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Whole grain intake and cardiovascular disease: A meta-analysis

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Abstract *Background and aims:* Whole grain food sources have been associated with lowered risk of cardiovascular disease (CVD). Studies in recent years have strengthened this observation and elucidated potential mechanisms for this association. This study sought to quantitate the available observational evidence on whole grain intake and clinical cardiovascular events.

Methods and results: Seven prospective cohort studies with quantitative measures of dietary whole grains and clinical cardiovascular outcomes were identified from MEDLINE searches and a review of the literature. Based on event estimates adjusted for cardiovascular risk factors, greater whole grain intake (pooled average 2.5 servings/d vs. 0.2 servings/d) was associated with a 21% lower risk of CVD events [OR 0.79 (95% CI: 0.73–0.85)]. Similar estimates were noted for different CVD outcomes (heart disease, stroke, fatal CVD) and in sex-specific analyses. Conversely, refined grain intake was not associated with incident CVD events [1.07 (0.94–1.22)].

Conclusions: There is a consistent, inverse association between dietary whole grains and incident cardiovascular disease in epidemiological cohort studies. In light of this evidence, policy-makers, scientists, and clinicians should redouble efforts to incorporate clear messages on the beneficial effects of whole grains into public health and clinical practice endeavors.

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Introduction

Cardiovascular disease (CVD) accounts for one-third of deaths worldwide, and the World Health

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Organization estimates that, over the next two decades, developing countries will bear the brunt of the increasing burden of CVD [1]. Over thirty years ago, Dr. Trowell noted that sub-Saharan Africa had a lower prevalence of ischemic heart disease than industrialized European and American populations, hypothesizing that observed differences were attributable to the relative intake of refined versus whole plant food sources [2]. This came to be known as the “fiber hypothesis”, which related fiber intake from cereal and plant sources to chronic heart and gastrointestinal diseases. The first prospective evaluation of the “fiber hypothesis” with respect to heart disease came from the United Kingdom [3]. Morris et al. found that cereal fiber (but not vegetable fiber) was negatively associated with incident ischemic heart disease. The first study to prospectively associate *whole grain* consumption with cardiovascular events was the Seventh Day Adventists’ study, in which individuals who consumed wheat bread had a 55% lower risk of non-fatal MI than those who ate white bread [4]. In 2003, Dr. Anderson synthesized data from thirteen studies evaluating intake of whole grains, fruits, vegetables, and fiber with respect to risk for clinical cardiovascular disease [5]. Of five studies prospectively evaluating whole grain intake and cardiovascular risk, higher intake of whole grains was associated with a 29% lower risk for cardiovascular events (adjusted RR 0.71, 95% CI 0.48–0.94). However, since this analysis, multiple observational studies have replicated this association and important causal pathways have been elucidated, including effects on glucose homeostasis, serum lipids, and endothelial function. We sought to quantitate the available observational evidence on whole grain intake and clinical cardiovascular events and review the potential mechanisms of this association.

Methods

We identified observational studies that evaluated the association between whole grain intake and clinical cardiovascular events using the following inclusion criteria: 1. the studies were performed using self-reported quantitative measures of whole grain intake (e.g. servings/day); 2. cardiovascular events were ascertained prospectively; and 3. the studies provided adequate data to generate adjusted event rates. Studies were identified from a MEDLINE search for ‘whole grain’ and ‘cardiovascular disease’ from 1966 to April 2006. Additional studies were drawn from reference lists of relevant manuscripts. Data were extracted by two independent investigators, and inconsistencies were

resolved by mutual agreement. For within-study comparisons, individuals in the highest quantile of whole grain intake were compared to individuals with the lowest whole grain intake. Covariate-adjusted event rates were derived from published event rates and adjusted relative risk estimates. For studies that reported risk estimates for multiple cardiovascular endpoints, the most comprehensive cardiovascular disease endpoint was utilized for the primary analysis. For studies that evaluated this association in multiple models, we evaluated estimates based on demographic-adjusted models and more fully-adjusted models (i.e. including cardiovascular risk factors) separately. Secondary analyses evaluated specific endpoints (coronary heart disease (CHD)/CHD mortality, ischemic stroke/stroke mortality) and subgroups (men, women) based on risk-factor adjusted estimates. Additionally, the relationship between refined grain intake and cardiovascular events was assessed using studies that provided this information.

