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Dietary fiber intake and risk of gallstone: a case–control study

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Abstract

Background Gallstone disease (GSD) and its complications are major public health issues globally. Although many community-based studies had addressed the risk factors for GSD, little is known about the associations between dietary factors and risk of disease. The present study aimed to investigate the potential associations between dietary fibers with the risk of gallstone disease.

Methods In this case–control study, 189 GSD patients with less than one month of diagnosis and 342 age-matched controls were enrolled. Dietary intakes were assessed using a 168-item semi-quantitative validated food frequency questionnaire. Crude and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated through cox proportional hazards regression models.

Results Comparing the highest versus the lowest tertile, significant reverse associations were observed between odds of GSD and each category of dietary fiber intake including total (OR_{T3 vs. T1} = 0.44, 95% CI: 0.37–0.7, P for trend = 0.015), soluble (OR_{T3 vs. T1} = 0.51, 95% CI: 0.3–0.8, P for trend = 0.048) and insoluble (OR_{T3 vs. T1} = 0.56, 95% CI: 0.3–0.9, P for trend < 0.001). The relationship between dietary fiber intake and the risk of gallstones was more prominent in overweight and obese subjects than in subjects with a normal body mass index.

Conclusion Comprehensive assessment of the associations of dietary fiber intake with GSD showed that higher intakes of dietary fiber were significantly associated with reduced GSD risk.

Keywords Gallstone, Dietary fiber, Cholelithiasis

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Background

Gallstone disease (GSD) is a major public health concern with a worldwide prevalence of 2–20% [1, 2]. Age and gender are two crucial factors in the prevalence of GSD. Compared to younger age, the prevalence of GSD increases more than 10 times in men and women over 60 and 50 years, respectively [3]. In addition to genetic predisposition, there are several pathogenic factors related to GSD, including increased biliary mucin secretion, hepatic hypersecretion of cholesterol and supersaturated bile, faster cholesterol crystallization and gallbladder stasis [4, 5]. Furthermore, there is an association between GSD and parameters related to metabolic syndrome such as obesity, type 2 diabetes and dyslipidemia [6, 7].

Recently, rising attention has been addressed to detect the association of dietary factors and GSD. It has been reported that high prevalence of gallbladder diseases can be explained by increased intake of sugar and fat and decreased intake of whole grains and high-fiber foods [8]. Moreover, a cohort study of 5000 women participating in National Health and Nutrition Examination Survey indicated that the increased risk of GSD-related hospitalization following dieting could be due to reduced dietary fiber intake [9]. Westernized diets (low-fiber, high-refined carbohydrate, high-fat) have also been shown to be associated with an increased risk of gallstones [4]. Fiber may have protective effects against gallstones by reducing the intestinal transit time and reducing the production of bile acids [10].

Since detecting the protective dietary factors is important in the management of GSD, thus, the purpose of the present study is to explore the association of dietary fiber and gallstone risk.

Methods and materials

This case–control study was conducted in the Research Institute for Gastroenterology and Liver Diseases of Taleghani hospital affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran. Subjects with the age of 18 years and older, eagerness to participate, had approved GSD and a month or less passed from GSD diagnosis were considered to be included in the present study. Pregnant and lactating mothers and subjects with a history of intestinal disorders, autoimmune diseases, cancers, inflammatory and infectious diseases were excluded. Controls were matched to cases regarding the age (± 5 years) and sex. Patients admitted to other departments of the same hospital with no history of GSD and other liver ailments confirmed by ultrasonography, were randomly allocated to control group. It is worth mentioning that hospital controls are preferred over community controls when the cases obtained from the hospitals [11]. Because, the intended exposures such as health problems

and debilitated behaviors of this type of controls are more likely to be similar to hospital cases. In fact, the prevalence of diseases in hospital controls is higher than that of the population-based controls [12]. Considering the exclusion of 5 cases with outrange mean energy intake ($\pm 3SD$) and subjects with uncompleted data, 189 cases and 342 controls ($n = 531$) remained for analyses. The protocol of the present study was approved by Research Institute of Gastroenterology and Liver Diseases Ethics Committee (IR.SBMU.RIGLD.REC.1396.159). All participants signed a written informed consent.

