ASSOCIATION BETWEEN CAFFEINE INTAKE AND GALLSTONE FORMATION: A GENDER-SPECIFIC ANALYSIS

STAT 51200: APPLIED REGRESSION ANALYSIS

Mahesh Moodukonaje
mamoodu@iu.edu

Nakul Gupta
guptanak@iu.edu

Tejas Jadhav
tjadhav@iu.edu

ABSTRACT

The occurrence of gallstones with cholesterol has increased due to the widespread adoption of a western diet. Coffee has been associated with several health benefits, including a possible reduction in gallstone formation, particularly in men. However, research findings on this association have been inconsistent, highlighting the need for further investigation. This study aims to examine the connection between caffeine consumption and the risk of developing gallstones or undergoing gallbladder removal (cholecystectomy). It also seeks to determine whether this relationship varies according to gender. To achieve this, we will analyze data from the NHANES 2017–2018 survey, categorizing participants by their daily caffeine intake levels and using logistic regression to assess the relationship while adjusting for factors such as age, sex, BMI, and diet.

1. Introduction

The increase in gallstones and gallbladder disease, driven in part by the adoption of a western diet. In the U.S. alone, approximately 20 million people are affected, leading to a significant burden on healthcare systems (1). Gallstone formation involves a complex process, including cholesterol buildup, lipid abnormalities, and inflammation. These issues are commonly seen in individuals with conditions such as diabetes and high cholesterol (2).

The prevalence of gallstones and gallbladder disease is increasing rapidly, driven in part by the adoption of a western diet. In the U.S. alone, approximately 20 million people are affected, leading to a significant burden on healthcare systems (1). Gallstone formation involves a complex process, including cholesterol buildup, lipid abnormalities, and inflammation. These issues are commonly seen in individuals with conditions such as diabetes and high cholesterol (2).

Diet and demographics also play a significant role in gallstone risk. Low-fat, high-fiber diets and adequate hydration can lower cholesterol levels in bile by promoting excretion and reducing absorption. Vitamin C may also help protect against gallstones. Demographically, gallstones are more common among middle-aged Caucasians, Hispanics, and Native Americans and individuals with lower education levels. Women are 2–3 times more likely to develop gallstones than men, mainly due to the effects of female hormones (8). Interestingly, one study suggested that the protective effect of coffee on gallstones may depend on estrogen levels (9).

Despite these findings, it remains unclear whether the relationship between caffeine intake and gallstones varies by sex. This study aims to investigate how different levels of caffeine intake are associated with gallstones and cholecystectomy, identify other dietary and demographic risk factors, and explore the role of sex in modifying this relationship.

2. Dataset

The National Health and Nutrition Examination Survey is a large-scale study conducted every two years by the Centers for Disease Control and Prevention. Collect information on the health and nutrition of adults and children in the United States. The primary goal of NHANES is to assess the nutritional and health status of the population and to inform public health policies (1 0). The survey uses a nationally representative sample and gathers data through interviews, physical exams, and laboratory tests conducted by trained professionals. Information such as demographic details, socioeconomic factors, dietary habits, and health-related measurements, including height, weight, blood pressure, and biomarkers, is collected. For this study, data on caffeine intake, gallstones, cholecystectomy, and other relevant factors like demographics, lifestyle, and diet were analyzed.

2.1. Data Subjects

The study focused on participants from the NHANES 2017–2018 survey cycle. A total of 9,254 individuals completed interviews, and 8,705 underwent physical examinations. Participants were excluded if they were under 20 years of age, pregnant, or diabetic at the time of screening. Additionally, individuals missing key data on gallstones, cholecystectomy, caffeine intake, or other covariates—such as sex, age, race/ethnicity, education, weight, BMI, physical activity, smoking and drinking habits, and dietary intake of fiber, fat, cholesterol, vitamin C, and water—were also excluded. After these exclusions, 3,793 participants remained for analysis, representing a 56% reduction in the initial sample size.

