Nut consumption and risk of heart failure in the Physicians’ Health Study I1–3
Luc Djoussé, Tamara Rudich, and J Michael Gaziano

ABSTRACT
Background: Heart failure is highly prevalent among older adults and is associated with high cost and societal burden. Although previous studies have reported beneficial effects of dietary factors on heart failure predictors, no previous study has examined whether frequent consumption of nuts is associated with a lower risk of heart failure in a large prospective cohort.
Objective: We examined the association between nut consumption and incident heart failure to determine whether such a relation is modified by overweight or obesity.
Design: This was a prospective cohort study of 20 976 participants from the Physicians’ Health Study I. Nut consumption was assessed with a simple abbreviated food questionnaire, and self-reported heart failure was ascertained by follow-up questionnaires. We used Cox regression to estimate relative risks of heart failure.
Results: After an average follow-up of 19.6 y, 1093 new cases of heart failure occurred. Nut consumption was not associated with the risk of developing heart failure in this cohort: multivariable adjusted hazard ratios were 1.0 (reference), 0.98 (95% CI: 0.83, 1.15), 1.06 (95% CI: 0.89, 1.27), and 1.01 (95% CI: 0.84, 1.22) for nut consumption of <1, 1, and ≥2 servings/wk, respectively (P for linear trend: 0.64). The lack of a meaningful relation between nut intake and incident heart failure was seen in both lean and overweight or obese participants (P for interaction: 0.96).
Conclusion: Our data do not provide evidence for an association between nut consumption and incident heart failure in US male physicians. However, our data cannot rule out possible benefits of nut consumption on subtypes of heart failure not prevalent in this cohort.

INTRODUCTION
Heart failure is a condition that could result from heterogeneous factors, including myocardial damage, heart valve pathology, dysregulation in volume homeostasis, hormonal changes, etc. It is the leading cause of hospitalization among the elderly and is associated with higher costs. At age 40 y, it is estimated that 1 in every 5 adults will develop heart failure during the remaining lifetime (1). Despite advances in medical and surgical management of heart failure, the rate of mortality after onset of heart failure remains high, thus underscoring the importance of primary prevention of this disease. Several predictors of heart failure can be influenced by modifiable lifestyle factors. For example, healthy diet, exercise, not smoking, and maintaining healthy weight were shown to favorably influence heart failure risk factors, including coronary artery disease (2–6), diabetes (7–11), and hypertension(12, 13). Among dietary factors, nuts are low in sodium and also provide a variety of nutrients, including monounsaturated and polyunsaturated fatty acids, minerals such as magnesium and potassium, fiber, antioxidants, and vitamins with beneficial influence on blood pressure. Nut consumption was previously associated with improved blood pressure (14–18), lower risk of diabetes (19), weight loss (20), and lower risk of sudden death or death of coronary heart disease (21). However, it is not known whether consumption of nuts is associated with a lower risk of heart failure. The current project sought to prospectively assess whether nut consumption was associated with a lower risk of heart failure among US male physicians.

SUBJECTS AND METHODS
Study population
We used data from the Physicians’ Health Study (PHS) I; this was a randomized, double-blind, placebo-controlled trial designed to study low-dose aspirin and β-carotene for the primary prevention of cardiovascular disease and cancer. A detailed description of the PHS I was previously published (22). Of the total 22 071 participants, we excluded 615 subjects because of missing data on nut consumption, 27 subjects with prevalent heart failure at the time of exposure assessment, and 453 subjects who died before collection of data on nut consumption or with missing covariates. Thus, a final sample of 20 976 participants was used for the current analyses. Each participant signed an informed consent, and the Institutional Review Board at Brigham and Women’s Hospital approved the study protocol.

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Nut consumption

We used an abbreviated food-frequency questionnaire to obtain self-reported information on nut consumption at 12 mo after randomization (1983–1985). Participants were asked to report how often, on average, they have consumed nuts (small packet or 1 oz) during the past year (possible responses were rarely or never, 1–3 servings/mo, 1 serving/wk, 2–4 servings/wk, 5–6 servings/wk, daily consumption, and ≥2 servings/d). Because of the limited number of subjects in the higher frequency categories, we combined the last 4 categories to obtain stable estimates as previously published (21). Although the food-frequency questionnaire was not validated in this cohort, it was validated in several cohorts (23–26).

