Breakfast Cereals and Risk of Heart Failure in the Physicians’ Health Study I

Luc Djousse, MD, MPH, DSc; J. Michael Gaziano, MD, MPH

Background: Heart failure (HF) is the leading cause of hospitalization among the elderly population in the United States. Consumption of grain products and dietary fiber has been shown to reduce the risk of hypertension and myocardial infarction. However, it is not known whether a higher consumption of breakfast cereals is associated with risk of HF.

Methods: This study evaluated prospectively the association between breakfast cereal intake and incident HF among 21,376 participants of the Physicians’ Health Study I. Cereal consumption was estimated using a semiquantitative food frequency questionnaire. Incident HF was ascertained through annual follow-up questionnaires and validated using Framingham criteria. We used Cox regression models to estimate adjusted relative risk of HF across categories of cereal intake.

Results: During an average follow-up of 19.6 years, 1018 incident cases of HF occurred. For average weekly cereal consumption of 0 servings, 1 or fewer, 2 to 6, and 7 or more, hazard ratios (95% confidence intervals) for HF were 1 (reference), 0.92 (0.78-1.09), 0.79 (0.67-0.93), and 0.71 (0.60-0.85), respectively ($P < .001$ for trend), adjusting for age, smoking, alcohol consumption, vegetable consumption, use of multivitamins, exercise, and history of atrial fibrillation, valvular heart disease, and left ventricular hypertrophy. However, the association was limited to the intake of whole grain cereals ($P < .001$ for trend) but not refined cereals ($P = .70$ for trend).

Conclusions: Our data demonstrate that a higher intake of whole grain breakfast cereals is associated with a lower risk of HF. Additional studies are warranted to confirm these findings and determine specific nutrients that are responsible for such a protection.

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The lifetime risk of heart failure (HF) is estimated at 20% (1 in 5) for both men and women aged 40 years. While advanced age, hypertension, diabetes mellitus, obesity, valvular heart disease, and myocardial infarction have been recognized as predictors of HF, limited data are available on the effects of modifiable lifestyle factors on the risk of HF. Studies have suggested that a higher consumption of grain products may confer a lower risk of hypertension, coronary heart disease, hypercholesterolemia, and mortality. Breakfast cereals and cereal products play an important role in the US diet. Cereals contain important nutrients such as vitamins, minerals, fiber, and oil that have been reported to lower cardiovascular risk factors and positively influence glucose and insulin metabolism. In addition, cereals contain phytoestrogens and phenolic acids, which have been shown to have health benefits. It is not known whether a higher consumption of breakfast cereals is associated with a lower risk of HF. Our primary objective was to prospectively examine whether a higher consumption of total breakfast cereals was associated with a lower risk of HF among US male physicians. In addition, since some of the nutrients are lost or added (fortification) in refined cereals, we sought to examine whether a higher intake of whole grain as well as refined breakfast cereals was associated with a lower incidence of HF in this population.

Methods

Study Population

This study used data from a previously reported randomized trial among US male physicians, the Physicians’ Health Study I (PHS I). Briefly, in 1981, 261,248 US male physicians were invited to participate in the trial. After exclusions, 33,223 participants were enrolled in an 18-week run-in period. Following the run-in period, 22,071 subjects were randomized to regimens of low-dose aspirin, beta carotene, both agents, or placebo. For the current project, we excluded 695 participants because of (1)
missing information on baseline breakfast cereals (n=25), (2) prevalent HF (n=18), and/or (3) missing covariates (n=652). A total of 21,376 individuals with complete data were included in the present analyses. Each participant gave written informed consent, and the study protocol was approved by the institutional review board at Brigham and Women’s Hospital.

BREAKFAST CEREAL CONSUMPTION

Information about consumption of cold breakfast cereals was self-reported using a simple semiquantitative food-frequency questionnaire. A detailed description of the assessment of breakfast cereal intake in the PHS I has been published.8 Briefly, participants were asked to report their average number of servings of cold breakfast cereals consumed (1 serving = 1 cup [250 mL]) during the past year. Possible response categories included rarely or never consumed cereal, 1 to 3 servings per month, 1 per week, 2 to 4 per week, 5 to 6 per week, 1 per day, and 2 or more per day. In addition, the brand of cereals consumed was queried at baseline. We used an algorithm developed by Jacobs and colleagues16 to classify breakfast cereals into those that contain at least 25% whole grain or bran by weight were classified as whole grain. This information was obtained at baseline, 18 weeks, and 24, 48, 72, 96, and 120 months after randomization.

