A Prospective Study of Coffee Consumption and the Risk of Symptomatic Gallstone Disease in Men

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Gallstone disease affects more than 20 million Americans and causes 800,000 hospitalizations each year,1 with a direct cost of more than $2 billion.2 Coffee is one of the most widely consumed beverages in the country,3 and coffee and individual coffee constituents affect various metabolic processes that are involved in cholesterol lithogenesis. Coffee stimulates cholecystokinin release,4 increases gallbladder motility,5 and possibly enhances large bowel motility.6 Caffeine inhibits biliary cholesterol crystallization,7 decreases gallbladder fluid absorption,8 and increases hepatic bile flow.9 Cafestol, a lipid component contained in coffee beans, may affect bile cholesterol concentration.10 Thus, metabolic studies addressing the effects of coffee suggest a possible preventive role of coffee consumption on risk for gallstone formation.4-9

Given widespread consumption of coffee and the high prevalence of gallstone disease, any association between these would have considerable clinical and public health relevance. However, epidemiological evidence regarding the relationship between coffee consumption and gallstone disease is sparse, with most studies compatible with a decreased risk of gallstone disease among persons with high coffee intakes,11-15 but some suggesting an increased risk.16-18 The lack of a statistically significant association observed in all but 1 prospective study11 may be due to imprecise assessments of coffee intake, limited control for potential confounders, or small sample sizes.

Context Coffee has several metabolic effects that could reduce the risk of gallstone formation.

Objective To examine the association between coffee consumption and the risk of symptomatic gallstone disease in men.

Design and Setting The Health Professionals Follow-up Study, a prospective cohort study, in which the consumption of coffee and other caffeinated drinks was assessed starting in 1986 as part of the 131-item food frequency questionnaire given to US male health professionals with follow-up through 1996.

Participants A total of 46,008 men, aged 40 to 75 years in 1986, without history of gallstone disease.

Main Outcome Measures Newly symptomatic gallstone disease (diagnosed by ultrasonography or x-ray) or a cholecystectomy.

Results During 404,166 person-years of follow-up, 1081 subjects reported symptomatic gallstone disease, of whom 885 required cholecystectomy. After adjusting for other known or suspected risk factors, compared with men who did not consume regular coffee in 1986 and 1990, the adjusted relative risk (RR) for those who consistently drank 2 to 3 cups of regular coffee per day was 0.60 (95% confidence interval [CI], 0.42-0.86) and for those who drank 4 or more cups per day the RR was 0.55 (95% CI, 0.33-0.92). All coffee brewing methods showed a decreased risk. The risk of symptomatic gallstone disease also declined with increasing caffeine intake (P for trend = .005).

After controlling for known or suspected risk factors, the RR for men in the highest category of caffeine intake (>800 mg/d) compared with men in the lowest category (<25 mg/d) was 0.55 (95% CI, 0.35-0.87). In contrast, decaffeinated coffee was not associated with a decreased risk.

Conclusions In this cohort of US men, coffee consumption may have helped to prevent symptomatic gallstone disease.

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Although gallstone occurrence and mild symptoms related to gallstones are less frequent in men than in women, severe biliary events leading to surgery are equally common among both sexes after gallstones have developed. To address further the association between coffee and caffeine consumption and symptomatic gallstone disease, we examined intake of coffee, tea, decaffeinated coffee, decaffeinated soft drinks, and caffeine from all sources as well as coffee brewing methods in relation to risk of symptomatic gallstone disease in a large cohort of US men.

METHODS

Population for Analysis

The Health Professionals Follow-up Study began in 1986 when 51,529 US male dentists, veterinarians, optometrists, osteopathic physicians, and podiatrists who were 40 to 75 years of age returned a mailed questionnaire regarding diet and medical history. Follow-up questionnaires were sent biennially to update information on exposures and newly diagnosed illnesses. Diet was assessed in 1986, 1990, and 1994. For this analysis, we excluded men who reported a cholecystectomy or gallstone diagnosis at baseline, men with cancer (other than nonmelanoma skin cancer) prior to 1986, men with an energy intake outside the range of 3347 to 17,572 kJ/d (800-4200 kcal/d), men with 70 or more blank food items, and men providing no information on beverage consumption. After exclusions, the study population consisted of 46,068 eligible men who were followed up from 1986 to 1996. The overall follow-up response was 94%.

