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Association of Proton Pump Inhibitor Use with the risk of kidney stones in NHANES population

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Abstract

Objective Several studies have suggested a potential link between proton pump inhibitors (PPIs) use and the risk of kidney stones, attributed to alterations in urine mineral levels. Our study aimed to investigate the association between PPI use and kidney stones in US adults.

Design Cross-sectional study.

Setting National Health and Nutrition Examination Survey (NHANES) (2007–2018).

Participants A total of 27,075 individuals with complete information for PPI use and history of kidney stones were included in this study.

Primary and secondary outcome measures Nonlinear analysis, logistic regression analysis, and subgroup analysis were conducted to estimate the relationship of PPI use with incident and recurrent kidney stones, after adjusting for potential confounding factors.

Results Multivariate logistic regression analysis revealed a significant association between PPI use and incident kidney stones (odds ratio [*OR*] 1.31, 95%*CI* 1.07–1.60), with a 4% increase in the incidence of kidney stones for each additional year of PPI use ($P < 0.001$). Similarly, PPI use was significantly associated with recurrent kidney stones (*OR* 1.49, 95%*CI* 1.04–2.13), with a 7%

increase in the incidence of recurrent kidney stones for each additional year of PPI use ($P < 0.001$). Furthermore, these associations remained significant even after conducting propensity score matching analysis on a subset of PPI users and non-users (all $P \leq 0.001$). Subgroup analyses showed that the effects of PPI use on kidney stones differed by age, sex, race, and BMI.

Conclusions This study indicated that long-term use of PPI was associated with a higher risk of both incident and recurrent kidney stones.

Keywords: NHANES; urolithiasis; proton pump inhibitors; risk factors; drug effects

STRENGTHS AND LIMITATIONS OF THIS STUDY

The NHANES dataset comprises a representative sample of the national population to ensure that our findings can be extrapolated to the broader population.

This is the first study to explore the positive relationship between PPI use and recurrent kidney stones in patients with history of nephrolithiasis.

Multiple potential confounders were adjusted and PSM design was performed to ensure the reliability of the results.

It is difficult to draw causal conclusions from such cross-sectional analyses.

NHANES may did not record information regarding the time and type of kidney stones and the dosage and type of PPI use.

Introduction

Kidney stone is a common disease in US, with a high prevalence of 12% of men and 10% of women, and caused high cost and morbidity(1, 2). Some drugs may affect the risk of kidney stones by altering active compounds crystallizing in urine or substances impairing urine composition(3-5).

Proton pump inhibitors (PPIs) are commonly prescribed medications worldwide for the treatment of gastric acid-related diseases such as gastroesophageal reflux disease (GERD), H. pylori infection, and gastric ulcers(6). However, the escalating prevalence of PPI overuse, especially for long-term therapy, has become a concerning issue(6, 7). Long-term PPI intake is associated with a reduction in intestinal absorption of essential vitamins and minerals and increased susceptibility to infections, chronic kidney disease, and dementia(7). Given that PPI can

inhibit gastric acid secretion, thereby affecting the intestinal absorption of essential minerals and altering the levels of calcium, magnesium, and citrate(8, 9), several studies have investigated the impact of PPI use on the risk of kidney stones(10-12). For instance, Sui et al. found that PPI use might elevate the risk of kidney stones by lowering the levels of urinary citrate and magnesium, which could compromise their inhibitory effect on kidney stone formation(11). However, it should be noted that all participants in their study were GERD patients. Similarly, Simonov et al. identified a correlation between PPI use and kidney stones primarily based on a sample of young individuals and males(10), thereby limiting the generalizability of their findings to not only the general population but also specific patient groups, such as recurrent stone formers(13).

This study aimed to investigate the potential association between PPI use and kidney stones by analyzing National Health and Nutrition Examination Survey (NHANES) data from 2007 to 2018. Our hypothesis was that PPI use increases the risk of both kidney stone formation and recurrence.

Materials and methods

Study Population and Design

The NHANES is an ongoing cross-sectional survey that employs a sophisticated multistage sample methodology to investigate the health and nutritional status of the non-institutionalized population in US. The protocol was approved by the National Center for Health Statistics (NCHS) Ethics Review Board, and informed consent was obtained from all participants. Additional information regarding data collection can be accessed on the NHANES website(14).

Six NHANES cycles were used in the study from 2007 to 2018. Initially, 34,709 participants aged 20 years and older were included. However, some participants were excluded: 372 participants who were pregnant, 90 participants with incomplete kidney stone questionnaire, and 7,026 participants with incomplete variables. In addition, given the limited number of participants who had taken PPI for more than 15 years, the standard errors for model estimates increased substantially(15), thus 146 participants were excluded. Finally, 27,075 participants were included in the analysis, consisting of 13,711 females and 13,364 males. Fig. 1 illustrates the filtering process used in this study.

Assessment of Outcomes

The primary outcome was the response to the question, “Have you ever had kidney stones?”

(NHANES 2007–2018). Participants who responded "yes" were defined as kidney stone formers. The secondary outcome was the response to the question, "How many times have you passed a kidney stone?" (NHANES 2007–2014). Participants who reported passing at least two stones were classified as recurrent stone formers.

Medication Use

The independent variables in this study were whether participants had taken PPI and the duration of their PPI use. Information on the types and duration of acid suppressant medication was obtained through prescription medication questionnaires. The types of PPI in this study included omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole. For participants using PPI, the duration of use was equal to the years since initiating therapy. Participants who did not use PPI had a duration of use recorded as zero. Data on specific dosages or previously discontinued prescription medications were unavailable.

Ascertainment of Covariates

The study collected three types of detailed information about covariates through standardized personal interviews. The first group included demographic factors including age, sex, race, education level, smoking status, and alcohol consumption. The second group consisted of factors that impact the body's metabolism level, including body mass index (BMI), mean arterial pressure, HbA1c, triglyceride levels, history of cardiovascular disease (CVD), thiazide use, loop diuretic use, and histamine-2 receptor antagonists (H2RA) use. The third group focused on risk factors related to kidney stone formation, including sedentary time, total water intake, albumin-adjusted calcium levels, estimated glomerular filtration rate (eGFR), and history of gout. History of CVD (including congestive heart failure, coronary heart disease, myocardial infarction, and stroke) was defined if participants self-reported a history of these conditions. Gout was defined as a self-reported diagnosis of gout, and/or the use of anti-gout medication.

Statistical Analyses

All statistical analyses considered NHANES survey design characteristics with sampling weights. Descriptive statistics were used to evaluate the demographic and clinic characteristics of the study population. The variance inflation factor (VIF) was utilized to evaluate multicollinearity among covariates and between covariates and kidney stones. A VIF value over 10 indicates multicollinearity, but none was observed in this study (Supplementary Table 1) (16). To explore the

relationship between PPI use and kidney stones, we performed four weighted logistics regression models and controlled for the aforementioned explanatory variables by modeling PPI as continuous variables based on the time of use. To evaluate the potential non-linear relationship between the time of PPI use and kidney stones, restricted cubic splines were used with three knots at the 5th, 50th, and 95th centiles. Subgroup analyses were also performed to explore whether the relationship between the time of PPI use and kidney stones differed by age, sex, race, and BMI, and potential effect modifiers were tested using the Wald test for multiplicative interactions. Additionally, a 1:1 propensity score matching (PSM) analysis was performed to balance population differences between PPI users and non-users while adjusting for all confounding variables. We conducted a meta-analysis using the 'meta' package, which allowed us to combine data from relevant studies and estimate an overall effect size for the association between PPI use and kidney stones. All statistical tests were two-sided, and P-values < 0.05 (two-sided) were considered statistically significant. R 4.2.2 software was used for modeling.

Results

Population Characteristics

This study included 27,075 participants aged 20 years and older from the NHANES database (2007–2018), representing 203,076,872 adults. And table 1 presents their demographic and clinic characteristics based on PPI use. The mean age of all participants was 47.46 ± 0.26 (standard error) years, with roughly equal representation of females (51.13%) and males (48.87%). PPI users were more likely to be older, females, non-Hispanic white, obese, have lower education level, alcohol consumption, total water intake, eGFR, higher sedentary time, mean arterial pressure, HbA1c, triglycerides, albumin-adjusted calcium. PPI users were taking more thiazide, loop diuretics, and H2RAs medications compared to non-users. Furthermore, CVD, gout and kidney stone diseases were more common in PPI users (all $P < 0.05$).

Multivariate Logistics Regression Analysis

Weighted univariate and multivariate-adjusted logistics regression models were used to investigate the independent association between PPI use and incident kidney stones, with PPI non-user as the reference group (Table 2). In the crude model, PPI use showed a significantly positive association with incident kidney stones (OR = 1.86, 95%CI = 1.55–2.22). Moreover, the incidence of kidney stones increased by 9% for each additional year of PPI use. In the fully adjusted model

(model 3), PPI use still maintained a significantly positive association with incident kidney stones (*OR* = 1.31, 95%*CI* = 1.07–1.60), and for each additional year of PPI use, the incidence of kidney stones increased by 4%. Additionally, we also explored the association between PPI use and recurrent kidney stones. In the crude model, PPI use showed a significantly positive association with recurrent kidney stones (*OR* = 1.49, 95%*CI* = 1.05–2.09), and for each additional year of PPI use, the incidence of recurrent kidney stones increased by 7%. In the fully adjusted model (model 3), PPI use still maintained a significantly positive association with recurrent kidney stones (*OR* = 1.49, 95%*CI* = 1.04–2.13). The incidence of recurrent kidney stones increased by 7% for each additional year of PPI use.

Dose-response Relationships Between the Time of PPI Use and Kidney Stones

According to the restricted cubic spline analyses, a significantly positive relationship was observed between the duration of PPI use and incident kidney stones (*P* for overall < 0.001, *P* for non-linearity = 0.651) (Fig. 2A) and recurrent kidney stones (*P* for overall = 0.001, *P* for non-linearity = 0.484) (Fig. 2B).

Subgroup Analyses

Moreover, subgroup analyses were performed to assess whether the relationship between the duration of PPI use and kidney stones were influenced by age, sex, race, and BMI (Table 3). After adjusting for all covariates, it was found that the duration of PPI use was significantly associated with incident kidney stones in participants aged 50 years or order, females, non-Hispanic White, and those with a BMI of 25 kg/m^2 or higher. On the other hand, a significant positive association between time of PPI use and recurrent kidney stones was observed only in participants non-Hispanic White, and those with a BMI of 25 kg/m^2 or higher (all *P* for interaction > 0.05).

Sensitivity Analyses

A 1:1 matched cohort analysis was conducted through PSM to minimize potential bias, given the significant difference in PPI use and non-use group (Table 1). This approach confirmed 4864 participants in the matched cohort. The descriptive statistics results showed that no significant differences observed in most variables between the PPI non-user and PPI user groups (Supplementary Table 2). In the fully adjusted model, the dose–response curve still displayed a positive association between the duration of PPI use and kidney stones (*OR* = 1.05, 95%*CI* = 1.02–1.08, *P* for overall < 0.001, *P* for non-linearity = 0.956) (Supplementary Fig. 1A) and recurrent

kidney stones (*OR* = 1.10, 95%*CI* = 1.02–1.18, *P* for overall = 0.001, *P* for non-linearity = 0.488) (Supplementary Fig. 1B).

Discussion

In this large cross-sectional study based on NHANES data from 2007 to 2018, we found that PPI use was significantly associated with an increased risk of incident kidney stones. The duration of PPI use demonstrated a dose-response association with incident kidney stones. Furthermore, our study uncovered a novel association between long-term PPI use and recurrent kidney stones in patients with a history of kidney stones, demonstrating a significant linear correlation. Additionally, subgroup analysis found that the effects of age, sex, race, and BMI varied in their influence on the relationship between PPI use and incident kidney stones.

Several studies have shown that PPI use could increase the risk of kidney stones, with a dose-response relationship(10-12). A retrospective study conducted on the Women's Veterans Cohort, which included 465,891 individuals, revealed that PPI use was linked to a 1.25-fold higher risk of kidney stones (95% CI = 1.19–1.33) (Supplementary Fig. 2)(10). It should be noted that this study included mainly young individuals (with a median age of 32 years) and was predominantly males (86%), thus having a certain degree of selection bias(13). Another study by Sui et al. also found a positive association between PPI use and kidney stones in patients with GERD, with a 1.46-fold increased risk (95%CI = 1.38–1.55), which could help in assessing the potential risk of kidney stones associated with PPI exposure (Supplementary Fig. 2)(11). Nevertheless, both studies were limited to specific populations, limiting the generalizability of their findings to the general population. In contrast, a nationwide population cohort from Korea, without selection bias, also showed a positive association between PPI use and kidney stones, displaying a dose-response relationship(12). Similarly, the current study, based on data from the NHANES database representing over 203 million individuals, found that PPI use was significantly associated with not only a higher risk of incident kidney stones, but also recurrent kidney stones. Furthermore, the risk of developing kidney stones was found to be higher in individuals who used PPI for a longer duration, highlighting the importance of monitoring this potential side effects of long-term PPI treatment, especially for patients with a history of kidney stones.