ASCERTAINMENT OF INCIDENT HF

A questionnaire was mailed to each participant every 6 months during the first year and has been mailed annually thereafter to obtain information on compliance with the intervention and the occurrence of new medical diagnoses including HF. In a pilot study, we found a higher confirmation rate (90%) of HF using the Framingham criteria.17 A detailed description of HF validation has been published elsewhere.18

OTHER VARIABLES

Information on age, height, weight, body mass index, cigarette smoking, vegetable consumption, hypertension, use of multivitamins, atrial fibrillation, valvular disease, diabetes mellitus, and physical activity was collected at baseline. Incidence of major chronic disease was ascertained through annual follow-up questionnaires.

STATISTICAL ANALYSIS

We used total breakfast cereals as the main exposure. However, we conducted stratified analyses by whole grain vs refined breakfast cereals. Because there was a good correlation between reported breakfast cereals at baseline and at 18 weeks (weighted κ = 0.71), we substituted missing values at baseline using reported cereals at 18 weeks in 756 individuals. Excluding these individuals with missing baseline cereal data did not alter the results (P < .001 for trend in fully adjusted model; data not shown). Since the distribution of total, refined, and whole grain cereals was skewed to the right, we did not use quartiles to categorize cereal consumption. We grouped adjacent categories to allow sufficient number of person-times per category and to maintain a gradient of exposure as previously described.8 Thus, we classified each subject into 1 of the following categories of average number of cereal servings consumed per week: 0, 1 or fewer, 2 to 6, and 7 or more. We calculated person-time of follow-up from baseline until the first occurrence of (1) HF, (2) death, or (3) censoring date—date of receipt of last follow-up questionnaire.

Within each breakfast cereal group, we calculated the incidence rate of HF by dividing the number of HF cases by the corresponding person-time. We used Cox proportional hazard models to compute multivariable adjusted hazard ratios with corresponding 95% confidence intervals (CIs) using subjects in the cereal category of 0 servings per week as the reference group. We assessed confounding by using 10% change in hazard ratio. Assumptions for the proportional hazard models were tested (by including main effects and product terms of covariates and a logarithmic transformed time factor) and were met (P > .05 for all). We obtained P value for linear trend by treating the cereal variable as ordinal (taking values of 0, 1, 2, and 3 from the lowest to the highest category of cereal intake).

The initial model controlled for age. The fully adjusted model included age, smoking status (never, past, or current smokers), alcohol consumption (<1, 1-4, 5-6, or ≥7 drinks per week), vegetable consumption (<3, 3-4, 5-6, 7-13, or ≥14 servings per week), use of multivitamin (never, past, or current), physical activity (<1 or ≥1 time per week), and history of atrial fibrillation, left ventricular hypertrophy, and valvular heart disease. To examine whether the effect of breakfast cereals on HF was mediated by body mass index, diabetes mellitus, coronary heart disease, and hypertension, we included these variables in the full model to see if their inclusion led to an attenuation of the hazard ratios.

In secondary analyses, we excluded individuals with a follow-up time of 2 years of less. Finally, we repeated the main analysis using updated cereal consumption data at 24, 48, 72, 96, and 120 months. For the last analysis, we used pooled logistic regression. Results from pooled logistic regression have been shown to be equivalent to those obtained from Cox regression model.19 All analyses were completed using SAS, version 9.1 (SAS Institute, Cary, North Carolina). Significance level was set at P = .05.

RESULTS

Among 21,376 participants in the PHS I, the mean±SD age at randomization was 53.7±9.5 years (age range, 40-86 years). Table 1 summarizes the baseline characteristics of the study participants. Frequent consumption of breakfast cereals was associated with (1) older age; (2) higher consumption of vegetables; (3) a higher proportion of current drinkers, those engaging in physical activity at least once a week, and users of multivitamins; (4) a lower proportion of current smokers; and (5) a lower prevalence of hypertension.