Dietary intake assessment

A valid reproducible semi-quantitative food frequency questionnaire (FFQ) [13] was used in order to determine the food intake of cases and controls before GSD diagnosis and hospital admission respectively, during a previous year. The frequency of food intake for each subject described on daily, weekly, monthly or yearly basis. The collected data were analyzed using Nutritionist IV software. The United States Department of Agriculture (USDA) food composition table (FCT) was used to calculate energy and nutrient contents. In addition to total fiber, the contents of insoluble and soluble fiber were calculated and expressed as gram per day.

Data collection

Information on socio-demographic factors, anthropometric measurements and other variables like physical activity, comorbidities, smoking habit and alcohol consumption in previous year collected by a trained interviewer through face-to-face interview. Participants body weight were measured to the nearest 100 g [14] while standing on digital scales (Soehnle, Berline, Germany). Measurement of height was done by a portable non-stretch meter to the nearest 0.5 cm. Body mass index (BMI) was calculated by division of weight in kilograms to square of height in meter. Data for physical activity was acquired by a valid questionnaire and described as metabolic equivalents hour per day (METs h/d). MET levels included in this questionnaire ranged from light (0.9 METs) to high-intensity activities (> 6 METs) [15, 16].

Statistical analysis

Statistical analysis was performed by SPSS software version 19 (SPSS Inc., Chicago, Illinois). We used the Kolmogorov–Smirnov test and histogram chart to check the normality of variables. In the present study, we described participant's baseline characteristics and dietary intakes as mean \pm SD for quantitative variables and numbers (percentage) for qualitative variables. Independent sample t-test and chi-square were applied for

Table 1 Baseline general characteristics and dietary intakes of study participants

	Total (n = 531)	Case (n = 189)	Control (n = 342)	P value
Men, n (%)	202 (38%)	55 (29%)	147 (43%)	0.002
Age (y)	53 ± 13	55 ± 15	52 ± 12	0.005
Alcohol drinker	13 (2.4%)	6 (3.2%)	7 (2%)	0.559
Smoker, %	78 (15%)	31 (16%)	47 (14%)	0.443
IPAQ level, %				< 0.001
1	400 (75%)	174 (92%)	226 (66%)	
2	115 (22%)	10 (5%)	105 (31%)	
3	16 (3%)	5 (3%)	11 (3%)	
Weight, kg	73 ± 12	72 ± 13	73 ± 11	0.637
Height, cm	164 ± 9	163 ± 8	165 ± 9	0.262
BMI, kg/m ²	26.8 ± 4	26.9 ± 5	26.7 ± 4	0.645
Calorie intake (Kcal/d)	2387 ± 665	2426 ± 724	2365 ± 630	0.320
Carbohydrate %	49 ± 7	49.5 ± 9	49 ± 7	0.883
Protein%	12 ± 2	12 ± 3	13 ± 2	0.287
Fat%	41 ± 10	42 ± 13	40 ± 7	0.040
Total fiber (g/d)	31 ± 14	29 ± 14	32 ± 13	0.007
Total fiber (g/1000 kcal)	13 ± 5	12 ± 5	14 ± 4	0.001
Soluble fiber (g/d)	0.6 ± 0.4	0.6 ± 0.5	0.7 ± 0.4	0.080
Insoluble fiber (g/d)	3.1 ± 2	2.7 ± 1.7	3.3 ± 2.1	< 0.001

Values are means ± SDs for continuous variables and percentages for categorical variables

ANOVA for quantitative variables and χ^2 test for qualitative variables

IPAQ International Physical Activity Questionnaire, BMI Body Mass Index

Table 2 Baseline general characteristics and dietary intakes of study participants by tertile of total dietary fiber intake

