Long-term Use of Proton Pump Inhibitors is Associated With An Increased Risk of Nonalcoholic Fatty Liver Disease

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Backgrounds: The adverse effects of long-term use of proton pump inhibitors (PPIs) have led to growing concern. The association between PPIs use and the risks of nonalcoholic fatty liver disease (NAFLD) remains controversial.

Goal: The aim of this study was to investigate the association between PPIs use and the risks of NAFLD among the general adult population in the United States.

Study: We performed a cross-sectional study by extracting data from the National Health and Nutrition Examination Survey of 2017 to 2018. The association between PPIs use and NAFLD risks was analyzed by weighted multivariate logistic regression.

Results: Among the 4238 participants included in this study, 2167 were diagnosed with NAFLD. In the multivariate logistic regression model, PPIs use was associated with increased risks of NAFLD [odds ratio (OR): 1.318, 95% CI: 1.044-1.663; $P=0.020$]. This association was nonsignificant in participants taking PPIs for <5 years (OR: 0.846, 95% CI: 0.579-1.238; $P=0.390$), whereas it remained significant in participants taking PPIs for more than 5 years (OR: 2.016, 95% CI: 1.366-2.975; $P=0.031$). Further analysis showed that the use of PPIs was positively associated with risks of severe hepatic steatosis (OR: 1.451, 95% CI: 1.034-2.036; $P=0.031$) but not with mild-to-moderate steatosis (OR: 1.242, 95% CI: 0.886-1.741; $P=0.208$).

Conclusions: This study indicated that taking PPIs was associated with increased risks of NAFLD, especially severe hepatic steatosis. Awareness should be raised regarding the potential risks of NAFLD when prescribing PPIs.

Key Words: nonalcoholic fatty liver disease, proton pump inhibitors, cross-sectional study

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The epidemic of nonalcoholic fatty liver disease (NAFLD) has substantially expanded over the past few years.[1] The prevalence of NAFLD rose rapidly from 20.0% to 31.9% in the United States from 1988 to 2016, casting a shadow over the public health and creating an economic burden.[2] NAFLD is a multisystem disease and is strongly associated with extrahepatic complications, including cardiovascular disease, type 2 diabetes and chronic kidney disease.[3] A meta-analysis on 0.5 million individuals showed that NAFLD patients had a 2.19-fold risk of developing incident type 2 diabetes than the healthy controls, the association of which strengthened with the severity of hepatic steatosis and fibrosis.[4] However, public awareness of NAFLD does not correspond to its high prevalence and adverse complications.[5]

Proton pump inhibitors (PPIs) are potent suppressants of gastric acid and are commonly recommended for gastric acid-related diseases, including peptic ulcers and gastroesophageal reflux disease.[6] From 2000 to 2010, PPI prescriptions rose sharply from 3% to 7.2% among outpatient visits in the United States.[7] PPIs ranked ninth in prescription drug expenditures in 2015.[8] However, a steadily increasing list of adverse effects linked to long-term use of PPIs have been reported, such as dementia, myocardial infarction, chronic kidney disease, hepatic encephalopathy, and osteoporosis.[9] Keeping the duration and dose of PPIs to the essential minimum was recommended to reduce adverse effects.[10]

Epidemiological studies have reported that adults taking PPIs carry a higher risk of fatty liver disease, especially in those taking PPIs for more than 180 days.[11] Furthermore, a 1.4-fold risk of advanced liver fibrosis was observed among biopsy-confirmed NAFLD patients receiving PPIs treatment in contrast to the controls.[12] Nevertheless, contradictory results have been published. A population-based study involving 10,398 individuals demonstrated that no significant association was observed between the use of PPIs and prevalent NAFLD.[13] The association between PPIs treatment and NAFLD risks is still under debate and has not yielded consistent results. Considering the high prevalence of NAFLD and the broad use of PPIs, investigations of their relationship can have a profound influence on clinical practice.

In this study, we investigated the association between the use of PPIs and prevalent NAFLD risks. We further analyzed whether this association was different among PPIs users with a duration of more or less than 5 years. Moreover, the association of taking PPIs with the severity of hepatic steatosis was assessed.

METHODS

Study Population

The data were collected from the 2017 to 2018 cycle of the National Health and Nutrition Examination Survey

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(NHANES), a complex and stratified sample representing the noninstitutionalized population of the United States. We excluded participants according to the following criteria: (i) aged < 18 years old; (ii) ineligible or incomplete hepatic ultrasound transient elastography data; (iii) missing demographic data and laboratory variables of interest; and (iv) excessive alcohol consumption or positive for HBV or HCV infection (Fig. 1). The Centers for Disease Control and Prevention institutional review board provided ethics approval, and all participants gave written informed consent to participate.[14] Our report followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.[15]

