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Review Article

Dietary refined grain intake could increase the coronary heart disease risk: evidence from a meta-analysis

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Abstract: Background: Previous reports have suggested a potential association of dietary refined grain intake with the risk of coronary heart disease (CHD). Since such association is controversial, we conducted a meta-analysis to re-assess the relationship between dietary refined grain intake and the risk of CHD. Methods: The databases of Pubmed, Embase, Web of science and Medline were carefully searched until 30th of Sep in 2016, without limits of language and publication year. Odds Ratios (OR) with 95% Confidence Intervals (CI) was derived by using random-effects models. Quality assessment was conducted according to Newcastle-Ottawa-Scale (NOS), and analysis of the statistical heterogeneity using I^2. Results: Our study was based on 8 articles with 12 studies, involving 8059 CHD cases. The total OR (95% CI) of CHD risk for the highest vs. the lowest categories of refined grain intake was 1.094 (1.007-1.189), with no heterogeneity among studies (I^2 = 0.0%, P = 0.508). The average NOS score was 7.1, suggesting a high quality. And there was no publication bias (P = 0.17) of the meta-analysis about dietary refined grain intake and CHD risk. Subgroup analyses showed that higher dietary refined grain intake could increase the risk of CHD in all subgroups examined except in male populations and the disease outcome of myocardial infarction (MI). Conclusion: We found that higher dietary refined grain intake can significantly increase the risk of CHD.

Keywords: Refined grain, coronary heart disease, meta-analysis

Introduction

Coronary heart disease (CHD) remains the leading cause of death worldwide [1]. In particular, a large portion of premature deaths were due to CHD. It was estimated that the number of death from CHD will rise from 16.7 million in 2010 to 23.3 million in 2030 [2]. Therefore, effective prevention strategies are urgently needed to reduce mortality from CHD. Growing attention is paid to alter risk factors so as to attenuate incidence and death from CHD. Among the known risk factors, dietary factors, especially dietary whole grain intake, have been widely considered to provide cardioprotective effects [3].

Whole-grain foods contain fiber, vitamins, minerals, phenolic compounds, phytoestrogens, and other un-measured constituents [4], which may have favorable effects on health by lowering serum lipids [5] and blood pressure [6], improving glucose and insulin metabolism [7], endothelial function, and alleviating oxidative stress [8] and inflammation [9]. Refined grains, in contrast, do not appear to offer protection and may instead increase the risk of CHD. Up to date, a number of epidemiologic studies have been published to explore the relationship between dietary refined grain intake and CHD risk. However, the results are not consistent. Therefore, we conducted a meta-analysis to (1) first assess the CHD risk for the highest vs. lowest amount of dietary refined grain intake; and (2) assess the heterogeneity among studies and publication bias.

Materials and methods

Literature search

An electronic search of Pubmed, Embase, Web of science and Medline databases was performed until 30th of Sep in 2016. The keywords imputed are [cardiovascular disease (CVD) OR myocardial infarction (MI) OR coronary heart

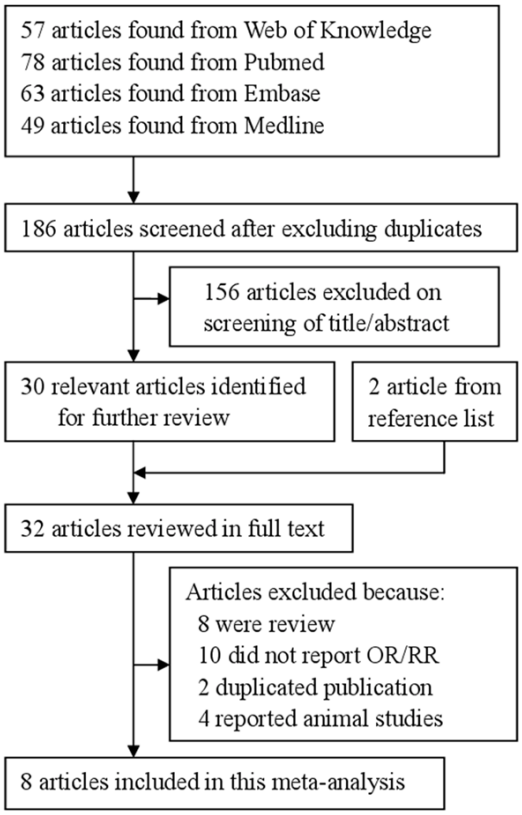

Figure 1. The flow diagram of screened, excluded, and analyzed publications.