Assessment of Diet

The consumption of regular coffee, decaffeinated coffee, tea, and decaffeinated soft drinks was assessed in 1986 as part of a 131-item semiquantitative food frequency questionnaire. For each beverage, a commonly used portion size was specified, and the participants were asked how often, on average over the past year, they consumed that amount.

There were 9 possible response categories ranging from “never” or “less than once per month” to “6 times or more per day.” Standard portion sizes were specified as 1 cup for coffee or tea, and 1 glass, bottle, or 354 mL (12 oz) can for decaffeinated soft drinks. Caffeine intake was calculated by multiplying the frequency of consumption of each beverage by the caffeine content of the specified portion size. Total caffeine intake for each participant was computed as the sum of the contributions from regular coffee (79% of the total for all participants), tea (12%), decaffeinated soft drinks (7%), and decaffeinated coffee, cocoa, chocolate, cookies, brownies, and candies (2%). To distinguish between methods of preparing coffee, on the 1990 questionnaire participants were asked to report whether they consumed mainly filtered, instant, or espresso type coffee.

To assess the validity of self-reported coffee consumption, estimated intakes from the food frequency questionnaire were compared with those from two 7-day dietary records in a sample of 127 Boston, Mass, area participants who had returned the 1986 baseline questionnaire and a second questionnaire in 1987. The Spearman correlation coefficient between coffee use as assessed by the questionnaires compared with the diet records was 0.82. (The Spearman correlation coefficient is a nonparametric measure of the strength and the direction of the relationship ranging from −1.0, perfect inverse correlation; 0, no correlation; +1.0, perfect positive correlation).

Assessment of Gallstone Cases

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. Subjects were also asked whether the gallstone diagnosis had been confirmed by ultrasonography or x-ray and whether their gallstones were symptomatic. To verify the self-reports of cholecystectomy and diagnosed but unremoved gallstones, we reviewed a sample of 441 medical records of subjects who reported a cholecystectomy or gallstones and of these, all but 5 confirmed the diagnosis. Furthermore, all self-reported symptoms and all but 1 of the self-reported diagnostic procedures were confirmed by medical record review. Although we did not assess the composition of the gallstones, in a similar cohort of men, nearly 80% were cholesterol or mixed stones.

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. Relative risks (RRs) were calculated as the incidence rate of symptomatic gallstone disease among men in different categories of exposure compared with the incidence rate among men in a specified reference group. Age-adjusted RRs were calculated using the Mantel-Haenszel rate ratio, and tests for trend were computed using the Breslow and Day χ statistic. For multivariate analyses, pooled logistic regression with 2-year time increments was used to estimate the RRs of symptomatic gallstone disease. This method accounts for varying time to the outcome event and is asymptotically equivalent to Cox regression if the time intervals are short and the probability of an event is small for each interval. The basic model included biennially updated age, body mass index (calculated as weight in kilograms divided by the square of height in meters), recent weight change, history of diabetes mellitus, smoking, physical activity, intake of cholesterol-lowering drugs, thiazide diuretics, and nonsteroidal anti-inflammatory drugs. Intakes of alcohol, energy-adjusted dietary fiber, energy-adjusted carbohydrates, and energy-adjusted dietary fat were also included in the basic model and were updated every 4 years. Tests for linear trend were calculated by assigning the median coffee intake for categories treated as a continuous variable.

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In a subanalysis, we corrected the RR estimate of coffee consumption for measurement error by using data from our validation study. This procedure provides an estimate of the association unattenuated by the effects of measurement error. All RRs are presented with 95% confidence intervals (CIs), and reported P values are based on 2-sided tests.

**RESULTS**

During 404,166 person-years of follow-up, we documented 1081 cases of self-reported symptomatic gallstone disease, of which 885 required cholecystectomy. Sixty-nine percent of the participants reported drinking regular coffee, 52% drank decaffeinated coffee, 56% drank tea, and 64% drank caffeinated soft drinks at least once per month. Compared with nondrinkers, men who drank regular coffee smoked more, consumed more dietary fat and less dietary fiber, and exercised less; but they drank more alcohol and had a lower carbohydrate intake (Table 1).