3. Study Design and Measurements

The main objective of this study was to assess the relationship between caffeine intake and the occurrence of gallstones and cholecystectomy, both of which were self-reported by participants. The outcome was defined as having ever experienced gallstones and/or cholecystectomy, coded as “yes” or “no.” Participants reporting both conditions were counted only once.

Daily caffeine intake was estimated using a 24-hour dietary recall. Based on their average caffeine consumption, participants were grouped into four categories: low ($\leq$ 50 mg), normal (51-200 mg), high (201-400 mg), and very high ($>$ 401 mg). These cutoff values were chosen based on prior research on caffeine and gallstones (5, 3) and the caffeine content of common beverages. The "normal" intake group served as the reference group because it represented the largest portion of the study population, providing a reliable basis for comparisons.

Demographic, lifestyle, and dietary variables were also included in the analysis to assess their potential influence on gallstones and cholecystectomy. Age, sex, race/ethnicity, education level, weight, BMI, physical activity, smoking and drinking habits, and dietary factors such as fiber, fat, cholesterol, vitamin C, and water intake were considered.

- Race/Ethnicity and Education:These were categorized into five groups as defined by the NHANES questionnaire.
- Physical Activity: This was dichotomized into whether participants met the American Heart Association’s recommended 150 minutes per week of moderate activity or 75 minutes per week of vigorous activity (22).
- Drinking Habits: Participants were grouped based on weekly alcohol consumption: less than 1 drink, 1–2 drinks, and more than 2 drinks.
- Smoking Status: Participants were classified as current smokers if they regularly used cigarettes or cigars; all others were considered non-smokers.

- Dietary Factors: Fiber and fat intake were assessed using a 24-hour dietary recall, similar to caffeine intake.

These variables were included as covariates to control for their potential confounding effects on the association between caffeine intake and gallstones.

4. Statistical Analyses

To account for the complex survey design of the dataset, statistical weights were applied to ensure the sample data accurately represented the U.S. population. Descriptive statistics summarized participants' characteristics, grouped by the presence or absence of gallstone disease. Continuous variables were presented as weighted means with standard errors (SE), while categorical variables were presented as counts with weighted percentages. Group comparisons were conducted using weighted two-sample t-tests for continuous variables and Pearson's chi-squared tests for categorical variables.

Residual diagnostics confirmed no violations of model assumptions. Linearity checks, using quadratic terms and logits plots, indicated a good fit for all continuous predictors. Sensitivity analysis, performed after removing seven influential points identified through leverage and Pregibon's dbeta plots (with dbeta values greater than 20), showed no significant changes in the model's findings.

The model development process began with an unadjusted logistic regression model, which included caffeine intake as the sole predictor. Demographic and dietary covariates, identified from prior literature, were then added to create an adjusted model. Interaction terms were tested to assess potential effect modification. Model fit was evaluated using metrics such as Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and pseudo-R^2. Diagnostic checks for collinearity (using variance inflation factor, VIF) and outliers (using leverage plots) ensured robustness.

Weighted multiple logistic regression was used to analyze the relationship between caffeine intake levels and the likelihood of gallstones. The Rao-Scott test, based on the estimated log-likelihood ratio, evaluated the predictability of categorical variables and compared model fits across different covariates. Three models were developed:

1. An unadjusted model with caffeine intake as the sole predictor.
2. An adjusted model including covariates such as age, sex, race/ethnicity, BMI, and dietary fat and fiber intake.
3. An adjusted model with an interaction term for caffeine intake and sex.

Collinearity among variables was minimal, with all VIF values below the threshold of 6. Linearity between continuous predictors and the logit of the outcome was confirmed through log-likelihood tests and logits plots. All statistical analyses were conducted with a significance level of $p < 0.05$.

