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A Prospective Cohort Study of Nut Consumption and the Risk of Gallstone Disease in Men

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Gallstone disease is a major source of morbidity in Western countries. Nuts are rich in several compounds that may be protective against gallstones. The objective of the study was to examine the relation between nut consumption and gallstone disease in the Health Professionals Follow-up Study. The consumption of nuts was assessed starting in 1986 as part of a 131-item semiquantitative food frequency questionnaire. The main outcome measure was newly diagnosed symptomatic gallstones. During 457,305 person-years of follow-up, 1,833 participants reported gallstone disease. After adjustment for age and other known or suspected risk factors, men consuming 5 or more units of nuts per week (frequent consumption) had a significantly lower risk of gallstone disease (relative risk = 0.70, 95% confidence interval: 0.60, 0.86; $p_{\text{trend}} < 0.001$) than did men who never ate or who ate less than 1 unit per month (rare consumption) (1 unit = 1 ounce (0.028 kg) of nuts). Further adjustment for fat consumption (saturated fat, *trans*-fat, polyunsaturated fat, and monounsaturated fat) did not materially alter the relation. In analyses examining consumption of peanuts and other nuts separately, both were significantly associated with a lower risk of gallstone disease in the age-adjusted and multivariate models. Our findings suggest that frequent nut consumption is associated with a reduced risk of gallstone disease in men.

gallstones; men; nuts; prospective studies

Abbreviation: CI, confidence interval.

Gallbladder disease is a common condition affecting approximately 10–25 percent of adults in the United States. It is a major source of morbidity and is a leading cause of digestion-related hospital admissions in developed countries (1, 2). Given the magnitude of the problem, preventive strategies to reduce the incidence of gallstone disease are required.

Most of the previous studies of the effect of diet on gallstone disease have considered intakes of alcohol, fat, and other nutrients (3–5). However, little attention has been paid to the intake of specific foods. Possibly the effect of diet on gallstone disease may depend on a combination of various nutrients and other constituents, many of which have unknown biologic activity. The influence of any particular food may depend on its unique combination of complex chemicals. An advantage of studying individual foods is the simplicity in conveying any resulting health education message.

In most Western countries, including the United States, an estimated 75–80 percent of gallstones are cholesterol stones (6). Cholesterol gallstones have many causes, but biliary hypersecretion of cholesterol is an important determinant (6). Low serum high-density lipoprotein cholesterol and high triglycerides may be also associated with the risk of gallstones (7–12). Nuts are rich in several compounds that have demonstrated beneficial effects on blood cholesterol and lipoprotein profiles (13–15). In addition, most of the fats in nuts are monounsaturated and polyunsaturated fats (16–18);

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the amount of saturated fat is relatively small. Dietary unsaturated fats may help reduce the occurrence of gallstones in hamsters (19, 20). Nuts are also a rich source of dietary fiber, magnesium, and antioxidant vitamins, particularly vitamin E (18), which may be beneficial in preventing gallstone formation. Given the prevalence and clinical significance of gallstone disease, any association between nut consumption and gallstone disease could have considerable clinical and public health relevance. Thus, we examined nut consumption in relation to risk of gallstone disease in a large cohort of US male health professionals.

MATERIALS AND METHODS

Study population

The Health Professionals Follow-up Study began in 1986 when 51,529 US male dentists (58 percent), veterinarians (20 percent), optometrists (7 percent), osteopathic physicians (4 percent), and podiatrists (3 percent) who were 40–75 years of age returned a questionnaire by mail regarding diet, medications, and medical history. Follow-up questionnaires were sent every 2 years to update information on exposures and to ascertain the occurrence of newly diagnosed illnesses, including gallstone disease. Diet was assessed in 1986, 1990, and 1994. At baseline, we excluded men who reported a cholecystectomy or a diagnosis of gallstone disease before 1986, men with a diagnosis of cancer before 1986, men with a daily energy intake outside the range of 800–4,200 kcal/day, men with 70 or more blank food items on the questionnaire, and men who provided no information on nut consumption. After exclusions, the study population consisted of 43,823 eligible men who were followed from 1986 to 1998. The average follow-up rate for biennial questionnaires was greater than 94 percent in each 2-year follow-up cycle.

