ORIGINAL INVESTIGATION

Nut Consumption and Decreased Risk of Sudden Cardiac Death in the Physicians' Health Study

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Background: Dietary nut intake has been associated with a reduced risk of coronary heart disease mortality; however, the mechanism is unclear. Since components of nuts may have antiarrhythmic properties, part of the benefit may be due to a reduction in sudden cardiac death.

Methods: We prospectively assessed whether increasing frequency of nut consumption, as ascertained by an abbreviated food frequency questionnaire at 12 months of follow-up, was associated with a lower risk of sudden cardiac death and other coronary heart disease end points among 21 454 male participants enrolled in the US Physicians' Health Study. Participants were followed up for an average of 17 years.

Results: Dietary nut intake was associated with a significantly reduced risk of sudden cardiac death after controlling for known cardiac risk factors and other dietary habits (*P* for trend, .01). Compared with men who rarely or never consumed nuts, those who consumed nuts 2 or more times per week had reduced risks of sudden cardiac death (relative risk, 0.53; 95% confidence interval, 0.30-0.92) and total coronary heart disease death (relative risk, 0.70; 95% confidence interval, 0.50-0.98). In contrast, nut intake was not associated with significantly reduced risks of nonsudden coronary heart disease death or nonfatal myocardial infarction.

Conclusion: These prospective data in US male physicians suggest that the inverse association between nut consumption and total coronary heart disease death is primarily due to a reduction in the risk of sudden cardiac death.

Arch Intern Med. 2002;162:1382-1387

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RECENT RANDOMIZED dietary trials have reported markedly reduced risks of recurrent events and cardiac death in patients assigned to the Mediterranean diet after a myocardial infarction.[1,2] In one trial, this benefit appeared to be at least partly due to an increase in the plasma level of α-linolenic acid (an n-3 fatty acid) in the Mediterranean diet arm.[3] Small to moderate amounts of n-3 fatty acids have been demonstrated to have antiarrhythmic effects[4] and to prevent sudden cardiac death in patients who have had a myocardial infarction.[5] Therefore, the protective effects on cardiac mortality of the Mediterranean diet may be partly related to antiarrhythmic effects of n-3 fatty acids and resultant reduction in sudden cardiac death.

Nuts are both an important component of the Mediterranean diet and a source of small to moderate amounts of α-linolenic acid.[6-8] In addition, nuts are a source of other unsaturated fats, magnesium, and vitamin E, and result in an improved lipoprotein profile when added to the diet[6-9] if caloric intake remains constant. On the basis of experimental and observational data, all of these potential effects would be expected to reduce sudden cardiac death.[10-12] In 3 large prospective observational studies,[13-15] reductions in coronary heart disease mortality were observed among those who consumed nuts more frequently, but none of these studies have specifically examined the end point of sudden cardiac death. To further understand the mechanism underlying the apparent protective effect of nut consumption, we examined the associations between nut consumption and risk of sudden cardiac death and other coronary heart disease end points in a cohort of 21 454 US male physicians followed up for an average of 17 years.

RESULTS

NUT INTAKE

The distribution of nut consumption among the 21 454 participants is displayed in the **Figure**. Twenty percent of the cohort rarely or never consumed nuts,

SUBJECTS AND METHODS

The Physicians' Health Study has been described in detail elsewhere.[16,17] Briefly, 22 071 male physicians who were 40 to 84 years old in 1982 and had no history of myocardial infarction, stroke, transient ischemic attacks, or cancer (except nonmelanoma skin cancer) were assigned at random by means of a 2×2 factorial design to receive aspirin, beta carotene, both active drugs, or both placebos. At baseline, the physicians completed questions on health status and risk factors for cardiovascular disease, including alcohol and vitamin use, dietary intake of selected foods, and exercise. Information on cardiovascular events was updated every 6 months for the first year and annually thereafter through brief follow-up questionnaires. Dietary intakes of selected foods were ascertained by 2 abbreviated semiquantitative food frequency questionnaires consisting of 20 items each[18] administered at baseline and 12 months.

