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Proton pump inhibitor use is associated with increased liver steatosis

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Abstract. Despite proton pump inhibitors (PPIs) being generally safe, there are questions about their potential long-term complications. The present study aimed to investigate the association between PPI therapy and the incidence of hepatic steatosis and liver fibrosis in the outpatient population of the United States. The present study included 7,395 individuals aged ≥20 years who underwent hepatic vibration-controlled transient elastography (VCTE) examination. The data were obtained from the January 2017 to March 2020 pre-pandemic National Health and Nutrition Examination Survey. Among the 7,395 adults who were included (mean age, 50.59 years; 3,656 male), 9.8% were prescribed PPIs. Following multivariable adjustment, the use of PPIs was significantly associated with hepatic steatosis [odds ratio (OR), 1.25; 95% confidence interval (CI), 1.02-1.53]. Prolonged use of PPIs was found to increase the risk of developing hepatic steatosis over time (P=0.006). Sensitivity analyses using different definitions of hepatic steatosis, such as a controlled attenuation parameter ≥285 dB/m (OR, 1.19; CI, 1.01-1.40), non-alcoholic fatty liver disease (OR, 1.50; 95% CI, 1.16-1.93) and metabolic dysfunction-associated steatotic liver disease (OR, 1.26; 95% CI, 1.05-1.52), consistently demonstrated an association between PPI prescription and hepatic steatosis. The administration of PPI therapy was linked with hepatic steatosis in US adults, although no significant association was observed with liver stiffness, as determined by VCTE.

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Introduction

Proton pump inhibitors (PPIs) are potent drugs used to suppress gastric acid secretion and are widely used worldwide. Despite several PPIs being available over the counter, the prevalence of prescription PPIs increased from an estimated 3.9% in 1999-2000 to 7.8% in 2011-2012 (1). Studies have shown that patients are often prescribed PPIs for inappropriate indications or are administered high doses of PPIs for extended periods, which is contrary to clinical guidelines (2,3). Additionally, it has been reported that patients are discharged from hospitals with PPIs that are not indicated for their condition (3). Although PPI therapy is an effective treatment strategy for a range of conditions, including gastroesophageal reflux disease (GERD), peptic ulcer disease and Zollinger-Ellison syndrome (which are generally deemed safe for treatment), evidence of potential long-term complications of PPI therapy is emerging: These complications include chronic kidney disease (4), dementia (5), bone fracture (6), myocardial infarction (7), infection (8), micronutrient deficiencies (9) and gastrointestinal malignancy (10).

To the best of our knowledge, the majority of research examining the association between exposure to PPIs and liver disease has focused on patients with cirrhosis (11-13). In both retrospective and prospective investigations, PPI exposure has demonstrated inconsistent associations with severe infection, hepatic decompensation, hepatocellular carcinoma and liver-related mortality (11-13). The prevailing hypothesis suggests that PPIs may increase the likelihood of complications by altering the intestinal microbiota via the suppression of gastric acid, thus resulting in bacterial overgrowth in the small intestine and an increase in bacterial translocation (14,15). To the best of our knowledge, however, there is limited research available regarding the effects of PPIs on the development and progression of liver fibrosis and hepatic steatosis in a general population cohort (11-13).

From January 2017 to March 2020, the National Health and Nutrition Examination Survey (NHANES) incorporated vibration-controlled transient elastography (VCTE)

measurements to assess prevalence of steatosis and fibrosis in a representative sample of the US population (16). VCTE is a non-invasive technique utilized for quantifying the severity of hepatic steatosis, determined by the controlled attenuation parameter (CAP) score, and assessing the degree of fibrosis via liver stiffness measurement (LSM) (16-18). The inclusion of LSM and CAP within a nationally representative dataset presents opportunity to investigate the association between PPI therapy and the risk of liver steatosis and fibrosis at a population level. To investigate the association between PPI therapy and risk of liver steatosis and fibrosis, the present study conducted a large, nationally representative cross-sectional study using data from the NHANES.

Materials and methods

Study population. The present study analyzed pre-pandemic data from the NHANES January 2017-March 2020, which is a nationally representative survey conducted by the National Center for Health Statistics (NCHS) to evaluate the health and nutritional status of adults and children in the US. Comprehensive participant data, encompassing demographic profiles, examination records (including liver ultrasound transient elastography), laboratory analyses and questionnaire responses, were gathered by well-trained examiners (cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?Cycle=2017-2020). Of the 15,560 patients included in the NHANES, 7,395 aged ≥20 years completed hepatic VCTE examinations. Exclusion criteria were as follows: i) aged <20 years (n=6,328); ii) missing elastography examination data (n=1,243) and iii) invalid elastography examination data (fasting <3 h, unable to obtain 10 valid measures, interquartile range/median >30% and CAP not performed) (n=594). Fig. 1 illustrates the sample selection flowchart. Researchers at the Centers for Disease Control and Prevention approved the NHANES (approval nos. #2011-17 and #2018-01) and all participants provided informed consent.

VCTE is a non-invasive imaging method widely used to assess liver fibrosis and steatosis in patients with liver disease (16-18). The present study utilized VCTE to evaluate the extent of liver fibrosis and steatosis. According to the American Association for the Study of Liver Diseases Practice Guidance on the Clinical Assessment and Management of Non-alcoholic Fatty Liver Disease (NAFLD) (17), steatotic liver disease is diagnosed histologically or through imaging techniques such as ultrasound, FibroScan (CAP), Computed Tomography, and Magnetic Resonance Imaging-Derived Proton Density Fat Fraction. Due to limitations in the available data from NHANES 2017-2020, the present study only used CAP for quantifying the severity of hepatic steatosis. Consequently, patients who did not undergo VCTE were excluded from the analysis.

Definition of PPI exposure. During the household sample person interview, survey participants were asked if they had taken prescription medications in the last 30 days. Those who answered 'yes' were requested to show the interviewer the pill containers for all utilized products. Participants in the survey were also asked when they took the drug and why they did so. The use of PPIs or H2-receptor antagonists (H2RAs) in 1 month preceding the interview was defined as exposure. The length of use was categorized as <0.5, 0.5-2.0 and >2.0 years. The PPIs included omeprazole, pantoprazole, esomeprazole and other (such as lansoprazole, rabeprazole and dexlansoprazole). The indication for prescribing PPI was based on the American Gastroenterological Association Clinical Practice Guidelines (2). The H2RAs included ranitidine and famotidine.