Assessment of diet

Dietary information was derived from a 131-item semiquantitative food frequency questionnaire (21). Participants were asked to indicate the frequency, on average, of consuming a typical serving size of selected foods during the previous year. There were nine options for respondents to choose from, ranging from never or less than once per month to six or more times per day. Nutrient scores were computed by multiplying the frequency of consumption of each unit of food from the semiquantitative food frequency questionnaire by the nutrient content of the specified portion according to food-composition tables (22). The frequency of nut intake was obtained from the dietary questionnaires in which the participants were asked how often, on average, during the previous year they had consumed nuts (1 unit being equivalent to 1 ounce (0.028 kg) of nuts). We collapsed categories for frequency of nut consumption to less than once per month, 1–3 times per month, once per week, 2–4 times per week, and five times or more per week. Nut consumption was assessed by two questions about peanuts and other nuts. Thus, consumption of total nuts was the sum of these two items. The correlation coefficient between intake of peanuts assessed by food frequency questionnaire and intake assessed by dietary records collected over 4 weeks was 0.66 (23). Peanut butter consumption (1 tablespoon equivalent to 1 ounce of peanuts) was also assessed in the baseline and follow-up questionnaires. A full description of the semiquantitative food frequency questionnaire and the procedures used for calculating nutrient intake, as well as data on reproducibility and validity in this cohort, were reported previously (24).

Ascertainment of endpoints

The primary endpoint was incident symptomatic gallstones. In 1986 and on each follow-up questionnaire, participants were asked whether they had undergone a cholecystectomy or had been diagnosed as having gallstones by a physician. Participants were also asked whether the gallstone diagnosis had been confirmed by ultrasonographic or radiographic procedures and whether their gallstones were symptomatic. To verify the self-reports of cholecystectomy and diagnosed but unremoved gallstones, we reviewed a random sample of 441 medical records of participants who reported a cholecystectomy or gallstones, and the diagnosis was confirmed in 99 percent of the random sample. Moreover, all but one of the self-reported diagnostic procedures were confirmed by medical record review.

Statistical analysis

For each participant, follow-up time accrued from the month of return of the 1986 questionnaire and ended at the month of cholecystectomy, diagnosis of symptomatic gallstones, death, or the end of the study period, whichever occurred first. Participants with asymptomatic gallstones or those whose gallstone diagnosis was not based on ultrasonography or radiography, as well as men with diagnosed cancer, were excluded from subsequent follow-up. Thus, the eligible population at risk comprised only those who remained free of gallstone disease and cancer at the beginning of each 2-year follow-up interval. Incidence rates were calculated by dividing the number of events by person-years of follow-up in each category. Relative risks were calculated as the incidence rate of gallstone disease among men in different categories of nut consumption compared with the incidence rate among men in the lowest intake category (less than once per month), with adjustment for age in 5-year categories. Age-adjusted relative risks were calculated using the Mantel-Haenszel summary estimator (25). For multivariate analyses, the estimated relative risks for gallstone disease were simultaneously adjusted for potential confounding variables by using a pooled logistic regression model with 2-year time increments (26). This method accounts for varying time to the outcome event and is asymptotically equivalent to Cox regression, with time-dependent covariates if the time intervals are short and if the probability of an event is small for each interval (27). Tests of linear trend across increasing quintiles of nut intake were conducted by assigning the median value to each quintile and treating these as a single continuous variable. The incidence of gallstone disease was related to the cumulative average of nut consumption from

TABLE 1. Baseline characteristics of US male health professionals according to frequency of total nut consumption, Health Professionals Follow-up Study, 1986