Total Dietary Fiber Intake				
	Tertile 1 (n = 172)	Tertile 2 (n = 170)	Tertile 3 (n = 171)	P value
Cases, n (%)	77 (43)	45 (25)	58 (32)	0.002
Men, n (%)	55 (29%)	57 (30%)	78 (41%)	0.017
Age (y)	54 ± 14	53 ± 13	52 ± 12	0.343
Alcohol drinker	4 (36%)	1 (9%)	6 (55%)	0.173
Smoker, %	26 (37)	18 (26)	26 (37)	0.365
IPAQ level, %				0.079
1	142 (37)	123 (32)	120 (31)	
2	27 (24)	42 (37)	44 (39)	
3	3 (20)	5 (33)	7 (47)	
Weight, kg	71 ± 13	73 ± 11	74 ± 12	0.051
Height, cm	163 ± 8	164 ± 8	165 ± 9	0.132
BMI, kg/m ²	26 ± 4	27 ± 4	27 ± 4	0.239
Calorie intake (Kcal/d)	2008 ± 551	2333 ± 473	2732 ± 644	< 0.001
Carbohydrate %	47 ± 8	49 ± 7	52 ± 7	< 0.001
Protein%	12 ± 3	12.5 ± 2	13 ± 2	0.075
Fat%	45 ± 12	42 ± 8	38 ± 7	< 0.001
Total fiber (g/d)	18 ± 4	29 ± 3	47 ± 11	< 0.001
Total fiber (g/1000 kcal)	9 ± 2	13 ± 3	18 ± 4	< 0.001
Soluble fiber (g/d)	0.4 ± 0.3	0.7 ± 0.4	0.7 ± 0.5	< 0.001
Insoluble fiber (g/d)	2 ± 1	3 ± 2	3.6 ± 2	< 0.001

Values are means ± SDs for continuous variables and percentages for categorical variables

ANOVA for quantitative variables and χ^2 test for qualitative variables

IPAQ International Physical Activity Questionnaire, BMI Body Mass Index

determining the differences between cases and controls for variables with normal distribution and categorical variables, respectively. Subjects were classified into tertiles regarding each category of fiber intake including total, insoluble and soluble fiber. *P*-value for the trend of GSD risk across each category of fiber intake was assessed using linear regression test. Occurrence of GSD and some of its risk factors including BMI, age and sex were illustrated across tertiles of each category of dietary fiber intake. The association between dietary fiber intakes with the odds of GSD was calculated using logistic regression. The analysis was adjusted for potential confounders including age and sex, energy intake, BMI, physical activity, smoking, and alcohol consumption. The odds ratio (OR) with 95% confidence interval (CI) of GSD across tertiles of each category of dietary fiber intake were reported in regard to some of the GSD risk factors including BMI, age and sex. *P* values < 0.05 were considered statistically significant.

Results

General characteristics of subjects and their dietary intakes are shown in Table 1. Patients diagnosed with GSD had higher mean age, consumed more fat and more likely to be female (*P* < 0.05) but they had less physical activity, total and insoluble dietary fiber intake (*P* < 0.05) than the control group (Table 1).

The subjects' characteristics and dietary intakes across the tertiles of dietary fiber intake are presented in Table 2. According to Table 2, there were no significant differences in age, alcohol consumption, smoking status, physical activity, weight and BMI between total dietary fiber intake tertiles whereas, significant differences in energy, carbohydrate and fat intakes were found to increase throughout the tertiles.