The final adjusted model included caffeine intake categories, sex, race/ethnicity, age, BMI, fiber, and fat intake as predictors. This model explained 19% of the variability in gallstone risk (pseudo-R^2 = 0.19). Notably, an interaction between caffeine intake and sex was observed (p = 0.014), indicating that the effect of caffeine intake on gallstones differs by sex. In men, higher caffeine intake was associated with a lower risk of gallstones (OR = 0.86; 95% CI: 0.28, 2.64), while no clear trend was observed in women.

5. Results

Table 1 summarizes the characteristics of the participants. The study included 1,789 males (47.2%) and 2,004 females (52.8%), with an average age of 46.27 years (SE = 0.57). Among all participants, 468 individuals

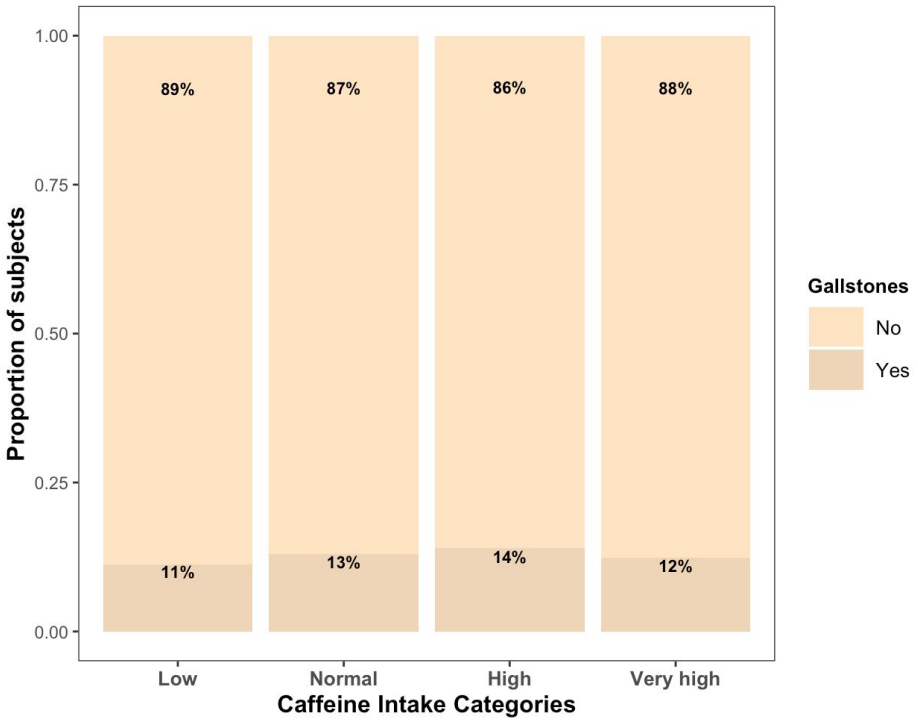

Figure 1: Proportion of participants with gallstones among the four caffeine intake categories.

(12.7%) reported having gallstones. The proportion of participants with gallstones across different caffeine intake levels is shown in Figure 1.

No significant difference was observed in caffeine intake between participants with and without gallstones (mean = 174.38 mg vs. 168.70 mg; p = 0.633, Table 1). However, significant differences were found in sex, age, and BMI between the two groups ($p < 0.001$). Participants with gallstones were more likely to be female (73.9% vs. 49.9%), older (mean age 54.42 vs. 45.08 years), and had a higher BMI (32.38 vs. 28.81 kg/m²).

Additionally, participants with gallstones consumed significantly less fat and fiber compared to those without ($p < 0.001$). These findings highlight key differences in demographics and dietary patterns between individuals with and without gallstones.

5.1. Association between gallstones and levels of caffeine

No significant association was found between caffeine intake and the presence of gallstones. Compared to the normal caffeine intake group, the odds of having gallstones were lower for both the low and very high caffeine intake groups, though these results were not statistically significant (low: OR = 0.85; 95% CI: 0.54, 1.39; p = 0.477; very high: OR = 0.94; 95% CI: 0.49, 1.81; p = 0.843, Table 2).

