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Original Article

Association between dietary patterns and coronary heart disease: a meta-analysis of prospective cohort studies

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Abstract: The associations of dietary patterns with coronary heart disease (CHD) risk remain unclear. Thereby, a meta-analysis was conducted to examine potential relations between dietary patterns and CHD. PubMed and EMBASE databases were searched up to March 2014 for eligible prospective cohort studies regarding the relationships between common dietary patterns and CHD. Random-effects models were applied to calculate the summary relative risk estimates (SRRE) for the highest versus the lowest category of dietary pattern. Sensitivity analyses were conducted and publication bias was assessed using Begg or Egger's tests. Twelve prospective cohort studies were included involving 409,780 participants and 6298 CHD cases. There was an inverse association between prudent/healthy dietary pattern and CHD risk (SRRE = 0.80, 95% CI: 0.74-0.87, *P*-value for heterogeneity = 0.497, I^2 = 0%). Furthermore, no significant association was observed between western/unhealthy dietary pattern and risk of CHD (SRRE = 1.05, 95% CI: 0.86-1.27, *P*-value for heterogeneity = 0.007, I^2 = 61.9%). However, increased risk was detected between western/unhealthy dietary pattern and CHD in the United States (USA) (SRRE = 1.45, 95% CI: 1.15-1.82, *P*-value for heterogeneity = 0.930, I^2 = 0%). In conclusion, our analysis provides evidence of an inverse association between prudent/healthy dietary pattern and CHD risk, and suggests null association between western/unhealthy dietary pattern and CHD. However, greater adherence to western/unhealthy pattern possibily increases by 45% the risk of CHD in USA. Further efforts are warranted to confirm these findings and clarify the role of dietary patterns and CHD risk.

Keywords: Coronary heart disease, dietary patterns, meta-analysis, nutrition

Introduction

Coronary heart disease (CHD) is the leading cause of death in adults throughout their lifetime, affecting millions of people in both developed and developing countries. Furthermore, it causes substantial mortality and morbidity [1, 2]. During the past decades, diagnostic intensity and treatment is improving, but prognosis is still poor. In addition, the rising incidence of CHD is alarming and there are little effective preventive measures against it [3]. In recent decades, the roles of dietary factors in the development of CHD have been received growing attention in epidemiologic investigations. Dietary factors are considered as the modifiable factors for CHD like smoking, physical inactivity, or alcohol [4].

Traditionally, the association of single nutrients with CHD has been widely studied. A major limitation of this approach is the little correlations between intakes of various nutrients or food items. To overcome the limitations of this approach, the studies of dietary patterns emerged, which could yield a more comprehensive understanding of how this complex factor affects the etiology of disease compared with analyzing single nutrient and food [5]. Dietary patterns can be defined either a priori or a posteriori. A posteriori methods derive patterns empirically based on the actual diet in a popula-

tion, of these methods, factor analysis (FA) and/or principal component analysis (PCA) has reasonable reproducibility and validity compared with other approaches [6, 7].

Since 2000, the association between dietary patterns on CHD has been more frequently studied. Furthermore, several prospective cohort studies, which are not prone to recall and selection bias, have explored the influence of dietary patterns on CHD risk [8-18]. However, their findings varied substantially across studies. Hence, to examine the association of dietary patterns with CHD risk, we performed this first meta-analysis of the existing prospective cohort studies on the relationship between dietary patterns and the risk of CHD.

Methods and materials

Literature search strategy

We performed this meta-analysis in accordance with Meta-analysis of Observatio0nal Studies in Epidemiology (MOOSE) guidelines [19]. We searched PubMed and EMBASE databases through March 2014 for the eligible prospective cohort studies that had evaluated the associations between dietary patterns and risk of CHD in humans. The keywords used in this study were: cardiovascular disease, coronary heart disease, myocardial infarction, ischemic heart disease, IHD, CHD, morbidity, incidence, risk, death, mortality, diet, dietary, patterns, factor analysis and principal component analysis. The two reviewers used no language or date restrictions in the searches. Furthermore, we assessed and searched the reference lists of all retrieved publications again for additional relevant publications. We identified articles for eligibility by a full-text review after initially screening by titles or abstracts.