Steatosis and fibrosis assessment. FibroScan® model 502 V2 Touch, equipped with either a medium (M) or extra-large (XL) wand (probe), was used to obtain elastography measurements within the NHANES Mobile Examination Center. A complete examination was defined as having a fasting time ≥3 h, obtaining ≥10 complete stiffness measurements and a liver stiffness interquartile range/median <30%. According to previous studies (19,20), an optimal CAP cut-off of ≥274 dB/m (sensitivity, 90%) is indicative of hepatic steatosis, whereas an optimal LSM cut-off of ≥9.7 kPa (sensitivity, 71%; specificity, 75%) is suggestive of advanced fibrosis (Metavir Fibrosis Stage ≥F3) (21).

Covariates. Based on the literature (22-25), the following covariates were included: Age, sex, race/ethnicity, educational level, ratio of family income to poverty (calculated by dividing family or individual income by the poverty guidelines specific to the survey year), smoking status, notable alcohol consumption and vigorous activity. To avoid overadjustment, obesity was not included as a covariate, as previously described (22-25). Race/ethnicity was classified into five groups, including non-Hispanic White, Hispanic, non-Hispanic Black, non-Hispanic Asian and other (including multiracial). Education level was categorized into four groups: Less than high school, high school graduate, some college or associate's degree and college or above. According to the ratio of family income to poverty, family income was categorized as low (<1.3), medium (1.3-4.9), or high (≥5.0). Smoking status was categorized into three groups, including never smoked, former smoker and current smoker. Notable alcoholic consumption was defined as >2 or 3 standard units)/day on average for female and male participants, respectively. Vigorous activity was defined as engaging in activity with a metabolic equivalent (ratio of the rate at which a person expends energy, relative to the mass) of ≥6, at least three times/week.

Statistical analysis. Continuous variables are expressed as the mean ± SD; categorical data are expressed as count and percentages. To compare clinical characteristics, linear regression for continuous variables and χ^2 test for categorical variables were used. To assess the effect of PPIs and H2RAs on the presence of steatosis and fibrosis, multivariable linear and logistic regression analyses were conducted. The multivariate test used three models: 1, no variables adjusted; 2, adjusted for age, sex and race/ethnicity and 3, further adjusted for education, the ratio of family income to poverty, smoking status, notable alcohol consumption and vigorous activity.

Three sensitivity tests were conducted. First, hepatic steatosis was defined by using a cut-off value of CAP ≥285 dB/m, which was chosen to optimize sensitivity and

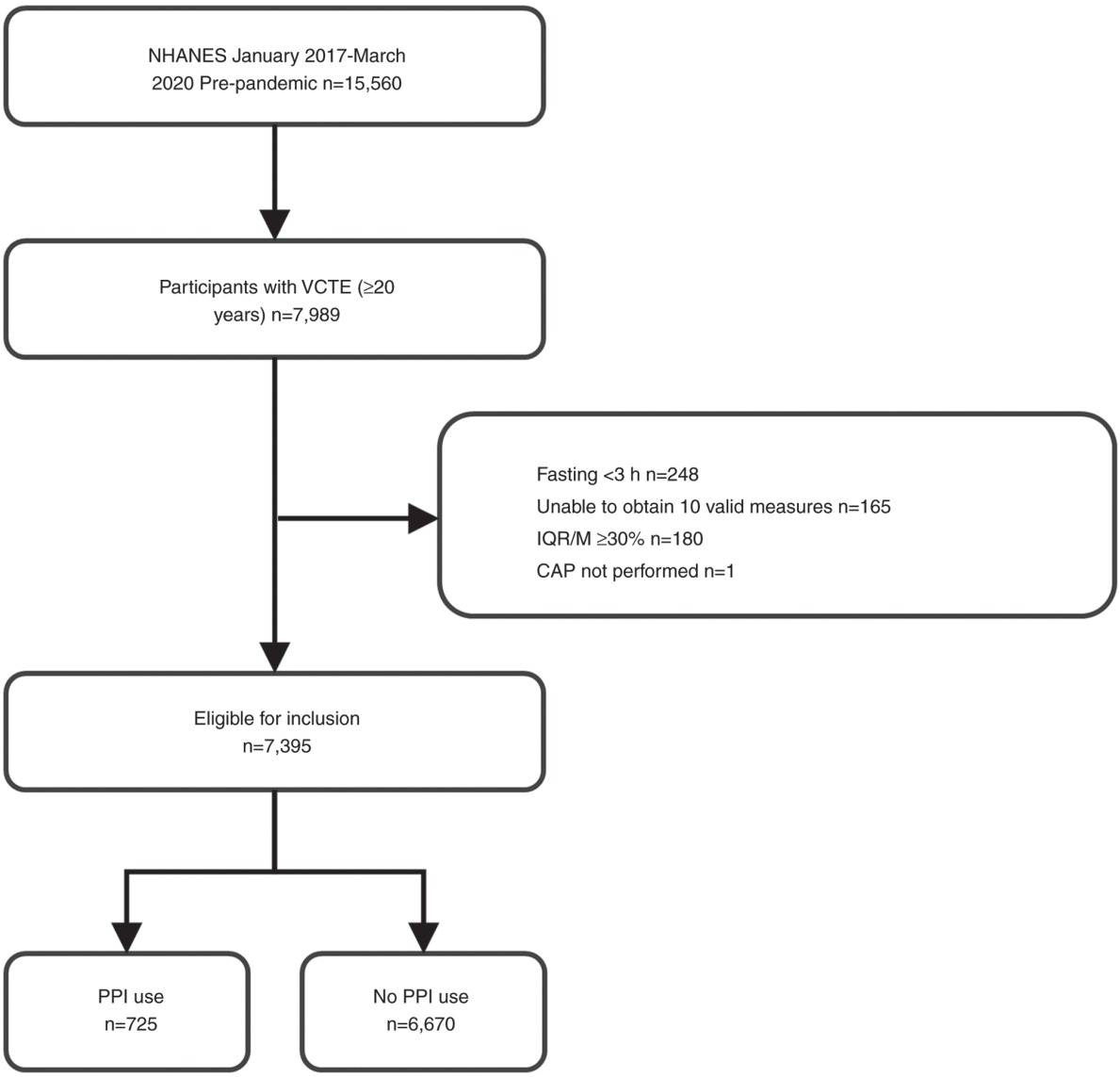

Figure 1. Study design. CAP, controlled attenuation parameter; IQR/M, interquartile range/median; PPI, proton pump inhibitor; VCTE, vibration-controlled transient elastography; NHANES, National Health and Nutrition Examination Survey.

specificity (26). Second, the target population was adjusted to include only patients with NAFLD (n=5,897) to eliminate the influence of certain factors (alcohol consumption, steatogenic medications,) on steatosis (27). Patients with hepatitis B (n=40) or C (n=165), notable alcoholic consumption (n=1,198), or use of steatogenic medications for >6 months (n=95) were excluded. The target population was refined to focus specifically on individuals with metabolic dysfunction-associated steatotic liver disease (MASLD; n=5,355). The diagnosis of MASLD was based on hepatic steatosis when no other underlying cause is identified and at least one of the cardiometabolic risk factors (general obesity, central obesity, diabetes, prediabetes, dyslipidemia, hypertension) is present (28).