In the adjusted model, the odds ratios for the low, high, and very high caffeine intake groups were 1.03 (95% CI: 0.47, 2,27; p = 0.907), 1.00 (95% CI: 0.49, 2.05; p = 0.999), and 0.85 (95% CI: 0.29, 2.50; p = 0.670), respectively. Figure 2 depicts the relationship between each predictor and gallstones.

Among the predictors, female sex had the strongest positive association with gallstones (OR = 2.53; 95% CI: 1.61, 3.99; p = 0.007), while being Black was inversely related to gallstones (OR = 0.45; 95% CI: 0.19, 1.07; p = 0.06). These results indicate that sex and race are significant factors influencing gallstone risk, whereas caffeine intake shows no clear relationship.

Characteristics	Total (n = 3793)	Ever had gallstones / cholecystectomy (n = 468)	Never had gallstones / cholecystectomy (n = 3325)	P-value
Age (y)	46.27 ± 0.57	54.42 ± 0.77	45.08 ± 0.58	**<0.001**
Sex				**<0.001**
Male	1789 (47.2%)	122 (26.1%)	1667 (50.1%)	
Female	2004 (52.8%)	346 (73.9%)	1658 (49.9%)	
Weights (pounds)	83.02 ± 0.81	88.66 ± 2.25	82.20 ± 0.80	**0.014**
BMI (kg/m^2)	29.26 ± 0.24	32.38 ± 0.62	28.81 ± 0.24	**<0.001**
Race/ethnicity				**0.021**
White	1374 (36.2%)	220 (47.0%)	1154 (34.7%)	
Black	889 (23.4%)	80 (17.1%)	809 (24.3%)	
Hispanic	844 (22.3%)	103 (22.0%)	741 (22.3%)	
Asian	498 (13.1%)	32 (6.8%)	466 (14.0%)	
Other	188 (5.0%)	33 (7.1%)	155 (4.7%)	
Education level				0.282
Under 9th grade	254 (6.7%)	29 (6.2%)	225 (6.8%)	
9-11th grade	405 (10.7%)	47 (10.0%)	358 (10.8%)	
High School	922 (24.3%)	136 (29.1%)	786 (23.6%)	
College	1261 (33.2%)	152 (32.5%)	1109 (33.4%)	
College graduate or above	951 (25.1%)	104 (22.2%)	847 (25.4%)	
Caffeine (mg)	169.42 ± 6.93	174.38 ± 7.84	168.70 ± 7.95	0.633
Caffeine categories				0.641
Low (≤50mg)	1362 (35.8%)	150 (32.1%)	1212 (36.5%)	
Normal (51-200mg)	1459 (38.5%)	193 (41.2%)	1266 (38.1%)	
High (201-400mg)	738 (19.5%)	96 (20.5%)	642 (19.3%)	
Very high (>401mg)	234 (6.2%)	29 (6.2%)	205 (6.1%)	
Fiber (gm)	17.05 ± 0.39	14.71 ± 0.28	17.39 ± 0.43	**<0.001**
Fat (gm)	89.23 ± 0.87	79.26 ± 2.33	90.67 ± 0.94	**<0.001**
Cholesterol (mg)	307.78 ± 5.08	268.48 ± 15.20	313.49 ± 6.01	**0.020**
Vitamin C (mg)	77.19 ± 2.37	72.20 ± 5.87	77.92 ± 2.28	0.314
Water (mL)	1301.60 ± 37.83	1289.18 ± 79.13	1303.40 ± 38.38	0.855
Alcohol				0.348
< 1 drink	3124 (82.4%)	416 (88.9%)	2708 (81.5%)	
1-2 drinks	205 (5.4%)	18 (3.9%)	187 (5.6%)	
> 2 drinks	464 (12.2%)	34 (7.2%)	430 (12.9%)	
Physical activity				0.080
Achieve AHA	1330 (35.1%)	138 (29.5%)	1192 (35.8%)	
Below AHA	2463 (64.9%)	330 (70.5%)	2133 (64.2%)	
Current smoker				0.628
Yes	734 (19.4%)	89 (19.0%)	645 (19.4%)	
No	3059 (80.6%)	379 (81%)	2680 (80.6%)	

Table 1: Characteristics of participants with and without gallstones or cholecystectomy Data are reported as mean ± SD or n (%). All values are weighted except for frequencies. Comparisons are based on weighted t-tests for continuous variables and weighted chi-squared tests for categorical variables.

