

# A Critical Review of Coffee Consumption and Gallstone Disease



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Coffee drinking is almost universal. Caffeine, a major component of coffee and to some extent tea, is known to have a transient stimulatory effect. While unpleasant side effects such as nervousness, palpitations, sleeplessness, and cardiac arrhythmias are better known, coffee is also gaining a reputation as a functional food. In particular coffee consumption is noted to reduce gallstone disease. In this paper the authors review the data on coffee consumption and the prevalence of gallstone disease.

## Teaching Points:

- Coffee is widely consumed for its property to improve quality of life, physical and mental performance.
- Caffeine, the major component of coffee, is also naturally present in tea as well as chocolate.
- Excessive use of coffee as well as withdrawal from the habit of coffee drinking is known to promote nervousness, irritability, anxiety, and cardiac arrhythmias.
- The less known information is that coffee has many beneficial roles making it a function food.
- A major benefit that is debated in the literature is the role of coffee drinking in preventing gallstone disease. Epidemiological studies meant to identify an association have come out with controversial results.

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## INTRODUCTION

### Physiological Qualities of Coffee

There is historical evidence that human beings have consumed coffee since the Stone Age.[1] Coffee has become an inescapable part of the cultures of both East and West and continues to be consumed in vast quantities for its perceived mood

*(continued on page 38)*

### A SPECIAL ARTICLE

(continued from page 36)

and cognitive-enhancing properties, as well as for its metabolism-promoting effects.[2] Caffeine, the major component of coffee and a few other beverages, is easily absorbed from the stomach and small intestine within 45 minutes of consumption and is distributed well throughout all tissues of the body.[3] Peak concentration in the blood is reached within one hour.

Common natural sources of caffeine are coffee, tea, and to a lesser extent, chocolate. The caffeine content of coffee, as well as tea, varies depending on different brews and method of preparation. Even a standardized commercial coffee product can have as much as half or double its average caffeine content on any given day.[2] The most important source of caffeine is the coffee bean. Many recent studies have found a number of benefits of coffee consumption which may be attributed to either caffeine or other ingredients not yet recognized in coffee. The general belief is that excessive coffee consumption is somewhat detrimental to health because it promotes nervousness, irritability, anxiety, tremulousness, muscle twitching, headaches, sleeplessness and cardiac arrhythmias. Coffee has also been at least tangentially associated with unpleasant GI side effects, such as dyspepsia and heartburn, as well as tremor and headaches during withdrawal.[4] Aggravation of symptoms related to peptic ulcers, irritable bowel syndrome, and other disorders is known to occur.

### Aim of this Paper

An interesting observation is that coffee or caffeine is not always injurious; indeed, it may be health promoting at times. Many studies have wrestled to quantify the effect of coffee drinking, if any, on the progression or symptomatology of gallstones. The aim of this paper is to critically analyze the publications for an association between coffee drinking and gallbladder disease. In this review, a Medline search was performed using the keywords “coffee and gallstones” and “caffeine and gallstones.” The search parameter limits were articles from January 1<sup>st</sup>, 1999 to June 30<sup>th</sup>, 2011, journal articles, English language, and humans only. In all, 16 articles were obtained for the “coffee and gallstones” search and 7 articles were obtained for the “caffeine and gallstones” search. After excluding articles due to irrelevance and overlapping in the two searches, there were a total of 13 unique articles involving coffee/caffeine and its effect on gallstones. The articles are mostly epidemiological in nature and a few are related

to gallstone pathogenesis.

### Epidemiology of Gallstone Disease

It would be proper to compare overall rates of gallbladder disease to coffee consumption in various countries and see if any relationship exists. In addition, if specifically caffeine (and not coffee) has an effect on gallbladder disease, various other sources of caffeine, including tea, sodas, and energy drinks, should be examined in further studies. Thus, variability in samples as well as the plethora of caffeinated products can make definitive conclusions about gallstone disease based upon a single factor, such as a coffee consumption, quite difficult to examine objectively.

