HHS Public Access

Author manuscript

*J Clin Gastroenterol*. Author manuscript; available in PMC 2017 August 01.

Published in final edited form as:

*J Clin Gastroenterol*. 2016 August ; 50(7): 596–601. doi:10.1097/MCG.0000000000000503.

# Histamine H2-Receptor Antagonists Use Is Associated with Lower Prevalence of Nonalcoholic Fatty Liver Disease: A Population-Based Study from the National Health and Nutrition Examination Survey, 2001-2006

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## Abstract

**Background & Aim—**Recent basic mechanistic studies found that proton pump inhibitors (PPIs) or histamine antagonists inhibited multiple pathways involved in non-alcoholic fatty liver disease (NAFLD) development. The aim of this study was to investigate an association between PPIs or H1/H2-receptor antagonists (H1RAs/H2RAs) use and NAFLD prevalence in the general US population.

**Methods—**We conducted a cross-sectional analysis of data from the National Health and Nutrition Examination Survey, 2001 – 2006. We included 10,398 adults aged 20 – 74 years who had alanine aminotransferase (ALT) data; of those, 2,058 were identified as having NAFLD and 8,340 as controls. PPIs or H1RAs/H2RAs use was defined as use of prescription medications in the preceding month. The length of use was categorized as ≤ 60 days and > 60 days. NAFLD was defined as elevated serum aminotransferases without any indication of other causes of chronic liver disease.

**Results—**In the multivariate unconditional logistic regression analysis, H2RAs use was inversely associated with prevalent NAFLD (odds ratio [OR] = 0.43, 95% confidence interval [CI] 0.18 – 0.99), a finding that was primarily limited to men (OR = 0.18, 95% CI 0.04 – 0.79) and those with insulin resistance (OR = 0.22, 95% CI 0.05 – 0.95). However, no significant associations were found between PPIs or H1RAs use and prevalent NAFLD.

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Both authors have read and approved the manuscript for submission. Both have made a substantial contribution to the conception, design, gathering, analysis and/or interpretation of data and a contribution to the writing and intellectual content of the article; and acknowledge that they have exercised due care in ensuring the integrity of the work

**Conflicts of Interest:** Both authors report no conflicts of interest relevant to this manuscript

Part of this work was presented at the Digestive Disease Week 2015, Washington, DC

**Conclusion—**These findings, from the first human study to investigate an association of PPIs or H1RAs/H2RAs use with NAFLD, suggest that H2RAs use may be associated with a lower prevalence of NAFLD, primarily among men with insulin resistance.

### Keywords

histamine antagonists; proton pump inhibitor; NAFLD

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases worldwide. It comprises of the spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from simple steatosis to steatohepatitis (NASH) and cirrhosis[1]. While simple steatosis is quite benign with slow histological progression, NASH is associated with hepatic injury and inflammation; which can lead to the development of fibrosis and cirrhosis[1].

The molecular mechanism triggering NASH is poorly understood. Histologically, NASH is manifested by inflammatory cell infiltration. Sustained inflammation in the liver is critical in the progression of NAFLD. Compelling data indicates that inflammatory cells play a key role in the initiation and perpetuation of the inflammatory response and the progression of liver disease in NASH[2-4].

A histamine antagonist consists of two common types of drugs: histamine H1-receptor antagonists (H1RAs) and histamine H2-receptor antagonists (H2RAs). H1RAs are commonly used to treat allergic reactions[5]. H2RAs act on the H2 histamine receptors commonly found at the parietal cells on the gastric mucosa[6]. Blocking this receptor reduces gastric acid secretion[6]. Proton pump inhibitors (PPIs) are another class of drugs with potent inhibition of gastric acid secretion[7]. In addition to anti-allergic and anti-acid secretory effects, these medications have been found to have anti-oxidant properties and direct effects on inflammatory cells including monocytes that might prevent inflammation[7-9]. The anti-inflammatory properties of these commonly used medications might influence the inflammatory cascades within and outside respiratory and gastrointestinal tracts.