In multivariate analyses, intake of regular coffee had a strong, inverse association with risk of symptomatic gallstone disease (P value, test for trend, <.001). Compared with men with no consumption of regular coffee, the RR for those who drank 4 or more cups of regular coffee per day was 0.67 (95% CI, 0.53-0.84) (Table 2).

To examine the possibility that latent gallstone symptoms caused a decrease in coffee consumption, thereby biasing our results, we conducted an analysis excluding all cases that occurred during the first 2-year follow-up period. The relationship became slightly stronger (RR for men consuming ≥4 cups of regular coffee per day compared with men with no consumption of regular coffee, 0.64; 95% CI, 0.49-0.84).

To evaluate the potential for bias due to an increased medical surveillance among men with no consumption of regular coffee, we additionally excluded men without a routine medical check-up between 1986 and 1988. The RR for men consuming 4 or more cups of regular coffee per day compared with men with no consumption of regular coffee was 0.59 (95% CI, 0.42-0.82). When we additionally excluded cases that occurred during the first 4 years of follow-up, the RR was 0.75 (95% CI, 0.53-1.06).

We further addressed the possibility of detection bias by excluding cases with unremoved gallstones (who were presumably less symptomatic) and limiting the analysis to cholecystectomy cases. The RR for men consuming 4 or more cups of regular coffee per day compared with men with no consumption of regular coffee was 0.69 (95% CI, 0.53-0.89).

We next cumulatively updated coffee exposure in 1990 and in 1994 to provide a better estimate of the effect of long-term average coffee consumption. Specifically, the incidence of symptomatic gallstone disease from 1986 through 1990 was related to the average intake reported on the 1986 questionnaire; the incidence from 1990 through 1994 was related to average intake reported on the 1986 and 1990 questionnaires, and the incidence from 1994 through 1996 was related to average intake reported on the 1986, 1990, and 1994 questionnaires. The RR among men drinking 4 or more cups of regular coffee per day compared with men with no consumption of regular coffee was 0.60 (95% CI, 0.46-0.79).

The inverse association was stronger among men with evidence of consistent coffee intake over time. Considering cases that occurred after 1990 only, men who consistently reported drinking 2 to 3 cups of regular coffee...
per day in the 1986 and 1990 questionnaires had an RR of 0.60 (95% CI, 0.42-0.86), and those drinking 4 or more cups of regular coffee per day had an RR of 0.55 (95% CI, 0.33-0.92) compared with men who in 1986 and in 1990 consistently reported no consumption of regular coffee (TABLE 3).

To examine the impact of measurement error in our assessment of coffee intake, we used regular coffee as a continuous variable in a multivariate logistic model. An increase in coffee consumption of 1 cup per day was associated with an RR of 0.94 (95% CI, 0.91-0.98). After correction for measurement error, the RR was 0.91 (95% CI, 0.86-0.98).

We also looked for possible differences in the association of coffee brewing method with symptomatic gallstone disease. For this subanalysis, we used 469 cases of gallstone disease occurring between 1990 and 1996 with no missing information on brewing methods. After mutually adjusting for brewing methods and using nondrinkers of regular coffee as the common reference group, the RR of symptomatic gallstone disease for men consuming any level of regular filtered coffee was 0.77 (95% CI, 0.62-0.96), for men consuming regular instant coffee, the RR was 0.74 (95% CI, 0.53-1.04), and for men consuming regular espresso, the RR was 0.68 (95% CI, 0.43-1.08).

We examined the association between caffeine and risk for symptomatic gallstone disease. Higher intakes of caffeine were associated with a decreasing risk of gallstone disease (P value, test for trend, .005). The RR for men in the highest category of caffeine intake (>800 mg/d, equivalent to ≥5-6 cups of coffee per day) compared with men in the lowest category (≤25 mg/d, equivalent to less than one fifth of a cup of coffee per day) was 0.55 (95% CI, 0.35-0.87) (TABLE 4).

No significant associations were observed between the consumption of tea, decaffeinated coffee, or low-calorie types of caffeinated soft drinks and the risk of gallstone disease. A positive association was observed for regular types of caffeinated soft drinks and gallstone disease (based on 22 cases), although the trend was not statistically significant (Table 2).