Rates of coffee consumption are generally greatest in the Scandinavian countries, with Finland having the highest rate at 12 kg per capita/year, followed closely by Norway, Iceland, Denmark, the Netherlands, and Sweden at 8.2 kg per capita/year.[5] The United States stands at nearly half that rate, at 4.2 kg per capita/year of coffee consumption; yet, the prevalence of gallstone disease in the US is similar to that of Northern Europe at 10-20% of the population.[6]

In the United States gallstone disease is extremely common with approximately 20-25 million adults harboring gallstones.[7] This vast extent of disease puts an enormous strain on our healthcare dollars, with costs of around \$6.5 billion annually.[7] Various factors have been proven to contribute to an increased risk of gallstone formation, such as being female (as related to fertility), obese, older in age, and having a family history of gallbladder disease.[8] Some of these risk factors are simply unavoidable, such as aging and being female, but many others may be modifiable.

In the US, ethnicity highly impacts the likelihood of developing gallstone disease. In general, the highest prevalence of gallstone disease occurs in indigenous Indians in North and South America, with North American Pima Indians leading the pack with a prevalence of “73% of Pima Indians over the age of 30 years.” [9] Native Indians of South America are not far behind with a rate of 49.4% of female Mapuche Indians of Chile. The rate of gallstone disease appears to be proportional to the amount of indigenous blood in the population; thus, Mexican Americans with less native Indian ancestry exhibit decreased rates of gallstone disease.[10] The rates of gallstone disease in Caucasians hover in the 10-20% range, with intermediate rates in Asians (5-20% range) and the lowest rates evident in

Black Africans, with rates of <5%. In fact, the Masi and Bantu tribes of Africa have virtually no prevalence of gallstone disease.[11] Western developed countries tend to have a high proportion of cholesterol gallstones (>80%) with the remainder primarily being black pigment stones.[7]

### Gastrointestinal Effects of Coffee

What must be made clear from the start is that coffee's actions on the GI system cannot solely be attributed to caffeine.[4] As the studies in the articles to be discussed below will suggest, decaffeinated coffee can have similar effects on the GI tract as its caffeinated cousin. The notion of coffee causing peptic ulcer disease has been refuted since the discovery of *H. pylori*. [4, 12] However, some people do experience dyspeptic symptoms after the ingestion of coffee. The data on this association is mixed at best, since decaffeinated coffee also appears to behave like caffeinated coffee. On the other hand, there is stronger evidence that coffee may be related to heartburn or gastroesophageal reflux disease (GERD). This effect does not seem to be caused by the slight acidity of the coffee drink itself (pH in the 5-6 range), but instead possibly via increased gastrin secretion.[13] The caffeine in coffee does not appear to be solely responsible, as increased gastrin secretion was noted for decaffeinated coffee as well. In one study, ingesting a caffeine/tap water mixture (with caffeine levels comparable to those of regular coffee) did not induce more reflux than simply drinking tap water, while both caffeinated and decaffeinated coffee did in fact promote further reflux.[14]

Moving from one end of the GI tract to the other, the effect of coffee drinking on the urge to defecate (quantified by colonic motor activity) was measured by Rao et al. They concluded that caffeinated coffee promotes colonic motility at a level similar to that of a 1000 kcal meal, 23% more than decaffeinated coffee and 60% more than water.[15]

### The Relationship between Diet and Gallstone Disease

The most established risk factor involving diet and gallstone disease is not the type of food ingested but the quantity. Obesity from simply consuming a high calorie diet carries a markedly increased risk of gallstone disease compared to normal weight controls. In fact, women with a BMI  $\geq 40$  kg/m<sup>2</sup> have seven times the risk of gallstone disease when compared to those with a BMI