ASSESSMENT OF NUT CONSUMPTION

At 12 months, the physicians were asked to indicate how often, on average, they had consumed nuts (small packet or 1 oz) during the past year. There were 7 possible response categories (≥2 times per day, daily, 5-6 times per week, 2-4 times per week, once per week, 1-3 times per month, and rarely or never), and on the basis of the frequency distribution of the responses, 4 categories of nut consumption were created (rarely or never, 1-3 times per month, once per week, and ≥2 times per week). The validity of this question was assessed in a cohort of female nurses, and the correlation coefficient was found to be 0.66[19] compared with repeated 1-week dietary records. Of the total cohort, 21 454 men returned the 12-month questionnaire and provided information on nut consumption. We chose not to exclude participants who developed evidence of cardiovascular disease during follow-up, but controlled for evidence of cardiovascular disease before the return of the 12-month questionnaire in the multivariate model, since previous disease could have influenced nut consumption.

END POINT ASCERTAINMENT AND DEFINITIONS

Information on cardiovascular events was updated every 6 months for the first year and annually thereafter. The ascertainment of cardiovascular disease events was by self-report on follow-up questionnaires, and deaths were generally reported by postal authorities or next of kin. All such events were reviewed by an end points committee of physicians for confirmation by medical records obtained from hospitals and attending physicians. The next of kin was interviewed regarding the circumstances surrounding the death if not adequately documented in the medical record. Deaths in which there was evidence of coronary heart disease at or before death and in which a noncoronary cause of death was not found were classified as coronary heart disease deaths (*International Classification of Diseases, Ninth Revision,* codes 410-414). Cases of nonfatal myocardial infarction were confirmed with the use of the World Health Organization criteria.[20]

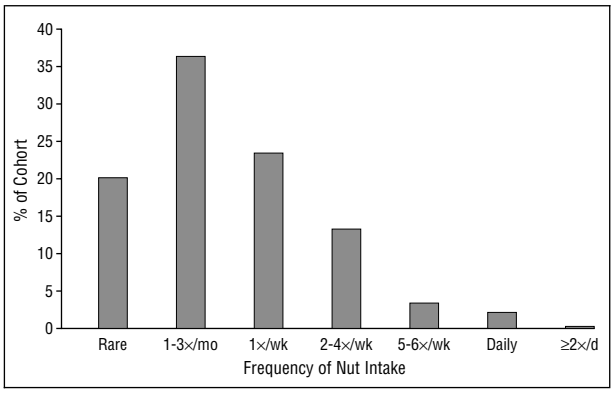
To ascertain the specific end point of sudden cardiac death, medical records and reports from next of kin for all cardiovascular deaths (excluding strokes) were reviewed by 2 cardiologists (including C.M.A.) unaware of exposure status, and agreement was reached. Sudden cardiac death was defined as death within 1 hour of symptom onset and/or a witnessed cardiac arrest or abrupt collapse not preceded by more than 1 hour of symptoms that precipitated the terminal event. Information from the death certificate was not used in the determination of the timing of death. To increase our specificity for "arrhythmic death," we excluded anyone who had evidence of collapse of the circulation (hypotension, exacerbation of congestive heart failure, and/or altered mental status) before the disappearance of the pulse.[21]

Unwitnessed deaths with no information on timing but with an autopsy consistent with arrhythmic cardiac death (ie, acute coronary thrombosis or severe coronary artery disease without myocardial necrosis or other pathologic findings to explain death) were considered possible sudden cardiac deaths, and the analysis was performed both including and excluding these deaths.

STATISTICAL ANALYSIS

Participants contributed follow-up time from the date of return of the 12-month questionnaire. Age-adjusted means or proportions of baseline risk factors and treatment group assignment were computed for the 4 categories of nut consumption (rarely or never, 1-3 times per month, once per week, and ≥2 times per week). The significance of associations was tested with the Mantel-Haenszel χ^2 test for trend for categorical variables and linear regression for continuous variables. Relative risks were computed with Cox proportional hazards models,[22] controlling for age and randomized aspirin and beta carotene assignment. Multivariate Cox proportional hazards models were used to control for potential confounders, including previous cardiovascular disease, body mass index, smoking, history of diabetes, history of hypertension, history of hypercholesterolemia, alcohol consumption, vigorous exercise, vitamin E use, vitamin C use, multivitamin use, and other dietary factors associated with nut intake (fish, red meat, vegetables, fruits, and dairy products). Participants with missing data on covariates included in the multivariate model were excluded from analysis. For each relative risk, 2-sided *P* values and 95% confidence intervals were calculated. Tests for trend were performed by assigning an ordinal variable for each level of consumption and then modeling this as a continuous variable in separate Cox proportional hazards models. SAS software (SAS Institute Inc, Cary, NC) was used for all analyses.

