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Dietary flavonoids intake and the risk of coronary heart disease: A dose-response meta-analysis of 15 prospective studies

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ABSTRACT

Introduction: Epidemiological studies evaluating the association of flavonoids intake with risk of coronary heart disease (CHD) have produced inconsistent results. We conducted a meta-analysis to summarize the evidence from prospective cohort studies regarding the association between flavonoids intake and risk of CHD.
Materials and Methods: Pertinent studies were identified by searching Web of Knowledge, Pubmed and Wan Fang Med Online up to April 2014. Fixed-effect or random-effect model was used to combine the results based on the heterogeneity. Dose-response relationship was assessed by restricted cubic spline. Publication bias was estimated using Begg' funnel plot and Egger's regression asymmetry test.
Results: Fourteen articles with 15 prospective studies involving 7,233 CHD cases and 452,564 participants were included in this meta-analysis. Pooled results suggested that highest flavonoids intake versus lowest intake was significantly associated with the risk of CHD [summary relative risk (RR) = 0.850, 95% confidence interval (CI) = 0.794-0.910, I^2 = 26.0%, τ^2 = 0.041]. Inverse associations were found both in Europe and in USA. Linear dose-response relationship was found between flavonoids intake and CHD risk. However, no significant association was found through the dose-response analysis (an increment of 20 mg/day, summary incidence rate ratios (IRR) = 0.95, 95%CI = 0.88-1.02).
Conclusions: Our results from this meta-analysis suggested that elevated flavonoids intake might have a protective effect on CHD.

Introduction

Coronary heart disease (CHD) is the leading cause of death in industrialized countries [1], accounting for up to 40% of all lethal events [2], and it is expected to be the leading cause of disease burden worldwide by 2020 [3]. Health behaviors including nutrition should be taken into account to reduce the risk of CHD according to the American Heart Association [4]. Flavonoids are a family of bioactive polyphenolic compounds that are present in many commonly consumed fruits, vegetables, and other plant-based foods [5]. According to the complexity of structure, they can be mainly classified as flavonoids, flavones, flavanones, flavan-3-ols and anthocyanins. Among those, flavonoids are the most widely distributed flavonoids in nature and are present in considerable amounts in our normal diet (20–35 mg/day) [5,6]. They exhibit a wide range of biological activities and are considered as the most active compounds within the flavonoids group [6]. Although flavonoids did not support a protective role against CHD in the previous meta-analysis [7], findings from recent two large population-basedprospective studies indicated an inverse association between flavonoids and CHD risk [8,9]. Hence, we chose to conduct a meta-analysis to update the evidence and further evaluate whether there is a dose-response relationship between flavonoids intake and the risk of CHD.

Materials and Methods

Literature Search and Selection

We performed a comprehensive literature search up to April 2014 using the databases of PubMed, Web of Knowledge and Wan Fang Med Online. The following search terms were searched throughout the entire article: "flavonoids," "flavonols," "quercetin," "kaempferol," "myricetin," combined with "coronary artery disease," "coronary heart disease," "ischemic heart disease," "myocardial infarction," and "cardiovascular diseases" and restricting studies conducted in humans. The relevant articles were reviewed in full after reviewing the title/abstract. The reference lists of all selected publications were checked to retrieve relevant publications that were not identified in the computerized search. References of screened and included articles, abstracts and

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available conference proceedings were also hand searched by one of the authors and included publications, posters, abstracts or conference proceedings.

Two investigators independently reviewed all identified studies, and studies were included if they met the following criteria: (1) using a prospective design; (2) the exposure of interest was flavonoids class; (3) the outcomes of interest were CHD; (4) relative risk (RR) with 95% confidence interval (CI) was provided; and (5) for dose-response analysis, the flavonoids intake for each category must also be provided (or data available to calculate them). If data were duplicated in more than one study, we included the study with the largest number of cases.