<25 kg/m<sup>2</sup>; moreover, this high BMI affords them a 2% chance of developing gallstones every year.[7] The risk increases linearly with BMI and is strongest for women and generally attributed to increased hepatic secretion of cholesterol. However, high LDL cholesterol only has a weak relationship to gallstones, while high HDL and low levels of triglycerides are protective against developing gallstone disease.[16] A potential benefit of coffee drinking in reducing gallstone disease may be that coffee reduces the risk of type 2 diabetes.[17]

In terms of more specific types of foods, refined carbohydrates were shown to be a risk factor for gallstone disease, while fiber, nuts, vitamin C, and calcium intake exerted a protective effect.[7] Interestingly, there is no vitamin C in coffee. Eating more saturated and trans-fat was associated with a higher rate of gallstones. Conversely, intake of polyunsaturated (such as fish oil) and monounsaturated fat was linked to a decreased incidence of gallstones.[18] Studies in rabbits showed that simply replacing sucrose with starch decreased the rates of gallbladder disease.[19] This supports the notion that refined sugars have a deleterious effect on the disease, but other studies in humans have yielded mixed results. Vegetarian diets may also be protective, possibly owing to their natural increased intakes of fruits and vegetables or vegetable protein such as soy.[20, 21] Fitting with the "healthy eating" theme, increased fiber intake, with wheat bran being studied in particular, seems to protect against gallstone disease by decreasing the production of the lithogenic deoxycholic acid and increasing the formation of chenodeoxycholic acid, which is used therapeutically (as Chenodiol) to help dissolve gallstones.[22-25] Finally, vitamin C has been shown to decrease the prevalence of gallbladder disease in women but not in men. In a study by Simon and Hudes, serum ascorbic acid levels were measured in both sexes and then compared to the rates of both clinical and asymptomatic gallbladder disease in these individuals. The results showed that each standard deviation increase in ascorbic acid concentration (27  $\mu$ mol/L) decreased the rates of clinical gallbladder disease and asymptomatic gallstones by 13% in women.[26] This may be due to ascorbic acid's role as a cofactor for 7 $\alpha$ -hydroxylase, the rate-limiting step in the breakdown of cholesterol to its component bile acids.[18] However, if this truly is the reason for vitamin C's protective effect, then individuals with adequate serum levels of the vitamin should not see any benefit from increased ingestion.