All statistical analyses were performed by using R version 4.3.0 (R Foundation for Statistical Computing). and EmpowerStats (version 4.1) software (https://www.empowerstats.net/cn/index.php#). Two-sided P-values were utilized. P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline characteristics. Out of the 15,560 participants who were included in the NHANES January 2017-March 2020 pre-pandemic database, 8,195 individuals were excluded because they were aged <20 years or had missing or invalid elastography examination data. This resulted in a final sample size of 7,395 patients. Among these adults, the mean age was 50.59 years, with 3,656 being male. The M probe was used to evaluate 5,381 adults (72.77%), whereas the XL probe was used for 2,014 adults (27.23%). The baseline characteristics of individuals based on current use of PPIs are presented in Table I. Compared with individuals who did not use PPIs, patients who took PPIs were significantly older, more likely to be female and Non-Hispanic White and had higher rates of obesity and comorbidities. Furthermore, PPI users demonstrated a greater prevalence of advanced liver fibrosis (7.72 vs. 5.73%) and hepatic steatosis (52.14 vs. 42.56%).

Table I. Features of the study populations according to current PPI use.

Characteristic	Total (n=7,395)	No PPI use (n=6,670)	PPI use (n=725)	P-value
Mean age, years	50.59±17.27	49.26±17.10	62.82±13.72	<0.01
Male (%)	3,656 (49.44)	3,332 (49.96)	324 (44.69)	<0.01
Race/ethnicity (%)				
Non-Hispanic White	2,510 (33.94)	2,167 (32.49)	343 (47.31)	<0.01
Hispanic	1,648 (22.29)	1,510 (22.64)	138 (19.03)	
Non-Hispanic Black	1,967 (26.60)	1,803 (27.03)	164 (22.62)	
Non-Hispanic Asian	904 (12.22)	855 (12.82)	49 (6.76)	
Other	366 (4.95)	335 (5.02)	31 (4.28)	
Education level (%)				<0.01
Less than high school	1,357 (16.35)	1,190 (17.84)	167 (23.03)	
High school graduate	1,781 (24.08)	1,598 (23.96)	183 (25.24)	
Some college or associate's degree	2,401 (32.47)	2,152 (32.26)	249 (34.34)	
College or above	1,847 (24.98)	1,722 (25.82)	125 (17.24)	
Body mass index, kg/m^2 (%)				<0.01
Underweight (<18.5)	101 (1.37)	95 (1.42)	6 (0.83)	
Normal weight (18.5-24.9)	1,810 (24.48)	1,692 (25.37)	118 (16.28)	
Overweight (25.0-29.9)	2,389 (32.31)	2,157 (32.34)	232 (32.00)	
Obese (>30.0)	3,028 (40.96)	2,673 (40.07)	355 (48.97)	
Ratio of family income to poverty (%)				0.72
<1.3	1,772 (23.96)	1,598 (23.96)	174 (24.00)	
1.3-4.9	2,492 (33.70)	2,240 (33.58)	252 (34.76)	
≥5.0	993 (13.43)	1,941 (29.10)	197 (27.17)	
Smoking status (%)				<0.01
Never smoked	4,325 (58.49)	3,957 (59.33)	368 (50.76)	
Former smoker	1,732 (23.42)	1,482 (22.22)	250 (34.48)	
Current smoker	1,338 (16.09)	1,231 (18.46)	107 (14.76)	
Alcohol abuse (%)	1,236 (16.71)	1,144 (17.15)	92 (12.69)	<0.01
Vigorous activity (%)	2,636 (36.65)	2,424 (36.34)	212 (29.24)	<0.01
Laboratory features				
Total cholesterol, mmol/l	4.82±1.05	4.84±1.05	4.67±1.07	<0.01
HDL-cholesterol, mmol/l	1.38±0.41	1.39±0.41	1.36±0.40	0.15
Triglycerides, mmol/l	1.57±1.23	1.55±1.22	1.77±1.35	<0.01
Glycohemoglobin, %	5.85±1.10	5.81±1.08	6.14±1.20	<0.01
AST, U/l	21.96±14.44	21.98±14.66	21.82±12.26	0.89
ALT, U/l	22.48±18.86	22.59±19.21	21.48±15.19	0.20
GGT, U/l	32.18±45.78	31.46±44.64	38.84±54.81	<0.01
Total bilirubin, μmol/l	7.84±4.72	7.86±4.74	7.65±4.50	0.21
Albumin, g/l	40.67±3.30	40.76±3.28	39.85±3.32	<0.01
Creatinine, μmol/l	79.51±40.21	78.62±38.36	87.75±53.79	<0.01
Uric acid, μmol/l	321.48±87.08	320.61±86.92	329.51±88.21	0.02
Platelet count, x10^9/μl	246.13±65.17	246.32±64.51	244.38±70.99	0.15
hsCRP, mg/l	3.98±8.27	3.78±7.00	5.86±15.62	<0.01
LSM≥9.7 KPa (%)	438 (5.92)	382 (5.73)	56 (7.72)	0.03
CAP≥274 dB/m (%)	3,217 (43.50)	2,839 (42.56)	378 (52.14)	<0.01
Comorbidities (%)				
Diabetes	1,390 (18.80)	1,139 (17.08)	251 (34.62)	<0.01
Hypertension	2,807 (37.96)	2,348 (35.20)	459 (63.31)	<0.01
Hypercholesterolemia	2,658 (35.84)	2,229 (33.42)	429 (59.17)	<0.01
Congestive heart failure	202 (2.73)	156 (2.34)	46 (6.34)	<0.01

Table I. Continued.