There have been no reported human studies that explored the association between anti-histamines or PPIs and NAFLD. The objective of this study was to investigate an association between anti-histamines or PPIs use and the prevalence of NAFLD in the US population using the data from the National Health and Nutrition Examination Survey (NHANES) 2001-2006.

## METHODS

### Study population

The data were obtained from three continuous cycles of the NHANES conducted between 2001 and 2006 using a complex, multistage, stratified, clustered, probability sample design to select a representative sample of the civilian, non-institutionalized US population. The three survey cycles of 13,248 participants included data interviews, physical examinations,

and laboratory tests with blood and urine samples collection. Parameters were transformed according to the provided guidelines to make the data comparable between the cycles[10]. A detailed description of the survey and its sampling procedures are available elsewhere. The study was approved by the National Center for Health Statistics (NCHS) Ethics Review Board.

The inclusion criteria were age 20 – 74 years old and the availability of complete demographic, social, clinical, and laboratory data. We excluded 1,435 subjects without alanine aminotransferase (ALT) data and 1,415 subjects with conditions other than NAFLD that might cause serum aminotransferases elevation. These conditions included excessive alcohol consumption, viral hepatitis, iron overload, and use of medications associated with hepatotoxicity (androgens, antivirals medications, antifungals medications, nitrofuratoin, phenytoin, sulfonamides, trazadone, or tetracycline). A total of 10,398 participants were eligible for analysis (Figure 1).

## Data collection

Standardized questionnaires were used to obtain self-reported data on sex, age, race or ethnicity, education, income, smoking, alcohol consumption, physical activity, medical conditions, and drug use[11]. Body mass index was calculated based on the standardized measurements of height and weight. Systolic and diastolic blood pressure was considered the mean of six or fewer measurements obtained at the household interview (maximum of three) and the physical examination (maximum of three).

Race or ethnicity was categorized as non-Hispanic whites, non-Hispanic blacks, Mexican-American, other Hispanics, and other, which included Aleut, Eskimo, American Indian, Asian or Pacific Islander. Education, according to completed years of schooling, was categorized as ≤ 8 years, 9 – 12 years, and ≥ 12 years. Economic status, according to the subject's household income for the previous year, was categorized as ≤ $15,000, $15,001 – $25,000, and ≥ $25,000.

Smoking status was categorized as never, former, and current. Current smokers were defined as persons who reported having smoked > 100 cigarettes during their lifetime and who currently smoke some days or every day. Former smokers were those who reported having smoked > 100 cigarettes during their lifetime but did not smoke at the time of interview. Never smokers were those who smoked < 100 cigarettes during their lifetime[12]. Excessive alcohol consumption was defined as ≥1 drink/day for women and ≥2 drinks/day for men[13]. Participants were categorized as sedentary if they chose the option: "you sit during the day and do not walk about very much".

Proton pump inhibitors (PPIs) or H1/H2-receptor antagonists (H1RAs/H2RAs) use was defined as the use of these medications during the month prior to the interview. The length of use was categorized as ≤ 60 days and > 60 days.

Insulin resistance was defined as a homeostasis of model assessment score (HOMA ) > 3.0[14]; elevated serum aminotransferases were defined as ALT > 40 U/L or aspartate

aminotransferase (AST) > 37 U/L in men, and ALT or AST > 31 U/ L in women; and transferrin saturation was considered as elevated when the values were ≥ 50%[15].

### Definitions of NAFLD and controls

NAFLD was defined as the presence of elevated serum aminotransferases without any indication of other causes of chronic liver disease such as viral hepatitis infection (defined as a positive HCV RNA or HBsAg test), iron overload, or excessive alcohol consumption. This definition is in accordance with our previous study and previous publications on NAFLD using NHANES dataset[16-18]. Controls were defined as participants with normal liver enzymes and no evidence of chronic liver disease.