Characteristic	Frequency of total nut consumption (1-ounce* serving)				
	<1/month	1–3/month	1/week	2–4/week	≥5/week
No. of participants	11,194	17,760	6,051	4,323	4,495
Mean age (years)	53.4	53.3	53.2	53.5	53.5
Current smoker (%)	9.5	9.3	9.6	9.2	9.2
Mean current body mass index (kg/m^2)	24.9	25.0	25.0	24.7	24.8
Mean physical activity (MET†)	18.9	19.5	20.7	21.1	22.5
Mean daily intake					
Carbohydrate (g)	240	235	234	232	223
Protein (g)	93	92	92	91	91
Alcohol (g)	10	11	12	13	14
Caffeine (mg)	264	244	229	225	219
Saturated fat (g)	24	25	25	24	24
trans-Fat (g)	2.9	2.9	2.8	2.7	2.4
Polyunsaturated fat (g)	12	13	13	14	16
Monounsaturated fat (g)	26	27	27	28	31
Dietary fiber (g)	20	21	21	22	23
Diabetes (%)	2.8	2.3	2.2	3.3	3.6
Regular use of medications (%)					
Aspirin and NSAIDs†	33.4	33.7	34.1	36.4	36.4
Thiazide diuretics	9.4	8.3	7.3	8.5	7.8

* One ounce = 0.028 kg.

† MET, metabolic equivalent (1 MET is defined as the energy expended in sitting quietly, which is equivalent to an oxygen uptake of 3.5 ml per kg of body weight per minute for an average adult); NSAIDs, nonsteroidal antiinflammatory drugs.

all available questionnaires up to the start of each 2-year follow-up interval, using methods for repeated measurement (28). In the main multivariate analyses, we simultaneously included intake of total energy and potential confounding covariates, including age, body mass index (weight (kg)/height (m)^2), recent weight change during the past 2 years, cigarette smoking, history of diabetes mellitus, physical activity, use of thiazide diuretics and nonsteroidal anti-inflammatory drugs, and intakes of alcohol, caffeine, and dietary fiber. All relative risks are presented with 95 percent confidence intervals, and all reported p values are two sided. All analyses were performed with Statistical Analysis System software, release 6.12 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

At baseline in 1986, approximately 33.9 percent of the participants reported eating 1 unit of nuts (equivalent to 1 ounce of nuts) at least once per week. Among the participants, 13.8 percent reported eating nuts once per week, 9.9 percent reported eating nuts 2–4 times per week, and 10.2 percent reported eating nuts five times or more per week. Men with frequent nut consumption in 1986 tended to be slightly more physically active and to drink more alcohol but less caffeine than did men who rarely consumed nuts (table 1). Frequent nut consumption was associated with lower intakes of *trans*-fat and saturated fats and higher intakes of polyunsaturated fat, monounsaturated fat, and fiber. Body mass index as well as consumption of meat, fish, and dairy foods was similar in men who frequently ate nuts and in those who rarely ate nuts.

During 457,305 person-years of follow-up from 1986 to 1998, we documented 1,833 cases of gallstone disease, of which 1,033 cases required cholecystectomy. The baseline frequency of total nut consumption was significantly inversely associated with subsequent gallstone disease in the age-adjusted analysis (for men consuming nuts five times or more per week compared with those who rarely ate nuts: relative risk = 0.73, 95 percent confidence interval (CI): 0.61, 0.88; $p_{trend} < 0.001$) (table 2). After controlling for potential confounding variables, we found that the association was slightly attenuated (relative risk = 0.78, 95 percent CI: 0.65, 0.95; $p_{trend} = 0.004$), reflecting the more favorable risk profile for gallstone disease in men who frequently consumed nuts.

We cumulatively updated nut intake in 1990 and 1994 to provide a better estimate of the effect of long-term average

TABLE 2. Relative risks of gallstone disease according to frequency of total nut consumption based on cumulative average and baseline intakes among men, Health Professionals Follow-up Study, 1986–1998

	Frequency of total nut consumption (1-ounce* serving)†									p_{trend}
	<1/month (relative risk)	1–3/month		1/week		2–4/week		≥5/week		
		Relative risk	95% confidence interval	Relative risk	95% confidence interval	Relative risk	95% confidence interval	Relative risk	95% confidence interval	
Cumulative average intake										
Model 1‡	1.00	0.97	0.86, 1.09	0.91	0.80, 1.04	0.81	0.69, 0.97	0.65	0.54, 0.80	<0.001
Model 2§	1.00	0.98	0.87, 1.10	0.94	0.82, 1.07	0.86	0.72, 1.03	0.70	0.60, 0.86	<0.001
Model 3¶	1.00	0.99	0.88, 1.11	0.95	0.83, 1.09	0.89	0.74, 1.07	0.73	0.58, 0.92	0.005
Baseline intake										
Model 1‡	1.00	1.05	0.94, 1.18	0.84	0.72, 0.99	0.90	0.76, 1.07	0.73	0.61, 0.88	<0.001
Model 2§	1.00	1.06	0.95, 1.19	0.87	0.74, 1.03	0.94	0.79, 1.13	0.78	0.65, 0.95	0.004
Model 3¶	1.00	1.07	0.96; 1.20	0.88	0.75, 1.05	0.97	0.82, 1.17	0.83	0.67, 1.02	0.05

* One ounce = 0.028 kg.