disease (CHD) OR ischemic heart disease (IHD)] AND (refined grain OR diet OR lifestyle) and restricting studies conducted in humans with no language or publication year restriction. The full text of relevant citations from all the results identified has been inspected and analyzed. Relative references in the main outcomes have also been searched and reviewed. The study selection process was performed following the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement [10].

Selection criteria

All the studies evaluating the linkage between dietary refined grain and CHD risk are considered to be included in this meta-analysis. We made the strict criteria for our studies as following: (1) The design of the studies is prospective cohort, case-control or cross-sectional studies. (2) Human population studies. (3) The outcomes of interest were CHD or MI or CVD or IHD. (4) The numbers of case and control and the total numbers were reported or the risk estimates, such as Relative Risk (RR) and Odds Ratio (OR) with 95% Confidence Interval (CI) was reported. If data were duplicated in more than one study, we included the study with the largest number of cases.

Data extraction and quality assessment

The following data were extracted from each study by two investigators: author name, year of publication, design of study, sex of population, age, length of follow-up, number of case and participants, value of OR with 95% CI and relative adjustments. The third reviewer was sought to make a common consensus on the abstracted data. The methodological quality of each study was assessed separately. We used Newcastle-Ottawa-Scale (NOS) mentioned by Wells et al. [11] to assess the studies quality, which can either be used as a checklist or scale.

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 dietary refined grain intake and the risk of CHD. Random-effects model was used to combine study-specific RR (95% CI), which considers both within-study and between-study variation [12]. The I^2 was used to assess heterogeneity, and I^2 values of 0, 25, 50 and 75% represent no, low, moderate and high heterogeneity [13], respectively. Publication bias was evaluated using Begg' funnel plot [14] and Egger regression asymmetry test [15]. A study of influence analysis [16] was conducted to describe how robust the pooled estimator is to removal of individual studies. All statistical analyses were conducted with STATA version 10.0 (StataCorp LP, College Station, Texas, USA). Two-tailed $P \leq 0.05$ was accepted as statistically significant.

Results

Study selection

A flow diagram of the study selection process was showed in **Figure 1**. Database search led to retrieval of 247 records from Pubmed, Embase, Web of science and Medline databases. There were 61 duplicated records, which