5.2. Analysis by sex

The interaction between sex and caffeine intake was found to be significant (p = 0.014, Table 2), suggesting that sex modifies the relationship between caffeine intake and gallstones. After including the interaction term, the adjusted odds ratio (OR) for the low caffeine intake group increased to 1.36, though it remained non-significant (95% CI: 0.68, 2.71; p = 0.402). Adding the interaction term also improved the model's overall predictability and fit.

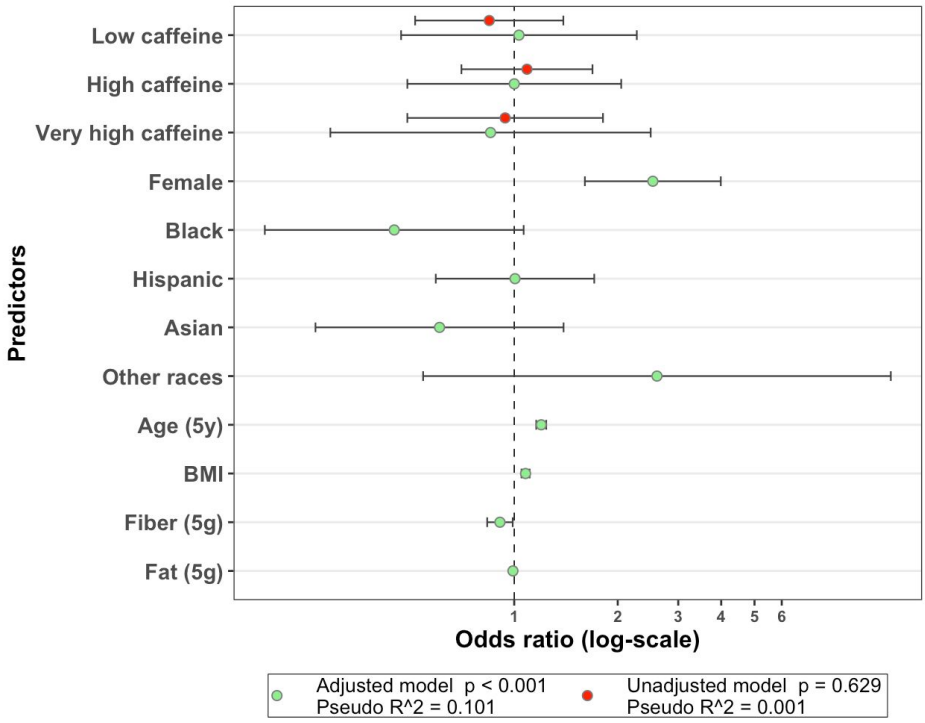

Figure 2: Association Between Gallstones/Cholecystectomy and Caffeine Intake Levels The adjusted model accounts for sex, race/ethnicity, age, BMI, fiber, and fat intake. White males with normal caffeine intake serve as the reference group. Age, fiber, and fat are analyzed in 5-unit increments.

Due to the significant interaction effect, the association between caffeine intake and gallstones was further analyzed separately for men and women. Caffeine intake was not significantly associated with gallstones in either group ($p = 0.758$ for men and $p = 0.972$ for women).

In men, the odds ratios decreased as caffeine intake increased, showing a potential protective trend (OR = 1.39, 1.10, and 0.77 for low, high, and very high caffeine intake, respectively; Table 2, Figure 3). However, in women, the odds ratios remained consistent across all levels of caffeine intake (OR = 0.90, 0.96, and 0.90 for low, high, and very high caffeine intake, respectively). These results suggest that higher caffeine intake may reduce the likelihood of gallstones in men, while no clear trend is observed in women.