† Cases of gallstone disease (person-years) per frequency of total nut consumption: <1/month: 550 cases (125,321 person-years); 1–3/month: 619 cases (153,028 person-years); 1/week: 379 cases (95,816 person-years); 2–4/week: 172 cases (46,008 person-years); ≥5/week: 113 cases (37,132 person-years).

‡ Adjusted for age.

§ Multivariate model adjusted for age (5-year categories), body mass index (five categories), weight change during the past 2 years (five categories), physical activity (quintiles), dietary fiber (quintiles), intake of thiazide diuretics (yes or no), intake of nonsteroidal antiinflammatory drugs (yes or no), diabetes (yes or no), pack-years of smoking (six categories), alcohol intake (five categories), caffeine intake (quintiles), and total energy intake (quintiles).

¶ Additional adjustment for fats, including saturated fat, *trans*-fat, polyunsaturated fat, and monounsaturated fat.

nut consumption. Specifically, the average intake reported on the 1986 questionnaire was related to the incidence of gallstone disease from 1986 through 1990, the average intake reported on the 1986 and 1990 questionnaires was related to the incidence from 1990 through 1994, and the average intake reported on the 1986, 1990, and 1994 questionnaires was related to the incidence from 1994 through 1998. The relative risk for men consuming nuts five times or more per week compared with men who rarely consumed nuts was 0.65 (95 percent CI: 0.54, 0.80; $p_{trend} < 0.001$) in age-adjusted analysis; the relative risk changed minimally after adjusting for multiple potential confounding variables (relative risk = 0.70, 95 percent CI: 0.60, 0.86; $p_{trend} < 0.001$) when extreme categories were compared (table 2). After further adjustment for intakes of saturated fat, polyunsaturated fat, *trans*-fat, and monounsaturated fat, the relative risk for gallstone disease from consuming nuts five times or more per week was 0.73 (95 percent CI: 0.58, 0.92; $p_{trend} = 0.005$).

To examine the possibility that latent gallstone symptoms might cause a decrease in nut consumption, thereby biasing the results, we conducted analyses on the cases (n = 1,650), excluding those that occurred during the first 2-year follow-up period, and on the cases (n = 1,226), excluding those that occurred during the first 4-year follow-up period, to address the concern of any potential change in diet due to preclinical conditions. The relation became slightly stronger. Compared with men who rarely consumed nuts, men who ate nuts five times or more per week had multivariate relative risks of 0.64 (95 percent CI: 0.50, 0.82; $p_{trend} < 0.001$) after excluding the first 2-year follow-up period (n = 183 cases) and of 0.67 (95 percent CI: 0.51, 0.89; $p_{trend} = 0.004$) after excluding the first 4-year follow-up period (n = 607 cases).

To evaluate the potential for detection bias due to an increased medical surveillance, we additionally excluded cases (n = 895) with a routine medical check-up between 1986 and 1988. The multivariate relative risk for men consuming nuts five times or more per week compared with men who rarely consumed nuts was 0.59 (95 percent CI: 0.43, 0.81; $p_{trend} < 0.001$). We further addressed the possibility of detection bias by limiting the analysis to cholecystectomy cases. The relative risk for men consuming nuts five times or more per week compared with men who rarely consumed nuts was 0.80 (95 percent CI: 0.61, 1.05; p_{trend} = 0.01).

To examine whether the association with nut consumption was modified by other risk factors for gallstone disease, we repeated the multivariate analyses within subgroups of potential confounding variables (table 3). The inverse associations between nut consumption and risk of gallstone disease persisted in virtually all subgroups, although they were not always statistically significant, and we found no apparent modification of the relation.