Multivariable-adjusted ORs and 95% CIs for gallstone across tertiles of each category of fiber intake were illustrated in Table 3. In the crude model, only insoluble fiber intake showed a significant association with the risk of GSD (OR_{T3 vs T1} = 0.54; 95% CI: 0.3–0.9, *P* for trend < 0.001). In the age and sex-adjusted model, subjects in the highest tertile of total (OR = 0.45; 95% CI: 0.3–0.7, *P* for trend = 0.007) and insoluble (OR = 0.53; 95% CI: 0.34–0.84, *P* for trend < 0.001) dietary fiber intake had lower odds of GSD compared to the first tertile as a reference group. Additionally, in the multivariable-adjusted model, after further adjusting for energy intake, BMI, physical activity, smoking and alcohol consumption, significant reverse associations were observed between odds of GSD and each category of dietary fiber intake including total (OR_{T3 vs T1} = 0.44, 95% CI: 0.37–0.7, *P* for trend = 0.015), soluble (OR_{T3 vs T1} = 0.51, 95% CI: 0.3–0.8, *P* for trend = 0.048)

Table 3 Odds and 95% confidence interval for occurrence of the gallstone in each tertile categories of fiber intake

	Tertiles of fiber intake			<i>P</i> trend
	T1 (< 24.5)	T2 (24.5–35)	T3 (35 ≤)	
Total fiber				
No. of cases	77	45	58	
Model 1	ref	0.63 (0.4–1)	0.49 (0.3–0.75)	0.091
Model 2	ref	0.73 (0.47–1.6)	0.45 (0.3–0.7)	0.007
Model 3	ref	0.65 (0.4–1.3)	0.44 (0.37–0.7)	0.015
Soluble fiber	T1 (< 0.37)	T2 (0.37–0.69)	T3 (0.69 ≤)	
No. of cases	98	122	122	
Model 1	ref	0.58 (0.4–0.9)	0.54 (0.2–0.7)	0.081
Model 2	ref	0.55 (0.3–0.9)	0.5 (0.3–0.8)	0.066
Model 3	ref	0.57 (0.3–0.9)	0.51 (0.3–0.8)	0.048
Insoluble fiber	T1 (< 2)	T2 (2–3.6)	T3 (3.6 ≤)	
No. of cases	101	116	125	
Model 1	ref	0.69 (0.4–1)	0.54 (0.3–0.9)	< 0.001
Model 2	ref	0.75 (0.48–1.2)	0.53 (0.34–0.84)	< 0.001
Model 3	ref	0.8 (0.4–1.3)	0.56 (0.3–0.9)	< 0.001

Based on multiple logistic regression model

Model 1: crude

Model 2: adjusted for age and sex

Model 3: additionally adjusted for energy intake, BMI, physical activity, smoking, alcohol

and insoluble (OR_{T3 vs T1} = 0.56, 95% CI: 0.3–0.9, *P* for trend < 0.001).

Multivariate odds ratios of total, soluble and insoluble fiber intake tertiles for risk of gallstone according to risk factor status at baseline are presented in Figs. 1, 2 and 3, respectively. According to Fig. 1, after adjusting for potential confounders, a significant relationship between total fiber intake and the risk of gallstones was found only in patients who were overweight (OR_{T3 vs T1} = 0.24, 95% CI: 0.1–0.6, *P* for trend = 0.002) or obese (OR_{T3 vs T1} = 0.55, 95% CI: 0.2–1.7, *P* for trend = 0.002), while, this relationship was not observed in people with normal BMI. Also, this relationship was significant in men and in people over 50 years old.

As shown in Fig. 2, a significant reverse association was observed between the highest and lowest tertiles of soluble dietary fiber intake and odds of GSD in subjects over 50 years old (OR = 0.36; 95% CI: 0.2–0.7, *P* for