The mechanisms underlying the impact of PPI on kidney stone formation remain unclear. Studies have suggested that PPI can elevate gastric pH, leading to a decrease in magnesium

absorption and urinary magnesium levels(9). Magnesium has been known to inhibit the formation of calcium oxalate crystals in urine(17, 18). A meta-analysis of nine observational studies found a significant increased risk of hypomagnesemia among patients using PPI(19). It should be noted that magnesium absorption occurs through both active and passive mechanisms, and alterations in pH do not affect passive absorption(19). Therefore, PPI use does not always result in hypomagnesemia, but patients with impaired gastrointestinal absorptive capacity may have an increased risk of developing hypomagnesemia. On the other hand, research has shown that citrate can inhibit the crystallization of calcium salts in urine, and a deficiency of citrate can increase the risk of stone formation(20, 21). A study of 301 nephrolithiasis patients with 24-hour urine data found that PPI exposure significantly reduced urinary citrate excretion, but did not affect urinary magnesium, pH, or other urinary minerals(8). Similarly, another study on GERD patients reported a significant correlation between PPI use and lower levels of urinary citrate and magnesium(11). Therefore, given the association between PPI use and hypomagnesemia and hypocitraturia, it may monitor the levels of urinary magnesium and citrate when using PPI.

PPIs are commonly prescribed for acid-related disorders, and patients with these conditions may be at higher risk for kidney stone formation(22). In this study, we employed the PSM analysis to minimize potential differences between PPI users and non-users, yet still identified a significant association between PPI use and incident and recurrent kidney stones. Subgroup analyses further revealed that certain patient groups, including the elderly, females, non-Hispanic Whites, and those with a BMI of 25 kg/m^2 or higher, exhibited a stronger positive association between PPI use and incident kidney stones, highlighting the importance of considering potential side effects of PPI use in these populations. While it is undeniable that PPI therapy has improved the quality of life for many patients with acid-related disorders(23), a growing body of literature suggested a relationship between long-term PPI use and adverse events(24). Caution should be exercised when discontinuing PPI use for evidence-based indications(25), but global concerns over long-term PPI overuse should not be overlooked(6, 7), especially in individuals with a history of kidney stones and high-risk factors, such as the elderly, females, non-Hispanic Whites, and those with a BMI of 25 kg/m^2 or higher, in order to reduce unnecessary use.

This study has several strengths. Firstly, the NHANES dataset comprises a representative sample of the national population, and we utilize NHANES-provided weights to ensure that our

findings can be extrapolated to the broader population. Secondly, this is the first study to explore the positive relationship between PPI use and recurrent kidney stones in patients with history of nephrolithiasis. Furthermore, multiple potential confounders were adjusted and PSM design was performed to ensure the reliability of the results. However, this study also has several limitations. Firstly, it is difficult to draw causal conclusions from such cross-sectional analyses. Although we adjusted for three types of detailed covariate information, there may still be unmeasured potential factors that could affect the association between PPI and nephrolithiasis. Secondly, the questionnaire survey may have been prone to recall bias and reporting bias, which could affect the accuracy of the data collected. Thirdly, NHANES may have missed some asymptomatic kidney stones without physical examination and did not record information regarding the time and type of kidney stones. Finally, the lack of information about the dosage and type of PPI use may limit the interpretability of the results.

Conclusions

In conclusion, our study demonstrated a significant relationship between PPI use and incident kidney stones, as well as an increased risk of recurrent kidney stones in patients with a history of nephrolithiasis. To mitigate this potential adverse effect, caution should be exercised regarding unnecessary long-term use of PPI.

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Contributors

W-L: conceptualization, methodology, data analysis, manuscript writing; J-W: methodology, data collection, data analysis, manuscript writing; M-W: methodology, data collection, data analysis; MM-W: data analysis, manuscript writing, supervision; M-L: conceptualization, supervision, manuscript editing, funding acquisition.

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Competing interests

None declared

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Ethical statement

The studies involving human participants were reviewed and approved by the Ethics Review Board of the NCHS (Protocol #98-12). The patients/participants provided their written informed consent to participate in this study.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be downloaded here: https://www.cdc.gov/nchs/nhanes/ (NHANES 2005-2006 and 2007-2008).

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Fig. 1 Study flowchart. Of 59,842 participants in the 2007–2018 National Health and Nutrition Examination Survey (NHANES), 27,075 remained after fulfilling inclusion and exclusion criteria.

Fig. 2 Dose-response relationships between time of PPIs use and kidney stones. (A) Time of PPIs use and kidney stones; (B) Time of PPIs use and recurrent kidney stones.

Abbreviations: OR, odds ratio; PPIs, proton pump inhibitors. Adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, gout, thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake, albumin-adjusted calcium, and eGFR. The shaded part represents the 95% CI.

Supplementary Fig. 1 Dose-response relationships between time of PPIs use and kidney stones after PSM. (A) Time of PPIs use and kidney stones; (B) Time of PPIs use and recurrent kidney stones.

Abbreviations: OR, odds ratio; PPIs, proton pump inhibitors; PSM, propensity score matching. Adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, gout, thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake, albumin-adjusted calcium, and eGFR. The shaded part

represents the 95% CI.

Supplementary Fig. 2 Forest plot showing the association between PPI use and kidney stones.

Table 1. Demographic and clinic characteristics according to PPIs use. NHANES 2007–2018*

Characteristics	Total Adults (N = 27,075)	Non-user (N = 24,643)	PPIs user (N = 2,432)	*P* value
Age, years, mean (SE)	47.46(0.26)	46.38(0.25)	59.05(0.47)	< 0.001
Female, n (%)	13711(51.13)	12335(50.63)	1376(56.43)	< 0.001
Race (Non-Hispanic White), n (%)	11470(66.93)	10153(65.94)	1317(77.61)	< 0.001
Education, n (%)				< 0.001
Grades 0–12	6368(23.03)	5671(14.72)	697(17.85)	
High school graduate/GED	6189(14.99)	5593(22.69)	596(26.69)	
Some college or above	14518(61.98)	13379(62.58)	1139(55.46)	
Smoking†, n (%)	5477(19.65)	5035(19.81)	442(17.93)	0.143
Alcohol consumption, n (%)	6469(26.38)	6010(26.73)	459(22.63)	0.017
BMI, kg/m‡², mean (SE)	29.05(0.09)	28.88(0.09)	30.89(0.22)	< 0.001
Weight status (≥ 25 kg/m²), n (%)‡	19423(70.54)	17439(69.47)	1984(81.95)	< 0.001
Sedentary time, hours/day, mean (SE)	368.10(2.86)	365.58(2.96)	395.13(5.96)	< 0.001
Mean arterial pressure, mmHg, mean (SE)	87.98(0.16)	87.83(0.17)	89.59(0.35)	< 0.001
Total water intake, g, mean (SE)	1171.48(15.90)	1180.99(16.29)	1069.41(30.63)	< 0.001
HbA1c, %, mean (SE)	5.63(0.01)	5.61(0.01)	5.89(0.03)	< 0.001
Triglycerides, mmol/L, mean (SE)	1.75(0.02)	1.73(0.02)	1.97(0.04)	< 0.001
Albumin-adjusted calcium, mmol/L, mean (SE)	2.28(0.00)	2.28(0.00)	2.30(0.00)	< 0.001
eGFR, mL/min, mean (SE)	94.33(0.33)	95.55(0.33)	81.23(0.61)	< 0.001
Gout, n (%)	403(1.25)	309(1.07)	94(3.23)	< 0.001
CVD, n (%)				
Congestive heart failure	805(2.20)	589(1.76)	216(6.88)	< 0.001
Coronary heart disease	1080(3.34)	829(2.87)	251(8.39)	< 0.001
Myocardial infarction	1082(3.01)	828(2.56)	254(7.82)	< 0.001
Stroke	984(2.78)	788(2.43)	196(6.47)	< 0.001
Thiazide user, n (%)	2748(8.66)	2256(7.81)	492(17.75)	< 0.001
Loop diuretics user, n (%)	876(2.46)	626(1.91)	250(8.35)	< 0.001
H2RAs user, n (%)	643(2.33)	550(2.26)	93(3.12)	0.030
Kidney stones, n (%)	2589(9.80)	2217(9.23)	372(15.88)	< 0.001

Abbreviations: NHANES, National Health and Nutrition Examination Survey; PPIs, proton pump inhibitors; SE, standard error; GED, General Equivalency Diploma; BMI, body mass index; eGFR, effective glomerular filtration rate; CVD, cardiovascular disease; H2RAs, H2-receptor antagonist.

*Means and percentages were adjusted for survey weights of NHANES.

†Smoking was defined as smoking at least 100 cigarettes during their lifetime.

‡BMI was calculated by dividing weight in kilograms (kg) by height in meters squared (m^2). Participants were classified as normal weight (BMI < 25 kg/m^2), and overweight/obese (BMI ≥ 25 kg/m^2).

Table 2. *OR* (95% *CI*) for kidney stones across PPIs use*

	Crude model	Model 1	Model 2	Model 3
Kidney stones (N = 2,589) VS Non-kidney stone (N = 24,486) (NHANES 2007–2018)				
PPIs use				
No	1[Reference]	1[Reference]	1[Reference]	1[Reference]
Yes	1.86(1.55,2.22)	1.42(1.18,1.72)	1.32(1.09,1.61)	1.31(1.07,1.60)
Time of use (years)	1.09(1.07,1.12)	1.05(1.02,1.08)	1.04(1.01,1.07)	1.04(1.01,1.07)
Recurrent kidney stones (N = 550) VS first kidney stone (N = 1,138) (NHANES 2007–2014)				
PPIs use				
No	1[Reference]	1[Reference]	1[Reference]	1[Reference]
Yes	1.49(1.05,2.09)	1.49(1.05,2.13)	1.47(1.03,2.10)	1.49(1.04,2.13)
Time of use (years)	1.07(1.01,1.12)	1.06(1.01,1.12)	1.06(1.01,1.12)	1.07(1.01,1.13)

Abbreviations: *OR*, odds ratio; *CI*, confidence interval; PPIs, proton pump inhibitors.

*Values are numerical values or weighted *OR* (95% *CI*).

Model 1 was adjusted for age, sex, race, education level, smoking, and alcohol consumption;

Model 2 was adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, thiazide use, loop diuretics use, and H2RAs use.

Model 3 was additionally adjusted for sedentary time, total water intake, albumin-adjusted calcium, eGFR and history of gout.

Table 3. *OR* (95% *CI*) for kidney stones across time of PPIs use stratified by selected factors*

	Kidney stones VS Non-kidney stone			Recurrent kidney stones VS first kidney stone		
	***OR* (95% *CI*)**	***P* value**	***P* for interaction**	***OR* (95% *CI*)**	***P* value**	***P* for interaction**
Age			0.439			0.419
< 50 years	1.05(0.98, 1.11)	0.150		1.11(0.98, 1.27)	0.104	
≥ 50 years	1.04(1.01,1.07)	0.004		1.07(1.00,1.14)	0.053	
Sex			0.856			0.623
Female	1.06(1.02,1.10)	0.004		1.08(0.99,1.18)	0.099	
Male	1.02(0.98,1.07)	0.258		1.06(0.98,1.14)	0.156	
Race			0.365			0.282
Non-Hispanic White	1.04(1.01,1.07)	0.005		1.11(1.01, 1.22)	0.037	
Other	1.02(0.98,1.06)	0.422		1.07(1.00,1.13)	0.038	
BMI			0.684			0.922
< 25 kg/m^2	1.06(0.98,1.14)	0.134		1.04(0.90, 1.22)	0.569	
≥ 25 kg/m^2	1.04(1.01,1.06)	0.013		1.07(1.01,1.15)	0.029	

Abbreviations: *OR*, odds ratio; *CI*, confidence interval; PPIs, proton pump inhibitors; BMI, Body mass index.

*Values are numerical values or weighted *OR* (95% *CI*).

Adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, gout, thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake, albumin-adjusted calcium, and eGFR, if not already stratified.

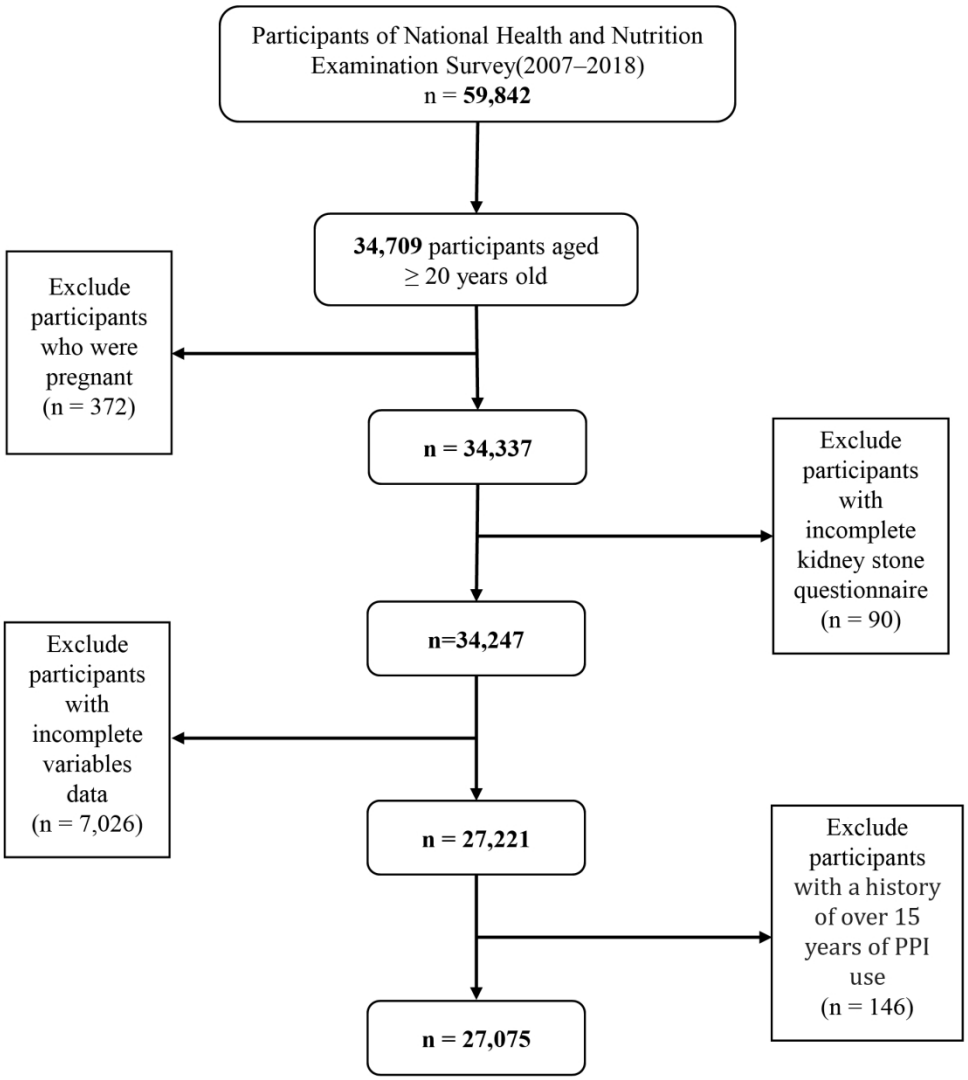

Fig. 1 Study flowchart. Of 59,842 participants in the 2007–2018 National Health and Nutrition Examination Survey (NHANES), 27,075 remained after fulfilling inclusion and exclusion criteria.