Covariates

Race/ethnicity was stratified as Mexican-American, other Hispanic, non-Hispanic white, non-Hispanic black and others. Smokers were defined as having smoked at least 100 cigarettes over one's life. Being physically active was identified as the sum of minutes of metabolic equivalent of task per week of > 600 minutes.[16] Overweight and obesity were defined as body mass indexes (BMI) ≥ 25 and ≥ 30 kg/m^2, respectively.[17] We diagnosed type 2 diabetes as fasting glucose ≥ 7.0 mmol/L or glycated hemoglobin A1c ≥ 6.5% and/or taking hypoglycemic agents.[18] Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg and/or a history of hypertension or receiving prescribed medications for hypertension.[19] Low high-density lipoprotein-cholesterol was identified as high-density lipoprotein-cholesterol <1.03 mmol/L for males or <1.29 mmol/L for females.[20] Overall diet quality was assessed by Healthy Eating Index (HEI) 2015 score.[21] It consisted of 9 adequacy components score and 4 moderation components score. HEI-2015 scores ranged from 0 to 100, with higher HEI scores reflecting better diet quality.

Medication Use

The Dietary Supplements and Prescription Medication Section of the Sample Person Questionnaire collected information on the use of prescription and nonprescription medications. Participants offered their data on medication use within the 30 days before the interview, including each medication name, the main reason for its use, and the duration of use. Frequency and dose were not recorded. PPIs use was based on self-reported prescription use of omeprazole, esomeprazole, pantoprazole, rabeprazole, and lansoprazole. The types of histamine-2 receptor antagonists taken by participants included cimetidine, famotidine, nizatidine, and ranitidine.

Diagnosis of NAFLD

Liver ultrasound transient elastography was performed to measure hepatic steatosis and fibrosis using the FibroScan Model 502 V2 Touch equipped with a medium or extra-large probe. Only participants with complete exams were included in this study, and they were defined as having ≥ 10 complete stiffness measures, with a liver stiffness interquartile range ≥ 30% and fasting for at least 3 hours. We defined hepatic steatosis as a median controlled attenuation parameter ≥ 261 dB/m. Mild-to-moderate and severe hepatic steatosis were identified as having controlled attenuation parameters of 261 to 311 and ≥ 312 dB/m, respectively, as suggested by a study conducted in the United States.[22] NAFLD was diagnosed as the presence of hepatic steatosis with exclusion of excessive alcohol consumption, hepatitis B virus surface antigen positivity or hepatitis C virus RNA positivity.[23] Excessive alcohol consumption was defined as alcohol intake > 210 g/week for males and 140 g/week for females.

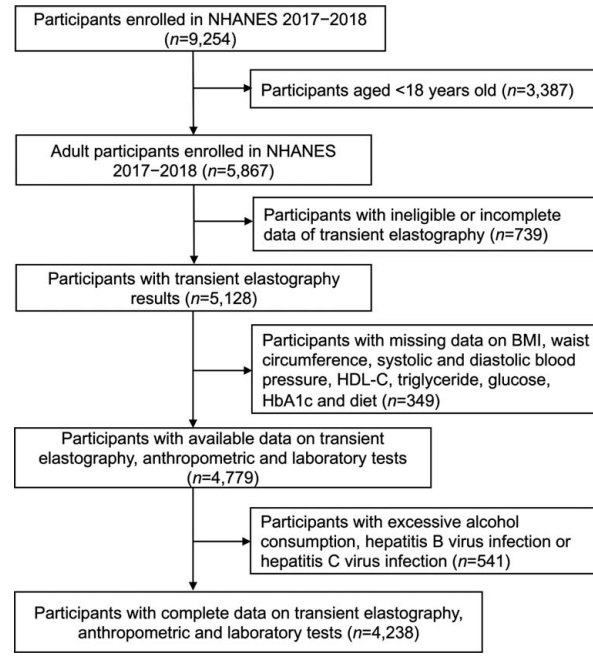

FIGURE 1. Flowchart of the study. BMI indicates body mass index; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol.

Statistical Analyses

The appropriate sampling weights of NHANES were applied to all the analyses to account for the unequal probabilities of selection. Continuous variables were presented as weighted means ± SDs or weighted medians and interquartile ranges. Categorical parameters were described as weighted percentages. The Student *t* test, Wilcoxon test and χ^2 test were adopted to compare the differences in variables between groups. We performed univariate and multivariate logistic regression analyses to evaluate the association between PPIs use and NAFLD risks. In addition, we performed sensitivity analyses by excluding participants taking histamine-2 receptor antagonists and with extreme BMIs (> 99th percentile or <1th percentile. All the analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC). A *P*-value <0.05 (2-tailed) was considered significant.