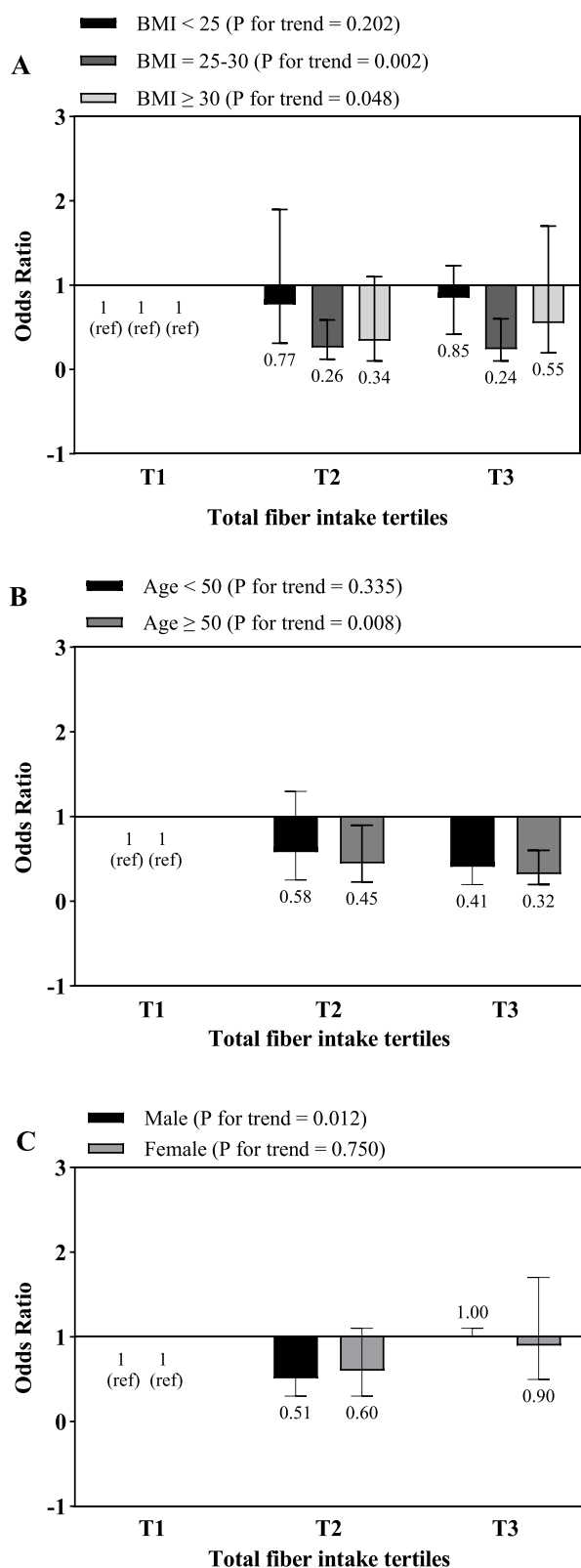


Fig. 1 Multivariate odds ratios of total fiber intake tertiles for risk of gallstone according to risk factor status at baseline (multivariate logistic regression models for estimating ORs and 95% CIs, multivariable models were adjusted for sex, age, energy intake, BMI, physical activity, smoking, alcohol, except for the respective stratifying factor). Data are reported as OR (95% CI). **A**, BMI < 25 vs 25–30 and ≥ 30 ($P=0.119$ for interaction); **B**, age < 50 years vs ≥ 50 years ($P=0.711$ for interaction); **C**, sex male vs female ($P=0.017$ for interaction). Ref indicates reference group

trend = 0.039) and male gender (OR = 0.37; 95% CI: 0.2–0.8, P for trend < 0.001).

Figure 3 indicates that subjects in the highest tertile of insoluble dietary fiber intake with age above 50 (OR = 0.3; 95% CI: 0.2–0.6, P for trend < 0.001) and female gender (OR = 0.11; 95% CI: 0.04–0.3, P for trend < 0.001) had lower odds of GSD compared to the reference group. Also, this association was significant for all BMI categories.

Discussion

To the best of our knowledge, the association of dietary total, soluble and insoluble fiber intake with the risk of gallstone has not been investigated yet. Comparing the highest versus the lowest tertile in the present case–control study showed that dietary total, soluble and insoluble fiber intake were associated with 56%, 49% and 44% lower GSD risk, respectively, after fully adjustment for potential confounders.