Data Extraction

The following data were extracted from each study by two investigators: the first author's last name, year of publication, geographic locations, sample source, the age range of study participants, and duration of follow-up. For dose-response analysis, we also extracted the number of cases, participants (person-years), and RR (95%CI) for each category of flavonoids intake. From each study, we extracted the RR that reflected the greatest degree of control for potential confounders. If there was disagreement between the two investigators about eligibility of the data, it was resolved by consensus with a third reviewer.

Statistical Analysis

Pooled measure was calculated as the inverse variance-weighted mean of the logarithm of RR with 95% CI, to assess the strength of association between flavonoids intake and the risk of CHD. I^2 describes the proportion of total variation attributable to between-study heterogeneity as opposed to random error or chance. In the presence of substantial heterogeneity ($I^2 > 50\%$), the DerSimonian and Laird random-effect model [10] was adopted as the pooling method; otherwise, the fixed-effect model was used as the pooling method [11]. The τ^2 is reported to describe the pooled between-study variance of true effects, thereby reflecting the magnitude of heterogeneity [12]. Publication bias were evaluated using Begg' funnel plot [13] and Egger regression asymmetry test [14]. A

Table 1
Characteristics of studies included in this meta-analysis on flavonoids and risk of CHD risk.

Author, year	Country	Age at baseline	Subjects (cases)	Follow-up years	RR (95%CI) for highest versus lowest category	Adjustment for covariates
Rimm et al. (1996)	USA	40-75	34789 (486)	6	1.08 (0.81-1.43)	Age, BMI, smoking, diabetes, intake of vitamin E, alcohol, hypertension, high cholesterol level, FHCHD, profession, and fiber, carotene, SFA (for mortality).
Yochum et al. (1999)	USA	55-69	34492 (438)	10	0.62 (0.44-0.87)	Age, total energy intake, BMI, WHR, high blood pressure, diabetes, ERT, alcohol, education, marital status, pack-years of smoking, physical activity, intake of cholesterol, saturated fat, vitamin E, dietary fiber, and whole grains.
Arts et al. (2001)	Netherlands	65-84	806 (90)	10	0.63 (0.36-1.10)	Prevalent myocardial infarction or angina pectoris at baseline (mortality analyses only), age, physical activity, total energy intake, BMI, alcohol, smoking status, intakes of fish, coffee, SFA, PUFA, dietary cholesterol, fiber, vitamin C, vitamin E, and β-carotene.
Hirvonen et al. (2001)	Finland	50-69	25732 (1122)	6.1	0.77 (0.64-0.93)	Age, supplementation group, SBP and DBP, serum total cholesterol, serum high-density lipoprotein cholesterol, BMI, smoking years, number of cigarettes smoked daily, history of diabetes mellitus or CHD, marital status, educational level, and physical activity.
Geleijnse et al. (2002)	Netherlands	≥55	4807 (146)	5.6	0.76 (0.49-1.18)	age, sex, BMI, smoking status, pack-years of cigarette smoking, education level, and daily intakes of alcohol, coffee, polyunsaturated fat, saturated fat, fiber, vitamin E, and total energy.
Knekt et al. (2002)	Finland	30-69	9131 (681)	28	0.93 (0.74-1.17)	Sex, age, geographic area, occupation, blood pressure, smoking, serum cholesterol, BMI, and diabetes.
Sesso et al. (2003)	USA	53.9	38445 (729)	6.9	0.82 (0.51-1.33)	Age, randomized aspirin treatment, randomized vitamin E treatment, and randomized β-carotene treatment, BMI, exercise, alcohol, smoking, postmenopausal hormone use, parental history of myocardial infarction at age < 60 y, diabetes, hypertension, high cholesterol, fruit, vegetable intake, fiber intake, folate, and saturated fat.
Marniemi et al. (2005)	Finland	65-99	755 (130)	10	0.79 (0.51-1.24)	Age, gender, smoking, functional capacity and weight adjusted energy intake.
van der Schouw et al. (2005)	Netherlands	49-70	16165 (372)	6.25	0.94 (0.68-1.30)	Age, BMI, smoking, physical activity, diabetes mellitus, hypertension, hypercholesterolemia, OC use, HRT use, energy intake, animal protein intake, MUFA, fiber, alcohol, fruit, and vegetable intake.
Lin et al. (2007)	USA	56.0	66360 (938)	12	1.05 (0.85-1.29)	Age, current smoking, parental history of myocardial infarction before age 60 years, history of hypertension, hypercholesterolem ia, and diabetes, menopausal status, postmenopausal hormone use, use of aspirin, multivitamin, vitamin E supplements, BMI, physical activity, alcohol, and total energy intake.
Kokubo et al. (2007)	Japan	40-59	27 063 (308)	12.5	0.77 (0.47-1.24) for male 0.37 (0.14-0.98) for female	Age, sex, smoking, alcohol, BMI, history of hypertension or diabetes mellitus, medication use for hypercholesterolemia, education level, sports, dietary intake of fruits, vegetables, fish, salt, and energy, menopausal status for women; and public health center.
Mursu et al. (2008)	Finland	42-60	1950 (102)	15.2	1.25 (0.74-2.11)	Age, examination years, BMI, SBP, hypertension medication, serum HDL- and LDL-cholesterol, serum triacylglycerol, maximal oxygen uptake, smoking, CVD in family, diabetes, alcohol, energy-adjusted intake of folate and vitamin E, total fat and saturated fat intake.
McCul lough et al. (2012)	USA	70 (M) 69 (F)	98469 (1286)	7	0.82 (0.73-0.92)	Age, smoking, beer and liquor intake, history of hypertension, history of cholesterol, family history of myocardial infarction, BMI, physical activity, energy intake, aspirin use, HRT (in women only), and sex.
Cassidy et al. (2013)	USA	25-42	93600 (405)	18	0.83 (0.61-1.12)	Age, physical activity, smoking, BMI, alcohol, energy, menopausal status, postmenopausal hormone use, aspirin use, oral contraceptive use, FHMI, cereal fiber, SFA, trans fatty acids, PUFA, MUFA, and caffeine.