RESULTS

Clinical Characteristics of The Participants

Of 4038 participants, 2167 (53.67%) were diagnosed with NAFLD. We compared the weighted characteristics of participants with and without PPIs use (Table 1). Compared with the controls, the PPIs users were older, had a greater waist circumference, and had higher serum levels of alanine transaminase, aspartate transaminase, γ-glutamyl transferase and triglyceride. PPIs users were more likely to have overweight, diabetes and hypertension and had a higher rate of NAFLD than the controls (64.78% vs. 47.40%, *P* <0.001). There was no significant difference in the systolic and diastolic

TABLE 1. Comparison of Clinical Characteristics of Participants With and Without PPIs Use

Variables	Without PPIs ($n = 3,840$)	With PPIs ($n = 398$)	P
Age (y)	47.60 ± 0.62	61.69 ± 1.27	< 0.001
Male (%)	48.25	40.15	0.083
Race/ethnicity (%)			0.006
Mexican-American	8.04	4.79	
Other Hispanic	7.04	5.16	
Non-Hispanic white	61.46	75.36	
Non-Hispanic black	12.18	8.65	
Other races	11.28	6.04	
Smokers (%)	36.82	44.97	0.017
Body mass index (kg/m^2)	29.34 ± 0.30	31.42 ± 0.58	0.339
Waist circumference (cm)	99.42 ± 0.82	106.45 ± 1.26	0.008
Systolic blood pressure (mmHg)	122.37 ± 0.39	130.17 ± 1.54	0.089
Diastolic blood pressure (mmHg)	72.11 ± 0.54	71.41 ± 0.83	0.555
Hypertension (%)	36.73	67.68	< 0.001
Overweight (%)	71.36	83.91	< 0.001
Diabetes (%)	13.05	30.76	< 0.001
Alanine aminotransferase (U/L)	22.12 ± 0.29	21.01 ± 0.73	< 0.001
Aspartate aminotransferase (U/L)	21.53 ± 0.22	21.64 ± 1.16	0.005
γ-Glutamyl transferase (U/L)	27.12 ± 0.76	33.07 ± 2.40	< 0.001
Triglyceride (mmol/L)	1.24 ± 0.04	1.58 ± 0.11	< 0.001
Total cholesterol (mmol/L)	4.89 ± 0.04	4.79 ± 0.11	0.726
HDL-C (mmol/L)	1.38 ± 0.01	1.35 ± 0.03	0.846
Fasting plasma glucose (mmol/L)	5.52 ± 0.04	6.14 ± 0.13	0.574
Glycated hemoglobin A1c (%)	5.68 ± 0.02	6.03 ± 0.06	0.835
Serum uric acid (μmol/L)	316.71 ± 2.26	330.54 ± 5.72	0.772
NAFLD (%)	47.40	64.78	< 0.001
H_2RA user (%)	2.22	2.72	0.605

Data were presented as weighted mean ± standard errors or weighted frequency ± standard errors.
H_2RA indicates histamine-2 receptor antagonist; HDL-C, high-densitylipoprotein-cholesterol; NAFLD, nonalcoholic fatty liver disease; PPI, proton pump inhibitor.

blood pressure, total cholesterol, high-density lipoprotein cholesterol, fasting plasma glucose, glycated hemoglobin A1c, and serum uric acid and the use of histamine-2 receptor antagonists between the 2 groups.

Association Between PPIs Use and Prevalence of NAFLD

We observed a positive association between PPIs use and NAFLD prevalence. That is, PPIs users had a significantly higher prevalence of NAFLD than non-PPI users (64.78% vs. 47.4%). We classified all NAFLD cases into mild-to-moderate hepatic steatosis and severe steatosis and found that the prevalence rates of mild-to-moderate hepatic steatosis and severe steatosis in PPIs users were 30.90% and 33.88%, respectively, whereas those in non-users were 24.46% and 20.94%, respectively (Fig. 2). These findings suggested that PPIs users were more likely to have NAFLD, especially severe steatosis, than non-PPIs users.

Association between PPIs Use and Risk of NAFLD

We further performed univariate and multivariate logistic regression to evaluate the association between PPIs use and NAFLD risks. In the univariate model, PPIs use was associated with a 2.014-fold risk of NAFLD [odds ratio (OR): 2.014, 95% CI: 1.683-2.475; P <0.001] (Fig. 3). This association was attenuated but remained significant after gradually adjusting for demographic variables, lifestyle, comorbidities and use of histamine-2 receptor antagonists (OR: 1.318, 95% CI: 1.044-1.663; $P = 0.020$). Furthermore, we analyzed the association between PPIs use and different degrees of hepatic steatosis. In the fully adjusted multivariate model, the odds ratio of severe steatosis was 1.451 (95% CI: 1.034-2.036; $P = 0.031$), whereas that of mild-to-moderate steatosis was 1.242 (95% CI: 0.886-1.741; $P = 0.208$). In addition, participants taking PPIs for more than 5 years had increased risks of NAFLD (OR: 2.016, 95% CI: 1.366-2.975; $P = 0.031$), whereas those taking PPIs for <5 years did not (OR: 0.846, 95% CI: 0.579-1.238; $P = 0.390$) (Fig. 4). These results indicated that the duration