### Statistical analyses

Sample weights were used to account for nonresponse and unequal probabilities of selection. Stratum and sampling units accounted for the complex survey design using Taylor series linearization. Demographic and clinical differences between study participants with and without prevalent NAFLD were compared using the student t-test or chi-square test, as appropriate. Unconditional multivariate logistic regression was used to assess the association between PPIs or H1RAs/H2RAs and NAFLD. Potential confounders, which included age, sex, ethnicity, socioeconomic status, BMI, physical activity, smoking status, diabetes or insulin resistance, hypertension or systolic/diastolic blood pressure, hypercholesterolemia or serum total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL), were assessed in stepwise regression models. The final models included for age, sex, ethnicity, socioeconomic status, waist circumference, physical activity, smoking status, insulin resistance (IR), systolic/diastolic blood pressure, and hypercholesterolemia as covariates. We also conducted analyses stratified on other risk factors, including sex, age, insulin resistance, hypertension, hypercholesterolemia, body mass index (BMI), and physical activity. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). A p-value ≤ 0.05 (2-sided) was considered statistically significant.

## RESULTS

### Demographic and clinical characteristics of the study participants

Of the 10,398 participants included for the main analyses, 2,058 were identified as having NAFLD and 8,340 as controls. Selected characteristics of the study participants, according to NAFLD status, are summarized in Table 1. On average, participants with NAFLD were nearly 1.5 years younger and had higher systolic and diastolic blood pressures; higher serum triglycerides and total and LDL-cholesterol and lower HDL-cholesterol levels; and higher circulating glycated hemoglobin, liver enzymes, and uric acid levels. Those with NAFLD were more likely to be men, obese, and Mexican-American. They had less education with higher prevalence of insulin resistance. Participants with NAFLD were less likely to take H1RAs/H2RAs and more likely to take PPIs in the prior month.

### Associations of H1RAs/H2RAs and PPIs and the prevalence of NAFLD

The results are summarized in Tables 2 and 3. After adjustment for potential confounders, the use of H2RAs was significantly associated with lower prevalence of NAFLD by 57%

regardless of the length of use, when compared to those who did not take H2RAs. The decreasing in the prevalence of NAFLD among H2RA users was only observed in men (OR 0.18, 95%CI 0.04-0.79) and those with insulin resistance (OR 0.22, 95%CI 0.05-0.95). There was no difference in the prevalent NAFLD among H1RA and PPI users (Tables 2, 4 and 5).

## DISCUSSION

Our cross-sectional study results to investigate an association of H1RAs/H2RAs or PPIs use with NAFLD suggest that only the use of H2RAs was associated with a lower prevalence of NAFLD in the general US population, primarily among men and those with insulin resistance.

The pathogenesis of NAFLD and the progression to NASH are complex, involving a combination of lipid oxidation, oxidative stress, inflammatory cells as well as proinflammatory cytokines[1, 16]. Alterations in lipid metabolism drive the polarization of the Kupffer cells into the proinflammatory phenotype; which trigger the recruitment of inflammatory cells and the progression of underlying NAFLD [2]. Several signaling cascades are also affected. Among them are the NFκB and the c-Jun-N terminal kinases (JNK). Their activation contribute to worsening steatosis and hepatic inflammation[2].

Histamine antagonists and PPIs are two medication classes which are most commonly used in the United States[19]. There are several proposed molecular mechanisms underlying the possible effectiveness of histamine antagonists and PPIs against NAFLD. Histamine can influence numerous functions of the cells involved in the regulation of immune response including macrophages[20]. In fact, macrophages express histamine receptors and also secrete histamine, which can selectively recruit the major effector cells into tissue leading to chronic inflammation[20]. Because of these reasons, it is speculated that modulation of histamine's function through the use of antagonists might interfere with its inflammatory effects. In fact, several studies have shown that both H1RAs and H2RAs suppress inflammatory responses via inhibition of NFκB, p38 MAP, and JNK[8, 21, 22]. PPIs are potent blockers of gastric acid secretion and have been found to have anti-oxidant properties through their effects on inflammatory cells thus mitigating inflammation[7, 23].