CHD: coronary heart disease; RR: relative risk; CI: confidence interval; BMI: body-mass index; CVD: cardiovascular disease; DBP: diastolic blood pressures; ERT: estrogen replacement therapy; FHCHD: family history of coronary heart disease; FHMI: family history of myocardial infarction; HDL: high-density-lipoprotein; HRT: hormone replacement therapy; LDL: low-density-lipoprotein; OC: oral contraceptive; SBP: systolic blood pressure; WHR: waist-to-hip ratio; SFA: saturated fatty acids; PUFA: polyunsaturated fatty acids; MUFA: monounsaturated fatty acids.

study of influence analysis [15] was conducted to describe how robust the pooled estimator is to removal of individual studies.

For the dose-response analysis, the method reported by Greenland et al. [16] and Orsini et al. [17] was used to calculate study specific slopes (linear trends) based on the results across categories of flavonoids intake. The method requires that the distribution of cases and person-years or noncases and the RR with the variance estimates for at least three quantitative exposure categories are known. In the first stage, a restricted cubic spline model with three knots at the 25th, 50th and 75th percentiles of the flavonoids intake was estimated using generalized least-square regression, taking into account the correlation within each set of published RR. Then the study-specific estimates were combined using the restricted maximum likelihood method in a multivariate random-effects meta-analysis [18]. A P-value for non-linearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to 0. All statistical analyses were conducted with STATA version 11.0 (StataCorp LP, College Station, Texas, USA). Two-tailed p-value ≤ 0.05 was accepted as statistically significant.

Results

Search Results and Study Characteristics

At the end, 14 articles [8,9,19–30] including 15 prospective studies (7,233 CHD cases and 452,564 participants) were used in this meta-analysis. Among the 15 prospective studies, 6 studies reported the result from United States, 7 studies from Europe and 2 studies from Japan. The characteristics of these studies are presented in Table 1.