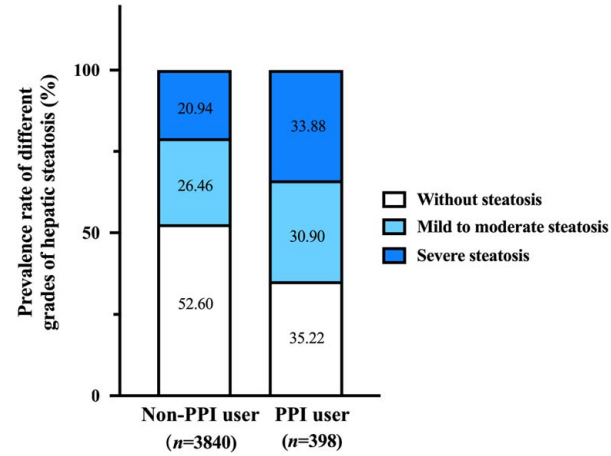

FIGURE 2. Association of proton pump inhibitor (PPI) use with prevalence rate of nonalcoholic fatty liver disease. (Mild-to-moderate and severe hepatic steatosis were identified as with a median controlled attenuation parameter 261 to 311 and ≥312 dB/m, respectively. χ^2 test was performed to compare the difference in prevalence rate of hepatic steatosis between PPIs users and non-users and χ^2 value was 70.69 with $P < 0.001$).

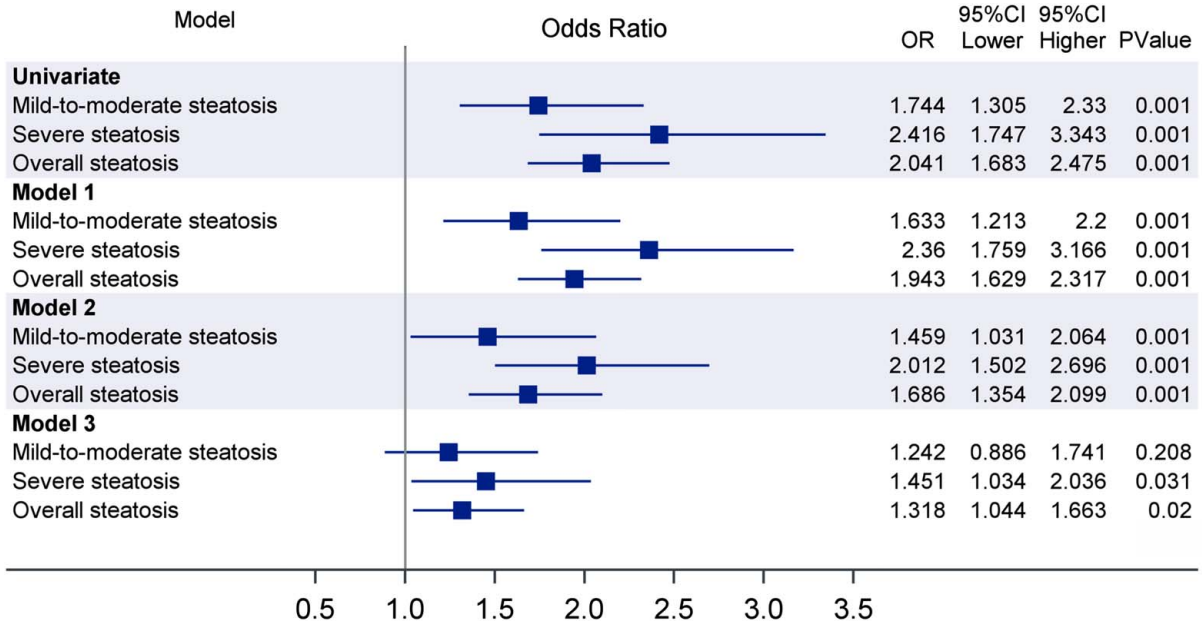

FIGURE 3. Association between proton pump inhibitor use and nonalcoholic fatty liver disease risks. Model 1 was adjusted for age, gender, and race/ethnicity. Model 2 was adjusted for variables in model 1+body mass index, waist circumference, physical activity, smoking, and diet quality. Model 3 was adjusted for variables in model 2+type 2 diabetes mellitus, hypertension, low high-density lipoprotein-cholesterol, and the use of histamine-2 receptor antagonist. OR indicates odds ratio.

of PPIs use was associated with the risk of NAFLD, and PPIs users were more likely to have severe hepatic steatosis rather than simple mild-to-moderate steatosis than non-PPI users.

Subgroup Analyses and Sensitivity Analyses

We divided the participants into subgroups such as young and middle-aged (age <65 y) and elderly (age ≥65 y), males and females, smokers and non-smokers, overweight and non-overweight, diabetic and non-diabetic, being physically active and controls. We performed univariate and multivariate logistic regression analyses to explore the association of PPIs use with NAFLD risks in these subgroups (Fig. 5).