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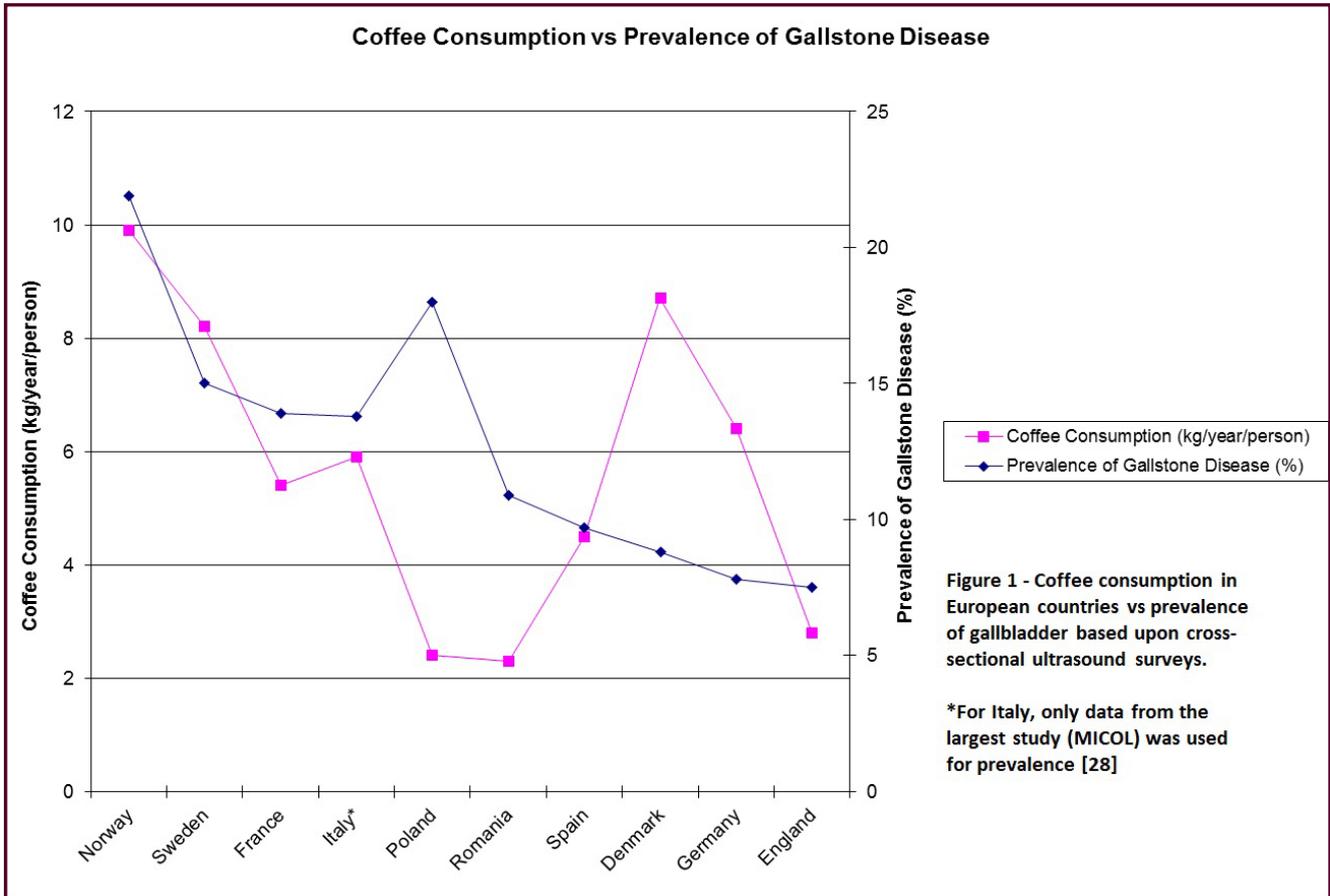
**Coffee Consumption and its Relation to Gallstone Disease**

When comparing the rates of gallstone disease to coffee consumption specifically in Europe, it does appear that Norway (#2 worldwide on the coffee consumption list at 9.9 kg per capita) has a higher rate of gallstone disease prevalence at over 20% of the populace when compared to England for example, with a coffee consumption of only 2.8 kg per capita/year and a gallstone prevalence of under 10%.[27] Thus some correlation may exist between these seemingly unrelated variables (Figure 1).[28] However, the correlation coefficient between these two variables using the data points in Figure 1 was only 0.318, implying a weak association at best. It is not prudent to look at one dietary factor, such as coffee consumption, solely as the etiologic cause or protective factor; however, it is judicious to look at the data in view of the ubiquity of coffee drinking and prevalence of gallstone disease.

**DISCUSSION**

**Pro: Coffee Prevents Gallstone Disease**

The two largest prospective studies (and thus likely reasons for citation by other articles) were conducted by Leitzmann et al. separately in men and women. For the study in men a survey that tracked eating/drinking habits, BMI, exercise, and smoking was sent out to over 46,000 individuals over 1986, 1990, and 1994; it assessed the development of gallstone disease over that period of time. Participants having a cholecystectomy within two years of the study start (1986) as well as those with asymptomatic gallstones were excluded. No ultrasound examinations were performed specifically for this study. The results showed that consistent coffee intake over time, as well as greater coffee intake ( $\geq 4$  cups per day), decreased the chances of developing gallstone disease. Certain brews of coffee (instant and espresso) were found not to be statistically significant



(continued on page 42)