Inclusion and exclusion criteria

Studies would be included in this meta-analysis if they met the following criteria: (1) There were prospective cohort studies that examined the relationship between dietary patterns and CHD in human being; (2) The outcome was risk of CHD, including incidence of CHD and CHD mortality; (3) The study has reported risk estimates (i.e., relative risk RRs or odds ratios ORs) and its variability (i.e., 95% confidence intervals CI). If the study has provided sufficient information (e.g.: raw data and *P*-value) for estimation, it would be included as well; (4) Food or dietary patterns in studies were examined by factor analysis (FA) and/or principal component analysis (PCA); (5) Only the most recent and informative one was included if there were more than one publications of the same or overlapping cohort.

To minimize error and combine the results, only the patterns sharing most foods with similar factor loadings were identified. In this analysis, we identified two common dietary patterns: Prudent/healthy dietary pattern was characterized by having high loadings of foods such as vegetables, fruits, fish, poultry, whole grains and low-fat dairy. While western/unhealthy dietary pattern tended to have a high intake of processed and/or red meat, refined grains, sweets, desserts, eggs and high-fat diary. Studies with dietary pattern having similar loadings of the foods common to prudent/healthy or western/unhealthy were also included in spite of naming differently [20, 21].

The exclusion criteria were (1) The studies were duplicates; (2) They had irrelevant data reported; (3) The studies were methodological studies, experimental studies, narrative reviews, editorial papers, case control or cross-sectional; (4) An identified dietary pattern did not fit into healthy or unhealthy dietary pattern categories; (5) The dietary patterns were not indentified by FA or PCA.

Data extraction

Two independent authors independently conducted literature search and extracted the data from all studies that were in the meta-analysis using an investigator-designed data extraction form. This included information about the first author, year of publication, geographic area, number of CHD cases, sample size, age range, study duration, follow-up duration, number of exposed cases, dietary assessment, identification method, naming dietary patterns, endpoints, RR or OR, 95% CIs, number of food items in Food Frequency Questionnaire (FFQ) and description of healthy and unhealthy dietary pattern adjustment variables. When one study presented different adjustment variables, we used the results from the main multivariable model that included the maximum number of adjusted confounders. The discrep-