During an average follow-up of 19.6 years, 1018 new cases of HF occurred. The crude incidence rates of HF were 26.7, 24.1, 22.2, and 23.3 cases per 10,000 person-years for cereal consumption of 0, 1 or fewer, 2 to 6, and 7 or more servings per week, respectively. In the multivariable Cox regression model, corresponding hazard ratios (95% CIs) for HF were 1 (reference), 0.92 (0.78-1.09), 0.79 (0.67-0.93), and 0.71 (0.60-0.85), respectively, after adjustment for age, smoking (never, past, or current smokers), alcohol consumption (<1, 1-4, 5-6, or ≥7 drinks per week), vegetable consumption (<3, 3-4, 5-6, 7-13, or ≥14 servings per week), use of multivitamin (never, past, or current), physical activity (<1 or ≥1 time per week), and history of atrial fibrillation, left ventricular hypertrophy, and valvular heart disease (P < .001 for linear trend) (Table 2).

The use of updated cereal consumption data at 24, 48, 72, 96, and 120 months yielded a similar inverse association
between cereal consumption and risk of HF ($P = .03$ for trend). Additional adjustment for potential intermediate factors such as body mass index, hypertension, myocardial infarction, and diabetes mellitus resulted in a modest attenuation of the effect measure with corresponding relative risks (95% CIs) of 1 (reference), 0.91 (0.77-1.08), 0.83 (0.71-0.99), and 0.80 (0.67-0.96), respectively ($P = .01$ for trend). Finally, exclusion of individuals whose follow-up times were 2 years or less had no effect on the relative risks ($P = .001$ for trend; data not shown).

However, when we stratified by the type of breakfast cereals consumed, we observed an inverse association between whole grain cereals and HF ($P < .001$ for trend) but not with refined cereals ($P = .70$ for trend) (Table 3). Adjustment for intermediate factors (body mass index, myocardial infarction, hypertension, and diabetes) attenuated the relative risks modestly with corresponding hazard ratios (95% CIs) of 1 (reference), 0.85 (0.68-1.06), 0.82 (0.68-1.01), and 0.81 (0.66-0.99), from the lowest to the highest category of whole grain breakfast cereals, respectively ($P = .02$ for trend).

In the present prospective study, we demonstrated that a higher consumption of breakfast cereals was associated with a lower risk of HF among US male physicians. However, this association was mainly present in individuals consuming whole grain breakfast cereals but not refined breakfast cereals. To our knowledge, this is the first study to prospectively examine the relation between breakfast cereal consumption and the risk of HF in a large cohort.

**COMMENT**

Dietary guidelines recommend a consumption of grain products for health benefits. Cereal grains and their products represent an important source of energy in the US population. Depending on the type (whole vs refined), cereals can provide substantial amounts of proteins, oils, fiber, potassium, selenium, and vitamins and other nutrients. Processing generally reduces the content of these nutrients and bioprotective substances. Previous epidemiologic studies have reported beneficial effects of fi-
Cereal consumption has been shown to favorably influence other risk factors for HF. A previous report from this cohort demonstrated an inverse association between total breakfast cereals and whole and refined cereals and body mass index and weight gain over time. In addition, higher consumption of whole grains and dietary fiber was inversely associated with weight and weight gain over 12 years among 74,091 US female nurses and US male physicians. In contrast, refined grain but not refined grains.

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Epidemiologic data on the effects of cereals or dietary fiber on the risk of coronary heart disease, weight, type 2 diabetes mellitus, and hypertension (all of which are determinants of HF). Specifically, in a randomized placebo-controlled trial, consumption of 5.52 g/d of oat cereals was associated with a 7.5–mm Hg reduction in systolic blood pressure (P < .01) and a 5.5–mm Hg reduction in diastolic blood pressure (P < .02) after 6 weeks of intervention among 18 men and women with hypertension and hyperinsulinemia; in contrast, no effect was observed in the placebo group of that trial. Other clinical trials using an intervention consisting of a high-fiber, low-fat, and low-sodium diet reported similar reductions in blood pressure. Data from the Coronary Artery Risk Development in Young Adults Study reported a lower incidence of elevated blood pressure with consumption of whole grain but not refined grains.