These findings are in line with several previous studies. Schwesinger et al. [17] have shown the protective effect of dietary soluble fiber against cholesterol gallstone formation. Two other observational studies have illustrated the inverse relationship between dietary fiber intake and the prevalence of gallstones [18, 19]. Another study investigating the effect of diet as a risk factor for cholesterol gallstone disease implicated that lower and higher intake of dietary fiber and refined sugar, were associated with propensity of gallstone formation, respectively [20]. In addition, consistent with our findings, a large number of epidemiological studies have reported an inverse association between insoluble dietary fiber and GSD [21–24].

In general, by decreasing the intestinal transit time, dietary fibers may reduce the persistence of bacteria located in the colon, which leads to a decrease in the production of secondary bile acids such as deoxycholate, and subsequently, less bile acids are absorbed [10, 25]. Lithogenicity of bile seems to be increased by deoxycholate, whereas chenodexycolate has contrary effect and thus it is used as a therapy to destruct gallstones [26]. Increasing the absorption of deoxycholate can stimulate biliary cholesterol saturation [27, 28]. This claim has been proved in an animal study conducted by Schwesinger et al., [17] who



Fig. 2 Multivariate odds ratios of soluble fiber intake tertiles for risk of gallstone according to risk factor status at baseline (multivariate logistic regression models for estimating ORs and 95% CIs, multivariable models were adjusted for sex, age, energy intake, BMI, physical activity, smoking, alcohol, except for the respective stratifying factor). Data are reported as OR (95% CI). **A**, BMI < 25 vs 25–30 and ≥ 30 ($P=0.119$ for interaction); **B**, age < 50 years vs ≥ 50 years ($P=0.711$ for interaction); **C**, sex male vs female ($P=0.017$ for interaction)

showed that fiber supplementation can prevent the formation of gallstones in prairie dogs on a lithogenic diet.

According to our findings, dietary fiber has the protective effect against GSD especially in older subjects and overweight and obese subjects. These findings are consistent with other published studies considering age and obesity as risk factors for GSD. Based on Masserat et al.'s [3] aging is an important factor leading to gallstone formation among Iranian. Moreover, higher BMI considered as an important risk factor for GSD [29, 30]. Additionally, we showed that women in the highest tertile of insoluble dietary fiber intake had the lowest risk of GSD. According to several studies, female gender is a possible risk factor for GSD [31, 32]. Thus, it seems that the protective effects of dietary fiber intake are more significant in people with related risk factors.

However, it is highly important to note that diets with low fiber content are usually accompanied by higher carbohydrate or/and fat intake, so the effect of fiber on GSD cannot be investigated independently [20]. There are some strengths attributed to current research. Contrary to previous studies, the current study has evaluated all types of biliary stone such as gallstone, common bile duct stone and the history of cholecystectomy during the last six months. Moreover, enrollment of newly diagnosed subjects declined the recall bias. The same interviewer proceeded the study so that the interviewer bias did not happen. Although, we had some limitations as well. First, due to the case–control design of the present study, it was not possible to show a causal relationship between dietary fiber intake and GSD. Second, due to the retrospective nature of the FFQ, the probability of recall bias should be considered. In order to be able to generalize the results, further research needs to be conducted, on a larger scale.

Conclusion

In conclusion, according to the findings of the current study, dietary fiber intakes have an inverse relationship with the risk of GSD.