Table 1. Characteristics of included studies on refined grains and CHD risk

Study, year	Study design	Quality scores	Country	Disease outcome	Participants (cases)	Follow-up (years)	Age (years)	RR (95% CI) for highest versus lowest category	Adjustment for covariates
Jacobs et al. 1998	Cohort	7	United States	IHD	34492 (438)	9	55-69	1.12 (0.77-1.62)	Adjusted for age, total energy intake, education, marital status, high blood pressure, diabetes, BMI, waist-to-hip ratio, physical activity, pack-years, alcohol intake, vitamin supplements, oral contraceptive pills, estrogen replacement therapy, Keys score, intake of fruit and vegetables except juice, intake of red meat, intake of fish and seafood, and sucrose intake.
Jacobs et al. 1999	Cohort	8	United States	CVD, CHD	38740 (1779)	9	55-69	1.09 (0.86-1.39) for CVD 1.15 (0.84-1.56) for CHD	Adjusted for age, total energy intake, educational attainment, marital status, high blood pressure, diabetes, heart disease, cancer, BMI, waist-to-hip ratio, physical activity, smoking, alcohol intake, vitamin supplements, estrogen replacement therapy use, total fat, saturated fat, intake of fruits and vegetables, intake of red meat, and intake of fish and seafood.
Liu et al. 2003	Cohort	8	United States	CVD, MI	86190 (1869)	5.5	40-84	1.04 (0.84-1.27) for CVD 0.96 (0.68-1.36) for MI	Adjusted for age, cigarette smoking, alcohol intake, physical activity, BMI, history of type 2 diabetes, high cholesterol, and hypertension, and use of multivitamins.
Steffen et al. 2003	Cohort	7	United States	CHD	15792 (535)	11	45-64	1.17 (0.82-1.66)	Adjusted for age at baseline, BMI, race, sex, time-dependent energy intake, education, smoking status, pack-years of smoking, physical activity, alcohol intake, and hormone replacement in women.
Sahyoun et al. 2006	Cohort	7	United States	CVD	535 (89)	10	60-98	2.16 (1.20-3.87)	Adjusted for age, sex, ethnicity, educational attainment, marital status, smoking, alcohol intake, exercise, BMI, energy intake, percentage saturated fatty acid intake, history of heart disease, and use of antihypertensive or lipid-lowering medication.
Jacobs et al. 2007	Cohort	7	United States	CVD, CHD	27312 (2934)	17	55-69	1.06 (0.91-1.24) for CVD 1.02 (0.82-1.27) for CHD	Adjusted for age, energy intake, BMI, waist-hip ratio, smoking, education, physical activity, estrogen use, multivitamin supplement use, and intakes of alcohol, refined grain, coffee, red meat, fish and seafood, and total fruit and vegetables.
Lockheart et al. 2007	Case-control	6	Norwegian	MI	211 (106)	--	45-75	1.41 (0.59-3.37)	Adjusted for age, marital status, and education, family history of heart disease, smoking, and energy intake.
Yu et al. 2013	Cohort	7	China	CHD	117366 (309)	Women: 9.8 Men: 5.4	40-74	1.53 (0.64-3.68) for women 2.01 (0.96-4.23) for men	Adjusted for educational level, income, smoking status, alcohol consumption, physical activity level, waist-to-hip ratio, history of hypertension, and dietary intakes of total energy, saturated fat, and protein.

Abbreviations: BMI = body mass index; CI = confidence interval; RR = relative risk; CVD = cardiovascular disease; CHD = coronary heart disease; MI = myocardial infarction; IHD = ischemic heart disease.