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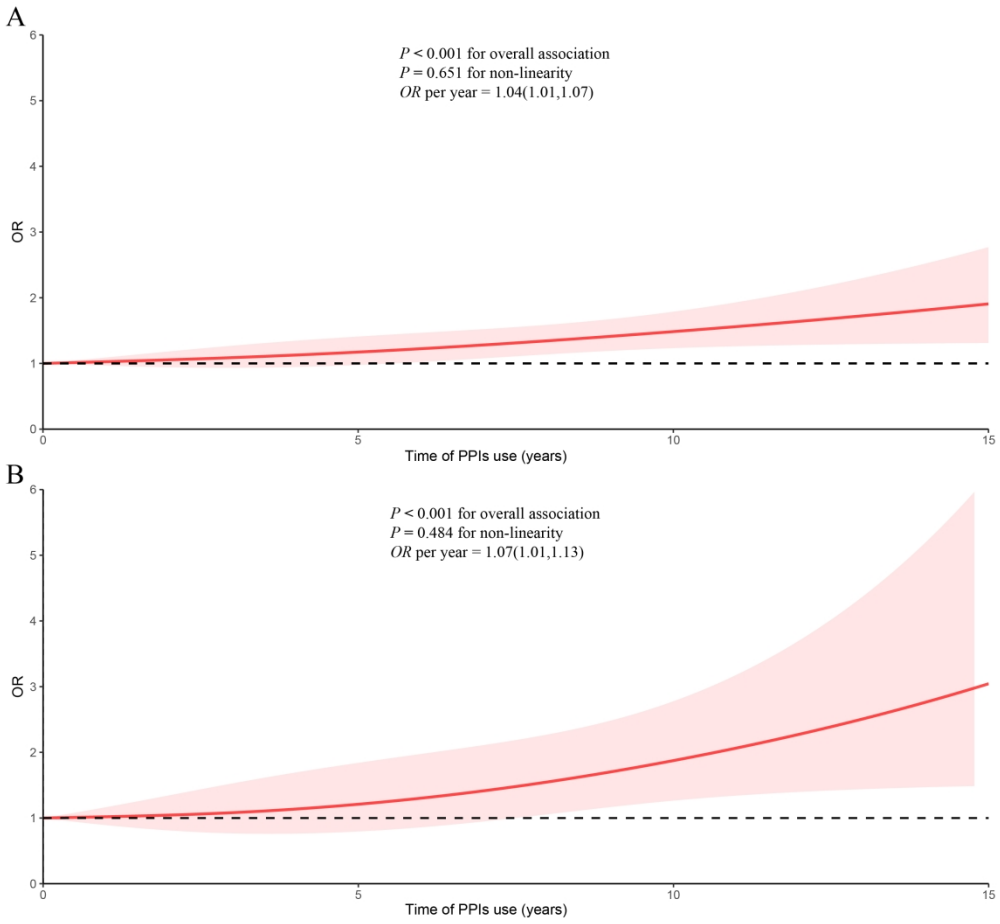

Fig. 2 Dose-response relationships between time of PPIs use and kidney stones. (A) Time of PPIs use and kidney stones; (B) Time of PPIs use and recurrent kidney stones.
Abbreviations: OR, odds ratio; PPIs, proton pump inhibitors. Adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, gout, thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake, albumin-adjusted calcium, and eGFR. The shaded part represents the 95% CI.

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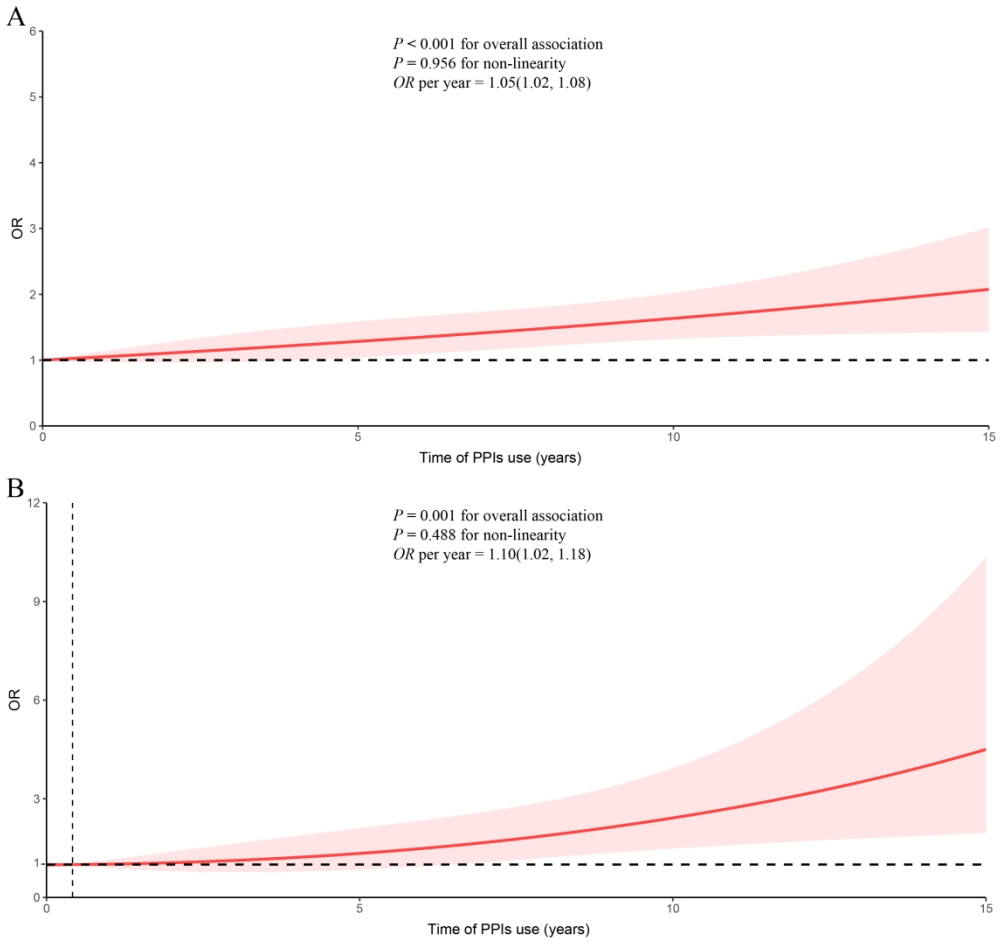

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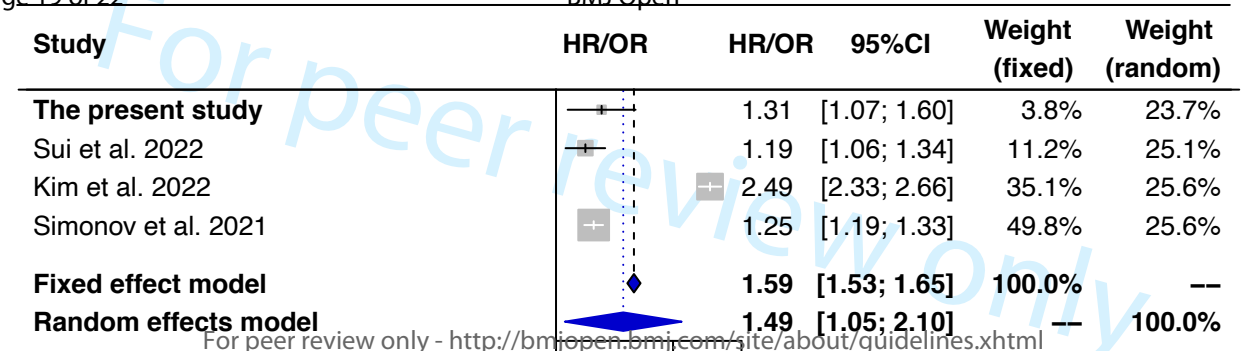

Supplementary Table 1. Collinearity analysis

Variables	VIF
Age	3.80
Sex	1.54
Race/ethnicity	1.85
Education	2.50
Smoking	2.08
Alcohol consumption	1.75
BMI	1.26
Sedentary time	1.54
Mean arterial pressure	1.25
Total water intake	1.99
HbA1c	1.81
Triglycerides	1.44
Albumin-adjusted calcium	1.97
eGFR	3.72
CVD	1.77
Thiazide use	1.78
Loop diuretics use	1.56
H2RAs use	1.27

Abbreviations: VIF, variance inflation factor; BMI, body mass index; eGFR, effective glomerular filtration rate; CVD, cardiovascular disease; H2RAs, H2-receptor antagonist.

Supplementary Table 2. Demographic and clinic characteristics according to PPIs use after PSM. NHANES 2007–2018*

Characteristics	Total Adults (N = 4,864)	Non-user (N = 2,432)	PPIs user (N = 2,432)	*P* value
Age, years, mean (SE)	59.15(0.35)	59.24(0.42)	59.05(0.47)	0.733
Female, n (%)	2679(56.73)	1303(57.02)	1376(56.43)	0.800
Race (Non-Hispanic White), n (%)	2634(78.13)	1317(78.63)	1317(77.61)	0.460
Education, n (%)				0.760
Grades 0–12	1379(17.54)	682(17.24)	697(17.85)	
High school graduate/GED	1217(26.31)	621(25.95)	596(26.69)	
Some college or above	2268(56.14)	1129(56.80)	1139(55.46)	
Smoking†, n (%)	904(18.71)	462(19.46)	442(17.93)	0.715
Alcohol consumption, n (%)	952(22.76)	493(22.89)	459(22.63)	0.902
BMI, kg/m‡², mean (SE)	30.64(0.17)	30.41(0.23)	30.89(0.22)	0.113
Weight status (≥ 25 kg/m²), n (%)‡	4013(82.25)	2029(82.531)	1984(81.948)	0.715
Sedentary time, hours/day, mean (SE)	390.48(4.72)	386.03(6.16)	395.13(5.96)	0.236
Mean arterial pressure, mmHg, mean (SE)	89.92(0.29)	90.25(0.40)	89.59(0.35)	0.194
Total water intake, g, mean (SE)	1058.14(24.20)	1047.33(32.08)	1069.41(30.63)	0.582
HbA1c, %, mean (SE)	5.89(0.02)	5.89(0.03)	5.89(0.03)	0.917
Triglycerides, mmol/L, mean (SE)	1.96(0.03)	1.95(0.03)	1.97(0.04)	0.716
Albumin-adjusted calcium, mmol/L, mean (SE)	2.30(0.00)	2.30(0.00)	2.30(0.00)	0.939
eGFR, mL/min, mean (SE)	81.68(0.45)	82.11(0.63)	81.23(0.61)	0.306
Gout, n (%)	169(2.83)	75(2.44)	94(3.23)	0.216
CVD, n (%)				
Congestive heart failure	365(5.64)	149(4.45)	216(6.88)	0.006
Coronary heart disease	435(7.39)	184(6.44)	251(8.39)	0.051
Myocardial infarction	430(6.67)	176(5.57)	254(7.82)	0.016
Stroke	380(6.52)	184(6.57)	196(6.47)	0.910
Thiazide user, n (%)	983(17.98)	491(18.20)	492(17.75)	0.776
Loop diuretics user, n (%)	436(7.13)	186(5.97)	250(8.35)	0.016
H2RAs user, n (%)	168(3.11)	75(3.10)	93(3.12)	0.979
Kidney stones, n (%)	658(13.51)	286(11.23)	372(15.88)	0.002

Abbreviations: PPIs, proton pump inhibitors; PSM, propensity score matching; NHANES, National Health and Nutrition Examination Survey; SE, standard error; GED, General Equivalency Diploma; BMI, body mass index; eGFR, effective glomerular filtration rate; CVD, cardiovascular disease; H2RAs, H2-receptor antagonist.

*Means and percentages were adjusted for survey weights of NHANES.

†Smoking was defined as smoking at least 100 cigarettes during their lifetime.

‡BMI was calculated by dividing weight in kilograms (kg) by height in meters squared (m^2). Participants were classified as normal weight (BMI < 25 kg/m^2), and overweight/obese (BMI ≥ 25 kg/m^2).