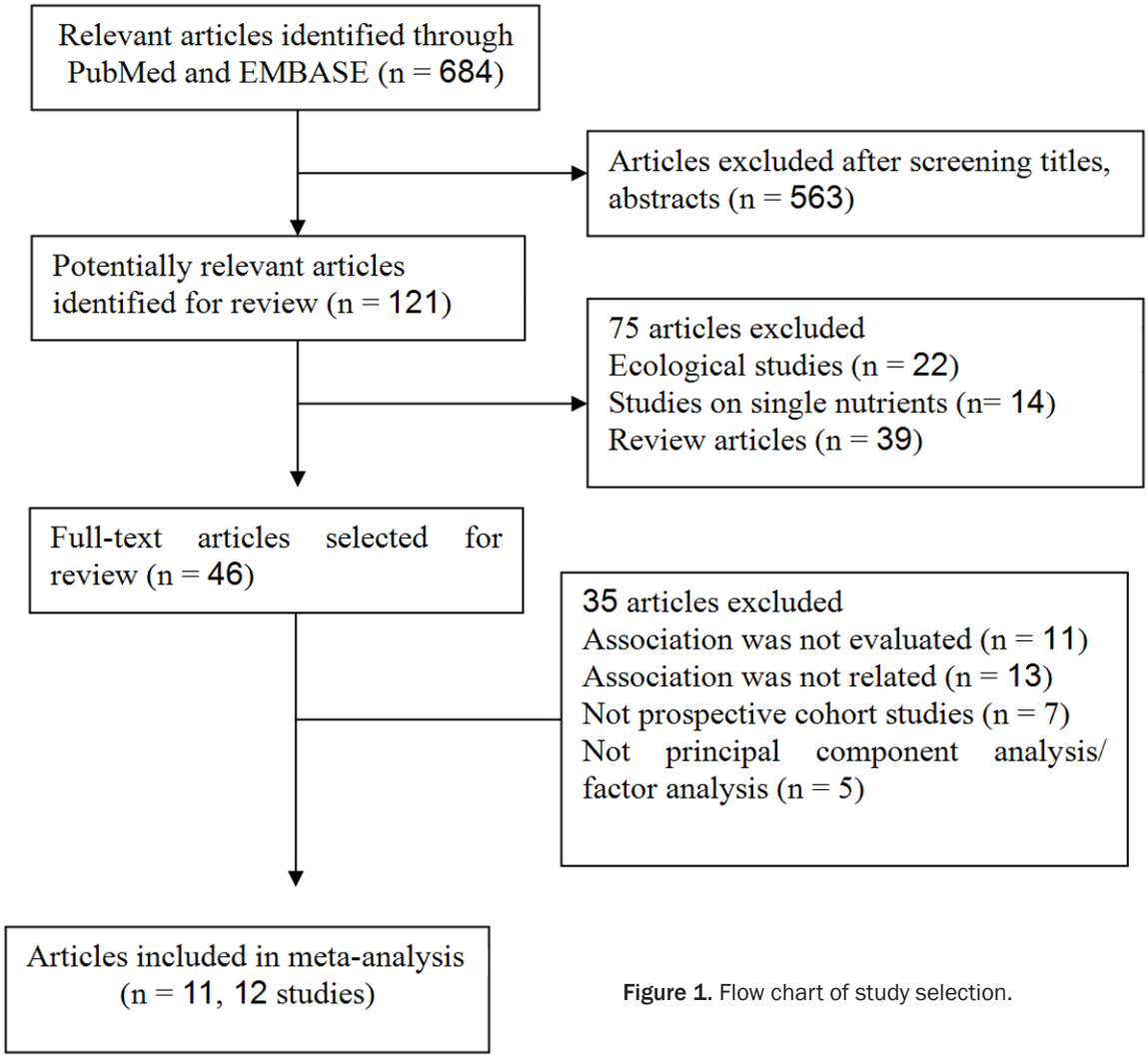

Figure 1. Flow chart of study selection.

ancy in data extraction was resolved by repeating the study review and discussion.

Quality assessment of each study was performed by reporting following crucial components of eligible studies: clear definition of participant characteristics, clear examination of exposure and outcome, study duration, sufficient follow-up duration, person-years of follow-up, no selective loss during follow-up and control for potential confounding factors. If a study did not clearly mention these key points, we considered that it had not been performed, but it's probably underestimated the reported characteristics.

Statistical analysis

We used summary relative risk estimate (SRRE) for a comparison of the highest with the lowest adherence of each dietary pattern intake type (prudent/healthy and western/unhealthy) in terms of tertiles, quartiles, or quintiles of dietary pattern in the included studies. The random effects meta-analysis models, which take into account within-and between-study variances considering the extent of variation, or heterogeneity, were applied to pool the study results and presented forest plots. Furthermore, we assessed the statistical heterogeneity across studies with a chi-square test (significant with a *P*-value of < 0.10), and quantified the inconsistencies using the I^2 statistic. Values of 25%, 50% and 75% for I^2 are defined to demonstrate low, moderate and high levels of heterogeneity, respectively [22].

Some studies provided more than one pattern models (i.e. vegetables, fruits, sweets, meat) that met the inclusion criteria in our meta-analysis for the prudent/healthy or western/

Table 1. Characteristics of studies included in meta-analysis of dietary patterns and coronary heart disease (CHD) risk