We identified eight publications from seven cohorts with both quantitative whole grain estimates and clinical cardiovascular event rates that included sufficient data for analysis (Table 1). Other reports of interest were excluded for the following reasons: retrospective study design [6], use of qualitative rather than quantitative whole grain measures (i.e. “What type of bread do you use?”) [4], and presentation of data subsequently updated [7]. Studies that met entry criteria and provided sufficient data were included in the analyses, with study weights based on the inverse variance. For the main and secondary analyses, we evaluated the Mantel-Haentzel test for heterogeneity. As there was no evidence of significant heterogeneity ($Q = 0.04-8.17$, $p = 0.07-0.83$), fixed-effects models were used. Publication bias was evaluated using funnel plots and the Egger test [8], and sensitivity analyses corrected for bias using the trim-and-fill method [9]. All analyses were performed using MIX v. 1.2 (Kitasato University, 2006; <http://www.mix-for-meta-analysis.info/index.html>).

Results

Six studies provided information for demographic-adjusted analyses [10–15], and seven included information for risk-factor-adjusted analyses [10–16] (Table 2). Among these cohorts, the pooled average intake of those with high intake was 2.5 servings/d, while consumption in the comparison group averaged 0.2 servings/day. High intake of whole grains was associated with a 37% lower risk of incident cardiovascular disease in the analyses

Table 1 Prospective cohort studies evaluating the association between quantitative measures of whole grain intake and clinical cardiovascular events

Cohort	Ref.	N ^a	Age range	Sex	Whole grain dietary measure	WG intake: low quantile ^b	WG intake: high quantile	Years of follow-up	Outcomes evaluated
Iowa Women's Health Study (IWHS)	10	34,492	55–69	Female	FFQ (servings/wk)	1.5 (0–3.5)	22.5 (18.5–84.5)	9	CHD death, stroke death, CVD death
Nurses' Health Study (NHS)	11, 17	75,521	38–63	Female	FFQ (servings/d)	0.13 (0–0.26)	2.7 (1.8–17.9)	10, 12	CHD, ischemic stroke
Norwegian County Study (NCS)	12	33,848	35–56	50% Female	FFQ (whole grain bread score)	(0.05–0.60)	(2.25–5.40)	14	CHD death, CVD death
Physicians' Health Study (PHS)	13	86,190	40–84	Male	FFQ (servings whole grain cereal/wk)	(0–1)	(≥7.0)	6	CHD death, stroke death, CVD death
Atherosclerosis Risk in Communities (ARIC)	14	11,940	45–64	56% Female	FFQ (servings/d)	0.1 (0–0.2)	3.0 (2.0–10.5)	11	CHD, ischemic stroke
Health Professionals' Follow-up Study (HPFS)	15	42,850	40–75	Male	FFQ (g/d)	3.3	49.6	14	CHD
Older community-dwelling adults, Boston, MA	16	535 ^c	60–98	67% Female	3-d food record (servings/d)	0.31 (0–0.56)	2.9 (>1.94)	12–15	CVD death

Abbreviations: Ref – reference; WG – whole grain; FFQ – food frequency questionnaire; CHD – coronary heart disease; CVD – cardiovascular disease.

^a Number of participants included in original article (all quantiles of whole grain intake).

^b Values represent the quantile median (range).

^c Included individuals with history of CVD.

based on demographic-adjusted estimates [OR .63 (95% CI 0.58–0.68)] (Fig. 1). This association was evident in analyses based on risk-factor-adjusted estimates, as well [0.79 (0.73–0.85)]. Though there was evidence of publication bias when evaluated with the Egger test (intercept = -2.32 , $p = 0.001$), the results were similar in analyses that corrected for this using the trim-and-fill method [0.81 (0.75–0.87)]. The results did not differ after removing one study [16] that included individuals with prevalent cardiovascular disease [0.79 (0.73–0.86)].

The findings were similar when analyses were restricted to studies that provided sex-specific results for men [0.82 (0.73–0.92)] [13,15] or women [0.79 (0.68–0.91)] [10,11]. Estimates were similar when analyses were limited to studies that reported fatal CVD endpoints [0.78 (0.70–0.88)] [10,12,13,16]. This association was also present when evaluating the endpoint of incident CHD [0.76 (0.69–0.83)] [7,11–15], but an apparent association was less significant for incident stroke [0.83 (0.68–1.02)] [10,13,14,17]. There was no evidence of decreased risk for cardiovascular events when comparing groups with high versus low refined grain intake [1.07 (0.94–1.22)] [10,13,14].