High Versus Low Analyses

Data from 14 articles including 15 prospective studies (7,233 CHD cases) were used in this meta-analysis. Inverse association of flavonoids intake with risk of CHD was reported in 4 studies, and no significant association was reported in 10 studies. Pooled results suggested that highest flavonoids intake versus lowest intake was significantly associated with the reduced risk of CHD [summary RR = 0.850, 95% CI = 0.794-0.910]. No evidence of heterogeneity (heterogeneity p-value = 0.168) was found with 26.0% of the variation in the overall pooled RR attributable to heterogeneity and $\tau^2 = 0.041$. (Fig. 1)

In subgroup analyses for geographic locations, inverse associations of flavonoids intake and CHD risk were found both in the Europe [summary RR = 0.842, 95%CI = 0.750-0.946] and in the USA [summary RR = 0.863, 95%CI = 0.791-0.941]. When we conducted the subgroup analysis by follow-up duration (<10 years and ≥10 years), significant associations were found both in <10 years follow-up and ≥10 years follow-up. When stratified analysis for study outcome (CHD mortality and AMI/coronary events), the associations were significant both in CHD mortality and AMI/coronary events. Furthermore, in subgroup analyses for mean age (<50 years and ≥50 years), inverse association of flavonoids intake and CHD risk was found in group of ≥50 years [summary RR = 0.849, 95%CI = 0.788-0.916]. The detailed results are summarized in Table 2.

Dose-response Analysis

Linear dose-response relationship was found between flavonoids intake and CHD risk. We observed a nonstatistically significant inverse association, with a 5% decreased risk [summary Incidence rate ratios (IRR) = 0.95, 95%CI = 0.88-1.02] for every 20 mg/day increment in flavonoids intake.

Influence Analysis and Publication Bias

Influence analysis showed that no individual study had excessive influence on the association of flavonoids intake and CHD risk. Begg's funnel plot and Egger's test ($P = 0.583$) showed no evidence of significant publication bias between flavonoids intake and CHD risk.

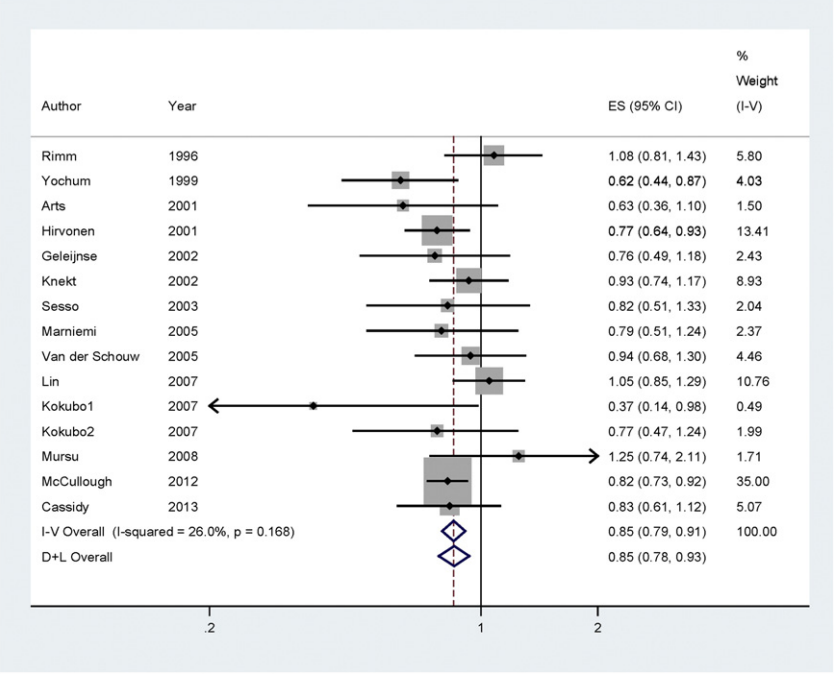

Fig. 1. The forest plot between highest versus lowest amount of flavonoids intake and risk of CHD.