In separate analyses, we examined individual consumption of peanuts, other nuts, and peanut butter. Comparing consumption of five times or more per week with less than once per month, we found that the multivariate relative risks were 0.69 (95 percent CI: 0.53, 0.91; $p_{trend} < 0.001$) for peanuts and 0.85 (95 percent CI: 0.70, 1.02; $p_{trend} = 0.17$) for

TABLE 3. Multivariate relative risks* of gallstone disease, stratified by risk factors, according to frequency of cumulative average total nut consumption, Health Professionals Follow-up Study, 1986–1998

Variables	Frequency of nut consumption (1-ounce† serving): <1/month (relative risk)	1–3/month		1/week		2–4/week		≥5/week		p_{trend}
		Relative risk	95% confidence interval	Relative risk	95% confidence interval	Relative risk	95% confidence interval	Relative risk	95% confidence interval	
Current smoking										
Yes	1.00	0.95	081, 1.10	0.90	0.75, 1.07	0.71	0.56, 0.91	0.68	0.52, 0.90	0.001
No	1.00	1.03	086, 1.24	1.00	0.81, 1.23	1.10	0.85, 1.42	0.73	0.52, 1.01	0.12
Current alcohol use										
Yes	1.00	0.93	0.77, 1.12	0.97	0.79, 1.18	0.88	0.69, 1.14	0.73	0.55, 0.99	0.04
No	1.00	1.02	0.88, 1.18	0.90	0.75, 1.08	0.83	0.64, 1.06	0.66	0.49, 0.89	0.002
Body mass index (kg/m^2)										
≥25	1.00	1.00	0.87, 1.17	0.93	0.78, 1.10	0.77	0.61, 0.97	0.57	0.43, 0.77	0.001
<25	1.00	0.94	0.77, 1.14	0.91	0.73, 1.14	0.95	0.72, 1.24	0.79	0.57, 1.09	0.20
Weight change during past 2 years (pounds†)										
>4	1.00	0.93	0.71, 1.21	0.84	0.61, 1.16	0.63	0.40, 1.00	0.71	0.44, 1.15	0.06
≤4	1.00	0.97	0.83, 1.14	0.91	0.76, 1.09	0.95	0.76, 1.19	0.65	0.49, 0.87	0.006
Physical activity‡ (MET§)										
High	1.00	1.00	0.84, 1.21	0.89	0.72, 1.10	0.75	0.57, 0.99	0.75	0.55, 1.10	0.01
Low	1.00	0.96	0.83, 1.12	0.97	0.82, 1.16	0.95	0.75, 1.19	0.66	0.50, 0.89	0.01
Caffeine intake‡										
High	1.00	1.03	0.87, 1.22	0.89	0.73, 1.09	0.95	0.74, 1.23	0.59	0.42, 0.83	0.002
Low	1.00	0.94	0.80, 1.10	0.98	0.82, 1.18	0.80	0.63, 1.03	0.79	0.61, 1.04	0.05
Dietary fiber intake‡										
High	1.00	1.05	0.89, 1.23	1.04	0.88, 1.24	1.03	0.84, 1.28	0.73	0.57, 0.94	0.02
Low	1.00	0.92	0.77, 1.09	0.81	0.66, 1.00	0.60	0.43, 0.84	0.71	0.48, 1.04	0.004

* Multivariate model adjusted for age (5-year categories), body mass index (five categories), weight change during the past 2 years (five categories), physical activity (quintiles), dietary fiber (quintiles), intake of thiazide diuretics (yes or no), intake of nonsteroidal antiinflammatory drugs (yes or no), diabetes (yes or no), pack-years of smoking (six categories), alcohol intake (five categories), caffeine intake (quintiles), and total energy intake (quintiles). The variable used for stratification was not included in the model.

† One ounce = 0.028 kg; 4 pounds = 1.814 kg.

‡ Median values were used as the cutoff point.

§ MET, metabolic equivalent (1 MET is defined as the energy expended in sitting quietly, which is equivalent to an oxygen uptake of 3.5 ml per kg of body weight per minute for an average adult).

peanut butter. For consumption of other nuts, we combined the top two categories because of the small number of cases. Compared with men who rarely ate nuts, men who ate other nuts two times or more per week had a multivariate relative risk of 0.75 (95 percent CI: 0.60, 0.93; $p_{trend} = 0.07$). All these associations with risk of gallstone disease were not materially changed after further adjustment for intakes of saturated fat, polyunsaturated fat, *trans*-fat, and monounsaturated fat (table 4).