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	3-4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3-4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3-4
Bias	9	*Describe any efforts to address potential sources of bias*	3-4
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3-4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-5
		(*b*) Describe any methods used to examine subgroups and interactions	4-5
		(*c*) Explain how missing data were addressed	4-5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	4-5
		(*e*) Describe any sensitivity analyses	4-5
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	3, 5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	5
Outcome data	15*	Report numbers of outcome events or summary measures	5-6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5-6
		(*b*) Report category boundaries when continuous variables were categorized	5-6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5-6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8-9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	7-8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association of Proton Pump Inhibitor Use with the risk of kidney stones in NHANES population: A cross-sectional study

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Association of Proton Pump Inhibitor Use with the risk of kidney stones in NHANES population: A cross-sectional study

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Abstract

Objective Several studies have suggested a potential link between proton pump inhibitors (PPIs) use and the risk of kidney stones, attributed to alterations in urine mineral levels. Our study aimed to investigate the association between PPI use and kidney stones in US adults.

Design Cross-sectional study.

Setting National Health and Nutrition Examination Survey (NHANES) (2007–2018).

Participants A total of 27,075 individuals with complete information for PPI use and history of kidney stones were included in this study.

Outcomes and analyses Nonlinear analysis, logistic regression analysis, and subgroup analysis were conducted to estimate the relationship between PPI use and the occurrence and recurrence of kidney stones, after adjusting for potential confounding factors.

Results Multivariable logistic regression analysis revealed a significant association between PPI use and kidney stones (odds ratio [*OR*] 1.31, 95%*CI* 1.07–1.60), with a 4% increase in the prevalence of kidney stones for each additional year of PPI use ($P < 0.001$). Similarly, PPI use was significantly associated with recurrent kidney stones (*OR* 1.49, 95%*CI* 1.04–2.13), with a 7%

increase in the recurrence of kidney stones for each additional year of PPI use ($P < 0.001$). Furthermore, these associations remained significant even after conducting propensity score matching analysis on a subset of PPI users and non-users (all $P \leq 0.001$). Subgroup analyses showed that the effects of PPI use on kidney stones differed by age, sex, race, and BMI.

Conclusions This study indicated that long-term use of PPI was associated with a higher risk of both the presence and recurrence of kidney stones.

Keywords: NHANES; urolithiasis; proton pump inhibitors; risk factors; drug effects

STRENGTHS AND LIMITATIONS OF THIS STUDY

The NHANES dataset comprises a representative sample of the national population to ensure that our findings can be extrapolated to the broader population.

This study explores the positive relationship between PPI use and recurrent kidney stones in patients with history of nephrolithiasis.

Multiple potential confounders were adjusted and PSM design was performed to ensure the reliability of the results.

It is difficult to draw causal conclusions from such cross-sectional analyses.

NHANES may did not record information regarding the time and type of kidney stones and the dosage and type of PPI use.

Introduction

Kidney stone is a common disease in US, with a high prevalence of 12% of men and 10% of women, and caused high cost and morbidity(1, 2). Some drugs may affect the risk of kidney stones by altering active compounds crystallizing in urine or substances impairing urine composition(3-5).

Proton pump inhibitors (PPIs) are commonly prescribed medications worldwide for the treatment of gastric acid-related diseases such as gastroesophageal reflux disease (GERD), H. pylori infection, and gastric ulcers(6). However, the escalating prevalence of PPI overuse, especially for long-term therapy, has become a concerning issue(6, 7). Long-term PPI intake is associated with a reduction in intestinal absorption of essential vitamins and minerals and increased susceptibility to infections, chronic kidney disease, and dementia(7). Given that PPI can

inhibit gastric acid secretion, thereby affecting the intestinal absorption of essential minerals and altering the levels of calcium, magnesium, and citrate(8, 9), several studies have investigated the impact of PPI use on the risk of kidney stones(10-12). For instance, Sui et al. found that PPI use might elevate the risk of kidney stones by lowering the levels of urinary citrate and magnesium, which could compromise their inhibitory effect on kidney stone formation(11). However, it should be noted that all participants in their study were GERD patients. Similarly, Simonov et al. identified a correlation between PPI use and kidney stones primarily based on a sample of young individuals and males(10), thereby limiting the generalizability of their findings to not only the general population but also specific patient groups, such as recurrent stone formers(13).

This study aimed to investigate the potential association between PPI use and kidney stones by analyzing National Health and Nutrition Examination Survey (NHANES) data from 2007 to 2018. Our hypothesis was that PPI use increases the risk of both kidney stone formation and recurrence.

Methods

Study Population and Design

The NHANES is an ongoing cross-sectional survey that employs a sophisticated multistage sample methodology to investigate the health and nutritional status of the non-institutionalized population in US. Demographic characteristics, clinical history, and self-reported dietary were collected from participants using a structured household interview. Physical examinations, including anthropometric measurements and blood samples, were collected within a mobile examination center. The protocol was approved by the National Center for Health Statistics (NCHS) Ethics Review Board, and informed consent was obtained from all participants. Additional information regarding data collection can be accessed on the NHANES website(14).

Six NHANES cycles were used in the study from 2007 to 2018. Initially, 34,709 participants aged 20 years and older were included. However, some participants were excluded: 372 participants who were pregnant, 90 participants with incomplete kidney stone questionnaire, and 7,026 participants with incomplete variables. In addition, given the limited number of participants who had taken PPI for more than 15 years, the standard errors for model estimates increased substantially(15), thus 146 participants were excluded. Finally, 27,075 participants were included in the analysis, consisting of 13,711 females and 13,364 males. Fig. 1 illustrates the filtering process

used in this study.

Assessment of Outcomes

The primary outcome was the response to the question, "Have you ever had kidney stones?" (NHANES 2007–2018). Participants who responded "yes" were defined as kidney stone formers. The secondary outcome was the response to the question, "How many times have you passed a kidney stone?" (NHANES 2007–2014). Participants who reported passing at least two stones were classified as recurrent stone formers.

Medication Use

The independent variables in this study were whether participants had taken PPI and the duration of their PPI use. Information on the types and duration of acid suppressant medication was obtained through prescription medication questionnaires. The types of PPI in this study included omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole. For participants using PPI, the duration of use was equal to the years since initiating therapy. Participants who did not use PPI had a duration of use recorded as zero. Data on specific dosages or previously discontinued prescription medications were unavailable.

Ascertainment of Covariates

The study collected three types of detailed information about covariates through standardized personal interviews. The first group included demographic factors including age, sex, race, education level, smoking status, and alcohol consumption. The second group consisted of factors that impact the body's metabolism level, including body mass index (BMI), mean arterial pressure, HbA1c, triglyceride levels, history of cardiovascular disease (CVD), thiazide use, loop diuretic use, and histamine-2 receptor antagonists (H2RA) use. The third group focused on risk factors related to kidney stone formation, including sedentary time, total water intake, albumin-adjusted calcium levels, estimated glomerular filtration rate (eGFR), and history of gout. Education level was categorized as follows: Grades 0–12, high school graduate/General Equivalency Diploma, and some college or above. Smokers was defined as smoking at least 100 cigarettes during their lifetime. BMI was calculated by dividing weight in kilograms (kg) by height in meters squared (m^2). History of CVD (including congestive heart failure, coronary heart disease, myocardial infarction, and stroke) was defined if participants self-reported a history of these conditions. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR(16). The CKD-EPI

equation is as follows: eGFR = 141 × min (Scr/κ, 1) $^{\alpha}$ × max (Scr/κ, 1) $^{-1.209}$ × 0.993 ^{Age} × 1.018 [if female] 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. Gout was defined as a self-reported diagnosis of gout, and/or the use of anti-gout medication.

Statistical Analyses

All statistical analyses considered NHANES survey design characteristics with sampling weights. Descriptive statistics were used to evaluate the demographic and clinic characteristics of the study population. The variance inflation factor (VIF) was utilized to evaluate multicollinearity among covariates and between covariates and kidney stones. A VIF value over 10 indicates multicollinearity, but none was observed in this study (Supplementary Table 1) (17). To explore the relationship between PPI use and kidney stones, we performed four weighted logistic regression models and controlled for the aforementioned explanatory variables by modeling PPI as continuous variables based on the time of use. To evaluate the potential non-linear relationship between the time of PPI use and kidney stones, restricted cubic splines were used with three knots at the 5th, 50th, and 95th centiles. Subgroup analyses were also performed to explore whether the relationship between the time of PPI use and kidney stones differed by age, sex, race, and BMI, and potential effect modifiers were tested using the Wald test for multiplicative interactions. Additionally, a 1:1 propensity score matching (PSM) analysis was performed to balance population differences between PPI users and non-users while adjusting for all confounding variables. Previous studies have established links between kidney stones and dietary factors, such as vitamin C intake, caffeine consumption, and the dietary inflammatory index (DII)(18-20). To address potential confounding effects, a sensitivity analysis was conducted using model 3 as the baseline, with additional adjustments made for three variables: vitamin C intake, caffeine intake, and DII. We conducted a meta-analysis using the 'meta' package, which allowed us to combine data from relevant studies and estimate an overall effect size for the association between PPI use and kidney stones. All statistical tests were two-sided, and P-values < 0.05 (two-sided) were considered statistically significant. R 4.2.2 software was used for modeling.

Results

Population Characteristics

This study included 27,075 participants aged 20 years and older from the NHANES database (2007–2018), representing 203,076,872 adults. And table 1 presents their demographic and clinic characteristics based on PPI use. The mean age of all participants was 47.46 ± 0.26 (standard error) years, with roughly equal representation of females (51.13%) and males (48.87%). PPI users were more likely to be older, females, non-Hispanic white, obese, have lower education level, alcohol consumption, total water intake, eGFR, higher sedentary time, mean arterial pressure, HbA1c, triglycerides, albumin-adjusted calcium. PPI users were taking more thiazide, loop diuretics, and H2RAs medications compared to non-users. Furthermore, CVD, gout and kidney stone diseases were more common in PPI users (all $P < 0.05$).

Multivariable Logistic Regression Analyses

Weighted univariable and multivariable logistic regression models were used to investigate the independent association between PPI use and the risk of kidney stones, with PPI non-user as the reference group (Table 2). In the crude model, PPI use showed a significantly positive association with the prevalence of kidney stones (*OR* = 1.86, 95%*CI* = 1.55–2.22). In the fully adjusted model (model 3), the association between PPI use and the prevalence of kidney stones remained significant (*OR* = 1.31, 95%*CI* = 1.07–1.60). When considering PPI use as a continuous variable, the restricted cubic spline analyses indicated a linear relationship between the duration of PPI use and the prevalence of kidney stones (*P* for non-linearity = 0.651) (Fig. 2A). With each additional year of PPI use, the prevalence of kidney stones increased by 4% (Table 2). Additionally, we explored the association between PPI use and recurrent kidney stones. In the crude model, PPI use showed a significantly positive association with the recurrence of kidney stones (*OR* = 1.49, 95%*CI* = 1.05–2.09). This positive association persisted in the fully adjusted model (model 3) (*OR* = 1.49, 95%*CI* = 1.04–2.13). The duration of PPI use exhibited a linear correlation with the recurrence of kidney stones (*P* for non-linearity = 0.484) (Fig. 2B), with a 7% increase for each additional year of PPI use (Table 2).

Subgroup Analyses

Moreover, subgroup analyses were performed to assess whether the relationship between the duration of PPI use and kidney stones were influenced by age, sex, race, and BMI (Table 3). After adjusting for all covariates, it was found that the duration of PPI use was significantly associated with the prevalence of kidney stones in participants aged 50 years or order, females, non-Hispanic

White, and those with a BMI of 25 kg/m^2 or higher. On the other hand, a significant positive association between time of PPI use and recurrent kidney stones was observed only in participants non-Hispanic White, and those with a BMI of 25 kg/m^2 or higher (all *P* for interaction > 0.05).

Sensitivity analyses and Meta-analysis

A 1:1 matched cohort analysis was conducted through PSM to minimize potential bias, given the significant difference in PPI use and non-use group (Table 1). This approach confirmed 4864 participants in the matched cohort. The descriptive statistics results showed that no significant differences observed in most variables between the PPI non-user and PPI user groups (Supplementary Table 2). In the fully adjusted model, the dose–response curve still displayed a positive association between the duration of PPI use and kidney stones (*OR* = 1.05, 95%*CI* = 1.02–1.08, *P* for non-linearity = 0.956) (Supplementary Fig. 1A) and recurrent kidney stones (*OR* = 1.10, 95%*CI* = 1.02–1.18, *P* for non-linearity = 0.488) (Supplementary Fig. 1B). Moreover, the results remained significant after making additional adjustments for vitamin C intake, caffeine consumption, and DII (Supplementary Table 3). Furthermore, we performed a meta-analysis based on our findings and previously published research, confirming a positive association between the PPI use and the risk of kidney stones (*OR* = 1.49, 95%*CI* = 1.05–2.10) (Supplementary Fig. 2)(10-12).

Discussion

In this large cross-sectional study based on NHANES data from 2007 to 2018, we found that PPI use was associated with an increased risk of kidney stones. The duration of PPI use demonstrated a dose-response association with kidney stones. Furthermore, our study uncovered a novel association between long-term PPI use and recurrent kidney stones in patients with a history of kidney stones, demonstrating a significant linear correlation. Additionally, subgroup analysis found that the effects of age, sex, race, and BMI varied in their influence on the relationship between PPI use and the prevalence of kidney stones.