Discussion

The inverse association between whole grain intake and cardiovascular disease has been consistently demonstrated in multiple observational studies. In analyses reflecting cardiovascular events from over 149,000 participants, we found

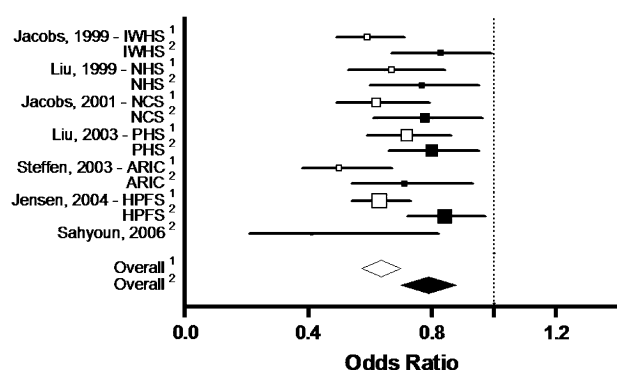


Figure 1 Odds ratios of incident cardiovascular disease, comparing high versus low whole grain intake. Abbreviations: IWHS – Iowa Women’s Health Study; NHS – Nurses’ Health Study; NCS – Norwegian County Study; PHS – Physicians’ Health Study; ARIC – Atherosclerosis Risk in Communities; HPFS – Health Professionals’ Follow-up Study. ¹Demographic-adjusted model. ²Demographic + risk factor adjusted model.

that consumption of 2.5 servings of whole grains was associated with a 21% lower risk of incident CVD compared to intake of 0.2 servings per day, after adjustment for cardiovascular risk factors. Similarly, whole grain intake is inversely associated with atherosclerosis, the common pathway for ischemic heart disease. In one study of 229 postmenopausal women, six or more servings of whole grain products per week was associated with 40% less coronary atherosclerotic progression [18]. As this evidence on the association of whole grain intake with atherosclerosis and clinical cardiovascular disease has been accumulating, other research continues to elucidate mechanisms whereby whole grains influence cardiovascular health.

Whole grain intake and CVD risk: potential mechanisms

Grains consist of bran, germ, and endosperm components. When refined, the carbohydrate-rich endosperm component is retained, while many biologically active agents, such as fiber, vitamins, minerals, antioxidants, and other plant compounds (lignans, phytosterols, etc.) are removed with the bran and germ [19]. These biological agents influence cardiovascular risk through effects on glucose homeostasis [20,21], lipids and lipoproteins [16,22], endothelial function [23], and other mechanisms [24–26], potentially accounting for much of the observed benefit of high intake of whole grains.

Whole grain intake, insulin resistance, and type 2 diabetes mellitus

The World Health Organization estimates the worldwide prevalence of type 2 diabetes mellitus (T2DM) to be 170 million, with an anticipated 50% increase by 2010. The greatest increase is occurring in countries undergoing the transition to “Western” lifestyle patterns [27]. In the United States, the prevalence of T2DM increased 765% from 1935 to 1996 [28]. Ecologic data suggest that the increasing prevalence of T2DM accompanies a parallel increase in total energy intake, the majority of which comes from refined carbohydrates [28,29]. This is supported by prospective data from the Nurses’ Health Study, in which intake of sugar-sweetened beverages was associated with weight gain and incident T2DM [30].

Conversely, higher intake of unrefined carbohydrates, such as whole grains, appears to be protective against insulin resistance and T2DM. Whole grain meals are associated with reduced glucose and

insulin responses [20], and longer feeding studies indicate that increased whole grain intake may improve insulin sensitivity or beta-cell function [31,32]. Cross-sectional studies have shown that whole grain intake is inversely associated with insulin resistance [21,33] and components of the metabolic syndrome [16,34]. Furthermore, multiple longitudinal cohort studies have demonstrated an inverse relationship between whole grain or cereal fiber intake and incident T2DM. In a meta-analysis by Liu, individuals with higher whole grain intake had a 30% lower risk of incident T2DM compared to those with low whole grain intake [35]. The beneficial effects of whole grains on glucose homeostasis are likely attributable to the specific carbohydrates found in whole grains (including fiber [36,37], resistant starches [38] and oligosaccharides [20]), physical factors that determine carbohydrate absorption [20], phytochemicals (e.g. lignans) [39], and magnesium [40].