and the majority of the men who consumed nuts did so between 1 to 3 times per month and 2 to 4 times per week. Few men reported consuming nuts 5 or more times per week (6.3%). **Table 1** shows the baseline cardiac risk factor profile across 4 categories of nut intake. The men who ate nuts more frequently were younger and less likely to smoke 20 or more cigarettes per day or have a history of hypertension. In addition, these men exercised more frequently and were more likely to take antioxidant supplements and drink light to moderate amounts of alcohol. Nut intake was also directly associated with various dietary factors. We therefore analyzed the relation-



Distribution of self-reported nut consumption (small packet or 1 oz) at 12 months of follow-up.

ship of nut consumption with sudden cardiac death with and without adjustment for all of these variables.

SUDDEN CARDIAC DEATHS

Among the 21 454 eligible participants, 201 sudden deaths (176 definite and 25 probable) were documented during 17 years of follow-up. The association between nut consumption at 12 months and subsequent risk of sudden cardiac death is presented in **Table 2**. After adjustment for age and aspirin and beta carotene assignment, men who ate nuts more frequently tended to have a lower risk of sudden cardiac death (*P* for trend, .04). This relationship persisted and was strengthened after adjustment for coronary risk factors, previous cardiovascular disease, and other dietary factors (*P* for trend, .01). Compared with men who consumed nuts less than monthly, the multivariate adjusted relative risk of sudden cardiac death for those who consumed nuts 2 or more times per week was 0.53 (95% confidence interval, 0.30-0.92). The relationship between nut consumption and sudden cardiac death appeared linear, and there was no clear evidence for a threshold effect over the distribution of nut consumption. When possible events were excluded from the analysis, the multivariate adjusted relative risk of sudden cardiac death for those who consumed nuts 2 or more times per week was similar at 0.51 (95% confidence interval, 0.28-0.94), and the *P* for trend across the 4 categories remained significant (*P*=.007).

OTHER CORONARY HEART DISEASE END POINTS

In contrast to the inverse relationship with sudden cardiac death, nut consumption was not significantly associated with risk of nonsudden coronary heart disease death or nonfatal myocardial infarction (**Table 3**). The risk of nonsudden coronary heart disease death was somewhat lower among the men who ate nuts 2 or more times per week; however, this reduction was not statistically significant. With respect to nonfatal myocardial infarction, there was no suggestion of any benefit associated with nut consumption. Rather, there was a slight elevation in risk among men who consumed nuts up to once per week compared with those who never consumed nuts;

Table 1. Relationship of Nut Intake at 12 Months to Coronary Heart Disease Risk Factors at Baseline*

Variable	Average Frequency of Dietary Nut Intake†			
	Rarely/ Never	1-3×/mo	1×/wk	≥2×/wk
No. of men	4347	7794	5068	4245
Age, mean, y	54.0	52.9	52.8	53.2
Smoking, %				
Current				
≥20 Cigarettes/d	8.3	6.9	6.4	6.7
<20 Cigarettes/d	3.9	3.8	4.0	3.7
Past	38.8	39.2	39.3	40.5
Never	49.0	50.1	50.3	49.1
Reported diagnosis, %				
Diabetes	2.6	2.1	2.0	3.1
High cholesterol‡	6.5	5.9	5.9	6.0
Hypertension§	15.7	14.3	12.7	12.8
Vigorous exercise (≥1×/wk), %	67.3	71.9	74.6	75.6
Alcohol use, %				
<1×/wk	30.2	25.5	24.0	25.1
1-6×/wk	44.5	49.6	53.4	48.0
Daily	25.3	24.9	22.6	26.9
Body mass index, mean‖	24.9	24.9	25.0	24.7
Parental history of MI before age 60 y, %	12.7	13.4	14.3	11.9
Vitamin supplement use, %				
Vitamin E	9.6	9.9	10.6	11.8
Vitamin C	21.7	22.2	23.4	25.5
Multivitamin	35.5	34.6	35.8	38.8
Food intake, servings/wk†				
Fish	2.3	2.4	2.6	2.7
Red meat	4.1	4.3	4.5	4.4
Chicken/turkey	1.9	1.9	2.0	2.0
Vegetables	10.0	10.1	10.4	10.7
Fruits	5.9	5.8	6.0	6.3
Dairy products	5.6	5.9	6.3	6.8