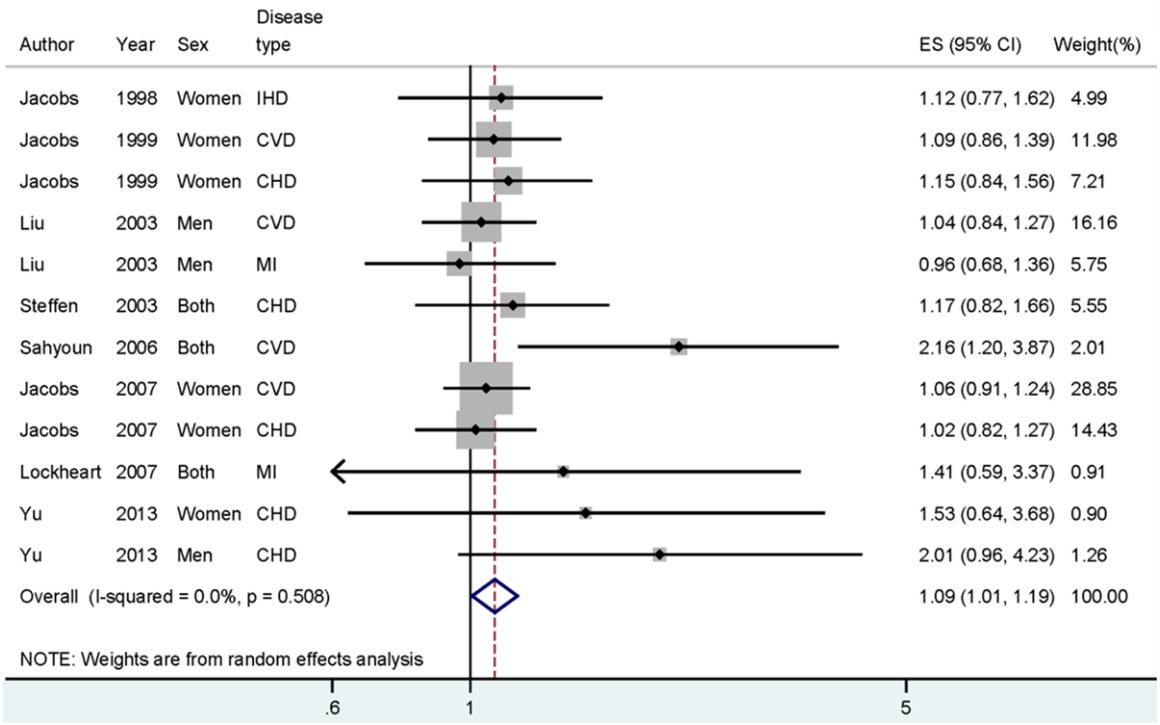

Figure 2. The forest plot between highest versus lowest amount of dietary refined grain intake and CHD risk.

were eliminated from further analyses. By reviewing the abstract and titles we removed studies that did not meet our demands. Examination of references cited in the remaining records resulted in addition of 2 more records to the initial collection. After carefully review of the full-text versions of each record, we finally ruled out 156 and focused on the remaining 32 reports for further assessment. Twenty-four articles are further except during various reasons. As a result, 8 references [17-24] with 12 studies involving 8059 CHD cases were chosen for our meta-analysis. All of the included studies were in relative high quality (over 6 stars), with the average NOS score was 7.1. The characteristics of the included studies are presented in **Table 1**.

High versus low analyses

The multivariate-adjusted OR of each study of the highest vs. the lowest dietary refined grain intake is available in **Figure 2**. The total RR of CHD for the highest vs. the lowest categories of dietary refined grain intake was 1.094 (95% CI = 1.007-1.189), with no heterogeneity was found (I^2 = 0.0%, P = 0.508). In subgroup analyses for study design, the pooled RR of CHD for the highest category of dietary refined grain intake versus the lowest category were 1.091 (95% CI = 1.004-1.186) for cohort studies. When we conducted the subgroup analysis by geographic locations, the significant associations were found between dietary refined grain intake and CHD both in American populations 1.079 (95% CI = 1.002-1.174) and other populations 1.670 (95% CI = 1.039-2.684). In subgroup analyses for disease outcome, the association of dietary refined grain intake and risk of CHD were also found in CHD [RR = 1.124, 95% CI = 1.004-1.310] and CVD [RR = 1.115, 95% CI = 1.007-1.312], but not in the MI. When we conducted the subgroup analysis by follow-up duration (< 10 years and ≥ 10 years) and Sex (Females and Males), the results was consistent with overall data except among the males populations. The details results are summarized in **Table 2**.

Influence analysis and publication bias

Influence analysis showed that no individual study had excessive influence on the association of dietary refined grain intake and CHD risk. Begg's funnel plot (**Figure 3**) and Egger's test (*P* = 0.17) showed no evidence of signifi-

Table 2. Summary risk estimates of the association between refined grains intake and CHD risk

Subgroups	No. (cases)	No. studies	RR (95% CI)	Heterogeneity test	
				I^2 (%)	*P*-value
All studies	8059	12	1.094 (1.007-1.189)	0.0	0.508
Study design					
Cohort	7947	11	1.091 (1.004-1.186)	0.0	0.448
Case-control	-	-	-	-	-
Geographic locations					
America	7644	9	1.079 (1.002-1.174)	0.0	0.572
Other	415	3	1.670 (1.039-2.684)	0.0	0.809
CHD outcome					
CHD	2560	5	1.124 (1.004-1.310)	0.0	0.453
CVD	4467	4	1.115 (1.007-1.312)	26.1	0.135
MI	594	2	1.012 (0.733-1.396)	0.0	0.422
Follow-up duration					
< 10	4395	7	1.092 (1.001-1.231)	0.0	0.671
≥ 10	3558	4	1.137 (1.009-1.376)	0.0	0.518
Sex					
Females	5271	6	1.075 (1.002-1.189)	0.0	0.952
Males	2058	3	1.087 (0.837-1.410)	37.6	0.201

Abbreviations: CVD = cardiovascular disease; CHD = coronary heart disease; MI = myocardial infarction; CI = confidence interval; RR = relative risk.