Table 3. Hazard Ratio of Heart Failure by Type and Quantity of Breakfast Cereal Consumed

<table>
<thead>
<tr>
<th>Cereal Intake, Servings/wk</th>
<th>Cases, No.</th>
<th>HR (95% CI)</th>
<th>P Value</th>
<th>Cases, No.</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>362</td>
<td>1 [Reference]</td>
<td></td>
<td>362</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>99</td>
<td>0.86 (0.69-1.08)</td>
<td>&lt;.001</td>
<td>52</td>
<td>1.11 (0.83-1.49)</td>
<td>.70</td>
</tr>
<tr>
<td>2-6</td>
<td>137</td>
<td>0.78 (0.64-0.96)</td>
<td>&lt;.001</td>
<td>52</td>
<td>1.10 (0.82-1.48)</td>
<td></td>
</tr>
<tr>
<td>≥7</td>
<td>129</td>
<td>0.72 (0.59-0.88)</td>
<td>&lt;.001</td>
<td>35</td>
<td>0.83 (0.58-1.18)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

- A common reference group of individuals who do not consume breakfast cereals was used for both types of cereal: adjusted for age, smoking (never, past, or current smokers), alcohol consumption (<1, 1-4, 5-6, or ≥7 drinks per week), vegetable consumption (<3, 3-4, 5-6, 7-13, or ≥14 servings per week), use of multivitamin (never, past, or current), physical activity (<1 or ≥1 time per week), and history of atrial fibrillation, left ventricular hypertrophy, and valvular heart disease.

- Cereal consumption was inversely associated with incident CVD in the Cardiovascular Health Study. Contrary to most cohort studies, the Diet and Reinforcement trial (DART) did not show any benefit of cereal fiber consumption on the risk of coronary heart disease, stroke, or all-cause mortality. Of note is that the DART was a secondary prevention trial in men with coronary disease, thus making it more difficult to detect a small effect of cereal fiber given the elevated baseline risk of CHD in the group that did not receive advice to consume more cereal fiber. Alternatively, residual confounding and/or uncontrolled confounding could partially explain the beneficial effects of cereals/fiber observed in cohort studies.

- There are several biological mechanisms by which whole grain cereals could protect against incident HF. Nutrients such as potassium contained in whole grain cereals have been shown to lower blood pressure. Phytoestrogens contained in whole grain cereals may improve lipid levels and insulin sensitivity. Slowing starch digestion or absorption and promoting satiety are possible mechanisms by which whole grain cereals may help control body weight. The attenuation of hazard ratios found after additional adjustment for body mass index, hypertension, myocardial infarction, and diabetes mellitus supports the hypothesis that beneficial effects of whole grain cereals on HF risk are mediated partially through these physiologic mechanisms. The fact that we still found a statistically significant P value for trend after adjusting for intermediate factors is more likely due to measurement errors in our data and/or unmeasured confounding.

- Our study has some limitations. First, we did not collect data to distinguish HF with and without preserved left ventricular function. Second, we used a simple semiquantitative food frequency questionnaire to collect dietary information. Thus, we were not able to control for total energy intake and other nutrients in the diet. Third, there is a possibility of inaccurate reporting of consumption of breakfast cereals, which might have led to exposure misclassification. Fourth, the fact that our sample...
consists of highly educated male physicians who may have different behaviors than the general population limits the generalizability of our findings. Finally, given the intercorrelation between cereal consumption and other dietary or lifestyle factors, our data cannot precisely estimate the net contribution of cereal consumption on the observed association. Nevertheless, the large sample size, the longer duration of follow-up, and the fact that participants were physicians who could recognize early signs of HF are strengths of the present study. In conclusion, our data showed an inverse association between consumption of whole grain breakfast cereals and incident HF. Such association is more likely to be mediated through beneficial effects of whole grains on risk factors of HF such as hypertension, myocardial infarction, diabetes mellitus, and obesity. If confirmed in other studies, a higher intake of whole grains along with other preventive measures could help lower the risk of HF.

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Correspondence: Luc Djousseé, MD, MPH, DSc, Division of Aging, Brigham and Women’s Hospital and Harvard Medical School, 1620 Tremont St, Third Floor, Boston, MA 02120 (ldjousse@rics.bwh.harvard.edu).

Author Contributions: Drs Djousseé and Gaziano have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Djousseé and Gaziano. Acquisition of data: Gaziano. Analysis and interpretation of data: Djousseé and Gaziano. Drafting of the manuscript: Djousseé. Critical revision of the manuscript for important intellectual content: Djousseé and Gaziano. Statistical analysis: Djousseé. Obtained funding: Djousseé and Gaziano. Administrative, technical, and material support: Gaziano. Study supervision: Gaziano.

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