*Standardized for age to the total cohort. MI indicates myocardial infarction.
†Small packet or 1 oz; information ascertained on the 12-month questionnaire.
‡Self-reported high cholesterol level of 240 mg/dL (6.2 mmol/L) or more, or taking cholesterol-lowering medications.
§Self-reported systolic blood pressure of 160 mm Hg or more, diastolic blood pressure of 90 mm Hg or more, or taking antihypertensive medication.
‖Calculated as weight in kilograms divided by the square of height in meters.

however, the *P* for trend was not significant (*P*=.87). When all fatal coronary heart disease events were examined, nut intake was associated with a trend toward a reduced risk of total coronary heart disease death (*P* for trend, .06), primarily because of a reduction in sudden cardiac death. However, the risk reduction was apparent only in the highest intake category. The men who consumed nuts 2 or more times per week had a 30% reduced risk of coronary heart disease death compared with those who rarely or never consumed nuts (*P*=.04).

COMMENT

In this large prospective cohort study of US male physicians, dietary nut intake was associated with a significantly reduced risk of sudden cardiac death, even after

Table 2. Relative Risk of Sudden Death According to Nut Intake*

Servings of Nuts Consumed	No. of Cases	Person-years	Age-Adjusted RR (95% CI)	Multivariate† RR (95% CI)
<1/mo	48	73 192	1.0 (Referent)	1.0 (Referent)
1-3/mo	79	133 361	0.98 (0.68-1.40)	0.80 (0.52-1.23)
1/wk	45	87 191	0.85 (0.57-1.28)	0.60 (0.36-1.00)
≥2/wk	29	73 007	0.64 (0.40-1.01)	0.53 (0.30-0.92)
P value for trend			.04	.01

*RR indicates relative risk; CI, confidence interval.

†Multivariate model includes age (continuous), aspirin and beta carotene treatment assignment, evidence of cardiovascular disease (angina, myocardial infarction, stroke, transient ischemic attack, percutaneous transluminal angioplasty, or coronary artery bypass grafting) before 12-month questionnaire, body mass index (quartiles), smoking (current: <20 cigarettes/d, ≥20 cigarettes/d, past, or never), history of diabetes, history of hypertension, history of hypercholesterolemia, alcohol consumption (monthly or less, weekly, or daily), vigorous exercise (less than weekly, 1-4×/wk, or ≥5×/wk), vitamin E, vitamin C, and multivitamin use at baseline. The model also adjusts for fish consumption (<1×/mo, 1-3×/mo, or ≥1×/wk) and red meat, fruit and vegetable, and dairy intake (all separated into quintiles of intake) at 12 months of follow-up.

Table 3. Relative Risk of Other Coronary Heart Disease End Points According to Nut Intake*

	Frequency of Nut Consumption				*P* Value for Trend
	<1×/mo	1-3×/mo	1×/wk	≥2×/wk	
Nonsudden CHD death					
No. of cases (n = 365)	88	125	84	68	. . .
Person-years	73 192	133 361	87 191	73 007	. . .
Age-adjusted RR (95% CI)	1.0	0.90 (0.68-1.18)	0.91 (0.68-1.23)	0.84 (0.61-1.15)	.33
Multivariate RR† (95% CI)	1.0	0.94 (0.66-1.34)	1.12 (0.77-1.63)	0.84 (0.55-1.28)	.72
Total CHD death					
No. of cases (n = 566)	136	204	129	97	. . .
Person-years	73 192	133 361	87 191	73 007	. . .
Age-adjusted RR (95% CI)	1.0	0.93 (0.75-1.15)	0.89 (0.70-1.13)	0.77 (0.59-1.00)	.05
Multivariate RR† (95% CI)	1.0	0.89 (0.67-1.16)	0.90 (0.67-1.22)	0.70 (0.50-0.98)	.06
Nonfatal myocardial infarction					
No. of cases (n = 1037)	217	383	250	187	. . .
Person-years	71 393	130 129	84 991	71 353	. . .
Age-adjusted RR (95% CI)	1.0	1.02 (0.86-1.21)	1.02 (0.85-1.23)	0.89 (0.73-1.08)	.28
Multivariate RR† (95% CI)	1.0	1.22 (1.00-1.51)	1.20 (0.96-1.50)	1.04 (0.82-1.33)	.87

*CHD indicates coronary heart disease; RR, relative risk; and CI, confidence interval.