First author and year	Study location	Cases[a]/ Subjiects	following-up/ Period	FFQ list	Dietary pattern	Endpoints	RR (95% CI)/Trend	*P*	Adjustments
Maruyama 2013 men [8]	Japan	272/26598	12.6/1998-2003	40	Vegetable	CHD mortality	0.73 (0.49-1.08)	0.150	Age, smoking, BMI, total energy intake, walking time, hours of sports, education, perceived mental stress, sleep duration, history of hypertension and diabetes
					Animal food	CHD mortality	0.72 (0.48-1.08)	0.140	
Maruyama 2013 women [8]	Japan	207/37439	12.6/1998-2003	40	Vegetable	CHD mortality	0.67 (0.43-1.06)	0.050	
					Animal food	CHD mortality	0.73 (0.42-1.26)	0.380	
Stricker 2013 [9]	Denmark	1843/40011	13/1993-2008	79	Prudent	CHD incidence	0.87 (0.75-1.00)	0.058	Age, gender, smoking, BMI, energy, education, type II diabetes, waist-hip-ratio, PA, blood pressure
					Western	CHD incidence	0.91 (0.76-1.08)	0.342	
Guallar-Castillón 2012 [10]	Spain	606/40757	11/1992-2004		Mediterranean	CHD incidence	0.73 (0.57-0.94)	0.013	Age, sex, smoking, BMI, energy intake, PA, center, hypercholesterolemia, diabetes, hypertension, cancer, waist, menopausal status, oral contraceptives, hormone replacement therapy, education
					Western	CHD incidence	0.86 (0.60-1.24)	0.510	
Nettleton 2009 [11]	USA	207/5316	4.6/2000-2007	120	Whole Grains and Fruit	CHD incidence	0.63 (0.34-1.16)	0.050	Age, sex, smoking, energy intake, PA, race-ethnicity, education, study center, weekly dietary supplement use
Harriss 2007 [12]	Australia	407/40653	10.4/1990-2003	121	Mediterranean foods	IHD mortality	0.59 (0.39-0.89)	0.030	Sex, smoking, BMI, total energy intake, PA, country of birth, education, waist-to-hip ratio, social isolation, dietary factors, CVD history, and family history of CVD, diabetes, hypertension
					Vegetables	IHD mortality	1.02 (0.73-1.42)	0.710	
					Fresh fruit	IHD mortality	0.82 (0.60-1.11)	0.360	
					Meat	IHD mortality	0.85 (0.60-1.21)	0.650	
Shimazu 2007 [13]	Japan	181/40547	7/1994-2001	40	Japanese	CHD mortality	0.82 (0.52-1.29)	0.290	Age, sex, smoking, BMI, total energy intake, walking duration, education, History of hypertension
					Animal food	CHD mortality	1.50 (0.95-2.37)	0.050	
Cai 2007 [14]	China	77/74942	5.7/1996-2004	71	Vegetable-rich	CHD mortality	1.10 (0.61-1.99)	0.504	Age, smoking, BMI, education, marriage, income per person, alcohol consumption, tea consumption, ginseng intake, PA, energy expenditure
					Fruit-rich	CHD mortality	0.71 (0.33-1.53)	0.550	
					Meat-rich	CHD mortality	1.58 (0.81-3.08)	0.176	
Akesson 2007 [15]	Sweden	308/24444	6.2/1997-2003	96	Health food	Myocardial infarction incidence	0.58 (0.39-0.88)	NR	Age, smoking, energy intake, PA, educational achievement, family history of MI, hormone therapy, aspirin, waist to hip ratio, cholesterol level, hypertension
Osler 2002 [16]	Denmark	280/5834	13/1982-1996	28	Healthy food index	CHD incidence	1.21(0.80-1.82)	0.229	Smoking, BMI, exercise, alcohol intake, education
Fung 2001 [17]	USA	821/69017	12/1984-1996	116	Prudent	CHD incidence	0.76 (0.60-0.98)	0.030	Age, smoking, BMI, caloric intake, hormone replacement therapy, PA, period, aspirin, family history, hypertension, multivitamin and vitamin E
					Western	CHD incidence	1.46 (1.07-1.99)	0.020	
Hu 2000 [18]	USA	1089/44875	8/1986-1994	131	Prudent	CHD incidence	0.75 (0.59-0.95)	0.020	Age, smoking, BMI, energy intake, PA, parental history of MI before age 60, multivitamin and vitamin E, alcohol, history of hypertension, profession, cereal fiber, folate intake
					Western	CHD incidence	1.43 (1.01-2.01)	0.004	

a:Number of cases in study; IHD: ischemic heart disease; CVD: cardiovascular disease; USA: the United States; FFQ: Food Frequency Questionnaire; NR: not reported; BMI: body mass index; PA: physical activity.

Table 2. Summary of meta-analysis results for dietary patterns (high intake vs. low intake[a]) and coronary heart disease (CHD) risk