We found that PPIs use was related to a nearly 2-fold increased risk of NAFLD in participants aged <65 years (OR: 1.844, 95% CI: 1.183-2.875; $P=0.007$), but this association was attenuated to be insignificant in participants aged ≥65 years (OR: 0.912, 95% CI: 0.683-1.219; $P=0.534$). Similarly, this association was significant in men (OR: 2.681, 95% CI: 1.639-4.387, $P<0.001$) but not in women (OR: 0.909, 95% CI: 0.680-1.215, $P=0.519$). In addition, PPIs users had a higher risk of NAFLD than nonusers among smokers (OR: 1.766, 95% CI: 1.050-2.970; $P=0.032$), physically active participants (OR: 1.639, 95% CI: 1.158-2.320; $P=0.005$), overweight participants (OR: 1.377, 95% CI: 1.090-1.740; $P=0.007$) and non-diabetic participants (OR: 1.344, 95% CI: 1.008-1.682; $P=0.047$). However, no significant association between PPIs use and NAFLD risks was observed among non-smoking, non-physically active, non-overweight, or diabetic participants. These results demonstrated that, compared with the corresponding controls, the positive association of PPIs use with NAFLD risks was more significant in males, smokers and physically active, overweight, non-diabetic, and young and middle-aged participants.

The use of histamine-2 receptor antagonists indicated that these participants had indications of gastric acid suppressants, such as peptic ulcer, dyspepsia, and gastroesophageal reflux disease. Therefore, in sensitivity analyses, we excluded participants taking histamine-2 receptor antagonists and observed that the association between PPIs use and NAFLD risks was not materially changed. In addition, we excluded participants with extreme BMI to minimize its influence, and this association remained significant (Fig. 6).

DISCUSSION

In this study, we found that PPIs use was positively associated with NAFLD risks. First, NAFLD patients had a higher rate of PPIs use than controls. Second, the prevalence of NAFLD was significantly elevated in PPIs users compared with non-PPI users. Third, PPIs use was associated with significantly increased risks of NAFLD, especially risks of severe hepatic steatosis. Fourth, the association between PPIs use and NAFLD risks was markedly stronger in males, smokers, and physically active, overweight, non-diabetic and young and middle-aged participants and in participants taking PPIs for more than 5 years than in the corresponding controls.

In this study, the prevalence rate of NAFLD was 53.67% among the adults included in NHANES 2017 to 2018. This rate seemed to be higher than the reported prevalence of NAFLD in the United States, which ranged from 24% to 34% in the general population.[24,25] We diagnosed the presence of hepatic steatosis by liver ultrasound transient elastography, adopting a cutoff value of 261 dB/m for the controlled attenuation parameter (CAP) scores.[22] The prevalence of NAFLD was also reported to be ~50% in published studies using the data from NHANES 2017 to 2018. For instance, a study using this database included

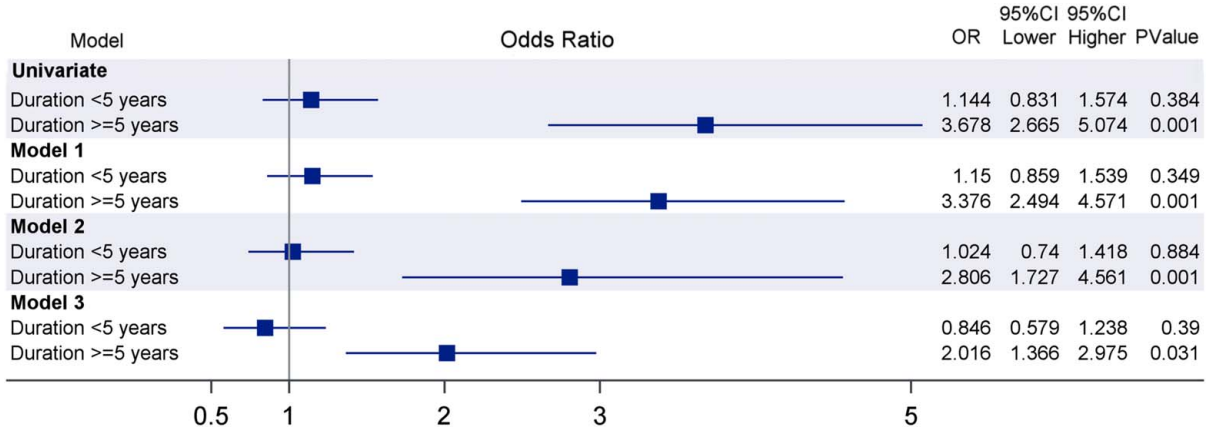

FIGURE 4. Association between duration of proton pump inhibitor use and nonalcoholic fatty liver disease risks. Model 1 was adjusted for age, gender, and race/ethnicity. Model 2 was adjusted for variables in model 1+body mass index, waist circumference, physical activity, smoking, and diet quality. Model 3 was adjusted for variables in model 2+type 2 diabetes mellitus, hypertension, low high-density lipoprotein-cholesterol, and the use of histamine-2 receptor antagonist. OR indicates odds ratio.