Characteristic	Total (n=7,395)	No PPI use (n=6,670)	PPI use (n=725)	P-value
Coronary heart disease	292 (3.95)	226 (3.39)	66 (9.10)	<0.01
Angina	171 (2.31)	129 (1.93)	42 (5.79)	<0.01
Stroke	342 (4.62)	259 (3.88)	83 (11.45)	<0.01
Asthma	1,144 (15.47)	986 (14.78)	158 (21.79)	<0.01
COPD	618 (8.36)	472 (7.08)	146 (20.14)	<0.01
Thyroid condition	849 (11.49)	704 (10.55)	145 (20.00)	<0.01
Arthritis	2,180 (29.48)	1,733 (25.98)	447 (61.66)	<0.01

AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transferase; hsCRP, high-sensitivity C-reactive protein; LSM, liver stiffness measurement; CAP, controlled-attenuation parameter; COPD, chronic obstructive pulmonary disease; HDL, high-density lipoprotein; PPI, proton pump inhibitor.

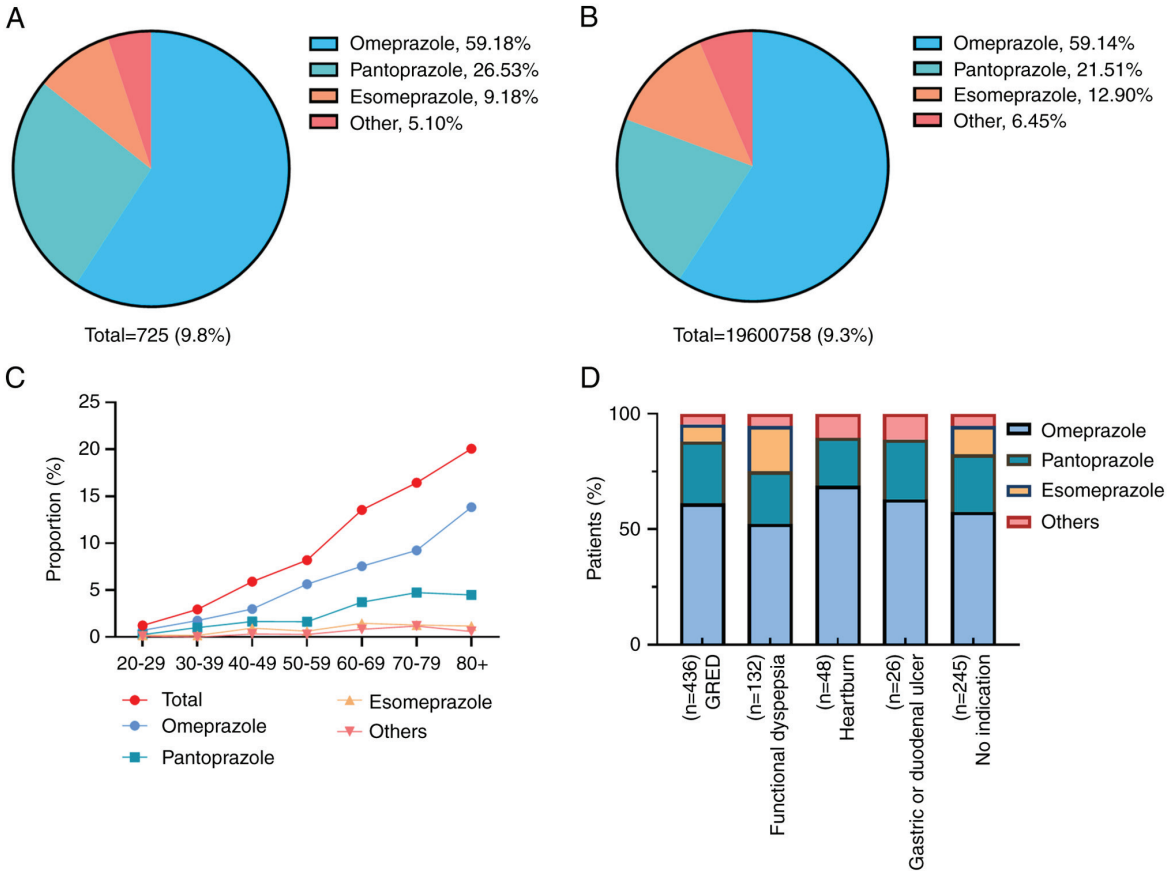

Figure 2. Proton pump inhibitor use. (A) Proportions of each type of prescribed proton pump inhibitor. (B) Proportions of prescriptions for each type of proton pump inhibitor were reanalyzed using the sampling weights provided by National Health and Nutrition Examination Survey. (C) Proportions of patients who received each type of proton pump inhibitor according to age. (D) Indications for proton pump inhibitor therapy. No indications indicate that individuals exhibited an unreasonable documented indication for prescription according to the American Gastroenterological Association Clinical Practice (2).

A total of 9.8% of individuals were prescribed PPIs (Fig. 2). Among the prescribed PPIs, omeprazole was the most commonly prescribed medication, accounting for 59.18% of prescriptions, followed by pantoprazole (26.53%), esomeprazole (9.18%) and other PPIs such as lansoprazole and rabeprazole (5.10%). The prevalence of prescription PPIs varied across age groups, with an estimated 1.25% of individuals aged 20-29 years having a prescription, compared with 20.08% of individuals aged >80 years. The primary indication for PPI use was gastro-esophageal reflux disease (60.14%), followed by functional dyspepsia (18.21%), heartburn (6.62%) and gastric or duodenal ulcers (3.59%). According to the American Gastroenterological Association Clinical Practice (2), 245 patients (33.79%) exhibited no indication for prescription.

Table II. Association between PPI use and hepatic steatosis.