We found that only H2RAs were significantly associated with lower prevalence of NAFLD. The explanation of our observations is unclear. . Though H1RAs and H2RA2 have been shown to inhibit inflammation[9], their role in the pathogenesis of NAFLD is still elusive. In fact, a previous study found that H1RAs exacerbate high fat diet-induced hepatic steatosis in mice[24]. While NAFLD with hepatic triglyceride accumulation was observed in H2RA null mice[25], the study by Wake et al., on the other hand, found that H2RAs inhibit the expression and the production of inflammatory cytokines in human peripheral blood mononuclear cells[26]. Additionally, though some of the anti-inflammatory actions that have been observed by PPIs, it is not clear that oral PPIs dosing can achieve the high drug concentrations in plasma and tissue to reproduce the effect observed in vitro studies[7].

The gender difference on the effect of H2RAs and the prevalence of NAFLD deserves further discussion. Flores et al conducted a study to determine if differences exist in the pharmacokinetic (PK) parameters of oral ranitidine caused by gender. Twenty subjects (10 men and 10 women) were enrolled when subjects received a tablet dose of 300 mg ranitidine (H2RA) and blood samples were drawn at several times after its ingestion for the PK analysis. It is interesting that the clearance of the medication was higher in women[27]. In another ranitidine PK study of 16 healthy volunteers (8 men and 8 women), the oral clearance is ~10.5% higher in women than that in men[28]. It is plausible that our findings reflect the gender differences in the PK of H2RAs.

It is unclear on why the effect of H2RAs is primarily observed in patients with insulin resistance. Gentile et al. evaluated the role of ranitidine on glucose, insulin levels in 9 healthy volunteers. Interestingly they found that ranitidine infusion influences hepatic clearance of glucose and insulin[29]. The effect of H2RAs on insulin/glucose hemostasis and its effect on NAFLD might need to be investigated further.

This study has several limitations. First, the cross sectional study design of NHANES prohibits the assessment for the causality between the use of H2RAs and NAFLD association. It is also important to note that the NHANES dataset only reports prescription medication use. Several H1RAs, H2RAs and PPIs are available without a prescription. It is possible that there were participants taking these medications from the over the counter sources which were not captured in the dataset. Additionally, the information on the exact doses of these medications and the duration of administration are also lacking. The study design also disallows us to determine the compliance with the medications in these subjects. Second, the data on inflammatory markers such as TNF alpha are not available. Hence, we cannot directly test the differences in their levels in these subjects, stratified by anti-histamine or PPI use. Lastly, the diagnosis of NAFLD was based on serum aminotransferases, but not confirmed by ultrasonography or liver biopsy; therefore, some study participants may have been misclassified as having NAFLD or not. We and others have used the definition of abnormal ALT in subjects without excessive alcohol use and other chronic liver disease etiologies, as the indirect marker for the presence of NAFLD[18, 30, 31]. In fact, when compared to those with normal ALT, these subjects were more obese and had several features of metabolic syndrome mimicking those with NAFLD[18]. Despite these weaknesses, our study is strengthened by the sample size and the study cohort representing the US population.

In conclusion, we found that the use of H2RAs may be associated with a lower prevalence of NAFLD, primarily among men with insulin resistance. Further studies are needed to confirm our observation.