4325 participants with an NAFLD prevalence of 56.47%, which was diagnosed at 263 dB/m CAP. Another study covering 2706 adults from NHANES 2017 to 2018 showed a prevalence of 46.3% of hepatic steatosis.[26] Compared with these studies, the prevalence of NAFLD with 37.1% was relatively lower in a study that used 274 dB/m as the cutoff

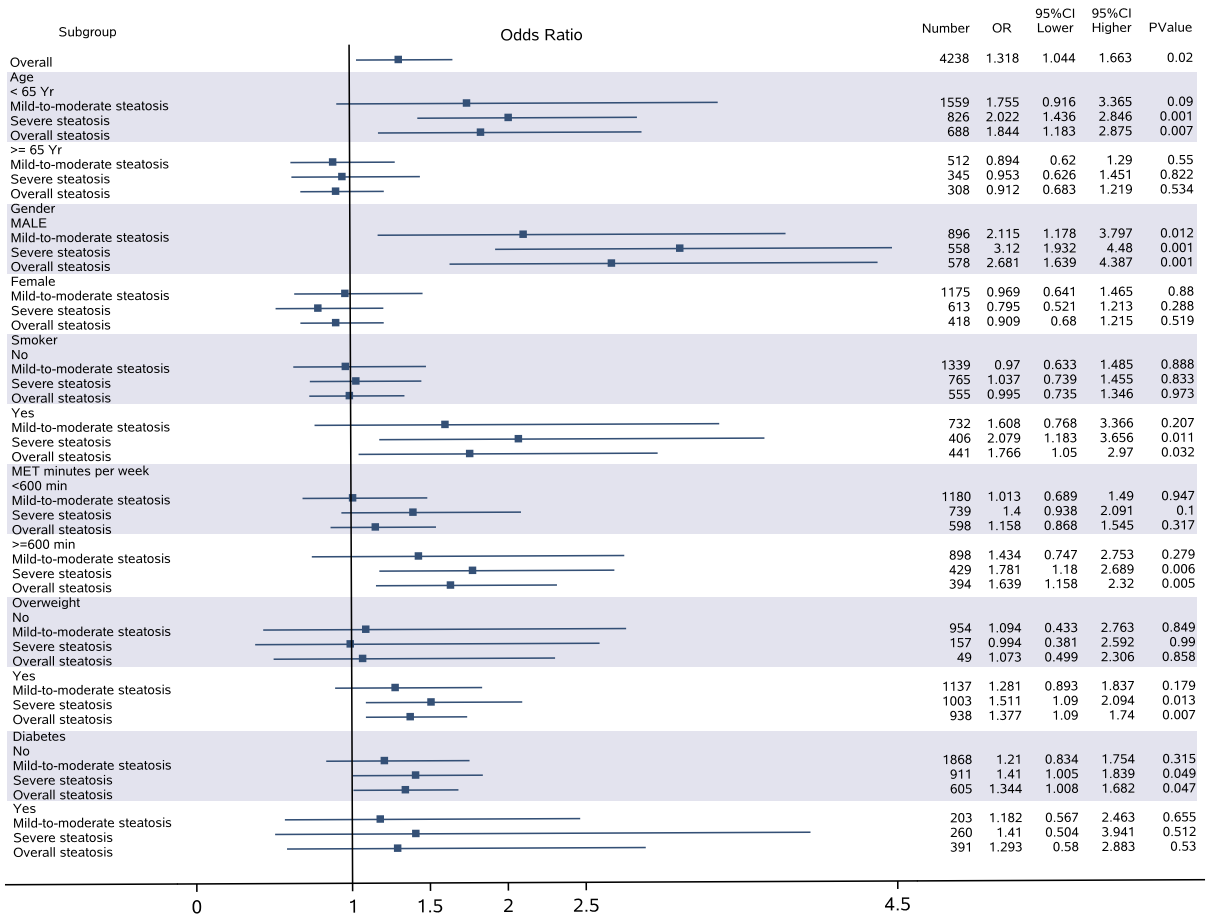

FIGURE 5. Subgroup analysis of the association between proton pump inhibitor use and nonalcoholic fatty liver disease risks. Results of multivariate logistic regression model adjusting for age, gender, race, smoking, physical activity, marital status, body mass index, hypertension, type 2 diabetes mellitus, low high-density lipoprotein-cholesterol and use of histamine-2 receptor antagonist. OR indicates odds ratio.