	Model 1		Model 2		Model 3	
Characteristic	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
PPI use						
No	1		1		1	
Yes	1.47 (1.26-1.71)	<0.01	1.24 (1.05-1.45)	0.01	1.22 (1.04-1.43)	0.02[a]
PPI						
None	1		1		1	
Omeprazole	1.54 (1.27-1.88)	<0.01	1.26 (1.03-1.54)	0.03	1.25 (1.02-1.53)	0.03[a]
Pantoprazole	1.36 (1.02-1.82)	0.04	1.21 (0.90-1.62)	0.22	1.18 (0.88-1.59)	0.28
Esomeprazole	1.20 (0.74-1.94)	0.46	1.05 (0.64-1.71)	0.85	1.02 (0.63-1.66)	0.94
Other	1.77 (0.92-3.40)	0.09	1.57 (0.81-3.05)	0.18	1.49 (0.77-2.89)	0.24
Length of PPI use, years						
Not applicable	1		1		1	
<0.5	1.06 (0.70-1.60)	0.79	0.96 (0.63-1.47)	0.85	0.97 (0.63-1.48)	0.87
0.5-2.0	1.07 (0.73-1.56)	0.74	0.96 (0.66-1.42)	0.85	0.94 (0.64-1.39)	0.77
>2.0	1.66 (1.39-1.99)	<0.01	1.36 (1.13-1.65)	<0.01	1.34 (1.11-1.62)	<0.01[a]
Sex						
Male	1.59 (1.26-2.00)	<0.01	1.35 (1.06-1.72)	0.01	1.33 (1.04-1.70)	0.02[a]
Female	1.44 (1.17-1.78)	<0.01	1.12 (0.90-1.39)	0.31	1.09 (0.88-1.36)	0.42
Age, years						
20-39	1.72 (0.97-3.03)	0.06	1.87 (1.04-3.36)	0.04	1.86 (1.03-3.34)	0.04[a]
40-59	1.57 (1.16-2.12)	<0.01	1.60 (1.18-2.18)	<0.01	1.57 (1.16-2.14)	<0.01[a]
≥60	1.11 (0.91-1.35)	0.30	1.08 (0.88-1.32)	0.46	1.06 (0.87-1.30)	0.57
Race/ethnicity						
Non-Hispanic White	1.81 (1.44-2.28)	<0.01	1.60 (1.26-2.03)	<0.01	1.54 (1.21-1.97)	<0.01[a]
Hispanic	1.19 (0.84-1.70)	0.32	0.99 (0.68-1.43)	0.95	0.98 (0.67-1.42)	0.91
Non-Hispanic Black	1.28 (0.92-1.78)	0.14	1.07 (0.76-1.49)	0.71	1.05 (0.75-1.48)	0.76
Non-Hispanic Asian	0.96 (0.53-1.74)	0.90	0.86 (0.47-1.59)	0.64	0.86 (0.46-1.60)	0.63
Other	1.12 (0.53-2.35)	0.77	0.78 (0.36-1.71)	0.54	0.72 (0.31-1.65)	0.44
BMI						
Normal weight	1.51 (0.92-2.47)	0.10	0.99 (0.59-1.66)	0.96	0.98 (0.58-1.65)	0.94
Overweight	1.42 (1.08-1.87)	0.01	1.22 (0.91-1.63)	0.18	1.22 (0.91-1.63)	0.18
Obese	1.14 (0.90-,1.45)	0.29	0.98 (0.761.27)	0.90	0.98 (0.76-1.27)	0.89

Model 1, no variables adjusted; model 2, adjusted for age, sex and race/ethnicity adjusted; model 3, further adjusted for education, ratio of family income to poverty, smoking status, notable alcohol consumption and vigorous activity. [a]P<0.05. PPI, proton pump inhibitor; BMI, body mass index.

Association between PPI use and hepatic steatosis. Table II and Fig. 3 show the results of multivariable logistic regression analysis. According to model 1, PPI use was significantly associated with hepatic steatosis (OR, 1.47; 95% CI, 1.26-1.71). This association was unchanged even after adjusting for multiple confounding factors (model 3) (OR, 1.22; 95% CI, 1.04-1.43), particularly regarding omeprazole (OR, 1.25; 95% CI, 1.02-1.53). Furthermore, use of PPIs for >2 years exhibited a significant positive association with hepatic steatosis (OR, 1.34; 95% CI, 1.11-1.62). The use of PPIs was associated with hepatic steatosis in individuals aged 20-39 (OR, 1.86; 95% CI, 1.03-3.34) and 40-59 years (OR, 1.57; 95% CI, 1.16-2.14), as well as in males (OR, 1.33; 95% CI, 1.04-1.70) and non-Hispanic whites (OR, 1.54; 95% CI, 1.21-1.97). Furthermore, use of PPIs and CAP demonstrated similar outcomes in the modelling of steatosis severity using multivariable linear regression (Table SI).

Association between PPIs and advanced fibrosis. The present study subsequently examined the association between PPIs and advanced fibrosis (Table III). According to model 1, a significant association was found between PPI use and advanced fibrosis (OR, 1.38; 95% CI, 1.03-1.84). However, in model 3, there was no association between any PPI use and advanced fibrosis (OR, 0.98; 95% CI, 0.72-1.33). In the