6. Discussion

6.1. Caffeine Intake and Gallstones

Study did not find a clear link between caffeine intake and the occurrence of gallstones. However, we observed that the relationship between caffeine intake and gallstones varies by sex, with men showing a slight decrease in gallstone risk as caffeine intake increases.

Caffeine may protect against gallstones by helping the gallbladder contract and lowering cholesterol levels in bile. This effect is thought to be caused by stimulating certain hormones and reducing cholesterol production in the liver (2). Despite these potential benefits, previous research has been inconsistent, likely due to differences in study participants and variations in caffeine consumption (4).

In this study, people with high caffeine intake had 15% lower odds of having gallstones compared to those with normal caffeine intake. Similar findings were reported in a study showing a 23% lower risk of gallstones

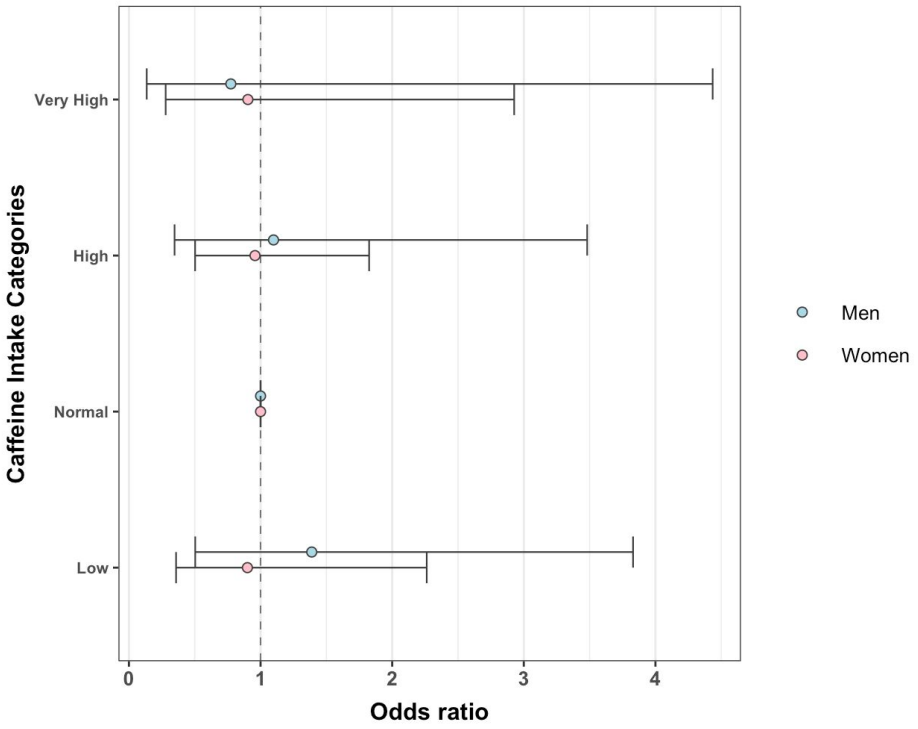

Figure 3: Association Between Gallstones/Cholecystectomy and Caffeine Intake Levels by Sex The model is adjusted for age, race/ethnicity, BMI, and fat and fiber intake.