Analysis specifications	Studies	SRRE (95% CI)	P^b	I^2
Prudent/health dietary pattern				
CHD risk	12	0.80 (0.74-0.87)	0.497	0
USA	3	0.75 (0.63-0.88)	0.854	0
Europe	4	0.82 (0.65-0.99)	0.104	30.7
Asia	4	0.72 (0.62-0.97)	0.767	0
Cases < 500	8	0.80 (0.73-0.89)	0.521	0
Cases ≥ 500	4	0.79 (0.67-0.92)	0.326	13.3
Participants < 50,000	7	0.81 (0.72-0.91)	0.221	27.2
Participants ≥ 50,000	5	0.75 (0.63-0.89)	0.843	0
Follow-up duration < 10 years	5	0.74 (0.62-0.87)	0.596	0
Follow-up duration ≥ 10 years	7	0.82 (0.74-0.91)	0.380	6.3
FFQ < 100 items	7	0.76 (0.66-0.88)	0.905	0
FFQ ≥ 100 items	4	0.82 (0.71-0.96)	0.232	0
Adjustment with energy	10	0.78 (0.66-0.88)	0.761	0
Adjustment without energy	2	1.08 (0.79-1.47)	0.405	0
Western/unhealthy dietary pattern				
CHD risk	9	1.05 (0.86-1.27)	0.007	61.9
Europe	2	0.90 (0.77-1.06)	0.784	0
USA	2	1.45 (1.15-1.82)	0.930	0
Asia	4	1.03 (0.67-1.59)	0.035	65.1
Cases < 500	5	1.12 (0.85-1.48)	0.011	73.1
Cases ≥ 500	4	0.98 (0.71-1.34)	0.058	56.2
Participants < 50,000	5	1.04 (0.83-1.80)	0.045	59.0
Participants ≥ 50,000	4	1.04 (0.68-1.61)	0.014	71.9
Follow-up duration < 10 years	3	0.92 (0.75-1.13)	0.054	54.0
Follow-up duration ≥ 10 years	6	1.05 (0.86-1.27)	0.962	0
FFQ < 100 items	5	0.98 (0.75-1.29)	0.063	55.3
FFQ ≥ 100 items	3	1.22 (0.87-1.71)	0.046	67.6
Adjustment with energy	8	1.02 (0.83-1.25)	0.007	63.7
Adjustment without energy	1	1.58 (0.81-3.08)	-	-

[a]The intake contrast (i.e., exposure vs. referent group) for each study is reported in **Table 1**. [b]P: *P*-value for heterogeneity; SRRE: summary relative risk estimate; 95% CI: 95% confidence intervals.

unhealthy dietary pattern. The separate risk estimates in individual study were combined to obtain a unique study-specific estimate for this pattern.

Sensitivity analyses were performed to assess the robustness of the effect estimates by excluding one study in turn from the analyses. Publication bias was assessed through the visual inspection of a funnel plot combined with Begg's rank correlation and Egger's linear regression test [23]. In addition, to explore potential sources of heterogeneity, subgroup analyses were also conducted on the basis of geographic area, number of cases (≥ 500 or < 500 cases) or participants (≥ 50,000 or < 50,000 persons), follow-up duration (≥ 10 or < 10 years), the number of food items in FFQ (≥ 100 or < 100 items) and whether energy intake was adjusted/unadjusted in studies. All statistical analyses were performed with STATA Statistical Software, version 11.0.

Results

Study selection

The initial search strategy identified 684 papers, of which 563 articles were excluded after screening by abstracts, titles or duplicate articles. Furthermore, 75 papers were excluded because of ecological studies, review articles or studies nutrients, whereas 46 papers were eligible for full text review. 23 articles were excluded because their effect sizes and the corresponding 95% confidence intervals were not reported or could not be estimated due to insufficient information. In addition, twelve papers were excluded because dietary patterns in those studies were not examined by FA/PCA, or the studies were not prospective cohort studies. The studies reported by Maruyama et al. [8] reported risk estimates for men and women individually. Thus, it was considered two separate studies when the observed items were pooled respectively. Finally, twelve prospective cohort studies form eleven papers were included in our meta-analysis, which were published between 2000 and 2014 [8-18]. **Figure 1** provides a flow summary of our selection proce.