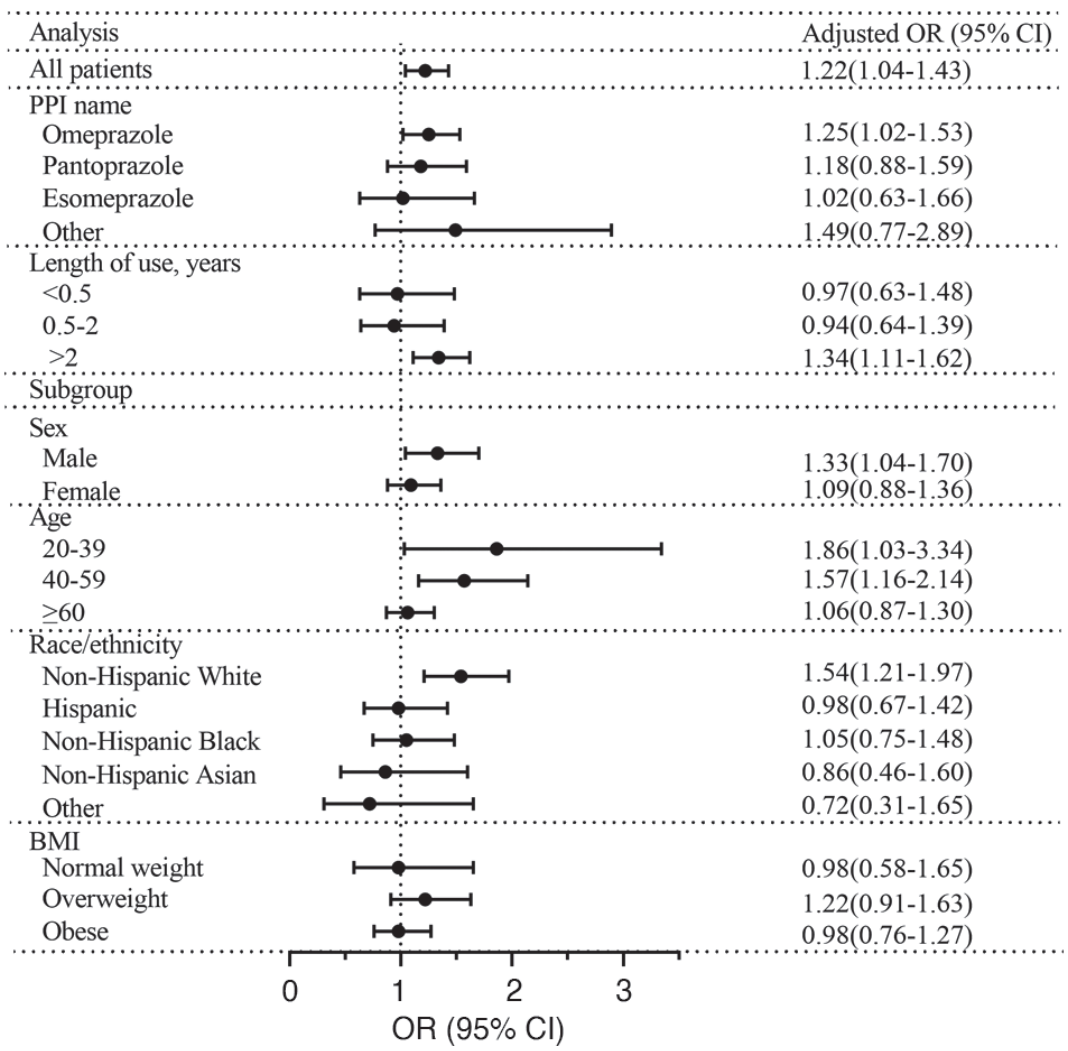

Figure 3. Association between PPI use and hepatic steatosis. Stratification was adjusted for age, sex, race/ethnicity, educational level, the ratio of family income to poverty, smoking status, notable alcohol consumption and vigorous activity, except for the stratification factor itself. PPI, proton pump inhibitor; BMI, body mass index.

subgroup analyses, stratified by sex, age, race/ethnicity, and body mass index, an insignificant association between use of PPIs and advanced fibrosis was observed in model 3. This was further supported by the multivariable linear regression, which showed no association between the use of any PPI and advanced fibrosis in all subgroups. (Table SII).

Sensitivity testing. Table SIII presents a summary of the findings of the sensitivity analyses. Following utilization of CAP ≥285 dB/m as a criterion for defining hepatic steatosis, the association between PPI use and hepatic steatosis was significant (OR, 1.19; 95% CI, 1.01-1.40). To mitigate the potential influence of other factors contributing to hepatic steatosis, the present study focused exclusively on patients with NAFLD. In logistic regression sensitivity analysis, use of PPIs was significantly associated with hepatic steatosis (OR, 1.50; 95% CI, 1.16-1.93; Table SIV). Furthermore, upon modifying the target population to individuals with MASLD and controlling for confounding variables, the association between the use of PPIs and hepatic steatosis persisted (OR, 1.26; 95% CI, 1.05-1.52; Table SV).

Associations between H2RAs and hepatic steatosis or advanced fibrosis. The findings are presented in Fig. 4 and Tables SVI and SVII. There was no significant difference in incidence of hepatic steatosis among users of H2RAs (OR, 1.20; 95% CI, 0.88-1.62; Table SVI). However, use of ranitidine was significantly associated with hepatic steatosis (OR, 1.56; 95% CI, 1.07-2.27; Table SVI). Furthermore, after adjusting for potential confounding factors (model 3), the use of H2RAs was significantly associated with an 85% greater incidence of advanced fibrosis, particularly in the case of ranitidine use and a duration of use >2 years (Fig. 4). There was a significant association between use of H2RAs and an elevated risk of advanced fibrosis in males (OR, 1.95; 95% CI, 1.04-3.64; Table SVII), individuals aged 40-59 years (OR, 3.65; 95% CI, 1.71-7.79; Table SVII) and individuals of Hispanic ethnicity (OR, 2.63; 95% CI, 1.12-6.15; Table SVII).

Discussion

In the present nationally representative cross-sectional study, use of PPIs was linked to hepatic steatosis. This association was

Table III. Association between PPI use and advanced fibrosis.

	Model 1		Model 2		Model 3	
Characteristic	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
PPI use						
No	1		1		1	
Yes	1.38 (1.03-1.84)	0.03	1.02 (0.75-1.38)	0.91	0.98 (0.72-1.33)	0.89
PPI						
None	1		1		1	
Omeprazole	1.32 (0.91-1.92)	0.15	0.95 (0.65-1.39)	0.79	0.91 (0.62-1.35)	0.65
Pantoprazole	1.52 (0.90-2.57)	0.12	1.15 (0.68-1.96)	0.60	1.09 (0.64-1.85)	0.76
Esomeprazole	1.03 (0.37-2.84)	0.96	0.83 (0.30-2.32)	0.73	0.83 (0.30-2.32)	0.73
Other	2.00 (0.70-5.66)	0.19	1.47 (0.51-4.22)	0.47	1.47 (0.51-4.23)	0.47
Length of PPI use, years						
Not applicable	1		1		1	
<0.5	0.76 (0.28-2.07)	0.59	0.66 (0.24-1.83)	0.43	0.68 (0.25-1.88)	0.46
0.5-2.0	1.45 (0.73-2.90)	0.29	1.22 (0.61-2.45)	0.57	1.16 (0.57-2.33)	0.68
>2.0	1.48 (1.07-2.06)	0.02	1.04 (0.74-1.46)	0.81	1.00 (0.71-1.40)	0.98
Sex						
Male	1.34 (0.90-1.99)	0.15	0.98 (0.65-1.48)	0.94	0.95 (0.63-1.44)	0.81
Female	1.52 (0.99-2.33)	0.06	1.05 (0.67-1.63)	0.85	1.00 (0.64-1.57)	0.99
Age, years						
20-39						
40-59	1.41 (0.80-2.51)	0.24	1.37 (0.77-2.44)	0.29	1.32 (0.73-2.37)	0.36
≥60	0.97 (0.68-1.37)	0.85	0.99 (0.69-1.40)	0.9	0.96 (0.67-1.37)	0.83
Race/ethnicity						
Non-Hispanic White	1.12 (0.73-1.73)	0.61	0.93 (0.60-1.46)	0.76	0.87 (0.56-1.37)	0.55
Hispanic	2.55 (1.48-4.38)	<0.01	1.67 (0.95-2.95)	0.08	1.69 (0.95-3,00)	0.08
Non-Hispanic Black	0.89 (0.431.87)	0.76	0.65 (0.31-1.39)	0.27	0.64 (0.30-1.37)	0.25
Non-Hispanic Asian	0.54 (0.07-4.00)	0.54	0.46 (0.06-3.49)	0.45	0.33 (0.04-2.72)	0.31
Other	1.69 (0.47-6.03)	0.42	1.62 (0.42-6.19)	0.48	1.62 (0.42-6.19)	0.53
BMI						
Normal weight	1.66 (0.58-4.76)	0.34	0.87 (0.29-2.56)	0.80	1.08 (0.35-3.29)	0.89
Overweight	1.22 (0.60-2.48)	0.58	0.72 (0.35-1.50)	0.38	0.62 (0.29-1.30)	0.21
Obese	1.09 (0.76-1.55)	0.64	0.89 (0.61-1.28)	0.52	0.88 (0.61-1.28)	0.51