	Unadjusted Model		Adjusted Model		Adjusted Model with Interaction	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Intercept	0.15 (0.09, 0.24)	**<0.001**	0.002 (0.001, 0.006)	**<0.001**	0.002 (0.001, 0.006)	**<0.001**
Caffeine categories	-	0.650	-	0.946	-	0.690
Low (≤50mg)	0.85 (0.52, 1.39)	0.477	1.03 (0.47, 2.27)	0.907	1.36 (0.68, 2.71)	0.402
Normal (51-200mg)	1.00	-	1.00	-	1.00	-
High (201-400mg)	1.09 (0.70, 1.69)	0.679	1.00 (0.49, 2.05)	0.999	1.16 (0.53, 2.54)	0.716
Very high (>401mg)	0.94 (0.49, 1.81)	0.843	0.85 (0.29, 2.50)	0.670	0.86 (0.28, 2.64)	0.797
Age (y)	-	-	1.04 (1.03, 1.05)	**0.002**	1.04 (1.03, 1.04)	**<0.001**
Sex	-	-	-	**0.007**	-	**0.001**
Male	-	-	1.00	-	1.00	-
Female	-	-	2.53 (1.61, 3.99)	**0.007**	2.98 (1.73, 5.14)	**0.001**
BMI (kg/m^2)	-	-	1.08 (1.05, 1.11)	**0.003**	1.08 (1.06, 1.10)	**<0.001**
Race/ethnicity	-	-	-	0.111	-	**0.025**
White	-	-	1.00	-	1.00	-
Black	-	-	0.45 (0.19, 1.07)	0.060	0.45 (0.23, 0.75)	0.008
Hispanic	-	-	1.01 (0.59, 1.71)	0.977	1.01 (0.72, 1.41)	0.965
Asian	-	-	0.61 (0.26, 1.39)	0.151	0.61 (0.37, 1.03)	0.078
Other	-	-	2.60 (0.54, 12.46)	0.147	2.57 (0.97, 6.77)	0.074
Fiber (gm)	-	-	0.98 (0.95, 1.01)	0.117	0.98 (0.96, 1.00)	**0.040**
Fat (gm)	-	-	0.99 (0.99, 1.00)	0.363	0.99 (0.99, 1.00)	0.323
Caffeine categories × Sex	-	-	-	-	-	**0.014**
Low × female	-	-	-	-	0.68 (0.25, 1.82)	0.455
High × female	-	-	-	-	0.82 (0.35, 1.87)	0.640
Very high × female	-	-	-	-	1.01 (0.24, 4.17)	0.992

Table 2: Association between gallstones/cholecystectomy and caffeine intake levels P-values were derived from weighted logistic regression. Overall predictability of categorical variables and interaction terms was assessed using Rao-Scott tests.

in people drinking more than six cups of coffee daily (5). However, some studies, such as a case-control study in Italy, found no connection between coffee consumption and gallstones. These mixed results may reflect differences in how the studies were designed.

6.2. The Role of Sex

Women are known to have a higher risk of developing gallstones due to the effects of estrogen, which increases cholesterol in bile (8). Our study supports this, as women had more than double the odds of developing gallstones compared to men.

Interestingly, in men, we observed that higher caffeine intake was linked to a lower risk of gallstones, with the odds decreasing by 23% in the highest caffeine group. In women, however, caffeine intake did not show a similar trend, and the odds of gallstones remained stable across all caffeine levels. These findings are consistent with previous research showing that coffee consumption may reduce gallstone risk more significantly in men . On the other hand, some studies, like NHANES III, found the opposite trend, with coffee reducing gallstone risk in women but not men (7). These differences highlight the need for more studies to understand how caffeine affects men and women differently.

6.3. Strengths and Limitations

This study has several strengths, including a large sample size that represents the U.S. population, the use of statistical adjustments for other factors, and the examination of how sex influences the relationship between caffeine and gallstones.

However, there are limitations. The dietary data relied on 24-hour recalls, which may not reflect long-term caffeine habits. We also could not separate the effects of different caffeine sources, such as coffee and tea, which might have different impacts (11). Additionally, gallstone data were self-reported, which could lead to errors, and the cross-sectional nature of the study means we cannot prove that caffeine causes changes in gallstone risk.