Several studies have shown that PPI use could increase the risk of kidney stones, with a dose-response relationship(10-12). A retrospective study conducted on the Women's Veterans Cohort, which included 465,891 individuals, revealed that PPI use was linked to a 1.25-fold higher risk of kidney stones (95% CI = 1.19–1.33)(10). It should be noted that this study included mainly young individuals (with a median age of 32 years) and was predominantly males (86%), thus having a

certain degree of selection bias(13). Another study by Sui et al. also found a positive association between PPI use and kidney stones in patients with GERD, with a 1.46-fold increased risk (95%CI = 1.38–1.55), which could help in assessing the potential risk of kidney stones associated with PPI exposure(11). Nevertheless, both studies were limited to specific populations, limiting the generalizability of their findings to the general population. In contrast, a nationwide population cohort from Korea, without selection bias, also showed a positive association between PPI use and kidney stones, displaying a dose-response relationship(12). Similarly, the current study, based on data from the NHANES database representing over 203 million individuals, found that PPI use was significantly associated with not only a higher risk of kidney stones, but also recurrent kidney stones. The findings from the meta-analysis conducted in this study have confirmed the positive association between PPI use and the risk of kidney stones. Furthermore, the risk of developing kidney stones was found to be higher in individuals who used PPI for a longer duration, highlighting the importance of monitoring this potential side effects of long-term PPI treatment, especially for patients with a history of kidney stones.

The mechanisms underlying the impact of PPI on kidney stone formation remain unclear. Studies have suggested that PPI can elevate gastric pH, leading to a decrease in magnesium absorption and urinary magnesium levels(9). Magnesium has been known to inhibit the formation of calcium oxalate crystals in urine(21, 22). A meta-analysis of nine observational studies found a significant increased risk of hypomagnesemia among patients using PPI(23). It should be noted that magnesium absorption occurs through both active and passive mechanisms, and alterations in pH do not affect passive absorption(23). Therefore, PPI use does not always result in hypomagnesemia, but patients with impaired gastrointestinal absorptive capacity may have an increased risk of developing hypomagnesemia. On the other hand, research has shown that citrate can inhibit the crystallization of calcium salts in urine, and a deficiency of citrate can increase the risk of stone formation(24, 25). A study of 301 nephrolithiasis patients with 24-hour urine data found that PPI exposure significantly reduced urinary citrate excretion, but did not affect urinary magnesium, pH, or other urinary minerals(8). Similarly, another study on GERD patients reported a significant correlation between PPI use and lower levels of urinary citrate and magnesium(11). Therefore, given the association between PPI use and hypomagnesuria and hypocitraturia, it may monitor the levels of urinary magnesium and citrate when using PPI.

PPIs are commonly prescribed for acid-related disorders, and patients with these conditions may be at higher risk for kidney stone formation(26). In this study, we employed the PSM analysis to minimize potential differences between PPI users and non-users, yet still identified a significant association between PPI use and the occurrence and recurrence of kidney stones. Subgroup analyses further revealed that certain patient groups, including the elderly, females, non-Hispanic Whites, and those with a BMI of 25 kg/m^2 or higher, exhibited a stronger positive association between PPI use and the prevalence of kidney stones, highlighting the importance of considering potential side effects of PPI use in these populations. While it is undeniable that PPI therapy has improved the quality of life for many patients with acid-related disorders(27), a growing body of literature suggested a relationship between long-term PPI use and adverse events(28). Caution should be exercised when discontinuing PPI use for evidence-based indications(29), but global concerns over long-term PPI overuse should not be overlooked(6, 7), especially in individuals with a history of kidney stones and high-risk factors, such as the elderly, females, non-Hispanic Whites, and those with a BMI of 25 kg/m^2 or higher, in order to reduce unnecessary use.

This study has several strengths. Firstly, the NHANES dataset comprises a representative sample of the national population, and we utilize NHANES-provided weights to ensure that our findings can be extrapolated to the broader population. Secondly, this study not only elucidates the correlation between PPI use and the prevalence of kidney stones but also probes its association with the recurrence of renal calculi in individuals with a history of nephrolithiasis.. Furthermore, multiple potential confounders were adjusted and PSM design was performed to ensure the reliability of the results. However, this study also has several limitations. Firstly, it is difficult to draw causal conclusions from such cross-sectional analyses. Although we adjusted for three types of detailed covariate information, there may still be unmeasured potential factors that could affect the association between PPI and nephrolithiasis. Secondly, the questionnaire survey may have been prone to recall bias and reporting bias, which could affect the accuracy of the data collected. Thirdly, NHANES lacks objective diagnostic imaging for the identification of kidney stones, potentially resulting in the omission of asymptomatic cases. Additionally, the dataset does not provide details on the timing and specific type of kidney stones. Finally, the lack of information about the dosage and type of PPI use may limit the interpretability of the results.

Conclusions

In conclusion, our study revealed a relationship between PPI use and the prevalence of kidney stones, as well as an increased risk of recurrent kidney stones in patients with a history of nephrolithiasis. To mitigate this potential adverse effect, caution should be exercised regarding unnecessary long-term use of PPI.

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Contributors

W-L: conceptualization, methodology, data analysis, manuscript writing; J-W: methodology, data collection, data analysis, manuscript writing; M-W: methodology, data collection, data analysis; MM-W: data analysis, manuscript writing, supervision; M-L: conceptualization, supervision, manuscript editing, funding acquisition.

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Competing interests

None declared

Patient and public involvement

None.

Patient consent for publication

Not applicable.

Ethical statement

Ethical review and approval for the research involving human participants were obtained from the Ethics Review Board of the NCHS (Protocol #98-12). The current analysis, which is based on publicly available data, did not necessitate any further ethics approval. Written informed consent was obtained from all patients or participants who were part of the study.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be downloaded here: https://www.cdc.gov/nchs/nhanes/ (NHANES 2005-2006 and 2007-2008).

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Fig. 1 Study flowchart. Of 59,842 participants in the 2007–2018 National Health and Nutrition Examination Survey (NHANES), 27,075 remained after fulfilling inclusion and exclusion criteria.

Fig. 2 Dose-response relationships between time of PPIs use and kidney stones. (A) Time of PPIs use and kidney stones; (B) Time of PPIs use and recurrent kidney stones.

Abbreviations: OR, odds ratio; PPIs, proton pump inhibitors. Adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, gout, thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake, albumin-adjusted calcium, and eGFR. The shaded part represents the 95% CI.

Supplementary Fig. 1 Dose-response relationships between time of PPIs use and kidney stones after PSM. (A) Time of PPIs use and kidney stones; (B) Time of PPIs use and recurrent kidney stones.

Abbreviations: OR, odds ratio; PPIs, proton pump inhibitors; PSM, propensity score matching. Adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, gout, thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake, albumin-adjusted calcium, and eGFR. The shaded part represents the 95% CI.

Supplementary Fig. 2 Forest plot showing the association between PPI use and kidney stones.

Table 1. Demographic and clinic characteristics according to PPIs use. NHANES 2007–2018*

Characteristics	Total Adults (N = 27,075)	Non-user (N = 24,643)	PPIs user (N = 2,432)	*P* value
Age, years, mean (SE)	47.46(0.26)	46.38(0.25)	59.05(0.47)	< 0.001
Female, n (%)	13711(51.13)	12335(50.63)	1376(56.43)	< 0.001
Race (Non-Hispanic White), n (%)	11470(66.93)	10153(65.94)	1317(77.61)	< 0.001
Education, n (%)				< 0.001
Grades 0–12	6368(23.03)	5671(14.72)	697(17.85)	
High school graduate/GED	6189(14.99)	5593(22.69)	596(26.69)	
Some college or above	14518(61.98)	13379(62.58)	1139(55.46)	
Smoking†, n (%)	5477(19.65)	5035(19.81)	442(17.93)	0.143
Alcohol consumption, n (%)	6469(26.38)	6010(26.73)	459(22.63)	0.017
BMI, kg/m‡², mean (SE)	29.05(0.09)	28.88(0.09)	30.89(0.22)	< 0.001
Weight status (≥ 25 kg/m²), n (%)‡	19423(70.54)	17439(69.47)	1984(81.95)	< 0.001
Sedentary time, hours/day, mean (SE)	368.10(2.86)	365.58(2.96)	395.13(5.96)	< 0.001
Mean arterial pressure, mmHg, mean (SE)	87.98(0.16)	87.83(0.17)	89.59(0.35)	< 0.001
Total water intake, g, mean (SE)	1171.48(15.90)	1180.99(16.29)	1069.41(30.63)	< 0.001
HbA1c, %, mean (SE)	5.63(0.01)	5.61(0.01)	5.89(0.03)	< 0.001
Triglycerides, mmol/L, mean (SE)	1.75(0.02)	1.73(0.02)	1.97(0.04)	< 0.001
Albumin-adjusted calcium, mmol/L, mean (SE)	2.28(0.00)	2.28(0.00)	2.30(0.00)	< 0.001
eGFR, mL/min, mean (SE)	94.33(0.33)	95.55(0.33)	81.23(0.61)	< 0.001
Gout, n (%)	403(1.25)	309(1.07)	94(3.23)	< 0.001
CVD, n (%)	2595(9.584)	2050(6.641)	545(17.438)	< 0.001
Congestive heart failure	805(2.20)	589(1.76)	216(6.88)	< 0.001
Coronary heart disease	1080(3.34)	829(2.87)	251(8.39)	< 0.001
Myocardial infarction	1082(3.01)	828(2.56)	254(7.82)	< 0.001
Stroke	984(2.78)	788(2.43)	196(6.47)	< 0.001
Thiazide user, n (%)	2748(8.66)	2256(7.81)	492(17.75)	< 0.001
Loop diuretics user, n (%)	876(2.46)	626(1.91)	250(8.35)	< 0.001
H2RAs user, n (%)	643(2.33)	550(2.26)	93(3.12)	0.030
Kidney stones, n (%)	2589(9.80)	2217(9.23)	372(15.88)	< 0.001

Abbreviations: NHANES, National Health and Nutrition Examination Survey; PPIs, proton pump inhibitors; SE, standard error; GED, General Equivalency Diploma; BMI, body mass index; eGFR, effective glomerular filtration rate; CVD, cardiovascular disease; H2RAs, H2-receptor antagonist.

*Means and percentages were adjusted for survey weights of NHANES.

†Smoking was defined as smoking at least 100 cigarettes during their lifetime.

‡BMI was calculated by dividing weight in kilograms (kg) by height in meters squared (m^2). Participants were classified as normal weight (BMI < 25 kg/m^2), and overweight/obese (BMI ≥ 25 kg/m^2).

Table 2. *OR* (95% *CI*) for kidney stones across PPIs use*

	Crude model	Model 1	Model 2	Model 3
Kidney stones (N = 2,589) VS Non-kidney stone (N = 24,486) (NHANES 2007–2018)				
PPIs use				
No	1[Reference]	1[Reference]	1[Reference]	1[Reference]
Yes	1.86(1.55,2.22)	1.42(1.18,1.72)	1.32(1.09,1.61)	1.31(1.07,1.60)
Time of use (years)	1.09(1.07,1.12)	1.05(1.02,1.08)	1.04(1.01,1.07)	1.04(1.01,1.07)
Recurrent kidney stones (N = 550) VS first kidney stone (N = 1,138) (NHANES 2007–2014)				
PPIs use				
No	1[Reference]	1[Reference]	1[Reference]	1[Reference]
Yes	1.49(1.05,2.09)	1.49(1.05,2.13)	1.47(1.03,2.10)	1.49(1.04,2.13)
Time of use (years)	1.07(1.01,1.12)	1.06(1.01,1.12)	1.06(1.01,1.12)	1.07(1.01,1.13)

Abbreviations: *OR*, odds ratio; *CI*, confidence interval; PPIs, proton pump inhibitors.

*Values are numerical values or weighted *OR* (95% *CI*).

Model 1 was adjusted for age, sex, race, education level, smoking, and alcohol consumption;

Model 2 was adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, thiazide use, loop diuretics use, and H2RAs use.

Model 3 was additionally adjusted for sedentary time, total water intake, albumin-adjusted calcium, eGFR and history of gout.

Table 3. *OR* (95% *CI*) for kidney stones across time of PPIs use stratified by selected factors*

	Kidney stones VS Non-kidney stone			Recurrent kidney stones VS first kidney stone		
	***OR* (95% *CI*)**	***P* value**	***P* for interaction**	***OR* (95% *CI*)**	***P* value**	***P* for interaction**
Age			0.439			0.419
< 50 years	1.05(0.98, 1.11)	0.150		1.11(0.98, 1.27)	0.104	
≥ 50 years	1.04(1.01,1.07)	0.004		1.07(1.00,1.14)	0.053	
Sex			0.856			0.623
Female	1.06(1.02,1.10)	0.004		1.08(0.99,1.18)	0.099	
Male	1.02(0.98,1.07)	0.258		1.06(0.98,1.14)	0.156	
Race			0.365			0.282
Non-Hispanic White	1.04(1.01,1.07)	0.005		1.11(1.01, 1.22)	0.037	
Other	1.02(0.98,1.06)	0.422		1.07(1.00,1.13)	0.038	
BMI			0.684			0.922
< 25 kg/m^2	1.06(0.98,1.14)	0.134		1.04(0.90, 1.22)	0.569	
≥ 25 kg/m^2	1.04(1.01,1.06)	0.013		1.07(1.01,1.15)	0.029	

Abbreviations: *OR*, odds ratio; *CI*, confidence interval; PPIs, proton pump inhibitors; BMI, Body mass index.

*Values are numerical values or weighted *OR* (95% *CI*).

Adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, gout, thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake, albumin-adjusted calcium, and eGFR, if not already stratified.