## Acknowledgments

**Sources of funding:** This study is supported by K08 AA016570 from the NIH/NIAAA, 1I01CX000361-01 from the Veterans Affairs Research and Administration, Indiana University Research Support Fund Grant, and W81XWH-12-1-0497 from United States Department of Defense (All to S.L)

## List of Abbreviations

| | |
|---|---|
| **BP** | Blood pressure |
| **H1RA** | histamine H1-receptor antagonist |
| **H2RA** | histamine H2-receptor antagonist |
| **NAFLD** | non-alcoholic fatty liver disease |
| **NHANES** | National Health and Nutrition Examination Survey |
| **PPI** | proton pump inhibitor |

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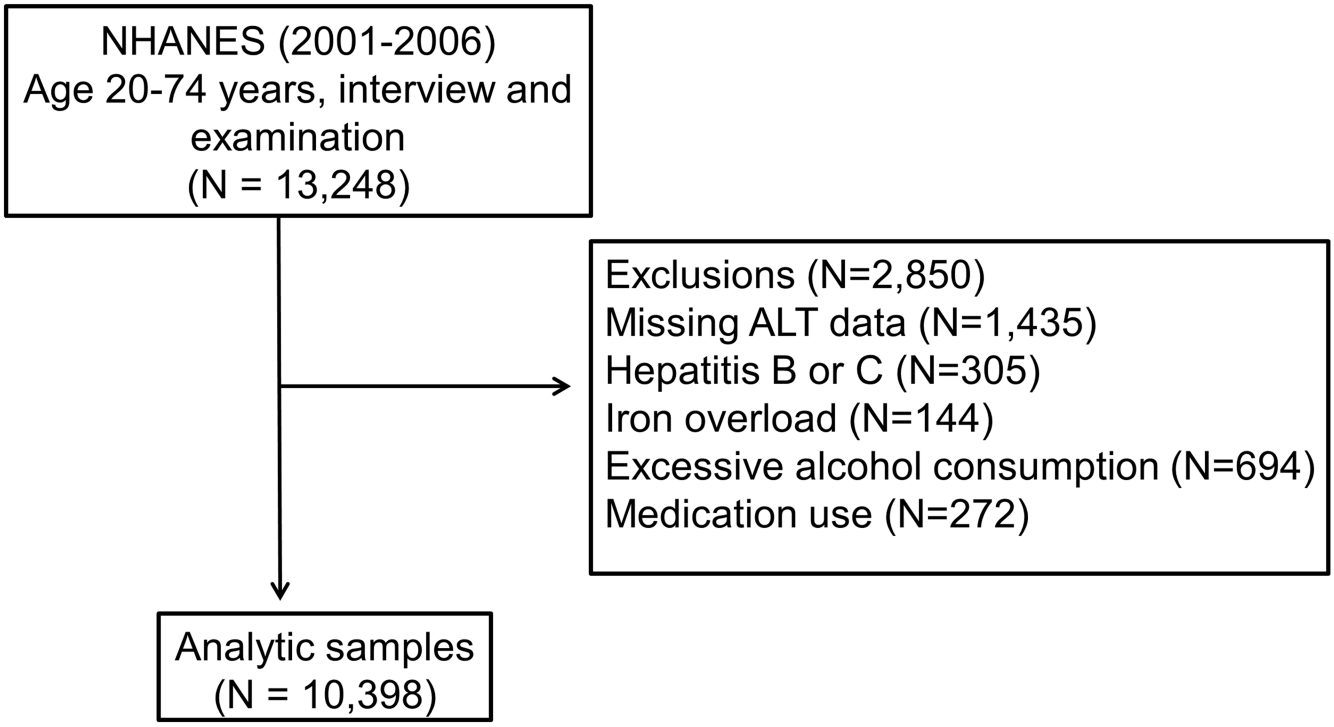