### Table 2. Relative Risk of Symptomatic Gallstone Disease in Relation to Average Daily Consumption of Coffee, Tea, and Caffeinated Drinks Among US Men: The Health Professionals Follow-up Study, 1986-1996*  

<table>
<thead>
<tr>
<th>Beverage</th>
<th>No. of cases</th>
<th>1 Cup per Day</th>
<th>2-3 Cups per Day</th>
<th>≥4 Cups per Day</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regular coffee</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>385</td>
<td>379</td>
<td>226</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>126,356</td>
<td>114,033</td>
<td>93,132</td>
<td>43,645</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>0.87 (0.75-1.00)</td>
<td>0.81 (0.69-0.96)</td>
<td>0.71 (0.56-0.89)</td>
<td>.002</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>0.87 (0.75-1.00)</td>
<td>0.79 (0.67-0.94)</td>
<td>0.67 (0.53-0.84)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Decaffeinated coffee</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>489</td>
<td>413</td>
<td>134</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>195,890</td>
<td>150,195</td>
<td>44,078</td>
<td>14,003</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>1.04 (0.91-1.18)</td>
<td>1.13 (0.93-1.36)</td>
<td>1.23 (0.90-1.66)</td>
<td>.11</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>1.05 (0.92-1.20)</td>
<td>1.05 (0.86-1.27)</td>
<td>1.08 (0.79-1.47)</td>
<td>.62</td>
</tr>
<tr>
<td><strong>Tea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>456</td>
<td>546</td>
<td>57</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>176,702</td>
<td>195,633</td>
<td>25,942</td>
<td>58,899</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>1.09 (0.97-1.24)</td>
<td>0.87 (0.66-1.15)</td>
<td>1.51 (0.98-2.32)</td>
<td>.77</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>1.13 (0.99-1.29)</td>
<td>0.87 (0.66-1.15)</td>
<td>1.42 (0.92-2.18)</td>
<td>.96</td>
</tr>
<tr>
<td><strong>Caffeinated soft drinks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-calorie types</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>694</td>
<td>344</td>
<td>43</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>258,879</td>
<td>132,301</td>
<td>12,986</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>1.06 (0.93-1.21)</td>
<td>1.59 (1.16-2.17)</td>
<td>...</td>
<td>.004</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>1.01 (0.88-1.15)</td>
<td>1.31 (0.96-1.80)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Regular types</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>651</td>
<td>408</td>
<td>22</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>226,371</td>
<td>171,967</td>
<td>58,28</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>0.95 (0.84-1.07)</td>
<td>1.79 (1.16-2.76)</td>
<td>...</td>
<td>.03</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>0.97 (0.85-1.11)</td>
<td>1.57 (1.01-2.45)</td>
<td>...</td>
<td>.08</td>
</tr>
</tbody>
</table>

*RR denotes relative risk compared with the group with no beverage intake; CI, confidence interval. The multivariate model included the following: age (5-year categories), body mass index (5 categories), weight change during the past 2 years (5 categories), history of diabetes mellitus (yes or no), pack-years of smoking (6 categories), physical activity (quintile groups), intake of cholesterol-lowering drugs (yes or no), thiazide diuretics (yes or no), aspirin and nonsteroidal anti-inflammatory drugs (yes or no), alcohol (5 categories), energy-adjusted dietary fat (quintile groups), energy-adjusted dietary fiber (quintile groups), and energy-adjusted carbohydrates (quintile groups). Ellipses indicate that the top 2 categories of caffeinated soft drink consumption were collapsed into 1 category.

ADDITIONALLY ADJUSTED FOR INTAKE OF REGULAR COFFEE (4 CATEGORIES).
verse association between consumption of regular coffee and risk of symptomatic gallstone disease. All brewing methods showed a decreased risk. No association was observed with intake of decaffeinated coffee or tea. The lack of association we observed with decaffeinated coffee and tea may be due to the low amount of caffeine in these beverages in our study population; men drinking 4 or more cups of decaffeinated coffee per day consumed only 140 mg/d of caffeine from all sources (approximately equivalent to 1 cup of regular coffee), and tea usually contains less than half the caffeine of regular coffee. In spite of the fact that we found a positive association with caffeinated soft drinks, only 1 multivariate RR value was statistically significant, and this finding was based on a small sample of 22 cases. Furthermore, the data did not appear to follow any significant dose-dependent trend.