†Multivariate model includes age (continuous), aspirin and beta carotene treatment assignment, evidence of cardiovascular disease (angina, myocardial infarction, stroke, transient ischemic attack, percutaneous transluminal angioplasty, or coronary artery bypass grafting) before 12-month questionnaire, body mass index (quartiles), smoking (current: <20 cigarettes/d, ≥20 cigarettes/d, past, or never), history of diabetes, history of hypertension, history of hypercholesterolemia, alcohol consumption (monthly or less, weekly, or daily), vigorous exercise (less than weekly, 1-4×/wk, or ≥5×/wk), vitamin E, vitamin C, and multivitamin use at baseline. The model also adjusts for fish consumption (<1×/mo, 1-3×/mo, or ≥1×/wk) and red meat, fruit and vegetable, and dairy intake (all separated into quintiles of intake) at 12 months of follow-up.

controlling for known cardiac risk factors and other dietary habits. The effect appeared linear with a significant trend across the range of nut intake in this study. Compared with men who rarely or never consumed nuts, those who consumed nuts 2 or more times per week had a 47% lower risk of sudden cardiac death and a 30% lower risk of total coronary heart disease death. In contrast, nut intake was not associated with significantly reduced risks of other types of coronary heart disease death and nonfatal myocardial infarction. This pattern of benefit on coronary heart disease end points suggests that at least part of the effect of nut consumption on sudden cardiac death may be due to a reduction in fatal ventricular arrhythmias. If the effect were due entirely to an effect on atherosclerosis or thrombosis, one would expect to observe a beneficial association with nonfatal myocardial infarction. Rather, there was a slight elevation in the risk among those consuming nuts up to once per week. If a component of nuts is antiarrhythmic, then fatal events could be converted to nonfatal events in the men who consumed nuts.

There are several components of nuts that, on the basis of observational and experimental data, may have antiarrhythmic properties. Nuts are a source of small to moderate amounts of α-linolenic acid,[6-8] the main nonmarine n-3 fatty acid in the diet. This fatty acid can be elongated and desaturated after ingestion to form eicosapentaenoic acid (C20:5n-3) and docosahexaenoic acid (C22:6n-3), the primary n-3 fatty acid found in fish.[4] This class of fatty acids has been demonstrated to have antiarrhythmic properties in experimental models[4] and to reduce the risk of sudden cardiac death among patients who have had myocardial infarctions in a randomized trial.[5] Walnuts, in particular, contain high amounts of α-linolenic acid (6.3 g per 100 g), whereas other nuts such as almonds, pistachios, and pecans contain much smaller amounts (0.4 to 0.7 g per 100 g).[8] Previous studies in this[23] and other[24,25] cohorts suggest that antiarrhythmic

effects may occur even with very small amounts of n-3 fatty acid intake. In addition to α-linolenic acid, nuts are rich in other polyunsaturated and monounsaturated fatty acids and result in an improved lipoprotein profile when substituted for other sources of fat in the diet.[6-9] Although not clearly antiarrhythmic, an improved lipoprotein profile could reduce the risk of plaque rupture, which is often an inciting event in sudden cardiac death.[12] Nuts are also rich in magnesium, potassium, and vitamin E, all nutrients with potential antiarrhythmic effects.[6-8,10-12] Finally, nuts also contain flavonoids,[8] which have been associated with reductions in coronary heart disease mortality in prospective studies[26,27]; however, the specific association between this constituent and sudden cardiac death has not been explored.

Our results regarding fatal coronary heart disease are consistent with other prospective studies; however, our results regarding nonfatal myocardial infarction are disparate from at least 1 prospective study. Three large-scale prospective studies have reported consistent inverse associations between nut consumption and fatal coronary heart disease. In the Adventist Health Study,[13] subjects who consumed nuts 5 or more times per week had significantly reduced risks of both fatal coronary heart disease (relative risk, 0.52) and nonfatal myocardial infarction (relative risk, 0.49). The Iowa Women's Health Study[14] reported similar reduced risks of fatal coronary heart disease among women who consumed nuts 2 to 4 times per week. Data on nonfatal events were not available in this study. Finally, the Nurses' Health Study[15] reported a 35% reduced risk of total coronary heart disease among women who consumed nuts 5 or more times per week. When fatal and nonfatal myocardial infarction were examined separately, the relationship with nut consumption remained significant only for fatal coronary heart disease after adjustment for other dietary variables.