Ascertainment of heart failure in the PHS

Ascertainment of endpoints, including heart failure, in the PHS was achieved with the use of self-reported information on follow-up questionnaires. A questionnaire was mailed to each participant every 6 mo during the first year and was mailed annually thereafter to obtain information on compliance with the intervention and the occurrence of new outcomes, including heart failure. A detailed description of heart failure validation in the PHS with the use of the Framingham criteria (27) was published elsewhere (28).

Other variables

Information on atrial fibrillation, coronary artery disease, valvular heart disease, hypertension, and diabetes mellitus was collected through self-reported annual follow-up questionnaires. A questionnaire was not validated in this cohort, it was validated in previously published (21). Although the food-frequency questionnaire was not validated in this cohort, it was validated in several cohorts (23–26).

Statistical analyses

We classified each subject into one of the following categories of nut consumption: none, <1, 1, and ≥2 servings/wk. We computed person-time of follow-up from exposure assessment (12 mo after randomization) until the first occurrence of 1) heart failure, 2) death, or 3) date of receipt of last follow-up questionnaire. We used Cox proportional hazard models to compute multivariable-adjusted hazard ratios with corresponding 95% CIs with the use of subjects in the lowest category of nut consumption as the reference group. We assessed confounding by established risk factors for heart failure. The initial model only adjusted for age (5-y categories, and a final model also controlled for body mass index (BMI; in kg/m²), smoking (never, former, and current smokers of 1–19 and ≥20 cigarettes/d), exercise (none, ≤1, 2–4, and ≥5 times/wk), alcohol consumption (none, <1, 1–4, 5–7, and ≥8 drinks/wk), multivitamin use (never, past, and current), aspirin assignment, hypercholesterolemia, fruit and vegetable intake (<5, 5–6, 7–13, and ≥14 servings/wk), and prevalent diabetes. Assumptions for proportional hazard models were tested (by including main effects and product terms of covariates and logarithmic-transformed time factor) and were met (all P values > 0.05). In a secondary analysis, we examined whether adiposity modified the association between nut intake and heart failure with BMI of 25 as the cutoff to separate lean from overweight or obese subjects. We then conducted stratified analyses by adiposity status (BMI < 25 or ≥25) and tested statistical interaction with the use of a product term of nut consumption and adiposity variable in a hierarchical model. All analyses were completed with the use of SAS, version 9.1 (SAS Institute, Cary, NC). Significance level was set at 0.05.

RESULTS

The baseline characteristics of 20 976 US male physicians according to nut consumption are presented in Table 1. The mean age of study participants was 54.6 ± 9.4 y (range: 40.7–87.1) at the time of nut consumption assessment. Of the total population, 36%, 24%, and 20% reported nut consumption with a frequency of <1, 1, and ≥2 servings/wk, respectively. Nut consumption was associated with a higher proportion of current drinkers, physical activity, and breakfast cereal consumption and with a lower proportion of current smokers and hypertension. During an average follow-up of 19.6 y, 1093 new cases of heart failure were documented. From the lowest to the highest category