(continued from page 40)

in this regard. In addition, decaffeinated coffee did not reduce the chance of developing gallstone disease; thus, caffeine was thought to be primarily responsible. However, both tea and caffeinated soft drinks did not exhibit any effect on gallstone disease in this study. This was attributed to the fact that soft drinks and tea generally have significantly lower quantities of caffeine than regular coffee.[29]

Leitzmann's study conducted in women followed very similar methods to the study in men and involved over 80,000 female nurses aged 34-59 from 1984-1994.[30] Once again, the results were similar to those of the previous study. Nevertheless, the authors said that these results may not be due entirely to caffeine but could have been influenced by other antioxidants in coffee, such as caffeic acid.[29] Reactive oxygen species (ROS) tend to precede the development of cholesterol monohydrate crystals; thus, the authors hypothesized that antioxidants in coffee may suppress the formation of gallstones. Other studies have supported this notion; indeed, Lichtenberg et al. even argued that "lipid peroxidation may play a significant role in gallbladder stone formation." [31] Moreover, studies on individuals after cholecystectomies due to gallstone disease showed higher levels of oxidized lipids in their gallbladders and lower levels of the antioxidant enzymes superoxide dismutase, glutathione, and catalase.[32]

The confounding factors in this as well as other studies of large groups of individuals were quite pronounced. For example, Leitzmann noted that coffee drinking males tended to be heavier, smoke more, and exercise less.[29] These factors are generally recognized to increase, not decrease, the risk of developing gallstone disease. While it is possible that the caffeine in coffee completely offset these risk factors, it is more likely that other confounding factors were at play in such a diverse subset of individuals. These factors make any study of this kind significantly more difficult to undertake, as multiple known and unknown aspects must be controlled for in order to achieve unbiased data. Moreover, the authors mentioned that their analysis was limited to symptomatic gallbladder disease and thus their study cannot be generalized to all gallbladder disease.[29]

The three other articles mentioning that coffee was protective against the development of gallbladder disease refer to the Leitzmann studies to support their conclusions. All three are informational articles and were not published to discuss original research

studies. Another study mentioned that adding caffeine to the drinking water of dogs prevented the formation of gallstones, likely due to the premise that caffeine stimulated bile flow.[18]

The question of whether or not coffee is a "functional food" is currently debated. Many beneficial physiological effects of coffee such as improved cognition, elevated mood, antioxidant properties of coffee, decreased LDL cholesterol, and lowered risk of type 2 diabetes are reported in support of the opinion that coffee is indeed a functional food.[2] Interesting to note is that the roasting process can significantly affect the antioxidant properties of the resulting coffee beverage. As the coffee bean is roasted for increasing periods of time, phenolic compounds such as caffeic acid and chlorogenic acid are diminished and Maillard reaction products (MRP) are created, which also possess their own antioxidant activity.[33] Intermediate-roasted beans possessed the highest level of antioxidant activity.[34] Also, the article mentioned high variability in the actual dosages of caffeine per cup of coffee. Both of these variables could theoretically affect many of the studies being examined in this paper and may account for a portion of the disagreement in the current literature.

The single article in the literature search that did not offer a stance on coffee's effect on gallbladder disease instead attempted to further explain this very subject. There is evidence that consumption of regular and decaffeinated coffee increases pancreatic secretions in humans.[35] The review article mentioned multiple other studies that suggested both regular and decaffeinated coffee increased CCK release and stimulated gallbladder contractility.[4] One study showed that while regular coffee increased gallbladder contractility, decaffeinated coffee also significantly increased contractility when compared to normal saline controls, albeit not as intensely as the regular coffee.[36] This study went on to recommend that people with symptomatic gallbladder disease be advised not to ingest coffee, implying that in those with gallstones coffee may precipitate symptoms.