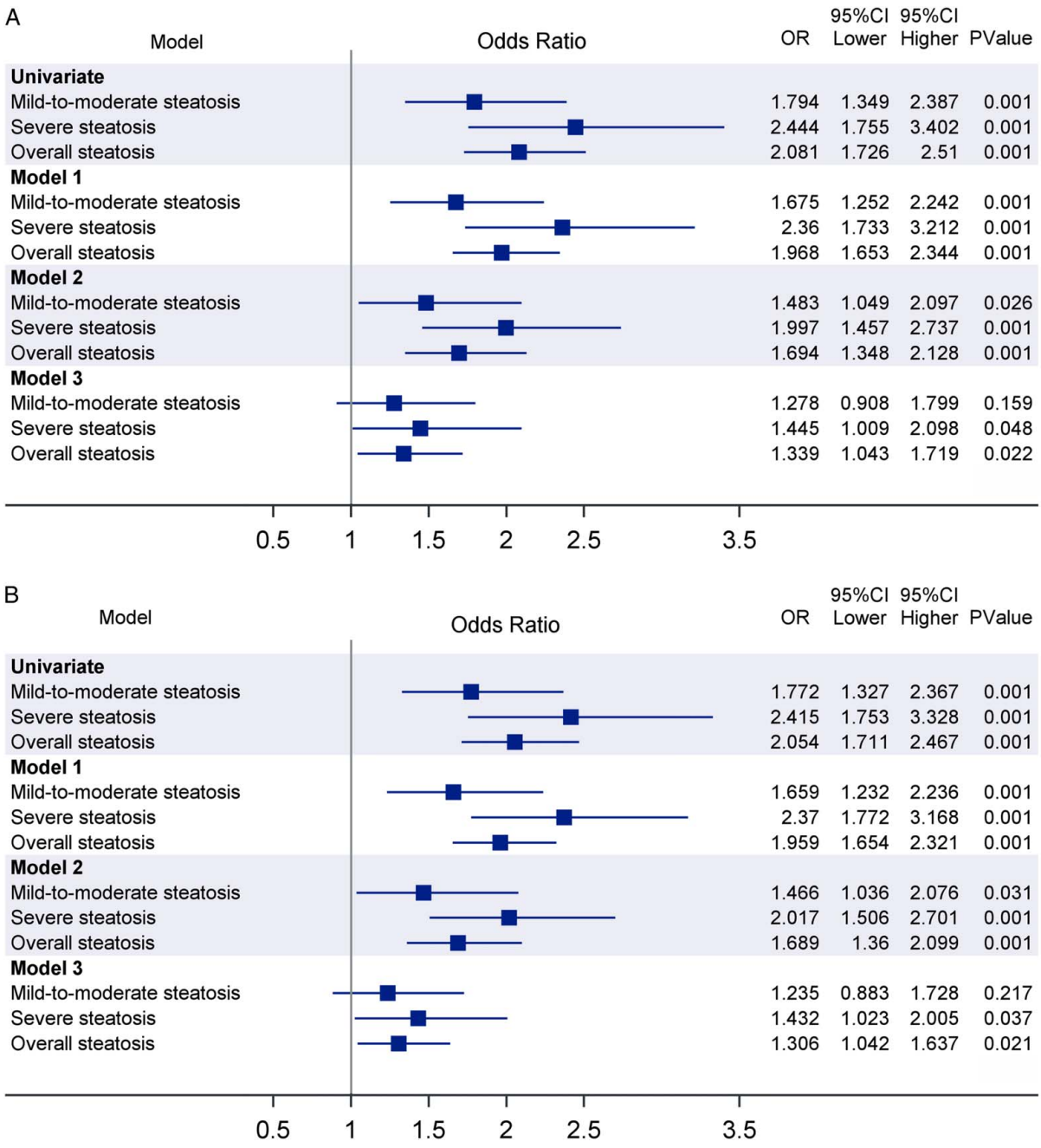

FIGURE 6. Sensitivity analysis of the association between proton pump inhibitor use and nonalcoholic fatty liver disease risks. A, Participants taking histamine-2 receptor antagonists were excluded. The number of patients with non-NAFLD, mild-to-moderate steatosis and severe steatosis were 2031, 1142, and 957, respectively. B, Participants with body mass index >99% (53.2 kg/m^2) or <1% (17.7 kg/m^2) were excluded. The number of patients with non-NAFLD, mild-to-moderate steatosis and severe steatosis were 2012, 1146, and 961, respectively. Model 1 was adjusted for age, gender and race/ethnicity. Model 2 was adjusted for variables in model 1+body mass index, waist circumference, physical activity, smoking, and diet quality. Model 3 was adjusted for variables in model 2+type 2 diabetes mellitus, hypertension, low high-density lipoprotein-cholesterol, and the use of histamine-2 receptor antagonist. OR indicates odds ratio.

value of CAP.[27] Notably, this value was cited from a study investigating the accuracy of CAP in assessing steatosis that was conducted in the United Kingdom, not in the United States.[28] In a similar study carried out in the United States, 274 dB/m was the cutoff value with 90% sensitivity for differentiating severe steatosis from controls.[29]

Intriguingly, long-term use of PPIs was reported to be associated with NAFLD risks but this association remains controversial. A population-based study first demonstrated that PPIs use was not significantly associated with prevalent NAFLD, but the use of histamine-2 receptor antagonists was.[13] This study was primarily limited to the diagnostic

criteria of NAFLD, which was based on elevated serum aminotransferase rather than imaging or histological findings of hepatic steatosis. A cross-sectional study covering 301 patients with celiac disease who were on a gluten-free diet showed that PPIs treatment was related to a 9.27-fold risk of hepatic steatosis, with a 95% confidence interval of 4.23 to 21.87.[30] Considering that possible confounding factors were not accounted for and the confidence interval was wide, this association among these participants requires further study.