**Figure 1. Schematic diagram on the selection of the study participants**

## Table 1

**Selected characteristics of the study participants, according to NAFLD prevalence; NHANES, 2001 – 2006***

| | Controls (n = 8,340) | NAFLD Cases (n = 2,058) | P-value£ |
|---|---|---|---|
| Age (yrs.) | 44.8 ± 0.2 | 43.2 ± 0.3 | < 0.01 |
| Men (%) | 39.8 ± 0.5 | 66.2 ± 1.0 | < 0.01 |
| Race or ethnicity (%) | | | |
| Mexican-American | 21.4 ± 0.4 | 30.4 ± 1.0 | < 0.01 |
| Other Hispanic | 3.5 ± 0.2 | 5.3 ± 0.5 | |
| Non-Hispanic White | 48.6 ± 0.5 | 45.5 ± 1.1 | |
| Non-Hispanic Black | 22.4 ± 0.5 | 15.0 ± 0.8 | |
| Other | 4.1 ± 0.2 | 3.7 ± 0.4 | |
| Annual household income (%) | | | |
| ≤ $15,000 | 13.9 ± 0.4 | 11.9 ± 0.7 | 0.03 |
| $15,001 – $25,000 | 15.1 ± 0.4 | 14.4 ± 0.8 | |
| > $25,000 | 71.0 ± 0.5 | 73.7 ± 1.0 | |
| Education (%) | | | |
| ≤ 8 years | 11.4 ± 0.3 | 14.8 ± 0.8 | < 0.01 |
| 9 – 12 years | 15.2 ± 0.4 | 14.9 ± 0.8 | |
| > 12 years | 73.3 ± 0.5 | 70.3 ± 1.0 | |
| Body mass index (kg/m$^2$) | 28.5 ± 0.1 | 30.3 ± 0.1 | < 0.01 |
| Waist circumference (cm) | 96.7 ± 0.2 | 102.3 ± 0.3 | < 0.01 |
| Physical activity (Sedentary) (%) | 23.3 ± 0.5 | 21.6 ± 0.9 | 0.10 |
| Smoking status (%) | | | |
| Never smokers | 54.8 ± 0.5 | 53.6 ± 1.1 | 0.07 |
| Former smokers | 23.0 ± 0.5 | 25.4 ± 1.0 | |
| Current smokers | 22.1 ± 0.5 | 21.0 ± 0.9 | |
| Diabetes† (%) | 9.9 ± 0.3 | 8.6 ± 0.6 | 0.09 |
| Hypertension† (%) | 28.2 ± 0.5 | 28.6 ± 1.0 | 0.78 |
| Hypercholesterolaemia† (%) | 39.3 ± 0.7 | 44.9 ± 1.4 | < 0.01 |
| Insulin resistance¥ (%) | 32.0 ± 0.7 | 56.2 ± 1.6 | < 0.01 |
| Glycated hemoglobin (%) | 5.5 ± 0.01 | 5.7 ± 0.02 | < 0.01 |
| Systolic BP (mm Hg) | 122.0 ± 0.2 | 123.3 ± 0.4 | < 0.01 |
| Diastolic BP (mm Hg) | 70.0 ± 0.1 | 72.9 ± 0.3 | < 0.01 |
| Serum triglycerides (mmol/L) | 1.6 ± 0.02 | 2.1 ± 0.06 | < 0.01 |
| Serum total cholesterol (mmol/L) | 5.2 ± 0.01 | 5.4 ± 0.03 | < 0.01 |
| Serum LDL-cholesterol (mmol/L) | 3.0 ± 0.01 | 3.2 ± 0.04 | < 0.01 |

| | **Controls (n = 8,340)** | **NAFLD Cases (n = 2,058)** | **P-value[£]** |
|---|---|---|---|
| Serum HDL cholesterol (mmol/L) | 1.4 ± 0.005 | 1.2 ± 0.008 | < 0.01 |
| Serum alanine aminotransferase (U/L) | 19.4 ± 0.1 | 47.0 ± 1.0 | < 0.01 |
| Serum aspartate aminotransferase (U/L) | 21.4 ± 0.1 | 35.9 ± 0.5 | < 0.01 |
| Serum γ-glutamyltransferase (U/L) | 21.8 ± 0.2 | 48.4 ± 1.5 | < 0.01 |
| Serum uric acid (μmol/L) | 303.1 ± 0.9 | 345.7 ± 1.9 | < 0.01 |
| PPIs use (%) | 6.1 ± 0.3 | 6.4 ± 0.5 | 0.59 |
| H2RAs use (%) | 1.8 ± 0.1 | 1.7 ± 0.3 | 0.91 |
| H1RAs use (%) | 3.4 ± 0.2 | 2.7 ± 0.4 | 0.14 |