Epidemiological data concerning the relationship between coffee and gallstone disease are sparse. Our results are consistent with a previous prospective Italian study using ultrasonography to assess cholelithiasis, which reported an odds ratio of 0.62 (95% CI, 0.40-0.98) for any vs no coffee drinking.11 One prospective study,12 1 case-control study,13 and 2 cross-sectional surveys14,15 also found inverse associations with coffee drinking.

In contrast, 1 cross-sectional survey16 and 1 case-control study17 observed positive associations with coffee intake, and 1 prospective study18 reported an inverse relationship with brewed coffee and a positive relationship with instant coffee. Thus, most studies that have examined this relationship support a benefit of coffee consumption in preventing gallstone disease. However, most studies were not statistically significant.12-18 Some did not address the dose-response relationship,11,12 and others could not rule out that coffee consumption may have been altered by the disease.14-16

Because our study restricted the outcome to men with symptomatic gallstone disease, the results may not be generalizable to all gallbladder disease. However, our analysis focuses on the clinically most relevant fraction of the disease.

Because no systematic screening of the study subjects with ultrasonography or other imaging tests for the presence of gallstones was performed, it is likely that there was considerable underascertainment of gallstones in this population, as most gallstones are asymptomatic.31 Thus, some of the gallstone cases were present but undiagnosed at baseline and may have preceded the reporting of coffee consumption. However, because it seems unlikely that the presence of asymptomatic gallstones at baseline is associated with the men's reporting of coffee consumption, this bias could not have been responsible for the decreased risk of symptomatic gallstone disease that we observed among men who consumed coffee in this study.

We considered the possibility of detection bias because coffee may cause pain in gallstone patients.32 Although some men who may have reduced or avoided coffee consumption because they had gastrointestinal symptoms could have consulted a physician more frequently, thus increasing the detection rate of gallstone disease, the magnitude of this bias would have to be substantial to account for the strong observed inverse association. Moreover, the relationship persisted after we excluded the first 2 years of follow-up, men without a routine medical check-up between 1986 and 1988, and men with unremoved gallstones who were presumably less symptomatic and more prone to detection bias.

The possibility of misclassification was of concern because information on

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**Table 3.** Relative Risk of Symptomatic Gallstone Disease in Relation to Consistent Intake of Regular Coffee in 1986 and 1990 Among US Men in the Health Professionals Follow-up Study, 1990-1996*

<table>
<thead>
<tr>
<th>Caffeine Intake, mg/d</th>
<th>None</th>
<th>≤1 Cup per Day</th>
<th>2-3 Cups per Day</th>
<th>≥4 Cups per Day</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>173</td>
<td>106</td>
<td>42</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>59,925</td>
<td>39,039</td>
<td>24,341</td>
<td>11,114</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>0.92 (0.72-1.17)</td>
<td>0.60 (0.43-0.84)</td>
<td>0.58 (0.36-0.84)</td>
<td>.002</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>0.88 (0.67-1.14)</td>
<td>0.60 (0.42-0.86)</td>
<td>0.55 (0.33-0.92)</td>
<td>.002</td>
</tr>
</tbody>
</table>

*RR denotes relative risk compared with the group with no intake of regular coffee; CI, confidence interval. See first footnote to Table 2 for variables included in the model.

**Table 4.** Relative Risk of Symptomatic Gallstone Disease in Relation to Average Daily Intake of Caffeine Among US Men in the Health Professionals Follow-up Study, 1986-1996*

<table>
<thead>
<tr>
<th>Caffeine Intake, mg/d</th>
<th>None</th>
<th>25-100</th>
<th>101-200</th>
<th>201-400</th>
<th>401-800</th>
<th>&gt;800</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>237</td>
<td>226</td>
<td>212</td>
<td>244</td>
<td>141</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>79,998</td>
<td>79,908</td>
<td>80,517</td>
<td>91,113</td>
<td>59,936</td>
<td>12,706</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.0</td>
<td>0.98 (0.82-1.18)</td>
<td>0.90 (0.75-1.09)</td>
<td>0.94 (0.79-1.13)</td>
<td>0.85 (0.69-1.04)</td>
<td>0.60 (0.38-0.94)</td>
<td>.05</td>
</tr>
<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.0</td>
<td>0.97 (0.81-1.17)</td>
<td>0.87 (0.72-1.06)</td>
<td>0.92 (0.76-1.10)</td>
<td>0.80 (0.64-0.99)</td>
<td>0.55 (0.35-0.87)</td>
<td>.005</td>
</tr>
</tbody>
</table>