In this study, we found that the use of PPIs was positively associated with NAFLD risks. Moreover, when we further divided PPIs users into individuals with use durations of less than or more than 5 years, this association was nonsignificant in the former but remained significant in the latter. This finding suggested that it was long-term use of PPIs that was independently associated with NAFLD risks, consistent with prior studies showing that the risks of diabetes, cardiovascular events, cancer and mortality were more evident among long-term PPIs users than among the controls. In addition, we analyzed the relationship between PPIs use and different grades of hepatic steatosis and found that PPI users had higher risks of severe hepatic steatosis but no increased risk of mild-to-moderate steatosis. This result was also supported by the finding that PPIs users had a higher proportion of hepatic steatosis, particularly severe hepatic steatosis. On the basis of the conflicting results about the association between PPIs treatment and NAFLD risks, this study provided further evidence and substantially expanded knowledge of the association between PPIs use and varying degrees of hepatic steatosis. Identifying the adverse effects of taking PPIs helped to raise awareness of reducing the unnecessary use of PPIs in clinical and public health practice. Collectively, this study offered opportunities for a more comprehensive understanding of the potential risks of NAFLD linked with taking PPIs and encouraged physicians to consider the appropriate duration of treatment in patients with PPIs indications.

The underlying mechanisms for the association between PPIs use and NAFLD risks remain to be elucidated. There are several possible explanations. First, emerging evidence suggested that gut microbiota dysbiosis may be responsible for this association. Previous studies have established that PPIs altered the composition of gut microbiota and reduced their diversity.[31] Gut microbiota dysbiosis plays an essential role in the pathogenesis of NAFLD by increasing intestinal permeability and increasing hepatic exposure to injuries [32,33] {Huang, 2022 #1}. For instance, both NAFLD patients and PPIs users were associated with increased *Escherichia*.[34,35] Furthermore, animal studies have reported that inhibiting gastric acid secretion promoted *Enterococcus faecalis* translocation to the liver, which subsequently activated Toll-like receptor 2 on Kupffer cells and triggered an inflammatory response in the liver.[36] Second, growing evidence suggested that the use of PPIs is associated with a range of metabolic dysfunction-related disorders, including type 2 diabetes mellitus,[37] metabolic syndrome,[30] weight gain,[38] and cardiovascular events.[39] It was reported that PPIs increased the plasma level of asymmetric dimethylarginine,[40] which is considered a risk factor for cardiovascular disease due to its inhibitory effects on endothelial nitric oxide synthases. In addition, elevated plasma asymmetric dimethylarginine promoted the development of insulin resistance,[41] and asymmetric dimethylarginine impaired insulin sensitivity of hepatocytes through mitogen-activated protein kinase-dependent pathways.[42] Insulin resistance was a cardinal hit that predisposed the development of hepatic steatosis.[43]

This study has several limitations. First, this was a cross-sectional study that could not capture the causal relationship between PPIs use and NAFLD risks. Second, we did not assess the dose-response effect of PPIs treatment on the risks of NAFLD due to a lack of data on the dose and frequency of PPIs use. We did not evaluate the impact of PPIs types on prevalent NAFLD, although they were recorded in the NHANES 2017 to 2018 database. As there were only 398 PPIs users among the participants ultimately included in this study, further classifying PPIs into too many groups may reduce the reliability of the results. Third, the indications of PPIs, including peptic ulcer, gastroesophageal reflux disease, and dyspepsia, were not adjusted in the multivariable logistic regression model because of a lack of these diagnosis data in the database. Nevertheless, the use of histamine-2 receptor antagonists, another type of gastric secretion suppressant that had similar indications as PPIs, was adjusted as a potential confounding factor in the multivariate models. The association of PPIs use and NAFLD risks was still significant after accounting for the use of histamine-2 receptor antagonists. Fourth, in subgroup analyses, we observed that the positive association of PPIs use with NAFLD risks was more significant in males, smokers and physically active, overweight, non-diabetic, and young and middle-aged participants compared with the corresponding controls. However, the explanations for these phenomenon remains unclear. Further research is warranted to elucidate the observed associations. Fifth, PPIs use was 6% in the non-NAFLD group and 11% in the NAFLD groups. In the Nurses' Health Study [44] and the Atherosclerosis Risk in Community Study,[45] nearly 6% to 25% of adults reported regular PPIs use. We acknowledge that the prevalence of PPIs use was relatively low in this study.

In conclusion, this study found that PPIs use was associated with increased risks of NAFLD, especially severe hepatic steatosis. Awareness should be raised regarding the potential risks of NAFLD when prescribing PPIs. Monitoring the development of NAFLD may be necessary for PPIs users, particularly for long-term users.

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