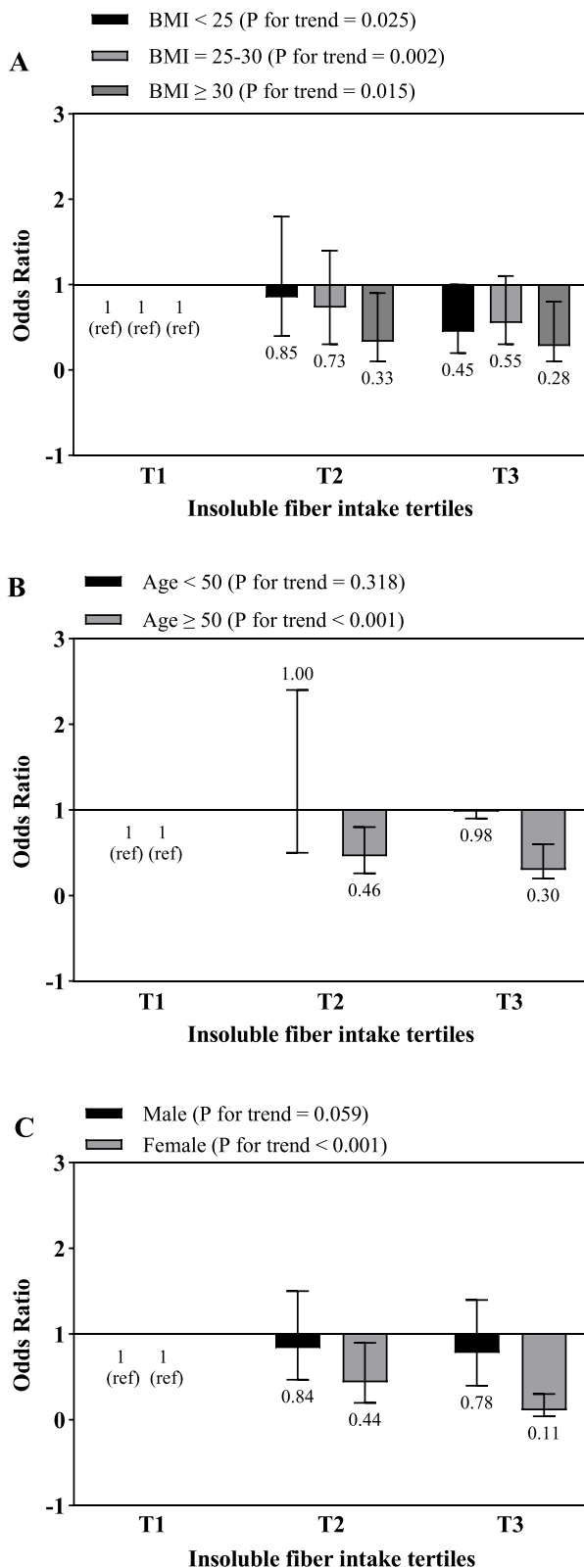


Fig. 3 Multivariate odds ratios of insoluble fiber intake tertiles for risk of gallstone according to risk factor status at baseline (multivariate logistic regression models for estimating ORs and 95% CIs, multivariable models were adjusted for sex, age, energy intake, BMI, physical activity, smoking, alcohol, except for the respective stratifying factor). Data are reported as OR (95% CI). **A**, BMI < 25 vs 25–30 and ≥ 30 ($P=0.138$ for interaction); **B**, age < 50 years vs ≥ 50 years ($P=0.581$ for interaction); **C**, sex male vs female ($P=0.356$ for interaction)

Abbreviations

ANOVA	Analyze of variance
BMI	Body mass index
CI	Confidence interval
FCT	Food composition table
FFQ	Food frequency questionnaire
HRs	Hazard ratios
IPAQ	International physical activity questionnaire
GSD	Gallstone disease
METS h/d	Metabolic equivalents hour per day
OR	Odds ratio
SD	Standard deviation
SPSS	Statistical Package Software for Social Science
USDA	United States Department of Agriculture

Acknowledgements

Authors have no acknowledgments to declare.

Authors' contributions

Conceptualization, ZY; Formal analysis, ZY; Methodology, Amir S, GD, SS and MG; Project administration, ANT and AH; Writing – original draft, ANT, Amin S and GD; Writing – review & editing, ZY and AH. All authors read and approved.

Funding

No funding has been received for this study.

Availability of data and materials

The datasets analyzed in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants adhered to the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol of the present study was approved by Research Institute of Gastroenterology and Liver Diseases Ethics Committee (IR.SBMU. RIGLD.REC.1396.159). All participants signed a written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 26 December 2022 Accepted: 29 March 2023

Published online: 11 April 2023

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