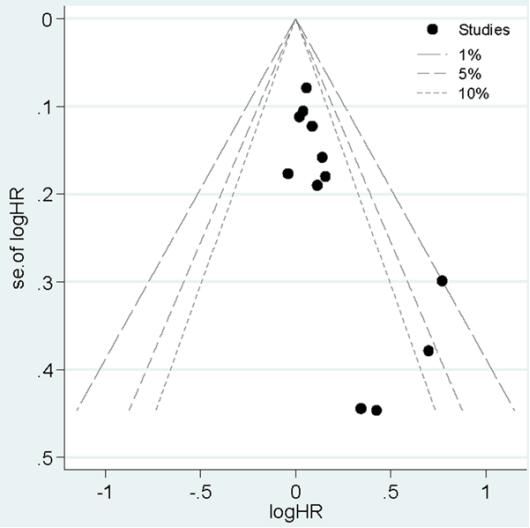

Figure 3. The Begg' funnel plot between highest versus lowest amount of dietary refined grain intake and CHD risk.

cant publication bias between dietary refined grain intake and CHD risk.

Discussion

Our study indicated that dietary refined grain intake has significant statistical association with the risk of CHD. The total RR of CHD for the highest vs. the lowest categories of dietary refined grain intake was 1.094 (95% CI = 1.007-1.189), with no heterogeneity among studies (I^2 = 0.0%, P = 0.508). The associations were also significant in cohort studies, American populations and female populations.

We only found the significant association in the female population, but not in the male population. Most of the included studies for female populations are post-menopausal women, at age about 55-69. It was previously reported that refined-grain intake in postmenopausal women in Iowa is associated with the mortality attributed to cardiovascular diseases, including that due to nonmalignant respiratory diseases [18]. It also suggest that refined grains are not rich in phytochemicals and other molecules that support the antioxidant defense, therefore, it could increase the risk of CHD [25]. Furthermore, dietary intake of refined grains is negative associated with plasma enterolactone concentrations. Therefore, it has also been linked to an increased risk of CHD [26].

A recent study has been conducted to assess the association between dietary whole grain intake and CHD risk [3]. They concluded that highest whole-grain intake amount compared with the lowest amount was significantly associated with reduced the risk of CHD. This may be due to whole-grain foods contain fiber, vitamins, minerals, phenolic compounds, phytoestrogens, and other phytochemicals that are removed during the refining process. However, refined grain did not contain that statement factor above. Furthermore, the associations were also significant in cohort studies and among American populations, which is consistent with our result.

To our knowledge, this is the first comprehensive meta-analysis conducted to assess the

association between dietary refined grain intake and CHD risk. For the results of analysis, we found an increased risk factor for CHD with higher dietary refined grain intake. Second, a major strength of this study was the large number of participants included in this meta-analysis, allowing a much greater possibility of reaching reasonable conclusions and conducting subgroup analysis. Third, no evidence of between-study heterogeneity and no publication bias were found, indicated that our results are stable.

There were some limitations should be considered in this meta-analysis. First, case-control studies are susceptible to potential bias inherent in the original studies, such as recall or selection bias. However, only one case-control study was included, and the association for cohort studies was significant. Second, of the 12 studies included, nine were come from America, one study was from Norwegian, and 2 were from China. We then combined the subgroup analysis for American populations and other populations. Therefore, more studies with other populations except America are wanted in the future studies. Third, we only found the significant association in female populations, but not in the male populations, perhaps due to the little cases and studies were included. Therefore, the results are applicable to female populations, but cannot be extended to male populations. Further studies originating in male populations are required to reassess the association between dietary refined grain intake and CHD risk. Finally, 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.

In summary, results from this meta-analysis suggested that the higher intake of refined grain might increase the risk of CHD, especially in American populations and female populations.

Disclosure of conflict of interest

None.

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