Model 1, no variables adjusted; model 2, adjusted for age, sex and race/ethnicity adjusted; model 3, further adjusted for education, ratio of family income to poverty, smoking status, notable alcohol consumption and vigorous activity. PPI, proton pump inhibitor; BMI, body mass index.

observed after adjusting for various factors, with omeprazole showing a particularly strong association. Furthermore, prolonged use of PPIs was found to significantly increase risk of developing hepatic steatosis. This association persisted when hepatic steatosis was redefined using a cut-off value of CAP ≥285 dB/m and when focusing specifically on individuals with NAFLD or MASLD. The subgroup analysis demonstrated a heightened OR in the relationship between the use of PPIs and hepatic steatosis among male individuals aged 20 to 59 years, as well as those who were Non-Hispanic White. By incorporating the NHANES design to acquire national estimates for the US, the present results may exhibit generalizability to the adult outpatient population.

NAFLD is the liver component of a cluster of diseases associated with metabolic dysfunction and it has emerged as being the predominant etiology of chronic liver disease on a global scale, with a prevalence of 25.04% (29). The 'multiple hit' hypothesis is gaining increasing support as a comprehensive explanation for the progression of NAFLD (17,27,28). This hypothesis encompasses factors such as genetic predisposition, insulin resistance, lipid metabolism imbalance, oxidative and endoplasmic reticulum stress, inflammation and dysbiosis of the gut microbiota. These factors serve key roles in the development of NAFLD across diverse pathogenic stages (30,31).

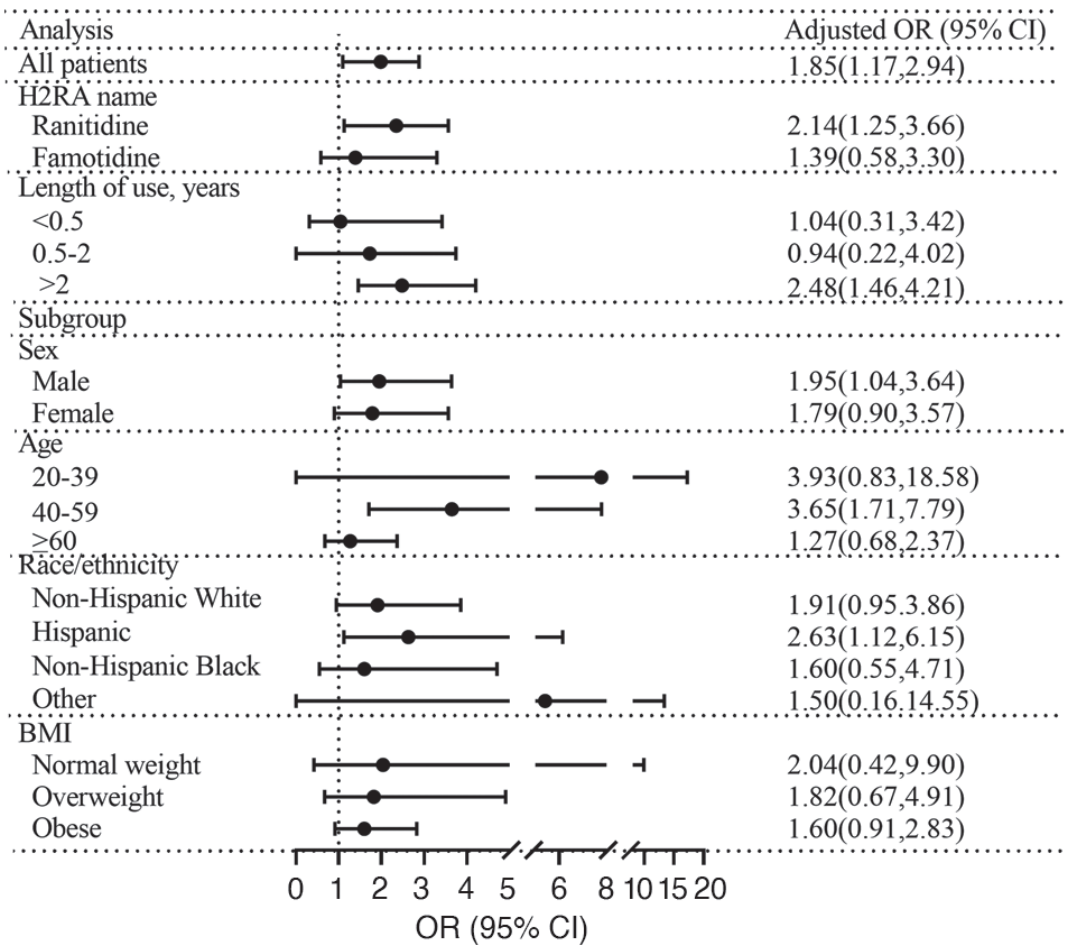

Figure 4. Association between the use of H2RA use and liver stiffness. Stratification was adjusted for age, sex, race/ethnicity, educational level, ratio of family income to poverty, smoking status, notable alcohol consumption and vigorous activity, except for the stratification factor. H2RA, H2-receptor antagonist.