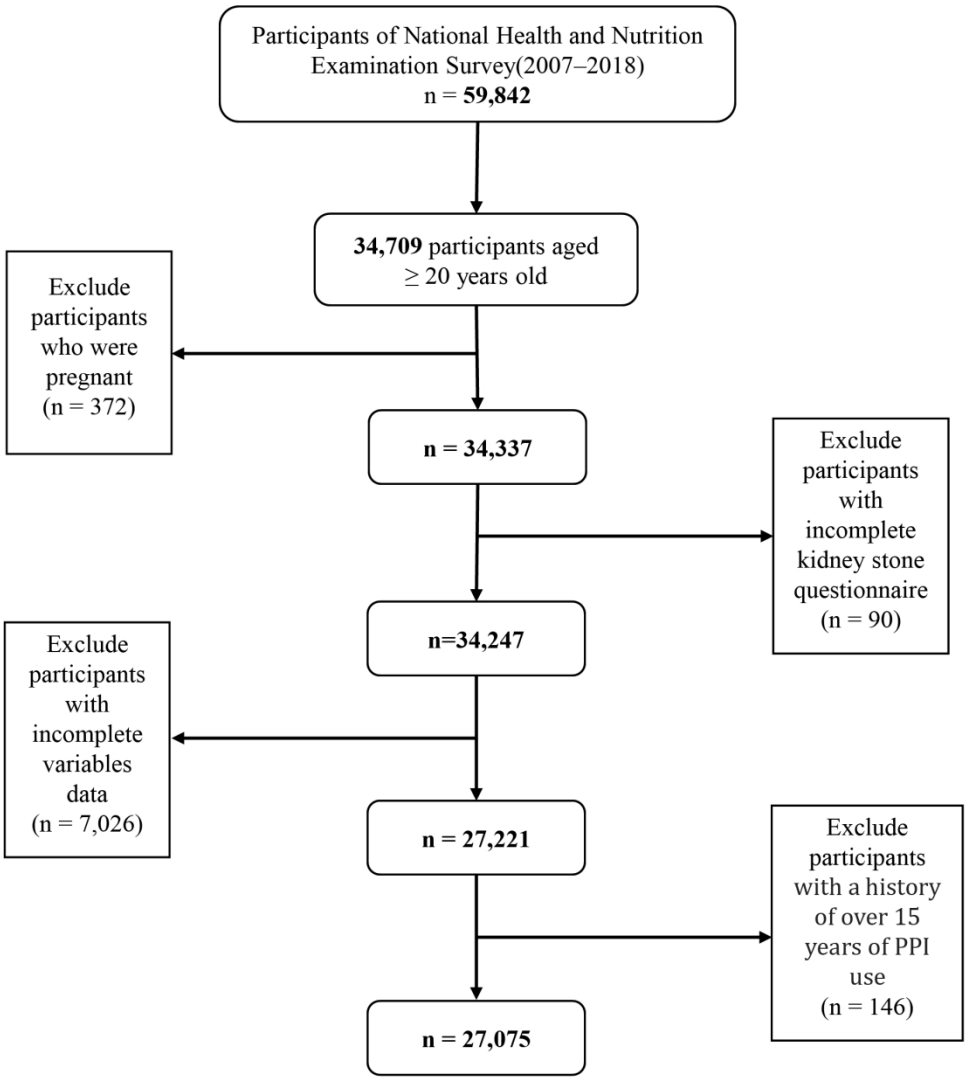

Fig. 1 Study flowchart. Of 59,842 participants in the 2007–2018 National Health and Nutrition Examination Survey (NHANES), 27,075 remained after fulfilling inclusion and exclusion criteria.

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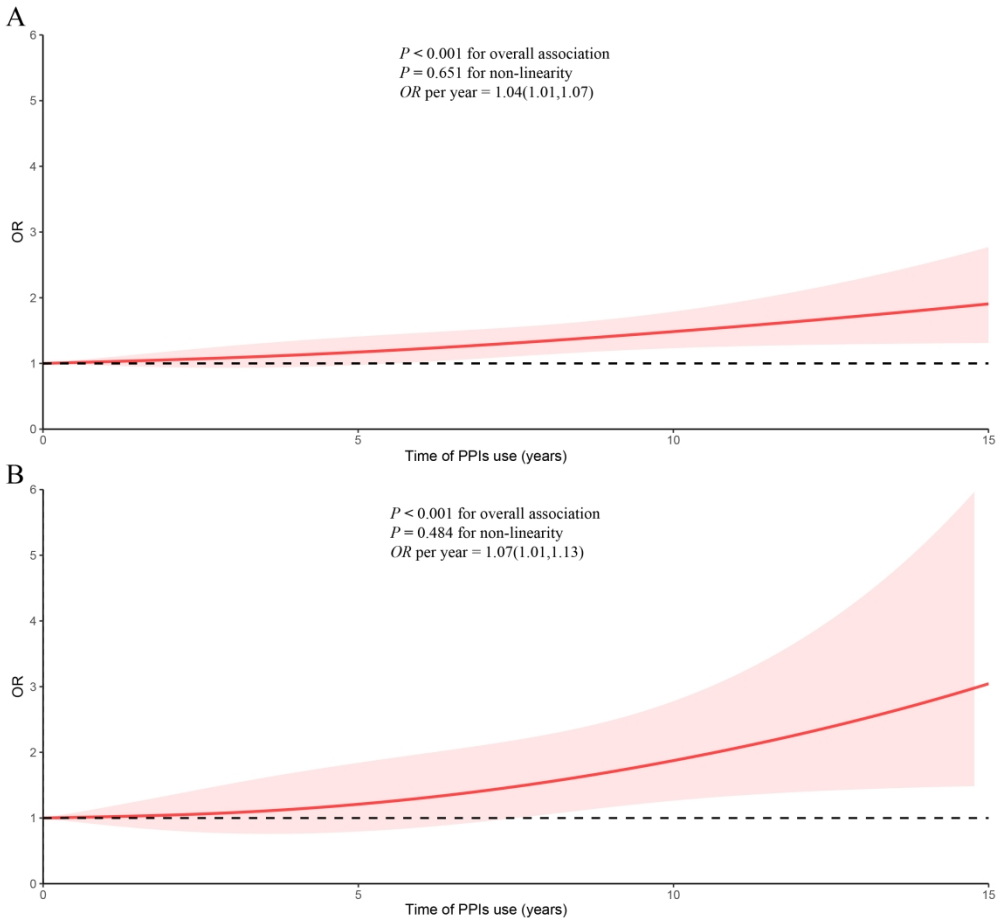

Fig. 2 Dose-response relationships between time of PPIs use and kidney stones. (A) Time of PPIs use and kidney stones; (B) Time of PPIs use and recurrent kidney stones.
Abbreviations: OR, odds ratio; PPIs, proton pump inhibitors. Adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, gout, thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake, albumin-adjusted calcium, and eGFR. The shaded part represents the 95% CI.

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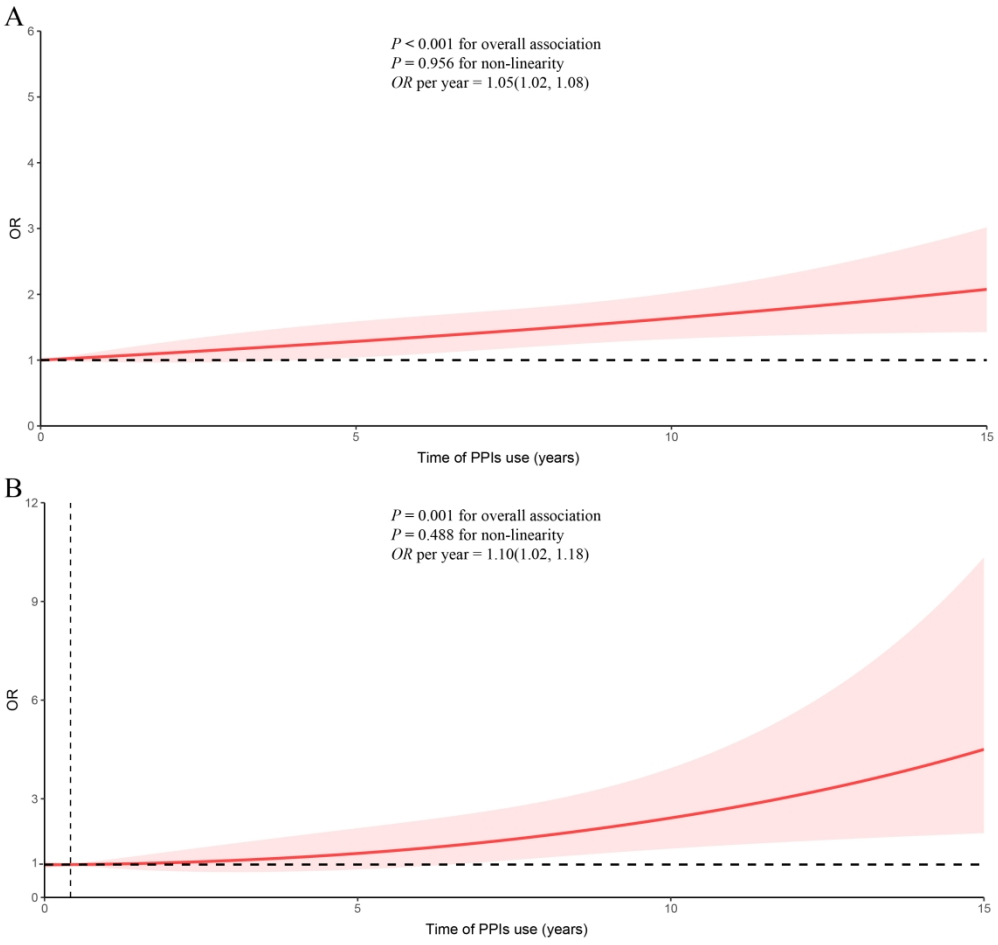

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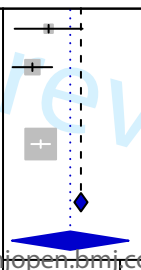

Study	HR/OR	95%CI	Weight (fixed)	Weight (random)
The present study	1.31	[1.07; 1.60]	3.8%	23.7%
Sui et al. 2022	1.19	[1.06; 1.34]	11.2%	25.1%
Kim et al. 2022	2.49	[2.33; 2.66]	35.1%	25.6%
Simonov et al. 2021	1.25	[1.19; 1.33]	49.8%	25.6%
Fixed effect model	**1.59**	**[1.53; 1.65]**	**100.0%**	**--**
Random effects model	**1.49**	**[1.05; 2.10]**	**--**	**100.0%**

Supplementary Table 1. Collinearity analysis

Variables	VIF
Age	3.80
Sex	1.54
Race/ethnicity	1.85
Education	2.50
Smoking	2.08
Alcohol consumption	1.75
BMI	1.26
Sedentary time	1.54
Mean arterial pressure	1.25
Total water intake	1.99
HbA1c	1.81
Triglycerides	1.44
Albumin-adjusted calcium	1.97
eGFR	3.72
CVD	1.77
Thiazide use	1.78
Loop diuretics use	1.56
H2RAs use	1.27

Abbreviations: VIF, variance inflation factor; BMI, body mass index; eGFR, effective glomerular filtration rate; CVD, cardiovascular disease; H2RAs, H2-receptor antagonist.

Supplementary Table 2. Demographic and clinic characteristics according to PPIs use after PSM. NHANES 2007–2018*

Characteristics	Total Adults (N = 4,864)	Non-user (N = 2,432)	PPIs user (N = 2,432)	*P* value
Age, years, mean (SE)	59.15(0.35)	59.24(0.42)	59.05(0.47)	0.733
Female, n (%)	2679(56.73)	1303(57.02)	1376(56.43)	0.800
Race (Non-Hispanic White), n (%)	2634(78.13)	1317(78.63)	1317(77.61)	0.460
Education, n (%)				0.760
Grades 0–12	1379(17.54)	682(17.24)	697(17.85)	
High school graduate/GED	1217(26.31)	621(25.95)	596(26.69)	
Some college or above	2268(56.14)	1129(56.80)	1139(55.46)	
Smoking†, n (%)	904(18.71)	462(19.46)	442(17.93)	0.715
Alcohol consumption, n (%)	952(22.76)	493(22.89)	459(22.63)	0.902
BMI, kg/m‡², mean (SE)	30.64(0.17)	30.41(0.23)	30.89(0.22)	0.113
Weight status (≥ 25 kg/m²), n (%)‡	4013(82.25)	2029(82.531)	1984(81.948)	0.715
Sedentary time, hours/day, mean (SE)	390.48(4.72)	386.03(6.16)	395.13(5.96)	0.236
Mean arterial pressure, mmHg, mean (SE)	89.92(0.29)	90.25(0.40)	89.59(0.35)	0.194
Total water intake, g, mean (SE)	1058.14(24.20)	1047.33(32.08)	1069.41(30.63)	0.582
HbA1c, %, mean (SE)	5.89(0.02)	5.89(0.03)	5.89(0.03)	0.917
Triglycerides, mmol/L, mean (SE)	1.96(0.03)	1.95(0.03)	1.97(0.04)	0.716
Albumin-adjusted calcium, mmol/L, mean (SE)	2.30(0.00)	2.30(0.00)	2.30(0.00)	0.939
eGFR, mL/min, mean (SE)	81.68(0.45)	82.11(0.63)	81.23(0.61)	0.306
Gout, n (%)	169(2.83)	75(2.44)	94(3.23)	0.216
CVD, n (%)				
Congestive heart failure	365(5.64)	149(4.45)	216(6.88)	0.006
Coronary heart disease	435(7.39)	184(6.44)	251(8.39)	0.051
Myocardial infarction	430(6.67)	176(5.57)	254(7.82)	0.016
Stroke	380(6.52)	184(6.57)	196(6.47)	0.910
Thiazide user, n (%)	983(17.98)	491(18.20)	492(17.75)	0.776
Loop diuretics user, n (%)	436(7.13)	186(5.97)	250(8.35)	0.016
H2RAs user, n (%)	168(3.11)	75(3.10)	93(3.12)	0.979
Kidney stones, n (%)	658(13.51)	286(11.23)	372(15.88)	0.002

Abbreviations: PPIs, proton pump inhibitors; PSM, propensity score matching; NHANES, National Health and Nutrition Examination Survey; SE, standard error; GED, General Equivalency Diploma; BMI, body mass index; eGFR, effective glomerular filtration rate; CVD, cardiovascular disease; H2RAs, H2-receptor antagonist.