### **Con: Coffee Has No Role in Preventing Gallstone Disease**

Two articles in the literature review linked coffee ingestion to an increased risk of gallbladder disease. A study conducted on middle-aged Japanese men found that the risk of previously diagnosed gallbladder disease in Japanese men had increased (OR 2.2, 95% CI 1.3-3.7) for those ingesting over 300 mg caffeine/day vs.

those ingesting <100 mg caffeine/day. Also the OR was 1.7 (95% CI of 1.1-2.8) for coffee consumption of  $\geq 5$  cups coffee/day vs. no coffee/day.[37] The authors of the Japanese study proposed that coffee drinking may lead to increased GI symptoms in people with previously diagnosed gallstone disease, leading them to seek medical attention. This explanation fits well with the recently noted studies on how CCK stimulation by coffee can increase the symptomatology of gallbladder disease.[36] The authors found no relationship between green tea and the development of gallbladder disease and they attributed this to the markedly decreased caffeine content in green tea as compared to coffee.[37]

The “Study of Health in Pomerania (SHIP)” study in northeastern Germany involved 4,202 participants, including both men and women aged 20-79 years. This study quantified coffee intake per day as 0 cups, 1-2 cups, 3-4 cups, and  $\geq 5$  cups and defined cholelithiasis as either current evidence of gallstones or previous history of cholecystectomy.[38] Results actually showed an *increased* risk of cholelithiasis in men only for coffee intake of 1-4 cups/day when compared to no coffee intake. The  $\geq 5$  cups/day group just missed statistical significance in this regard with a *p* value of 0.06. In men with previous cholecystectomy excluded, coffee intake of 3-4 cups/day also significantly increased the risk of gallstone disease, further strengthening the association. The same was not true for women. Furthermore, significant results were shown for the use of tea (no quantity specified in the study) as a risk factor for gallstone disease, once again for men only. Curiously, the results for tea were no longer significant when individuals with a prior cholecystectomy were excluded. The authors proposed that this may be due to either a change in dietary habits after cholecystectomy or a possible effect of tea causing gallstones to become symptomatic earlier than usual (likely due to increased contractility of the gallbladder by caffeine).[38]

### Inconclusive Studies

The majority of the literature published in the last 11 years has instead found that coffee has no statistically significant effect on gallbladder disease. Five out of the thirteen articles reviewed in this paper came to this conclusion. However, in many of these studies, coffee/caffeine and its effect on gallstones were measured on a questionnaire without being broken down in detail. For example, when assessing risk factors for gallstone formation in a high altitude Saudi population, coffee

use was simply asked in “yes” or “no” format, without quantifying the amount of coffee ingested or the frequency of consumption.[8] The same limited detail to coffee intake was evident in an Indian case-control study which compared a control of no milk/tea/coffee intake (odds ratio of 1 for development of gallstone disease) to intake of coffee alone (OR 0.81, 95% CI 0.34-1.96) or a combination of coffee and tea intake (OR 0.69, 95% CI 0.3-1.6). The quantity of beverages at  $>3$  cups/day was also assessed but as a separate variable in the univariate analysis, without regard to whether it was coffee, tea, or milk.[39] As the data clearly indicate, no association was readily apparent.

Another study attempted to analyze why Danish individuals had roughly double the rates of gallstone disease than their nearby northeastern German counterparts. The authors used questionnaires similar to those employed by Leitzmann’s studies to determine the reasons for this vast discrepancy.[40] However, in order to simplify reporting and ensure compatibility between the Danish study (“Monitoring of Trends and Determinants of Cardiovascular Disease,” or DANMONICA) and the German study (SHIP), the final data merely indicated either the presence or lack of coffee intake. Moreover, coffee use was grouped together with alcohol use and cigarette smoking. Consequently, unbiased results were not obtained solely for coffee intake as the independent variable. The study participants noted the lack of detail in the questionnaire as one of the limitations of the study. The Danish/German comparison study concluded that controlling for coffee intake (together with alcohol intake and smoking) did not significantly affect the roughly double rate of gallstone disease in northeastern Germany compared to Denmark.[40] Interestingly, the final results of this study found that the difference in gallstone disease rates between the two countries was partially attributable to the higher BMI, more unfavorable lipid levels, higher prevalence of diabetes, and more frequent usage of oral contraceptives in the Germans.[40]