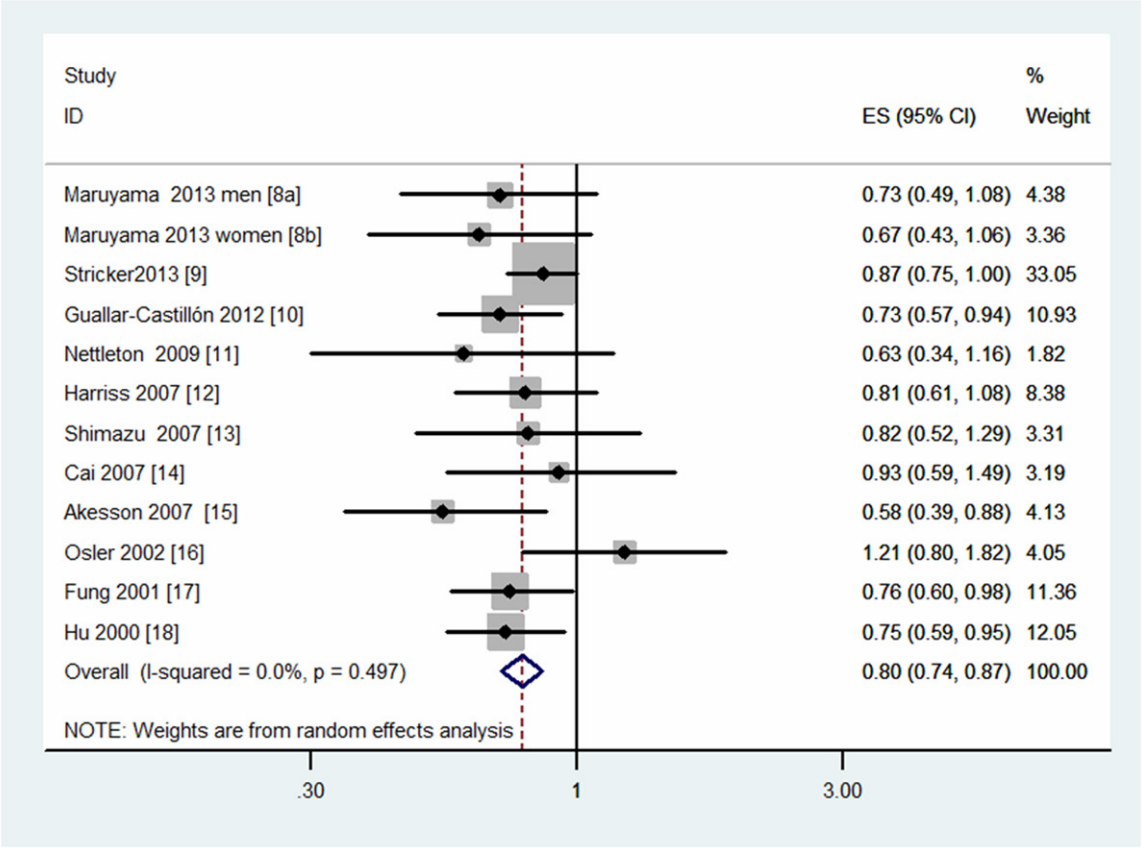

Figure 2. Meta-analysis of studies that examined the associations of prudent/health dietary pattern with coronary heart disease (CHD) risk.

Study characteristics

All of the included twelve studies were prospective cohort studies, three studies were conducted in the United States (USA) [11, 17, 18], three in Japan [8, 8, 13], two in Denmark [9, 16], one each in Spain [10], Australia [12], Sweden [15] and China [14]. Most of studies in our analysis used FFQ based on self-report or interviewer-administered questionnaires to ascertain dietary information, despite the length of items list in the questionnaire varied across studies. In summary, twelve studies were included in the present analysis with a sample size of 409,780 individuals and 6298 cases of CHD. **Table 1** has shown the characteristics of the included studies.

Prudent/healthy dietary patterns and CHD risk

The overall meta-analysis results are presented in **Table 2**. The pooled results showed an inverse association between prudent/healthy diet pattern and CHD risk (SRRE = 0.80, 95% CI: 0.74-0.87), and little variability was observed (*P*-value for heterogeneity = 0.497, I^2 = 0%) (**Table 2**; **Figure 2**). Furthermore, similar inverse associations were found in the subgroup analyses. The Begg (*P* = 0.837) and Egger (*P* = 0.382) tests, as well as visual inspection of the funnel plot (not shown), did not suggest a publication bias. Furthermore, further sensitivity test by exclusion each study at a time suggested that no single study could materially influence the overall results in our meta-analysis, with a narrow range from 0.75 (95% CI: 0.67-0.82) to 0.80 (95% CI: 0.73-0.86).

Western/unhealthy dietary patterns and CHD risk

The pooled results indicated that there was no evidence of a difference in the risk of CHD in the highest category compared with the lowest category of western/unhealthy diet pattern (SRRE = 1.05, 95% CI: 0.86-1.27). Substantial