Table 2
Pooled measures on the association of flavonoids and CHD risk. FEM, fixed effect model; REM, random effect model; CHD, coronary heart disease; AMI, acute myocardial infarction.

Studies	Number of studies	Number of cases	Risk estimate (95% CI)		Heterogeneity test	
			FEM	REM	I^2 (%)	P
Total flavonoids	15	7233	0.850(0.794-0.910)	0.853(0.779-0.933)	26.0	0.168
Geographic locations						
Europe	7	2643	0.842(0.750-0.946)	0.842(0.750-0.946)	0.0	0.475
USA	6	4282	0.863(0.791-0.941)	0.872(0.752-1.011)	41.3	0.098
Follow-up duration						
<10 years	6	4141	0.835(0.767-0.911)	0.835(0.767-0.911)	0.00	0.459
≥10 years	9	3092	0.876(0.783-0.981)	0.839(0.712-0.988)	42.2	0.086
Study Outcome						
CHD mortality	4	2551	0.817(0.742-0.900)	0.811(0.713-0.923)	22.2	0.278
AMI/coronary events	10	4580	0.874(0.792-0.965)	0.867(0.767-0.981)	25.1	0.212
Mean age						
<50 years	4	1394	0.854(0.721-1.011)	0.840(0.689-1.023)	16.2	0.302
≥50 years	11	5839	0.849(0.788-0.916)	0.857(0.768-0.955)	34.8	0.120

Discussion

Findings from this meta-analysis indicated that highest flavonoids intake amount versus lowest amount was significantly associated with the reduced risk of CHD. Inverse associations were also found in subgroup by geographic locations (Europe and USA), follow-up duration (<10 years and ≥10 years) and study outcome (CHD mortality and AMI/coronary events), respectively. The association was also significant in the group of ≥50 years.

Several potential mechanisms for the observed association have been proposed. Flavonoids, the natural alternatives to artificial colors, was found to exert protection on CHD risk by improving endothelial function by influencing NO levels, protecting against TNF–induced monocyte chemotactic protein 1 secretion in human endothelial cells, decreasing the extent of apoptotic and necrotic cell death in cultured cardiomyocytes and reducing infarct size after ischemia in rats, suppressing the induced secretion of several molecules related to inflammatory modulation, and reducing serum C-reactive protein concentration [31].

A major strength of this study was the large number of participants included from prospective studies, allowing a much greater possibility of reaching reasonable conclusions. And prospective studies do not suffer from recall bias and are anticipated to be less likely to have selection bias relative to case-control studies. Second, no evidence of between-study heterogeneity and no publication bias were found, indicated that our results are stable. However, there were some limitations in this meta-analysis. First, although we extracted the RR that reflected the greatest degree of control for potential confounders, the extent to which they were adjusted and the possibility that the observed association was due to unmeasured or residual confounding should be considered. Second, although food-frequency questionnaires reflect habitual and long-term intakes relative to biochemical indicators such as urinary excretion, they cannot capture all potential sources of flavonoids and are not the accurate measure of the flavonoids available in human body. Third, the any meta-analysis results are (in general) important to make hypotheses or to design intervention studies, or to explore mechanism(s), but are not sufficient to reach definite conclusions. Fourth, when we conducted the subgroups analysis by study outcome, only 2 studies were conducted for CVD mortality (CVD death also included stroke death). Therefore, due to the small number of studies included, we did not combine the results for CVD mortality. More studies originating in CVD mortality are required to investigate the association between flavonoids intake and CHD risk. Fifth, in subgroup analyses for mean age (<50 years and ≥50 years), the association was not significant in the group of <50. It is more likely that a modest effect did not reach the level of statistical significance with small sample size.

In summary, results from this meta-analysis suggested that the higher intake of flavonoids might have a protective effect on CHD.

Authorship

Conceived of the study: WLJ and HBW; Carried out the literature searching: WLJ, HBW and BH; Data extraction: WLJ, HBW and BH; Analyzed the data: HBW; Draft the manuscript: WLJ.

Conflict of Interest

None.

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