[*] Values are percentages ± standard errors (SE) for categorical variables and means ± SE for continuous variables

[£] From Student t-test for continuous variables and chi square test for categorical variables

[†] Self-reported doctor diagnosis and medication use

[¥] Insulin resistance was defined as a homeostasis of model assessment score, or HOMA, > 3.0

## Table 2

**Association of proton-pump inhibitors (PPIs) or H1/H2-receptor antagonists (H1RAs/ H2RAs) use with prevalent NAFLD; NHANES, 2001 – 2006**

| | Crude OR (95% CI) | Adjusted[¥] OR (95% CI) |
|---|---|---|
| *PPIs use* | | |
| No | 1.00 | 1.00 |
| Yes | 1.06 (0.87 – 1.29) | 0.97 (0.67 – 1.39) |
| *Length of use* | | |
| Never | 1.00 | 1.00 |
| ≤ 60 days | 1.31 (0.77 – 2.23) | 0.86 (0.24 – 3.08) |
| > 60 days | 1.03 (0.83 – 1.27) | 0.98 (0.67 – 1.43) |
| | | $P_{trend}^{*} = 0.70$ |
| *H2RAs use* | | |
| No | 1.00 | 1.00 |
| Yes | 0.98 (0.68 – 1.41) | **0.43 (0.18 – 0.99)** |
| *Length of use* | | |
| Never | 1.00 | 1.00 |
| ≤ 60 days | 1.74 (0.79 – 3.80) | 0.47 (0.05 – 3.97) |
| > 60 days | 0.85 (0.56 – 1.30) | 0.42 (0.16 – 1.09) |
| | | $P_{trend}^{*} = 0.67$ |
| *H1RAs use* | | |
| No | 1.00 | 1.00 |
| Yes | 0.80 (0.60 – 1.07) | 0.78 (0.46 – 1.31) |
| *Length of use* | | |
| Never | 1.00 | 1.00 |
| ≤ 60 days | 1.07 (0.57 – 2.03) | 0.44 (0.05 – 3.61) |
| > 60 days | 0.75 (0.54 – 1.04) | 0.81 (0.47 – 1.40) |
| | | $P_{trend}^{*} = 0.10$ |

Abbreviations: NAFLD, non-alcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; CI, confidence interval; IR, insulin resistance

[*] Cochran-Armitage trend test

[¥] Unconditional logistic regression model, adjusted for age, sex, ethnicity, socioeconomic status, waist circumference, physical activity, smoking status, insulin resistance (IR), systolic/diastolic blood pressure, and hypercholesterolemia

## Table 3

**Association of $H_2$-receptor antagonists (H2RAs) use with prevalent NAFLD according to selected risk factors; NHANES, 2001 – 2006**

| | Crude OR (95% CI) | Adjusted[¥] OR (95% CI) |
|---|---|---|
| Sex | | |
| *Male* | 0.88 (0.55 – 1.42) | **0.18 (0.04 – 0.79)** |
| *Female* | 1.04 (0.57 – 1.92) | 0.78 (0.26 – 2.35) |
| Age | | |
| *≤ 60 yrs.* | 1.03 (0.62 – 1.69) | 0.39 (0.11 – 1.38) |
| *> 60 yrs.* | 1.25 (0.72 – 2.17) | 0.46 (0.13 – 1.57) |
| BMI | | |
| *< 25* | 2.20 (0.94 – 5.12) | 2.15 (0.53 – 8.75) |
| *25-30* | 0.93 (0.51 – 1.69) | 0.31 (0.07 – 1.37) |
| *≥ 30* | 0.66 (0.37 – 1.15) | 0.13 (0.02 – 1.05) |
| IR | | |
| *No* | 0.80 (0.34 – 1.88) | 0.72 (0.25 – 2.11) |
| *Yes* | 0.33 (0.13 – 0.86) | **0.22 (0.05 – 0.95)** |