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Baseline characteristics of 20 976 US male physicians according to nut consumption</th>
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<tbody>
<tr>
<td></td>
<td>None (n = 4229)</td>
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<tr>
<td>Age (y)</td>
<td>55.4 ± 9.8²</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8 ± 2.9</td>
</tr>
<tr>
<td>Fruit and vegetables intake (serving/d)</td>
<td>1.1 ± 0.7</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>12.4</td>
</tr>
<tr>
<td>Current drinking (%)</td>
<td>70.0</td>
</tr>
<tr>
<td>Randomly assigned to aspirin (%)</td>
<td>50.4</td>
</tr>
<tr>
<td>Exercise (%)</td>
<td>81.9</td>
</tr>
<tr>
<td>Coronary heart disease (%)</td>
<td>2.9</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>1.5</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>26.6</td>
</tr>
<tr>
<td>Valvular heart disease (%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>3.5</td>
</tr>
<tr>
<td>Breakfast cereal intake (%)</td>
<td>59.1</td>
</tr>
<tr>
<td>Current use of multivitamins (%)</td>
<td>20.1</td>
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</tbody>
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<th>Notes:</th>
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<td>¹ Determined by linear regression for continuous variables and logistic regression for categorical variables.</td>
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<td>² ± SD (all such values).</td>
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of nut consumption, crude incidence rates for heart failure were 27.9, 25.3, 28.0, and 26.1 cases/10,000 person-years, respectively. No evidence was observed for a statistically significant association between nut consumption and incident heart failure. Multivariable adjusted hazard ratios for heart failure were 1.0 (reference), 0.98 (95% CI: 0.83, 1.15), 1.06 (95% CI: 0.89, 1.27), and 1.01 (95% CI: 0.84, 1.22) for nut consumption of none, <1, 1, and ≥2 servings/wk, respectively (P for linear trend: 0.64; Table 2). In secondary analysis, nut consumption was not associated with incident heart failure in lean subjects (BMI < 25) [multivariable adjusted hazard ratios of 1.0 (reference), 0.96 (95% CI: 0.75, 1.24), 1.11 (95% CI: 0.85, 1.46), and 1.00 (95% CI: 0.75, 1.32) from the lowest to the highest category of nut consumption, respectively, P for trend: 0.70] or overweight and obese subjects [corresponding multivariable adjusted hazard ratios of 1.0 (reference), 0.98 (95% CI: 0.79, 1.23), 1.03 (95% CI: 0.81, 1.30), and 1.01 (95% CI: 0.78, 1.31), respectively, P for trend: 0.80]. P value for interaction between nut consumption and obesity status was 0.96.

**DISCUSSION**

In this prospective study, we showed that nut consumption was not associated with incident heart failure in apparently healthy US male physicians. In addition, such relation was not modified by overweight or obesity status. To the best of our knowledge, this is the first large epidemiologic study to evaluate whether nut consumption is associated with the risk of heart failure. The lack of an association between nut consumption and heart failure risk is contrary to our a priori hypothesis of a lower risk of heart failure with frequent nut consumption and merits some comments.

Our inability to further differentiate the type of heart failure (with and without preserved left ventricular function) or conditions leading to heart failure development in this study prevent us from examining the relation between nut consumption and heart failure subtypes. In addition, we did not have detailed information on types of nuts consumed (ie, cashews, almonds, hazelnuts, walnuts, almonds, etc) to assess the amounts of saturated, polyunsaturated, and monounsaturated fatty acids and other nutrients provided by nuts. For example, walnuts would have more n-3 fatty acids than macadamia nuts, which would provide more monounsaturated fatty acids. In addition, we did not have data on the preparation of nuts such as salted, spiced, roasted, or raw nuts to examine the influence of the preparation method on the risk of heart failure. Because study participants were physicians, it is less likely that consumption of salted nuts was important in this population, given the positive association between sodium intake and hypertension. It is possible that, overall, nut consumption does not have a meaningful influence on the risk of heart failure. Alternatively, because of their medical knowledge, participants at risk of heart failure (those with diabetes, hypertension, coronary heart disease, or left ventricular dysfunction) may have been more likely to consume nuts, given previous reports on the beneficial effects of nut consumption on diabetes (19), weight control (20), coronary artery disease (21), or blood pressure (17, 18). Such scenario would bias the association toward the null and be consistent with our data. With a single measurement of nut consumption at baseline, it is difficult to disentangle such hypothesis.

Additional limitations of our study include the inability to generalize our findings to the general population because our participants consisted solely of male physicians who may have different lifestyle habits than the general population, the inability to account for changes in frequency of nut consumption over time, possible over- or underreporting of nut consumption, and the lack of data on other foods and energy intake in this population to account for confounding by other dietary factors. However, our study has important strengths, including the large sample size, a 20-year follow-up, and a standardized and comprehensive ascertainment of outcomes in this cohort.

In conclusion, our data do not provide evidence for an association between nut consumption and the risk of incident heart failure among US male physicians. However, given the heterogeneity of the heart failure syndrome, the current study cannot rule out possible beneficial effects of nut consumption on certain subtypes of heart failure (ie, heart failure resulting from diabetic causes).

We thank the participants in the PHS for their outstanding commitment and cooperation and the entire PHS staff for their expert and unfailing assistance.

The author’s responsibilities were as follows—LD: study concept and design, statistical analysis, and drafting of the manuscript; JMG: acquisition of data and funding; and LD, TR, and JMG: critical revision of the manuscript for important intellectual content. None of the authors had a personal or financial conflict of interest.

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