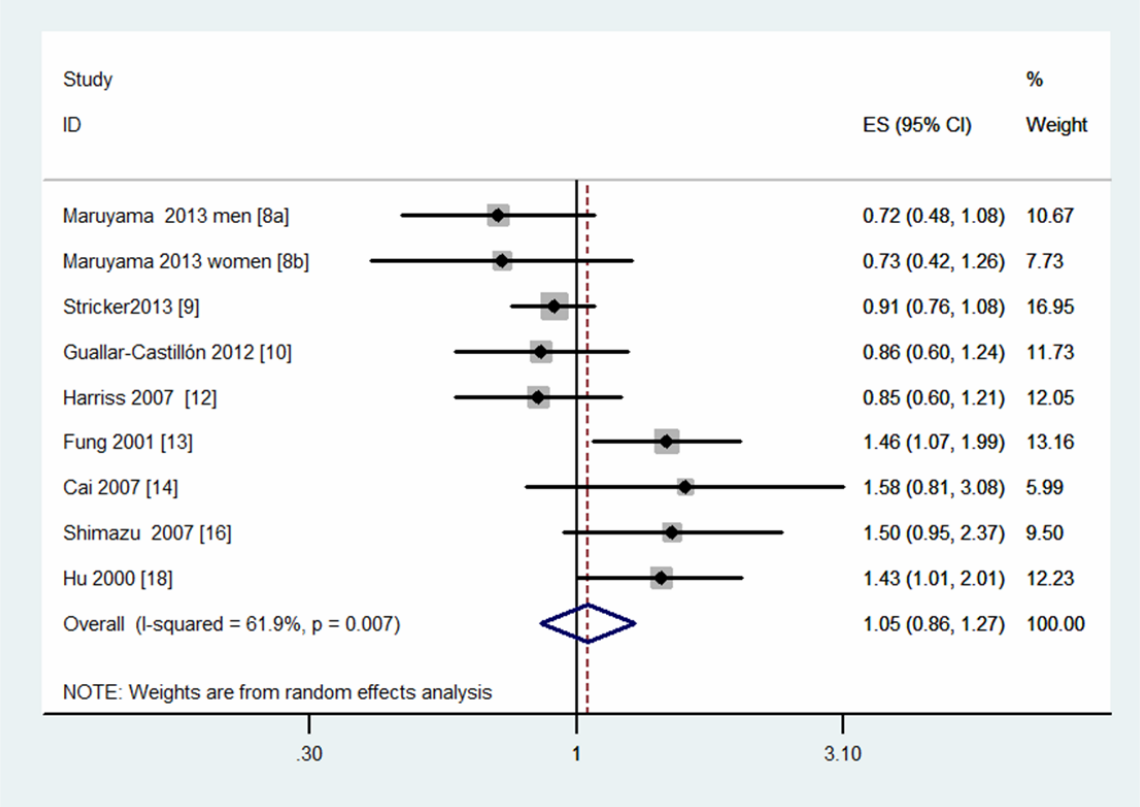

Figure 3. Meta-analysis of studies that examined the associations of western/unhealthy dietary pattern with coronary heart disease (CHD) risk.

heterogeneity was observed between studies (*P*-value for heterogeneity = 0.007, I^2 = 61.9%) (**Table 2**; **Figure 3**). No significant summary association was observed in most of subgroup analyses. To be noted, summarized results from a limited number of studies showed a positive association between CHD risk and western/unhealthy pattern in USA (SRRE = 1.45, 95% CI: 1.15-1.82; *P*-value for heterogeneity = 0.930, I^2 = 0%) (**Table 2**).

Visual inspection of the funnel plot (not shown) did not suggest substantial asymmetry. There was no statistical evidence of publication bias based on the Begg's rank correlation (*P* = 0.754) and the Egger's linear test (*P* = 0.541). None of any single study would affect the overall estimates of western/unhealthy dietary pattern and CHD risk, and the results indicated by sensitivity analyses ranged between 0.90 (95% CI: 0.79-1.02) and 0.96 (95% CI: 0.85-1.08).

Subgroup analyses

Subgroup analyses were conducted to examine the stability of our overall findings (**Table 2**). The associations of dietary patterns with risk of CHD were similar in most of our subgroup analyses, which were defined by study location, number of cases or participants, follow-up duration, number of food items in FFQ, and whether energy intake was adjusted in models.

Discussion

It has been suggested that dietary habits play a vital role in the development of CHD. Given the complex interaction between intakes of various nutrients or food items, and that nutrients and foods could never be eaten in isolation, The results revealing the effects through individual foods or nutrients consumption on a given health outcome may be spurious resulting in masking true associations [5, 24]. Recently, there has been growing attention in the identification of dietary patterns, representing a combination of nutrients and foods, as an alternative or complementary approach to single-food/nutrient analysis in relation to risk of disease or death. The study examined dietary patterns

has the advantage of studying the effect of the whole diet and may be a better predictor of health outcomes than analyzing single nutrient or food [25]. Up to date, considerable controversy exists regarding the associations of dietary patterns with CHD risk.