Plausible explanations for the disparate results with respect to nonfatal myocardial infarction within this cohort and the Adventist Health Study include differences in the amount of nuts consumed and other dietary habits of the participants. Twenty-four percent of the subjects in the Adventists study consumed nuts 5 or more times per week compared with only 6.3% of the physicians. If large quantities of nuts are required to obtain the benefit on nonfatal myocardial infarction, then it is possible that such a benefit could be missed in our cohort. Second, the Adventists study had a high proportion of vegetarians (approximately 50% of the cohort) who substituted nuts for meat as part of meals, whereas the physicians may have been consuming nuts as snacks. In the Adventist Health Study, the association between nut consumption and total coronary heart disease was significant in the nonvegetarians; however, the *P* for trend was weaker and the risk reduction was apparent only among those who ate nuts at least 5 times per week.[28]

There are several limitations of the present study. As with any observational study, the association between nut consumption and sudden cardiac death could be due, at least in part, to residual confounding. The men who consumed nuts had fewer coronary risk factors and practiced healthier lifestyle habits (Table 1) and, therefore, nut consumption may be a marker for a healthier lifestyle and/or diet. Arguing against this possibility, the association between nut consumption and sudden cardiac death became stronger after adjustment for lifestyle, cardiac risk factors, and diet. In addition, if nut consumption were simply a marker for a healthier lifestyle, a similar association should have been found for nonsudden coronary heart disease death and nonfatal myocardial infarction. Since we did not collect complete information on diet, this study cannot exclude the possibility that some other dietary factor associated with nut consumption could be responsible for the observed association. However, the relationship with nut consumption remained significant after controlling for intake of meat, fruits and vegetables, dairy products, and, more important, fish intake, the only other dietary factor known to be associated with sudden cardiac death.[23] Another important limitation of the study is the single measure of self-reported nut intake raising the possibility of misclassification, which, if random, would tend to underestimate the magnitude of benefit or risk. Health professionals have been found to reliably report nut intake[19]; however, the inability to account for changes in intake occurring over time would tend to obscure associations if the effect of nut intake is of short duration.

In summary, this large prospective cohort study suggests that increasing nut consumption among men is associated with a significantly reduced risk of sudden cardiac death and fatal coronary heart disease, but not nonfatal myocardial infarction. Since sudden cardiac death is often the first manifestation of coronary heart disease,[29] primary prevention is of the utmost importance in reducing the incidence of sudden cardiac death. However, despite the large numbers of sudden cardiac deaths in the population, the overall incidence is only 0.1% per year, and our ability to predict sudden cardiac death in the general population is poor.[30] Therefore, to reduce the incidence of sudden cardiac death, we must either accurately identify those at risk or develop safe, low-cost interventions that can be applied to the population at large. If the observed associations between dietary habits such as nut and fish consumption are causal, then these dietary interventions could be applied with little risk. In addition, further research directed at understanding the underlying mechanism by which nuts may protect against sudden cardiac death specifically and coronary heart disease in general could also lead to the development of novel preventive therapeutics.

Accepted for publication October 23, 2001.

This study was supported by grants CA-34944 and CA-40360 from the National Cancer Institute and HL-26490 and HL-34595 from the National Heart, Lung, and Blood Institute, Bethesda, Md. Dr Albert is supported by Mentored Clinical Scientist Development Award 1-K08-HL-03783 from the National Heart, Lung, and Blood Institute.

An earlier analysis of these data (12 years of follow-up) was presented in abstract form at the American Heart Association Meeting, Dallas, Tex, November 9, 1998.

We acknowledge the crucial contributions of the entire staff of the Physicians' Health Study, under the leadership of Charlene Belanger, MA, as well as Mary Breen, Vadim Bubes, PhD, Jean MacFadyen, Geneva McNair, David Pot-

ter, Leslie Power, Harriet Samuelson, MA, Miriam Schvartz, MD, Mickie Sheehey, Joanne Smith, and Phyllis Johnson Wojciechowski. We are also indebted to the 22 071 men who have participated and continue to participate in the Physicians' Health Study.

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