DISCUSSION

In this large prospective cohort study among men, we found a significantly inverse association between nut consumption and risk of gallstone disease. Men who consumed nuts five times or more per week appeared to have an approximately 30 percent lower risk. This inverse association was found not only for peanut consumption, which accounts for approximately half of all nuts consumed in typical American diets, but also for other nuts and for a combination of these. It is possible that confounding might explain the observed inverse association, because men who frequently consumed nuts tended to have dietary or behavioral factors that might be protective against gallstone disease in contrast to those who rarely ate nuts. However, in detailed multivariate analyses, these adjustments only slightly attenuated the associations, and a statistically significant risk reduction persisted. Because the population we

TABLE 4. Relative risks of gallstone disease according to frequency of cumulative average peanut, other nuts, and peanut butter consumption, Health Professionals Follow-up Study, 1986–1998

Type of nut	Frequency of nut consumption (1-ounce* serving)									p_{trend}
	<1/month (relative risk)	1–3/month		1/week		2–4/week		≥5/week		
		Relative risk	95% confidence interval	Relative risk	95% confidence interval	Relative risk	95% confidence interval	Relative risk	95% confidence interval	
Peanuts†										
Model 1‡	1.00	0.94	0.85, 1.04	0.92	0.77, 1.10	0.72	0.59, 0.87	0.64	0.49, 0.84	<0.001
Model 2§	1.00	0.95	0.86, 1.06	0.94	0.79, 1.13	0.75	0.62, 0.91	0.69	0.53, 0.91	<0.001
Model 3¶	1.00	0.96	0.87, 1.07	0.96	0.80, 1.16	0.77	0.63, 0.95	0.73	0.55, 0.97	0.008
Peanut butter#										
Model 1‡	1.00	0.86	0.77, 0.97	1.06	0.90, 1.24	0.87	0.75, 1.01	0.86	0.72, 1.03	0.18
Model 2§	1.00	0.85	0.76, 0.95	1.04	0.88, 1.22	0.87	0.75, 1.01	0.85	0.70, 1.02	0.17
Model 3¶	1.00	0.85	0.76, 0.95	1.04	0.89, 1.23	0.88	0.76, 1.03	0.88	0.73, 1.07	0.36
	<1/month (relative risk)	1–3/month		1/week		≥2/week**				
		Relative risk	95% confidence interval	Relative risk	95% confidence interval	Relative risk	95% confidence interval			
Other nuts††										
Model 1‡	1.00	0.83	0.75, 0.92	0.95	0.77, 1.18	0.71	0.57, 0.88			0.01
Model 2§	1.00	0.86	0.77, 0.95	0.99	0.80, 1.24	0.75	0.60, 0.93			0.06
Model 3¶	1.00	0.86	0.78, 0.96	1.03	0.83, 1.29	0.80	0.63, 1.01			0.29

* One ounce = 0.028 kg.

† Cases of gallstone disease per frequency of peanut consumption: <1/month: 791 cases; 1–3/month: 715 cases; 1/week: 145 cases; 2–4/week: 124 cases; ≥5/week: 58 cases.

‡ Adjusted for age.

§ Multivariate model adjusted for age (5-year categories), body mass index (five categories), weight change during the past 2 years (five categories), physical activity (quintiles), dietary fiber (quintiles), intake of thiazide diuretics (yes or no), intake of nonsteroidal antiinflammatory drugs (yes or no), diabetes (yes or no), pack-years of smoking (six categories), alcohol intake (five categories), caffeine intake (quintiles), and total energy intake (quintiles).

¶ Additional adjustment for fats, including saturated fat, *trans*-fat, polyunsaturated fat, and monounsaturated fat.

\# Cases of gallstone disease per frequency of peanut butter consumption: <1/month: 766 cases; 1–3/month: 501 cases; 1/week: 198 cases; 2–4/week: 233 cases; ≥5/week: 135 cases.