	Male		**Female**	
	Odds ratio (95 % CI)	p-value	Odds ratio (95 % CI)	p-value
Intercept	0.0008 (0.0007, 0.009)	0.004	0.007 (0.003, 0.025)	0.001
Caffeine categories	-	0.758	-	0.972
Low ($\leq$50mg)	1.39 (0.50,3.83)	0.419	0.90 (0.36, 2.26)	0.767
Normal (51-200mg)	1.00	-	1.00	-
High (201-400mg)	1.10 (0.35,3.48)	0.832	0.96 (0.50,1.82)	0.862
Very high ($\geq$401mg)	0.77 (0.14, 4.43)	0.705	0.90 (0.28,2.93)	0.823

Table 3: Association Between Gallstones/Cholecystectomy and Caffeine Intake Levels, Stratified by Sex. P-values for the Association Between Caffeine Intake and Gallstones/Cholecystectomy P-values were calculated using weighted logistic regression. Both models were adjusted for age, race/ethnicity, BMI, and fat and fiber intake.

7. Conclusion

This study did not find a clear link between caffeine intake and the risk of gallstones or gallbladder removal after considering factors like age, sex, race, BMI, and diet. However, people with the highest caffeine intake had the lowest odds of having gallstones. The results also showed that the effect of caffeine varies by gender, with a significant difference between men and women.

8. Future Work

Future work could explore non-linear relationships using methods like restricted cubic splines or GAMs to capture nuanced effects of caffeine, age, BMI, and dietary factors on gallstone risk. Analyzing caffeine sources (e.g., coffee, tea) could uncover variations due to different bioactive compounds, while examining broader dietary patterns with PCA or cluster analysis could highlight interactions with caffeine intake. Subgroup analyses by age, race, or BMI categories might reveal differential effects, and temporal analysis using NHANES data over multiple years could uncover trends in diet, caffeine intake, and gallstone prevalence.

9. References

1. Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. *Gut Liver*. 2012;6(2):172-187. doi:10.5009/gnl.2012.6.2.172
2. Douglas BR, Jansen JB, Tham RT, Lamers CB. Coffee stimulation of cholecystokinin release and gallbladder contraction in humans. *Am J Clin Nutr*. 1990;52:553-556.
3. Leitzmann MF, Willett WC, Rimm EB, et al. A prospective study of coffee consumption and the risk of symptomatic gallstone disease in men. *JAMA*. 1999;281:2106–12.
4. Zhang YP, Li WQ, Sun YL, Zhu RT, Wang WJ. Systematic review with meta-analysis: coffee consumption and the risk of gallstone disease. *Aliment Pharmacol Ther*. 2015;42(6):637-648. doi:10.1111/apt.13328
5. Nordestgaard AT, Stender S, Nordestgaard BG, Tybjaerg-Hansen A. Coffee intake protects against symptomatic gallstone disease in the general population: a Mendelian randomization study. *J Intern Med*. 2020;287(1):42-53. doi:10.1111/joim.12970
6. Misciagna G, Leoci C, Guerra V, et al. Epidemiology of cholelithiasis in southern Italy. Part II: Risk factors. *Eur J Gastroenterol Hepatol*. 1996;8:585–93.
7. Ruhl CE, Everhart JE. Association of coffee consumption with gallbladder disease. *Am J Epidemiol*. 2000;152(11):1034-1038. doi:10.1093/aje/152.11.1034
8. Novacek G. Gender and gallstone disease. *Wien Med Wochenschr*. 2006;156(19-20):527-533. doi:10.1007/s10354-006-0346-x
9. Nordenvall C, Oskarsson V, Wolk A. Inverse association between coffee consumption and risk of cholecystectomy in women but not in men. *Clin Gastroenterol Hepatol*. 2015;13(6):1096-1102.e1. doi:10.1016/j.cgh.2014.09.029
10. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2017-2018. Retrieved from `https://www.cdc.gov/nchs/nhanes/index.htm`.
11. Makiuchi T, Sobue T, Kitamura T, et al. Association between green tea/coffee consumption and biliary tract cancer: A population-based cohort study in Japan. *Cancer Sci*. 2016;107(1):76-83. doi:10.1111/cas.12843