7	0.006	16	0.83(0.79, 0.87)	14.9	0.282
Publication year												
≤2005	17	0.80(0.71, 0.90)	44.5	0.025	15	0.73(0.67, 0.80)	0.0	0.691	13	0.78(0.71, 0.86)	31.1	0.134
>2005	28	0.88(0.85, 0.91)	21.4	0.156	26	0.87(0.82, 0.93)	43.9	0.009	21	0.84(0.80, 0.87)	9.7	0.332

CVD=cardiovascular disease; CHD= Coronary heart disease; IHD=ischemic heart disease; RR=relative risk; CI=confidence interval.

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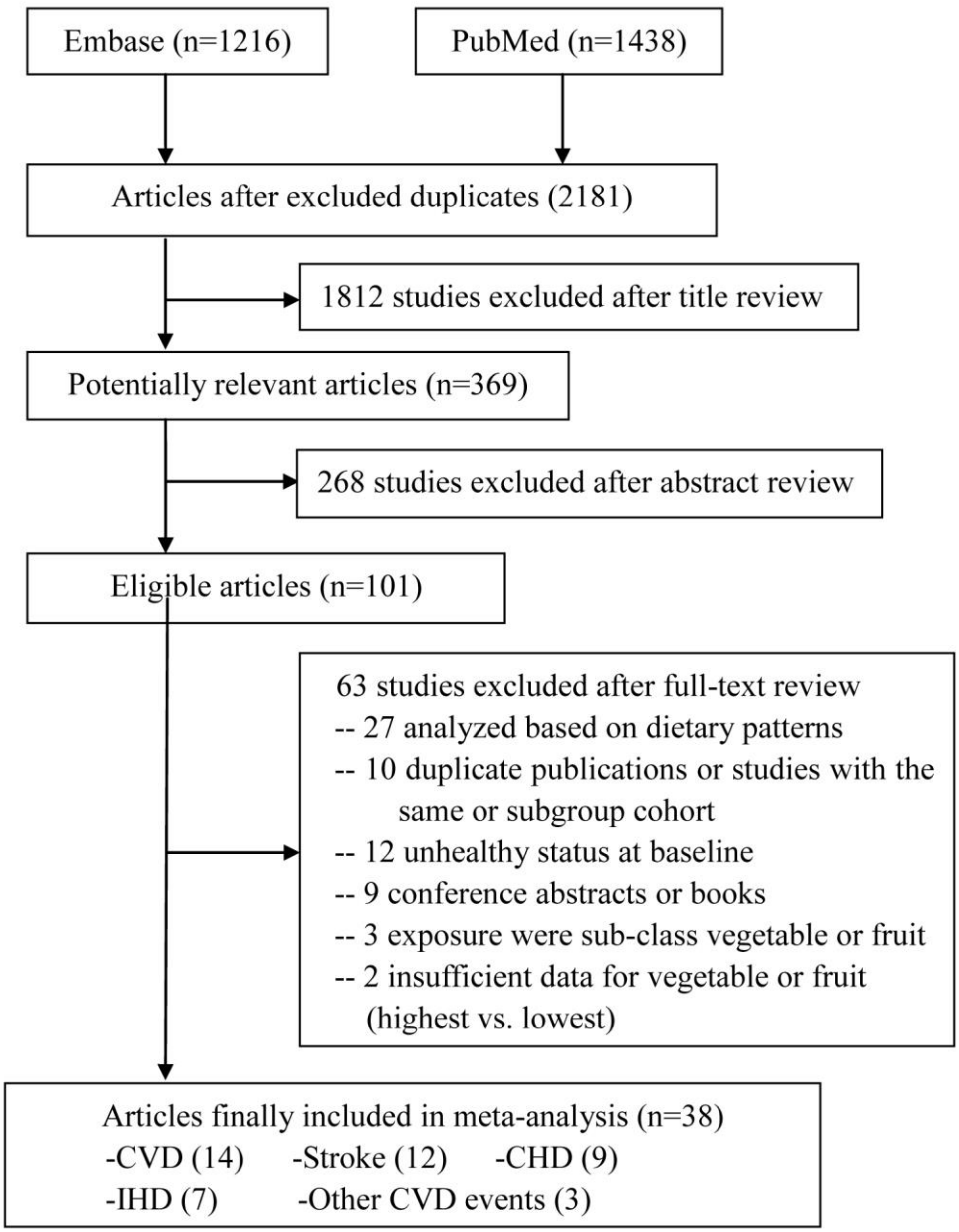