*RR denotes relative risk compared with the group representing the lowest category of intake; CI, confidence interval. See first footnote to Table 2 for variables included in the model.
COFFEE CONSUMPTION AND GALLSTONE DISEASE

Coffee intake was collected by self-report. However, this cohort provides accurate and reliable information on coffee consumption. Moreover, the correlation coefficient for consumption in 1986 and 1990 was 0.57, indicating that coffee intake tracks over time. Because the data concerning coffee consumption were gathered before the onset of symptoms of gallstone disease, misclassification would be nondifferential between cases and noncases and would tend to weaken any true relationship.

Extensive information on multiple risk factors enabled us to adjust for the effects of known confounding variables. However, we cannot rule out the possibility that the associations we observed were partly attributable to unmeasured dietary, behavioral, or genetic factors.

Several physiological mechanisms support a causal relationship between coffee intake and lower risk of gallstone disease. Coffee stimulates cholecystokinin release, enhances gallbladder contractility, and may increase colonic motility, factors that are related to development of cholesterol gallstone disease.

The inverse association between coffee intake and gallstone disease may be due specifically to the effect of caffeine. In animal models, caffeine prevents cholesterol crystallization, possibly by inhibiting gallbladder fluid absorption, which is increased in the early stages of cholesterol lithogenesis. Caffeine and other methylxanthines are excreted via the bile and may decrease bile cholesterol saturation by increasing bile flow or by stimulating ileal bile acid absorption and hepatic bile acid uptake. In addition, caffeine possesses significant thermogenic properties and could exert a preventive influence on gallstone development by increasing energy expenditure and reducing body fat stores.

In addition to caffeine, 1 or more of the many ingredients in coffee may contribute to the inverse relationship. For example, an insoluble hemicellulose fiber contained in coffee may decrease the colonic absorption of deoxycholic acid. Because coffee is rich in antioxidative compounds such as caffeic acid and other phenolics, the protective effect of coffee on gallstone formation could be mediated by an inhibition of reactive oxygen metabolites, which appear to precede the formation of cholesterol monohydrate crystals. Coffee may act through the effect of magnesium, which is a coffee constituent and was inversely associated with gallstone disease in our data and in a recent survey. Magnesium correlates inversely with γ-glutamyltransferase levels and is essential in maintaining membrane integrity and energy production, suggesting that it may modulate hepatic enzyme activity and gallbladder motility.

A more speculative possibility linking coffee intake with decreased gallstone risk is that certain lipid components contained in coffee modulate hepatic cholesterol metabolism. Unfiltered coffee contains cafestol and kahweol, which raise serum cholesterol levels, possibly by decreasing hepatic low-density lipoprotein receptor activity. The mechanism underlying the downregulation of low-density lipoprotein receptors may involve 7α-hydroxylase and 3-hydroxy-3-methylglutaryl coenzyme A reductase activity. If coffee diterpenes decrease bile cholesterol saturation, one might expect a lower risk of gallstone disease among consumers of unfiltered coffee, such as espresso. Our results show similar associations for filtered and unfiltered coffee.

In summary, these prospective data suggest a decreased risk of symptomatic gallstone disease with higher intake of regular coffee. Our results are most obviously generalizable to US men aged 40 years and older. The magnitude of the association, the evidence of a dose-response effect, the failure to explain this relationship on the basis of other risk factors for gallstone disease, the existence of several plausible metabolic pathways, and the consistency with experimental studies all support the causal nature of this association.

The fact that symptomatic gallstones are associated with considerable morbidity and are currently the most common digestive-related cause of hospitalization in the United States underscores the significant implications of these findings for health-related quality of life and the use of health care resources. Further studies are needed to evaluate the apparent benefits of coffee consumption for preventing gallstone disease and to assess the potential therapeutic effects of coffee and individual coffee components on gallstone disease. Because the overall effect of coffee intake on health may vary considerably according to acute or chronic consumption, level of intake, source and type of coffee, methods of roasting and preparation of the brew, and the development of tolerance, clinical recommendations on coffee consumption should be based on the patients' individual health risks and benefits.

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COFFEE CONSUMPTION AND GALLSTONE DISEASE