*Means and percentages were adjusted for survey weights of NHANES.

†Smoking was defined as smoking at least 100 cigarettes during their lifetime.

‡BMI was calculated by dividing weight in kilograms (kg) by height in meters squared (m^2). Participants were classified as normal weight (BMI < 25 kg/m^2), and overweight/obese (BMI ≥ 25 kg/m^2).

Supplementary Table 3. Sensitivity analyses of the associations between kidney stones and PPIs use after additional adjustment for vitamin C intake, caffeine intake and dietary inflammation index*

	Model (*OR* [95%*CI*])	*P*-value
Kidney stones (N = 2,589) VS Non-kidney stone (N = 24,486) (NHANES 2007–2018)		
PPIs use		0.01
No	1[Reference]	
Yes	1.31(1.07,1.60)	
Time of use (years)	1.04(1.01,1.07)	0.004
Recurrent kidney stones (N = 550) VS first kidney stone (N = 1,138) (NHANES 2007–2014)		
PPIs use		0.03
No	1[Reference]	
Yes	1.49(1.04,2.13)	
Time of use (years)	1.07(1.01,1.13)	0.03

Abbreviations: *OR*, odds ratio; *CI*, confidence interval; PPIs, proton pump inhibitors.

*Values are numerical values or weighted *OR* (95% *CI*).

Model was adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, thiazide use, loop diuretics use, H2RAs use, sedentary time, total water intake, albumin-adjusted calcium, eGFR history of gout, vitamin C intake, caffeine intake and dietary inflammation index.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	3-4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3-4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3-4
Bias	9	*Describe any efforts to address potential sources of bias*	3-4
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3-4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-5
		(*b*) Describe any methods used to examine subgroups and interactions	4-5
		(*c*) Explain how missing data were addressed	4-5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	4-5
		(*e*) Describe any sensitivity analyses	4-5
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	3, 5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	5
Outcome data	15*	Report numbers of outcome events or summary measures	6-7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-7
		(*b*) Report category boundaries when continuous variables were categorized	6-7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6-7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	7-9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association of proton pump inhibitor use with risk of kidney stones: an analysis of cross-sectional data from the US National Health and Nutrition Examination Survey (2007–2018)

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Abstract

Objective Several studies have suggested a potential link between use of proton pump inhibitors (PPIs) and the risk of kidney stones, attributed to alterations in urine mineral levels. Our study aimed to investigate the association between PPI use and kidney stones in US adults.

Design Cross-sectional study.

Setting National Health and Nutrition Examination Survey (NHANES) (2007–2018).

Participants 27,075 individuals with complete information for PPI use and history of kidney stones were included in this study.

Outcomes and analyses Nonlinear analysis, logistic regression analysis, and subgroup analysis were conducted to estimate the relationship between PPI use and the occurrence and recurrence of kidney stones, after adjusting for potential confounding factors.

Results Multivariable logistic regression analysis revealed a significant association between PPI use and kidney stones (odds ratio [*OR*] 1.31, 95%*CI* 1.07–1.60), with a 4% increase in the prevalence of kidney stones for each additional year of PPI use ($P < 0.001$). Similarly, PPI use was significantly associated with recurrent kidney stones (*OR* 1.49, 95%*CI* 1.04–2.13), with a 7% increase in the recurrence of kidney stones for each additional year of PPI use ($P < 0.001$). Furthermore, these associations remained significant even after conducting propensity score matching analysis on a subset of PPI users and non-users (all $P \leq 0.001$). Subgroup analyses showed that the effects of PPI use on kidney stones differed by age, sex, race, and BMI.

Conclusions This study indicated that long-term use of PPI was associated with a higher risk of both the presence and recurrence of kidney stones.

Keywords: NHANES; urolithiasis; proton pump inhibitors; risk factors; drug effects

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The NHANES dataset comprises a representative sample of the national population to ensure that our findings can be extrapolated to the broader population.
- Multiple potential confounders were adjusted for and a propensity score matching analysis was performed to ensure the reliability of the results.
- It is difficult to draw causal conclusions from cross-sectional analyses.
- NHANES did not record information regarding the time and type of kidney stones or the dosage and type of proton pump inhibitor use.

Introduction

Kidney stones are a common disease in US, with a prevalence of 12% in men and 10% in women, and have a substantial impact in terms of cost and morbidity(1, 2). Some drugs may affect the risk of kidney stones by altering active compounds crystallizing in urine or substances impairing urine composition(3-5).

Proton pump inhibitors (PPIs) are commonly prescribed medications worldwide for the treatment of gastric acid-related diseases such as gastroesophageal reflux disease (GERD), H. pylori infection, and gastric ulcers(6). However, the escalating prevalence of PPI overuse,

especially for long-term therapy, has become a concerning issue(6, 7). Long-term PPI intake is associated with a reduction in intestinal absorption of essential vitamins and minerals and increased susceptibility to infections, chronic kidney disease, and dementia(7). Given that PPI can inhibit gastric acid secretion, thereby affecting the intestinal absorption of essential minerals and altering the levels of calcium, magnesium, and citrate(8, 9), several studies have investigated the impact of PPI use on the risk of kidney stones(10-12). For instance, Sui et al. found that PPI use might elevate the risk of kidney stones by lowering the levels of urinary citrate and magnesium, which could compromise their inhibitory effect on kidney stone formation(11). However, it should be noted that all participants in their study were GERD patients. Similarly, Simonov et al. identified a correlation between PPI use and kidney stones primarily based on a sample of young individuals and males(10), thereby limiting the generalizability of their findings to not only the general population but also specific patient groups, such as recurrent stone formers(13).

This study aimed to investigate the potential association between PPI use and kidney stones by analyzing National Health and Nutrition Examination Survey (NHANES) data from 2007 to 2018. Our hypothesis was that PPI use increases the risk of both kidney stone formation and recurrence.

Methods

Study design and population

The NHANES is an ongoing cross-sectional survey that employs a sophisticated multistage sample methodology to investigate the health and nutritional status of the non-institutionalized population in US. Demographic characteristics, clinical history, and self-reported dietary were collected from participants using a structured household interview. Physical examinations, including anthropometric measurements and blood samples, were collected within a mobile examination center. The protocol was approved by the National Center for Health Statistics (NCHS) Ethics Review Board, and informed consent was obtained from all participants. Additional information regarding data collection can be accessed on the NHANES website(14).

Six NHANES cycles were used in the study from 2007 to 2018. Initially, 34,709 participants aged 20 years and older were included. However, some participants were excluded: 372 participants who were pregnant, 90 participants with incomplete kidney stone questionnaire, and 7,026 participants with incomplete variables. In addition, given the limited number of participants who

had taken PPI for more than 15 years, the standard errors for model estimates increased substantially(15), thus 146 participants were excluded. Finally, 27,075 participants were included in the analysis, consisting of 13,711 females and 13,364 males. Fig. 1 illustrates the filtering process used in this study.

Outcome assessment

The primary outcome was the response to the question, "Have you ever had kidney stones?" (NHANES 2007–2018). Participants who responded "yes" were defined as kidney stone formers. The secondary outcome was the response to the question, "How many times have you passed a kidney stone?" (NHANES 2007–2014). Participants who reported passing at least two stones were classified as recurrent stone formers.

Medication use

The independent variables in this study were whether participants had taken PPI and the duration of their PPI use. Information on the types and duration of acid suppressant medication was obtained through prescription medication questionnaires. The types of PPI in this study included omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole. For participants using PPI, the duration of use was equal to the years since initiating therapy. Participants who did not use PPI had a duration of use recorded as zero. Data on specific dosages or previously discontinued prescription medications were unavailable.

Covariates

The study collected three types of detailed information about covariates through standardized personal interviews. The first group included demographic factors including age, sex, race, education level, smoking status, and alcohol consumption. The second group consisted of factors that impact the body's metabolism level, including body mass index (BMI), mean arterial pressure, HbA1c, triglyceride levels, history of cardiovascular disease (CVD), thiazide use, loop diuretic use, and histamine-2 receptor antagonists (H2RA) use. The third group focused on risk factors related to kidney stone formation, including sedentary time, total water intake, albumin-adjusted calcium levels, estimated glomerular filtration rate (eGFR), and history of gout. Education level was categorized as follows: Grades 0–12, high school graduate/General Equivalency Diploma, and some college or above. Smokers was defined as smoking at least 100 cigarettes during their lifetime. BMI was calculated by dividing weight in kilograms (kg) by height in meters squared (m^2). History of

CVD (including congestive heart failure, coronary heart disease, myocardial infarction, and stroke) was defined if participants self-reported a history of these conditions. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR(16). The CKD-EPI equation is as follows: $eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. Gout was defined as a self-reported diagnosis of gout, and/or the use of anti-gout medication.

Statistical analyses

All statistical analyses considered NHANES survey design characteristics with sampling weights. Descriptive statistics were used to evaluate the demographic and clinic characteristics of the study population. The variance inflation factor (VIF) was utilized to evaluate multicollinearity among covariates and between covariates and kidney stones. A VIF value over 10 indicates multicollinearity, but none was observed in this study (Supplementary Table 1) (17). To explore the relationship between PPI use and kidney stones, we performed four weighted logistic regression models and controlled for the aforementioned explanatory variables by modeling PPI as continuous variables based on the time of use. We utilized restricted cubic splines to explore the potential non-linear link between PPI use duration and kidney stones. Assessing model fit, we employed the Akaike Information Criterion (AIC). Our knot selection process prioritized the model with the lowest AIC value, leading us to choose a model with three knots located at the 5th, 50th, and 95th centiles, as detailed in Supplementary Table 2. Subgroup analyses were also performed to explore whether the relationship between the time of PPI use and kidney stones differed by age, sex, race, and BMI, and potential effect modifiers were tested using the Wald test for multiplicative interactions. Additionally, a 1:1 propensity score matching (PSM) analysis was performed to balance population differences between PPI users and non-users while adjusting for all confounding variables. Previous studies have established links between kidney stones and dietary factors, such as vitamin C intake, caffeine consumption, and the dietary inflammatory index (DII)(18-20). To address potential confounding effects, a sensitivity analysis was conducted using model 3 as the baseline, with additional adjustments made for three variables: vitamin C intake, caffeine intake, and DII. We conducted a meta-analysis using the 'meta' package, which allowed us to combine data

from relevant studies and estimate an overall effect size for the association between PPI use and kidney stones. All statistical tests were two-sided, and P-values < 0.05 (two-sided) were considered statistically significant. R 4.2.2 software was used for modeling.

Patient and public involvement

None.

Results

Population characteristics

This analysis included 27,075 participants aged 20 years and older from the NHANES database (2007–2018), representing 203,076,872 adults. And table 1 presents their demographic and clinical characteristics based on PPI use. The mean age of all participants was 47.46 ± 0.26 (standard error) years, with roughly equal representation of females (51.13%) and males (48.87%). PPI users were more likely to be older, females, non-Hispanic white, obese, have lower education level, alcohol consumption, total water intake, eGFR, higher sedentary time, mean arterial pressure, HbA1c, triglycerides, albumin-adjusted calcium. PPI users were taking more thiazide, loop diuretics, and H2RAs medications compared to non-users. Furthermore, CVD, gout and kidney stone diseases were more common in PPI users (all $P < 0.05$).

Multivariable logistic regression analyses

Weighted univariable and multivariable logistic regression models were used to investigate the independent association between PPI use and the risk of kidney stones, with PPI non-user as the reference group (Table 2). In the crude model, PPI use showed a significantly positive association with the prevalence of kidney stones (*OR* = 1.86, 95%*CI* = 1.55–2.22). In the fully adjusted model (model 3), the association between PPI use and the prevalence of kidney stones remained significant (*OR* = 1.31, 95%*CI* = 1.07–1.60). When considering PPI use as a continuous variable, the restricted cubic spline analyses indicated a linear relationship between the duration of PPI use and the prevalence of kidney stones (*P* for non-linearity = 0.651) (Fig. 2A). With each additional year of PPI use, the prevalence of kidney stones increased by 4% (Table 2). Additionally, we explored the association between PPI use and recurrent kidney stones. In the crude model, PPI use showed a significantly positive association with the recurrence of kidney stones (*OR* = 1.49, 95%*CI* = 1.05–2.09). This positive association persisted in the fully adjusted model (model 3) (*OR* = 1.49, 95%*CI* = 1.04–2.13). The duration of PPI use exhibited a linear correlation with the recurrence of kidney

stones (*P* for non-linearity = 0.484) (Fig. 2B), with a 7% increase for each additional year of PPI use (Table 2).

Subgroup analyses

Moreover, subgroup analyses were performed to assess whether the relationship between the duration of PPI use and kidney stones were influenced by age, sex, race, and BMI (Table 3). After adjusting for all covariates, it was found that the duration of PPI use was significantly associated with the prevalence of kidney stones in participants aged 50 years or order, females, non-Hispanic White, and those with a BMI of 25 kg/m^2 or higher. On the other hand, a significant positive association between time of PPI use and recurrent kidney stones was observed only in participants non-Hispanic White, and those with a BMI of 25 kg/m^2 or higher (all *P* for interaction > 0.05).