Whole grain effects on lipids

Though effects on insulin sensitivity and glycemia are likely a major component of the cardioprotective benefit realized with increased consumption of whole grains, early evaluations of unrefined grain sources emphasized cholesterol as the central mechanism of cardiovascular benefit. Dr. Trowell's ecologic observations focused on total cholesterol levels as a reflection of carbohydrate source [2], noting that cholesterol levels across populations were more strongly associated with fiber intake than amount or type of fat. Since then, an abundance of evidence has demonstrated an inverse relationship between intake of soluble fiber (most often consumed as β -glucan from oats [41]) and LDL-cholesterol [42]. Animal models suggest that this effect is mediated, in part, by increased bile acid degradation and loss [43], disrupting enterohepatic bile circulation and reducing the amount of cholesterol available for LDL synthesis [44], which in turn leads to an upregulation of hepatic LDL receptors [45]. In addition to soluble fiber, whole grains are also rich in phytosterols, which compete with cholesterol for absorption in the small intestine, lowering LDL cholesterol [22,46]. Whole grains are also associated with a reduction in small LDL cholesterol [47]. In addition to effects on LDL, whole grains influence the insulin resistant lipid pattern (elevated triglycerides and low HDL cholesterol) associated with the metabolic syndrome [16]. Thus, whole grains could confer cardiovascular benefits by acting on numerous lipid intermediates, including LDL (amount and size), HDL,

and triglycerides, resulting in a lipid profile that is globally less atherogenic.

Whole grains and endothelial function

Whole grain constituents also appear to influence the vascular endothelium directly. Endothelial dysfunction is an early development in the pathophysiology of atherosclerosis [48]. Whole grain interventions have been shown to improve vascular reactivity, a marker of endothelial function, in response to a high fat meal [23], and dietary patterns associated with high intake of whole grains are associated with improved plasma markers of endothelial function [49,50]. Whole grains are rich in lignans, phytoestrogens whose intakes have been associated with decreased cardiovascular death [51], presumably through beneficial effects on the endothelium. Furthermore, whole grains are rich in antioxidants, including vitamin E, which may have a significant beneficial effect on the vascular endothelium [52].

Whole grains: other mechanisms of cardiovascular benefit

In addition to their effects on insulin sensitivity, lipids, and endothelial function, whole grains may influence other parameters that shape cardiovascular risk, including blood pressure [24], plasma homocysteine [25], and inflammation [26]. Thus, whole grains are a complex food source with pleotropic effects, and the cardiovascular benefits associated increased dietary whole grains involve multiple pathways.

Conclusions

Despite the abundant evidence in support of increasing whole grain intake and a diverse assortment of whole grain food sources (Table 3), intake remains low. Data from the National Health and Nutrition Examination Survey 1999–2000 found that only 8% of U.S. adults consume three or more servings of whole grain per day, with most whole grains consumed in snack foods (41%) [followed by cereals (32%), breads (18%) and other sources (9%)] [53]. The same data revealed that 42% of adults eat no whole grains on a given day. Many consumers and health professionals are unaware of the health benefits of whole grains [54]. This may improve as guidelines begin to make whole grain recommendations more explicit [53,55].

Table 3 Examples of whole grain foods and flours

Amaranth
Barley
Buckwheat
Corn (<i>whole cornmeal, popcorn</i>)
Millet
Oats (<i>oatmeal</i>)
Quinoa
Rice (<i>brown rice</i>)
Rye
Sorghum (<i>or milo</i>)
Teff
Triticale
Wheat (<i>varieties include spelt, emmer, farro, einkorn, Kamut[®], durum; forms include bulgur, cracked wheat, and wheatberries</i>)
Wild rice

When consumed in a form retaining the bran, germ, and endosperm components. Source: The Whole Grains Council (<http://www.wholegrainscouncil.org>).

In summary, dietary whole grains have been inversely associated with cardiovascular risk factors, atherosclerosis, and incident cardiovascular disease. In light of this consistent evidence, policymakers, scientists, and clinicians should redouble efforts to incorporate clear messages on the beneficial effects of whole grains into public health and clinical practice endeavors.

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