OR, odds ratio; CI, confidence interval; IR, insulin resistance

[¥]Unconditional logistic regression model, adjusted for PPIs and H1RAs use, age, sex, ethnicity, socioeconomic status, waist circumference, physical activity, smoking status, insulin resistance (IR), systolic/diastolic blood pressure, and hypercholesterolemia

## Table 4

**Association of $H_1$-receptor antagonists (H1RAs) use with prevalent NAFLD according to selected risk factors; NHANES, 2001 – 2006**

| | Crude OR (95% CI) | Adjusted[¥] OR (95% CI) |
|---|---|---|
| Sex | | |
| *Male* | 1.12 (0.76 – 1.65) | 1.20 (0.62 – 2.32) |
| *Female* | 0.65 (0.40 – 1.06) | 0.34 (0.11 – 1.13) |
| Age | | |
| *≤ 60 yrs.* | 0.74 (0.53 – 1.02) | 0.74 (0.39 – 1.40) |
| *> 60 yrs.* | 1.16 (0.63 – 2.13) | 1.05 (0.39 – 2.82) |
| BMI | | |
| *< 25* | 0.48 (0.19 – 1.19) | 0.79 (0.17 – 3.62) |
| *25-30* | 0.94 (0.60 – 1.48) | 1.01 (0.46 – 2.23) |
| *≥ 30* | 0.78 (0.50 – 1.21) | 0.54 (0.24 – 1.24) |
| IR | | |
| *No* | 0.57 (0.28 – 1.13) | 0.83 (0.38 – 1.78) |
| *Yes* | 0.96 (0.55 – 1.69) | 0.77 (0.37 – 1.62) |

OR, odds ratio; CI, confidence interval; IR, insulin resistance

[¥] Unconditional logistic regression model, adjusted for PPIs and H2RAs use, age, sex, ethnicity, socioeconomic status, waist circumference, physical activity, smoking status, insulin resistance (IR), systolic/diastolic blood pressure, and hypercholesterolemia

## Table 5

**Association of proton-pump inhibitors (PPIs) use with prevalent NAFLD according to selected risk factors; NHANES, 2001 – 2006**

| | Crude OR (95% CI) | Adjusted[¥] OR (95% CI) |
|---|---|---|
| Sex | | |
| *Male* | 0.85 (0.65 – 1.12) | 0.98 (0.59 – 1.62) |
| *Female* | 1.44 (1.08 – 1.93) | 0.98 (0.56 – 1.70) |
| Age | | |
| *≤ 60 yrs.* | 1.34 (1.06 – 1.70) | 1.09 (0.67 – 1.77) |
| *> 60 yrs.* | 0.86 (0.59 – 1.26) | 0.75 (0.42 – 1.35) |
| BMI | | |
| *< 25* | 1.30 (0.77 – 2.19) | 1.17 (0.48 – 2.90) |
| *25-30* | 0.80 (0.56 – 1.14) | 0.92 (0.49 – 1.75) |
| *≥ 30* | 1.07 (0.81 – 1.40) | 1.05 (0.62 – 1.78) |
| IR | | |
| *No* | 0.72 (0.44 – 1.17) | 0.76 (0.41 – 1.40) |
| *Yes* | 1.07 (0.75 – 1.53) | 1.10 (0.69 – 1.76) |

OR, odds ratio; CI, confidence interval; IR, insulin resistance

[¥]Unconditional logistic regression model, adjusted for H1RAs and H2RAs use, age, sex, ethnicity, socioeconomic status, waist circumference, physical activity, smoking status, insulin resistance (IR), systolic/diastolic blood pressure, and hypercholesterolemia