Therefore, we performed this fist meta-analysis of the existing prospective cohort studies on the associations of dietary patterns with risk of CHD. Twelve prospective cohort studies were included in our analysis with a total of 409,780 participants and 6298 cases of CHD. The summarized findings showed that greater adherence to prudent/healthy dietary pattern had an inverse association with CHD risk. However, there was an absence of significant association between western/unhealthy dietary pattern and risk of CHD. The findings were consistent with most of our subgroup analyses. To be noted, we found that higher adherence to western/unhealthy pattern was associated with 45% increased risk of CHD in USA.

Substantial heterogeneity was detected across studies of western/unhealthy pattern compared with prudent/healthy pattern. This might be caused by variability among the study populations, follow-up period, analytic methodology, dietary assessment method and adjustment for confounding factors. Based on our subgroups by geographical region, number of cases or participants, follow-up duration, number of food items in FFQ as well as adjustment for energy intake or not, little heterogeneity was observed among studies conducted in Europe and USA, and studies with follow-up period more than 10 years. In addition, our sensitivity analyses indicated that no individual study had a particularly large influence on the pooled estimates. Furthermore, there was no evidence of publication bias either with the Begg's or Egger's tests in the present study.

Considering the number and description of dietary patterns identified has varied widely, we identified two common dietary patterns named prudent/healthy or western/unhealthy dietary pattern in our analysis, which shares most foods with similar factor loadings. The dietary patterns could be identified according to several approaches including FA, PCA, cluster analysis, reduced rank regression, dietary scores and so on. Of these methods, FA/PCA used to derive dietary patterns has long term reproducibility, stability and validity compared with other approaches [5, 7]. Thereby, we only included the studies of FA/PCA as the dietary patterns identification method to could minimize the risk of bias and combine the result accurately.

High intakes of fresh fruits, vegetables, cereals, fish and olive oils are defining characteristics of the prudent/healthy dietary pattern. Because this pattern is rich in vitamins, minerals, antioxidants, fiber, monounsaturated fatty acids and n-3 fatty acids, it seems protective in people's cardiac health. The prudent/healthy pattern was found to be associated with a lower risk of CHD. The underlying mechanism could be favorably correlated with facilitating weight maintenance, markers of inflammation and endothelial dysfunction caused by greater adherence to the prudent pattern [17]. Furthermore, other biological mechanisms like lipid abnormalities or effects on oxidative stress, systolic and diastolic blood pressure rise, arrhythmias, and insulin sensitivity would be a possible explanation for this finding [25].

A frequent consumption of red meat, processed meat, refined grains, sweets, French fries, desserts, eggs and high high-fat dairy products characterizes the western/unhealthy dietary pattern. No significant association was found between the western dietary pattern and CHD. The pooled risk estimate was in line with most results emerging from the included studies. One explanation may be that cardioprotective roles mediated primarily through plants are reduced because of greater intakes of meat products in place of more beneficial plant foods in diet [26].

However, a positive association was observed between adherence to western dietary pattern and CHD risk in USA. The underlying mechanism involved in this association is uncertain. One plausible reason is the characteristics of the typical American diet by containing more red meat, high-fat dairy products and other animal products, less fish and plant-rich foods [27]. Many studies have demonstrated some foods or nutrients consumption of this pattern were significantly related to an increased CHD risk, such as heme iron, red meat, whole milk and a high glycemic index from carbohydrate-

loading foods [28-31]. In addition, we could not exempt the possibility that the associations could be explained by terms of genetic background and lifestyle in this area. Noticeably, the studies included in this model were limited. Therefore, the results should be interpreted with caution.

Several potential limitations in our current study should be acknowledged. First, although most included studies were adjusted for a wide range of dietary and lifestyle variables and established risk factor, we could not exempt the possibility that other variables are relevant to the observed outcomes. Second, there was substantial heterogeneity across studies that examined unhealthy dietary patterns, though we were able to partly find that geographic region and follow-up duration are potential source of heterogeneity through subgroup analyses. In addition, all the included studies in our analysis were prospective cohort designed. However, differences among follow-up period, measurement of CHD end point, etc, may lead us to misreport the true associations of dietary patterns on CHD risk.

In conclusion, our meta-analysis on the basis of 409,780 participants provides evidence of an inverse association between prudent/healthy dietary pattern and CHD risk, and suggests null association between western/unhealthy dietary pattern and risk of CHD. However, our findings indicates that greater adherence to western/unhealthy pattern possibly increases by 45% the risk of CHD in USA. Further studies are warranted to confirm these findings and clarify the role of dietary patterns and CHD risk.

Disclosure of conflict of interest

None.

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