Figure 1. Literature search and study selection

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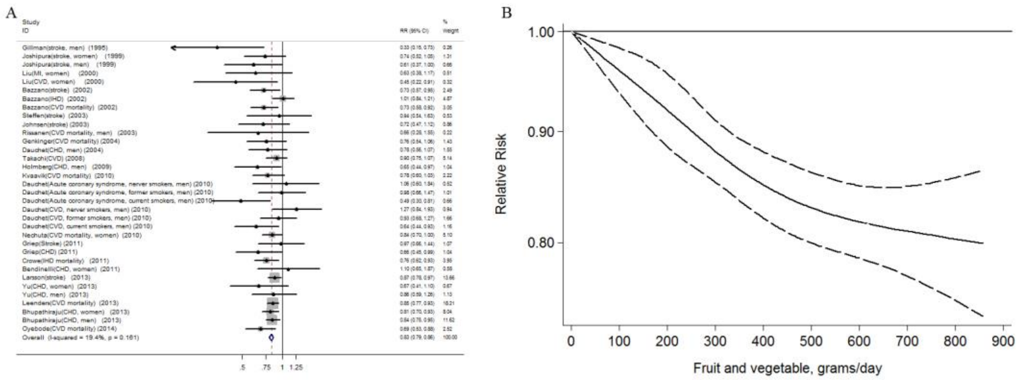

Figure 2. Total FV consumption and the risk of CVD (A: Forest plot of FV with the risk of CVD; B: Dose-response relation of FV with the risk of CVD)

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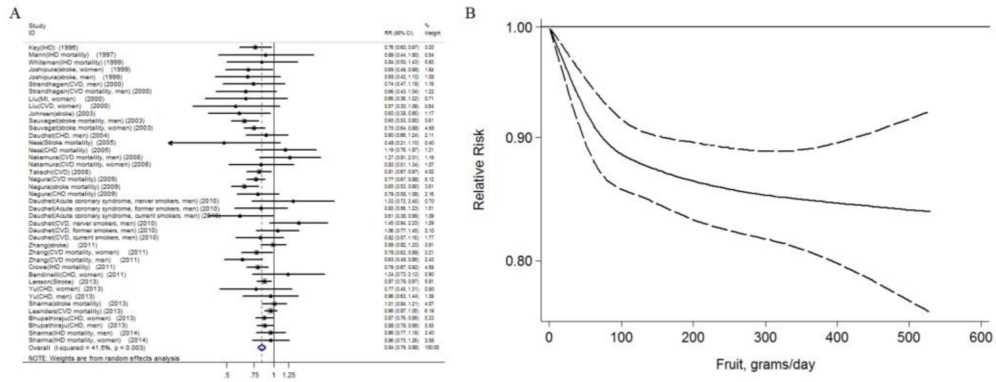

Figure 3. Fruit consumption and the risk of CVD (A: Forest plot of fruit with the risk of CVD; B: Dose-response relation of fruit with the risk of CVD)

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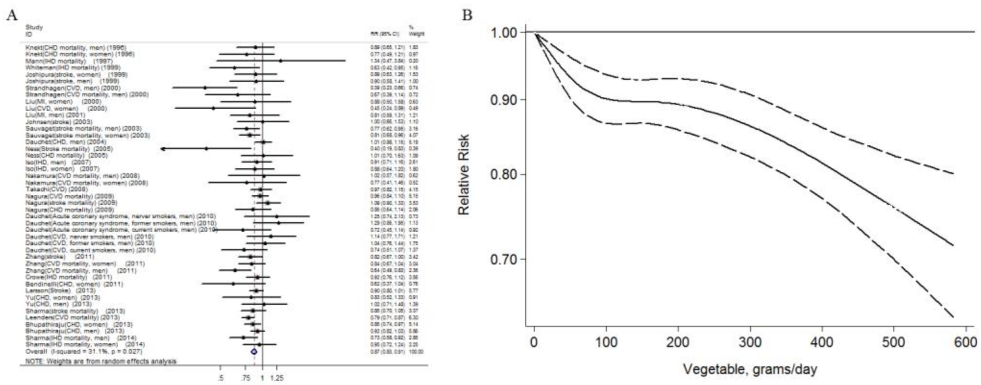

Figure 4. Vegetables consumption and the risk of CVD (A: Forest plot of vegetables with the risk of CVD; B: Dose-response relation of vegetables with the risk of CVD)

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