Now the discussion will turn to two studies which quantify caffeine intake (either in cups per day or times per week). One study which showed no effect of coffee on gallstone disease gave a questionnaire to over 2,400 individuals from Leutkirch, Germany and assessed for current or prior gallstone disease via ultrasound examination.[41] A previous cholecystectomy or current evidence of gallstones was indicative of gallbladder disease. This study was retrospective and grouped

coffee and tea consumption together and soft drinks separately. The authors did not find a significant difference of gallstone disease between those who drank coffee/tea “seldom or never” and those who drank coffee/tea “daily or several times per day.” In addition, no difference was found when comparing 1-3 cups of coffee/tea per day to >3 cups of coffee/tea per day. Furthermore, when consumption of just coffee was compared, no relationship was found to gallstone disease ( $p=0.21$ ).[41]

The results were not as clear in the second study to quantify caffeine intake. In a large questionnaire-based study conducted by Ruhl and Everhart, nearly 14,000 adult men and women were grouped into “previously diagnosed gallstone disease” and “new gallstone disease” based upon the first-time detection of gallstones via ultrasound examination.[42] The authors found that while there was no relation of total gallbladder disease and coffee, there was a slight protective effect when the analysis was restricted to previously diagnosed gallbladder disease ( $p=0.027$ ).[42] The authors came to this conclusion by examining coffee intake comparing no consumption to <1 cup per day, 1-2 cups per day, and >2 cups per day. This study was chosen to be grouped into the “neutral” category for coffee/caffeine and effects on gallbladder disease because the majority of its data overwhelmingly favors no association. Even in the statistically significant portion of the data for women with previously diagnosed gallbladder disease, the individual prevalence ratios for coffee intake at each level of consumption (<1 cup, 1-2 cups, >2 cups) were not statistically significant; in fact, simply the  $p$ -value for “trend” was significant. Even so, this study cannot be discounted due to the clear quantification of coffee intake and superb power, as evidenced by the large sample size. Moreover, this study chose to separate previous gallbladder disease from new disease, a feat which the highest power Leitzmann study did not undertake.[29] The reasons for this significant association may be multifactorial and the authors noted much uncertainty regarding the mechanisms behind their results.[42]

### SUMMARY AND CONCLUSIONS

In conclusion, it is clearly evident that there is no unanimity of opinion with regard to the protective effect of coffee or caffeine on gallstone disease. Multiple variables must be controlled for, including quite

challenging ones such as the exact caffeine content in a brew and even the type of brew most routinely consumed. As discussed, the roasting process of the bean may also play a significant part in the antioxidant quality of the beverage and, by extension, on any possible effect on gallstone formation.[33] In addition, caffeine drinkers may possess other confounding variables which may make them either more or less prone to develop gallstones over time when compared to non-caffeine drinkers, such as differing BMIs, exercise routines, incidence of cigarette smoking, and intake of saturated fats. It may not realistically be possible to control for all these variables because, based on the current data, all important causes of gallstones have yet to be clarified. Thus there will almost certainly be ‘contaminated data’ of some sort which may create the illusion of a relationship (either positive or negative) when such an association may instead be due to a confounding factor. More research must be done in this arena in order to further elucidate risk factors while accounting and controlling for as much confounding data as possible.

After exploring the complete set of data in this review and giving adequate credence to the quality, time, and number of participants in individual studies, it is the opinion of the authors that there is a preponderance of evidence in favor of coffee/caffeine possibly being protective in gallbladder disease, though this is by no means conclusive. The prudent advice at this time is to drink coffee in moderation if it does not produce adverse symptoms. We are not yet ready to advise the population to increase the intake of coffee to prevent gallstone disease. ■

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