Long-term PPI use has been reported to be associated with the risk of NAFLD, but this association remains controversial (32-35). Shen and Liangpunsakul (32) reported no significant association between the use of PPIs and the incidence of NAFLD (adjusted OR, 0.97; 95% CI, 0.87-1.29). However, the diagnosis of NAFLD relied solely on serum aminotransferase levels and was not confirmed by ultrasonography or liver biopsy. Consequently, certain study participants may have been misclassified as either having NAFLD or not. By contrast, a cohort study from South Korea reported that PPI use is associated with an increased risk of fatty liver disease [adjusted hazard ratio (aHR), 1.50; 95% CI, 1.44-1.57] (33). However, the aforementioned study investigated a single ethnic group (Koreans) (33) and future research should encompass diverse ethnicities. Furthermore, use of CAP for diagnosing steatosis may offer greater accuracy compared with diagnostic codes (which have a high rate of underdiagnosis in NAFLD). Moreover, Llorente *et al* (34) discovered that individuals who use PPIs are at a significantly greater risk of developing alcoholic liver disease than previous users (aHR, 1.37; 95% CI, 1.00-1.88) or those who never used PPIs (aHR, 1.52; 95% CI, 1.21–1.91). Llorente *et al* (34) focused on the relationship between PPI use and ALD and underlying mechanism (inducing overgrowth of intestinal *Enterococcus*). Huang *et al* (35) indicated that taking PPIs was associated with increased risk of NAFLD, especially severe hepatic steatosis (OR, 1.451, 95% CI, 1.034-2.036). The aforementioned study did not assess the dose-response effect of PPI treatment on the risk of NAFLD due to a lack of data on dosage and frequency of PPI use. In conclusion, the aforementioned studies were limited by a single ethnic group, inability to control for intricate confounding factors, inaccurate measures for categorizing liver disease such as diagnostic codes or indirect estimations of liver disease such as liver enzyme levels, absence of indications and categories for PPI use or inability to assess the degree of steatosis. Therefore, the present study conducted a large, nationally representative cross-sectional study using data from the NHANES.

Understanding of the potential mechanisms linking the use of PPIs to hepatic steatosis remains elusive. Numerous molecular mechanisms have been suggested for the increased risk of hepatic steatosis associated with PPI use. Primarily, PPIs may predispose patients to small intestinal bacterial overgrowth (8). Various pathogenetic mechanisms include diminished bacterial elimination, overgrowth of bacteria in the intestine, modified gastrointestinal motility, and augmented intestinal permeability (36). Llorente *et al* (34) conducted a study utilizing data from mouse models and humans and demonstrated that the use of gastric acid-suppressive medications contributes to the excessive

proliferation of *Enterococcus* in the intestine, thus facilitating the progression of liver disease. Likewise, multiple studies have indicated the potential role of the gut microbiota in mediating initiation and progression of NAFLD through the gut-liver axis (37-40). The potential underlying mechanisms include hepatic inflammatory response, impaired bile acid metabolic cycle, impaired choline metabolism, reduced production of short-chain fatty acids and endogenous alcohol production. These alterations have the potential to contribute to hepatic insulin resistance, inflammation (non-alcoholic steatohepatitis) and fibrosis. Furthermore, the administration of PPIs has been associated with a decrease in granulocyte and monocyte count, which is likely due to a decrease in oxidative bursts. This reduction in immune cell function may weaken systemic immunity (41). Several other potential mechanisms have been hypothesized to establish a connection between use of PPIs and development of hepatic steatosis. These mechanisms include PPI-induced hypomagnesemia, which leads to insulin resistance and low-grade systemic inflammation, decreased levels of insulin-like growth factor 1 and activation of the pregnane X receptor (42,43).

The present subgroup analysis showed demonstrated that among patients aged 20-9 years and male and Non-Hispanic White patients, those receiving PPI therapy had a greater risk of hepatic steatosis. This requires further investigation. A previous study reported that the one year change in body weight was 1.52±0.6 kilograms higher in male using PPI compared to men not using PPI, whereas female PPI users do not exhibit such a trend (44). The precise mechanisms underlying the association between weight gain and PPI use remain unclear, although there are no notable disparities in energy intake or indicators of energy expenditure (44). Here, the primary indication for prescribing PPIs was GERD. A double-blind randomized trial demonstrated that female patients with GERD may require lower dosages of PPIs than male patients (45). Nguyen *et al* (46) demonstrated a greater prevalence of Barrett's esophagus among Non-Hispanic Whites than African Americans. Additionally, Non-Hispanic Whites exhibit a greater likelihood of being male and using PPIs than African Americans (46). These findings potentially explain the outcomes of the present subgroup analysis. However, the present study had a limited sample size. Consequently, further well-designed prospective studies are warranted.

The present study examined the potential association between PPI therapy and VCTE-estimated liver fibrosis and hepatic steatosis, allowing more accurate determination of the degree of hepatic fibrosis and steatosis than other assessment methods. Additionally, the present study included PPI type and therapy duration as variables. The study sample was representative of the population at the national level and all of the patients had a comprehensive medical service utilization history. This contributes to a high level of generalizability of results and enables subgroup analyses with high statistical power. Furthermore, the present study employed rigorous exclusion criteria and effectively controlled for potential confounding factors by providing comprehensive data on lifestyles, including educational attainment, family income-to-poverty ratio, smoking status, alcohol misuse and vigorous physical activity. Additionally, the robustness of the present findings was substantiated through confirmation in multiple subgroups and sensitivity analyses.

The present study was subject to certain limitations due to its cross-sectional and observational design. First, as a cross-sectional analysis, it did not allow for the establishment of causality or identification of associations with clinical outcomes. Second, the exclusion of individuals who underwent unsuccessful VCTE examinations may result in the omission of a potentially significant at-risk group. Another limitation of the present study was that it used prescription data. Prescription data may not accurately reflect patient adherence and do not consider over-the-counter use of acid-suppressive therapies. Finally, potential influence of other confounding factors could not be eliminated.

In conclusion, PPI therapy was associated with an increased risk of hepatic steatosis in a representative sample of the US population. It may be advisable to prioritize the appropriate indication for PPIs and administer the lowest feasible dosage for the shortest possible duration in patients with fatty liver resulting from any etiology.

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Availability of data and materials

The data generated in the present study may be found in the NHANES database under accession number (NHANES 2017-March 2020 Pre-pandemic) or at the following URL: https://wwwn.cdc.gov/nchs/nhanes/.

Authors' contributions

HY and ML designed the study, performed the statistical analysis and drafted the manuscript. BL, HS, HJ, ZL and AS collected and analyzed the data. BW and YY revised the manuscript, conceived and designed the study and analyzed data. BW and YY confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

As the National Health and Nutrition Examination Survey data sets are completely de-identified and publicly available, this analysis was deemed exempt by the Institutional Review Board (Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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