** The highest two categories were combined because of the small number of cases.

†† Cases of gallstone disease per frequency of consumption of other nuts: <1/month: 1,067 cases; 1–3/month: 585 cases; 1/week: 92 cases; ≥2/week: 89 cases.

studied is relatively homogeneous with respect to education and occupation, confounding by socioeconomic status was minimized. Furthermore, the inverse association was consistently present in all subgroups of potential confounding variables, which suggested an apparent independent protective effect.

Nut consumption has been associated with a significantly lower risk of coronary heart disease, by approximately 30–50 percent, in several prospective large cohort studies (18, 29). However, the relation between nut intake and gallstone disease was undetermined despite the biologic plausibility that nut consumption can reduce the risk. Because up to 80 percent of energy in nuts comes from fat, the beneficial effects on blood lipids ascribed to nuts may be due to their high content of unsaturated fatty acids and a low content of saturated and *trans*-fatty acids (30–35). These health-promoting lipid profiles may be protective against cholesterol gallstone formation, because monounsaturated and polyunsaturated fats may act as inhibitors of cholesterol cholelithiasis (19, 20, 36). In hamsters, supplementation of the diet with oleic or linoleic acid resulted in the incorporation of these fatty acids into biliary phosphatidylcholines in the bile (20), which resulted in more stabilized cholesterol-phospholipid vesicles. Thus, by modifying the molecular species of phosphatidylcholine, the addition of unsaturated fatty acids to the diet in hamsters decreased bile lithogenicity and prevented cholesterol gallstone formation. Peanut butter had a weaker inverse association and no evidence of a dose-response relation, which could be due to the addition of hydrogenated fat to major American brands of peanut butter (22).

Because of their high fat content and relatively high energy density, concern may arise that higher nut consumption can result in weight gain and, hence, increased risk for gallstones. However, in our cohort, men who consumed more nuts did not tend to weigh more. In the Nurses' Health

Study and the Adventist Health Study (37, 38), participants with frequent nut consumption also did not tend to be heavier. This indicates that the energy contained in nuts tends to be balanced by decreased intake of other sources of energy or by more physical exercise.

As a complex plant food, nuts are a rich source of many nutrients and other bioactive compounds (39). The reduction in the risk of gallstone disease is probably not explained solely by the fatty acid profile of nuts, as an inverse association persisted after controlling for intakes of specific fatty acids. Other bioactive components may be present in nuts that further reduce the risk of gallstone disease; one candidate could be dietary fiber. Nuts are a rich source of dietary fiber: 1 ounce of peanuts or mixed nuts provides 2.4–2.6 g of dietary fiber. Studies have shown that dietary fiber may be protective against cholesterol gallstone formation by decreasing recirculation of secondary bile acids in the intestine as well as by improving insulin sensitivity (40–42). In addition, nuts are a rich source of magnesium and vitamin E. Dietary magnesium has been suggested to play a role in improving insulin sensitivity and, hence, may decrease the occurrence of gallstones (43, 44). Dietary vitamin E, as an antioxidant and by preventing mucin hypersecretion, may also play a role in reducing risk of gallstone formation (45).

The possibility of misclassification was of concern because information on nut consumption was collected by self-report. However, nut consumption was reported on dietary questionnaires with reasonable accuracy (23). Moreover, we assessed nut consumption repeatedly during the successive follow-up periods, and the updated analyses took into consideration any potential dietary changes. Because the data regarding nut consumption were collected before the onset of symptoms of gallstone disease, any misclassification would be nondifferential between cases and noncases and would most likely weaken any true relation toward the null.

We could not exclude the possibility that participants with latent gallstone disease might have decreased nut consumption in the presence of abdominal symptoms and, consequently, have consulted physicians more frequently, thus increasing the detection rate of gallstone disease. However, the magnitude of this bias would have to be quite substantial to account entirely for the observed inverse relation. Moreover, the inverse association persisted after the first 2 years and 4 years of follow-up were excluded. Additionally, we excluded men with unremoved gallstones who might be presumably less symptomatic and more prone to detection bias. The inverse associations still persisted after the exclusions.

In conclusion, our findings suggest that frequent nut consumption is associated with a reduced risk of gallstone disease in men. Further research is needed to determine whether this association is causal and, if so, how nuts confer this benefit and to assess the potential preventive effects of nuts and their bioactive components on gallstone disease.

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