Sensitivity analyses and meta-analysis

A 1:1 matched cohort analysis was conducted through PSM to minimize potential bias, given the significant difference in PPI use and non-use group (Table 1). This approach confirmed 4864 participants in the matched cohort. The descriptive statistics results showed that no significant differences observed in most variables between the PPI non-user and PPI user groups (Supplementary Table 3). In the fully adjusted model, the dose–response curve still displayed a positive association between the duration of PPI use and kidney stones (*OR* = 1.05, 95%*CI* = 1.02–1.08, *P* for non-linearity = 0.956) (Supplementary Fig. 1A) and recurrent kidney stones (*OR* = 1.10, 95%*CI* = 1.02–1.18, *P* for non-linearity = 0.488) (Supplementary Fig. 1B). Moreover, the results remained significant after making additional adjustments for vitamin C intake, caffeine consumption, and DII (Supplementary Table 4). Furthermore, we performed a meta-analysis based on our findings and previously published research, confirming a positive association between the PPI use and the risk of kidney stones (*OR* = 1.49, 95%*CI* = 1.05–2.10) (Supplementary Fig. 2)(10-12).

Discussion

In this large cross-sectional study based on NHANES data from 2007 to 2018, we found that PPI use was associated with an increased risk of kidney stones. The duration of PPI use demonstrated a dose-response association with kidney stones. Furthermore, our study uncovered a novel association between long-term PPI use and recurrent kidney stones in patients with a history of kidney stones, demonstrating a significant linear correlation. Additionally, subgroup analysis found that the effects

of age, sex, race, and BMI varied in their influence on the relationship between PPI use and the prevalence of kidney stones.

Several studies have shown that PPI use could increase the risk of kidney stones, with a dose-response relationship(10-12). A retrospective study conducted on the Women's Veterans Cohort, which included 465,891 individuals, revealed that PPI use was linked to a 1.25-fold higher risk of kidney stones (95% CI = 1.19–1.33)(10). It should be noted that this study included mainly young individuals (with a median age of 32 years) and was predominantly males (86%), thus having a certain degree of selection bias(13). Another study by Sui et al. also found a positive association between PPI use and kidney stones in patients with GERD, with a 1.46-fold increased risk (95%CI = 1.38–1.55), which could help in assessing the potential risk of kidney stones associated with PPI exposure(11). Nevertheless, both studies were limited to specific populations, limiting the generalizability of their findings to the general population. In contrast, a nationwide population cohort from Korea, without selection bias, also showed a positive association between PPI use and kidney stones, displaying a dose-response relationship(12). Similarly, the current study, based on data from the NHANES database representing over 203 million individuals, found that PPI use was significantly associated with not only a higher risk of kidney stones, but also recurrent kidney stones. The findings from the meta-analysis conducted in this study have confirmed the positive association between PPI use and the risk of kidney stones. Furthermore, the risk of developing kidney stones was found to be higher in individuals who used PPI for a longer duration, highlighting the importance of monitoring this potential side effects of long-term PPI treatment, especially for patients with a history of kidney stones.

The mechanisms underlying the impact of PPI on kidney stone formation remain unclear. Studies have suggested that PPI can elevate gastric pH, leading to a decrease in magnesium absorption and urinary magnesium levels(9). Magnesium has been known to inhibit the formation of calcium oxalate crystals in urine(21, 22). A meta-analysis of nine observational studies found a significant increased risk of hypomagnesemia among patients using PPI(23). It should be noted that magnesium absorption occurs through both active and passive mechanisms, and alterations in pH do not affect passive absorption(23). Therefore, PPI use does not always result in hypomagnesemia, but patients with impaired gastrointestinal absorptive capacity may have an increased risk of developing hypomagnesemia. On the other hand, research has shown that citrate can inhibit the

crystallization of calcium salts in urine, and a deficiency of citrate can increase the risk of stone formation(24, 25). A study of 301 nephrolithiasis patients with 24-hour urine data found that PPI exposure significantly reduced urinary citrate excretion, but did not affect urinary magnesium, pH, or other urinary minerals(8). Similarly, another study on GERD patients reported a significant correlation between PPI use and lower levels of urinary citrate and magnesium(11). Therefore, given the association of PPI use with hypomagnesuria and hypocitraturia, it may monitor the levels of urinary magnesium and citrate when using PPI.

PPIs are commonly prescribed for acid-related disorders, and patients with these conditions may be at higher risk for kidney stone formation(26). In this study, we employed the PSM analysis to minimize potential differences between PPI users and non-users, yet still identified a significant association between PPI use and the occurrence and recurrence of kidney stones. Subgroup analyses further revealed that certain patient groups, including the elderly, females, non-Hispanic Whites, and those with a BMI of 25 kg/m^2 or higher, exhibited a stronger positive association between PPI use and the prevalence of kidney stones, highlighting the importance of considering potential side effects of PPI use in these populations. While it is undeniable that PPI therapy has improved the quality of life for many patients with acid-related disorders(27), a growing body of literature suggested a relationship between long-term PPI use and adverse events(28). Caution should be exercised when discontinuing PPI use for evidence-based indications(29), but global concerns over long-term PPI overuse should not be overlooked(6, 7), especially in individuals with a history of kidney stones and high-risk factors, such as the elderly, females, non-Hispanic Whites, and those with a BMI of 25 kg/m^2 or higher, in order to reduce unnecessary use.

This study has several strengths. Firstly, the NHANES dataset comprises a representative sample of the national population, and we utilize NHANES-provided weights to ensure that our findings can be extrapolated to the broader population. Secondly, this study not only elucidates the correlation between PPI use and the prevalence of kidney stones but also probes its association with the recurrence of renal calculi in individuals with a history of nephrolithiasis. Furthermore, multiple potential confounders were adjusted and PSM design was performed to ensure the reliability of the results. However, this study also has several limitations. Firstly, it is difficult to draw causal conclusions from such cross-sectional analyses. Although we adjusted for three types of detailed covariate information, there may still be unmeasured potential factors that could affect the

association between PPI and nephrolithiasis. Secondly, the questionnaire survey may have been prone to recall bias and reporting bias, which could affect the accuracy of the data collected. Thirdly, NHANES lacks objective diagnostic imaging for the identification of kidney stones, potentially resulting in the omission of asymptomatic cases. Additionally, the dataset does not provide details on the timing and specific type of kidney stones. Finally, the lack of information about the dosage and type of PPI use may limit the interpretability of the results.

Conclusions

In conclusion, our study revealed a relationship between PPI use and the prevalence of kidney stones, as well as an increased risk of recurrent kidney stones in patients with a history of nephrolithiasis. To mitigate this potential adverse effect, caution should be exercised regarding unnecessary long-term use of PPI.

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Contributors

W-L: conceptualization, methodology, data analysis, manuscript writing; J-W: methodology, data collection, data analysis, manuscript writing; M-W: methodology, data collection, data analysis; MM-W: data analysis, manuscript writing, supervision; M-L: conceptualization, supervision, manuscript editing, funding acquisition.

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Competing interests

None declared.

Patient consent for publication

Not applicable.

Ethics statement

Ethical review and approval for the original research involving human participants were obtained from the Ethics Review Board of the NCHS (Protocol #98-12). Written informed consent was obtained from

all patients or participants who were part of the study. The current analysis, which is based on publicly available data, did not require any further ethics approval.

Data availability statement

Publicly available datasets were analyzed in this study. Data are available from https://www.cdc.gov/nchs/nhanes/ (NHANES 2005-2006 and 2007-2008).

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FIGURE TITLE/LEGENDS

Figure 1. Study flowchart

Of 59,842 participants in the 2007–2018 National Health and Nutrition Examination Survey (NHANES), 27,075 remained after fulfilling inclusion and exclusion criteria.

Figure 2. Dose-response relationships between time of PPIs use and kidney stones

(A) Time of PPIs use and kidney stones; (B) Time of PPIs use and recurrent kidney stones.

Abbreviations: OR, odds ratio; PPIs, proton pump inhibitors. Adjusted for age, sex, race, education

level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, gout, thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake, albumin-adjusted calcium, and eGFR. The shaded part represents the 95% CI.

SUPPLEMENTARY FIGURE TITLE/LEGENDS

Supplementary Fig 1. Dose-response relationships between time of PPIs use and kidney stones after PSM

(A) Time of PPIs use and kidney stones; (B) Time of PPIs use and recurrent kidney stones.

Abbreviations: OR, odds ratio; PPIs, proton pump inhibitors; PSM, propensity score matching. Adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, gout, thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake, albumin-adjusted calcium, and eGFR. The shaded part represents the 95% CI.

Supplementary Fig 2. Forest plot showing the association between PPI use and kidney stones

TABLES

Table 1. Demographic and clinic characteristics according to PPIs use, NHANES 2007–2018*

Characteristics	Total Adults (N = 27,075)	Non-user (N = 24,643)	PPIs user (N = 2,432)	*P* value
Age, years, mean (SE)	47.46(0.26)	46.38(0.25)	59.05(0.47)	< 0.001
Female, n (%)	13711(51.13)	12335(50.63)	1376(56.43)	< 0.001
Race (Non-Hispanic White), n (%)	11470(66.93)	10153(65.94)	1317(77.61)	< 0.001
Education, n (%)				< 0.001
Grades 0–12	6368(23.03)	5671(14.72)	697(17.85)	
High school graduate/GED	6189(14.99)	5593(22.69)	596(26.69)	
Some college or above	14518(61.98)	13379(62.58)	1139(55.46)	
Smoking†, n (%)	5477(19.65)	5035(19.81)	442(17.93)	0.143
Alcohol consumption, n (%)	6469(26.38)	6010(26.73)	459(22.63)	0.017
BMI, kg/m‡², mean (SE)	29.05(0.09)	28.88(0.09)	30.89(0.22)	< 0.001
Weight status (≥ 25 kg/m²), n (%)‡	19423(70.54)	17439(69.47)	1984(81.95)	< 0.001
Sedentary time, hours/day, mean (SE)	368.10(2.86)	365.58(2.96)	395.13(5.96)	< 0.001
Mean arterial pressure, mmHg, mean (SE)	87.98(0.16)	87.83(0.17)	89.59(0.35)	< 0.001
Total water intake, g, mean (SE)	1171.48(15.90)	1180.99(16.29)	1069.41(30.63)	< 0.001
HbA1c, %, mean (SE)	5.63(0.01)	5.61(0.01)	5.89(0.03)	< 0.001

Triglycerides, mmol/L, mean (SE)	1.75(0.02)	1.73(0.02)	1.97(0.04)	< 0.001
Albumin-adjusted calcium, mmol/L, mean (SE)	2.28(0.00)	2.28(0.00)	2.30(0.00)	< 0.001
eGFR, mL/min, mean (SE)	94.33(0.33)	95.55(0.33)	81.23(0.61)	< 0.001
Gout, n (%)	403(1.25)	309(1.07)	94(3.23)	< 0.001
CVD, n (%)	2595(9.584)	2050(6.641)	545(17.438)	< 0.001
Congestive heart failure	805(2.20)	589(1.76)	216(6.88)	< 0.001
Coronary heart disease	1080(3.34)	829(2.87)	251(8.39)	< 0.001
Myocardial infarction	1082(3.01)	828(2.56)	254(7.82)	< 0.001
Stroke	984(2.78)	788(2.43)	196(6.47)	< 0.001
Thiazide user, n (%)	2748(8.66)	2256(7.81)	492(17.75)	< 0.001
Loop diuretics user, n (%)	876(2.46)	626(1.91)	250(8.35)	< 0.001
H2RAs user, n (%)	643(2.33)	550(2.26)	93(3.12)	0.030
Kidney stones, n (%)	2589(9.80)	2217(9.23)	372(15.88)	< 0.001

Abbreviations: NHANES, National Health and Nutrition Examination Survey; PPIs, proton pump inhibitors; SE, standard error; GED, General Equivalency Diploma; BMI, body mass index; eGFR, effective glomerular filtration rate; CVD, cardiovascular disease; H2RAs, H2-receptor antagonist.

*Means and percentages were adjusted for survey weights of NHANES.

†Smoking was defined as smoking at least 100 cigarettes during their lifetime.

‡BMI was calculated by dividing weight in kilograms (kg) by height in meters squared (m^2). Participants were classified as normal weight (BMI < 25 kg/m^2), and overweight/obese (BMI ≥ 25 kg/m^2).

Table 2. OR (95% CI) for kidney stones across PPIs use*

	Crude model	Model 1	Model 2	Model 3
Kidney stones (N = 2,589) vs non-kidney stone (N = 24,486) (NHANES 2007–2018)				
PPIs use				
No	1[Reference]	1[Reference]	1[Reference]	1[Reference]
Yes	1.86(1.55,2.22)	1.42(1.18,1.72)	1.32(1.09,1.61)	1.31(1.07,1.60)
Time of use (years)	1.09(1.07,1.12)	1.05(1.02,1.08)	1.04(1.01,1.07)	1.04(1.01,1.07)
Recurrent kidney stones (N = 550) vs first kidney stone (N = 1,138) (NHANES 2007–2014)				
PPIs use				
No	1[Reference]	1[Reference]	1[Reference]	1[Reference]
Yes	1.49(1.05,2.09)	1.49(1.05,2.13)	1.47(1.03,2.10)	1.49(1.04,2.13)
Time of use (years)	1.07(1.01,1.12)	1.06(1.01,1.12)	1.06(1.01,1.12)	1.07(1.01,1.13)

Abbreviations: OR, odds ratio; CI, confidence interval; PPIs, proton pump inhibitors.

*Values are numerical values or weighted OR (95% CI).

Model 1 was adjusted for age, sex, race, education level, smoking, and alcohol consumption;

Model 2 was adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, thiazide use, loop diuretics use, and H2RAs use.

Model 3 was additionally adjusted for sedentary time, total water intake, albumin-adjusted calcium, eGFR and history of gout.

Table 3. OR (95% CI) for kidney stones across time of PPIs use stratified by selected factors*

	Kidney stones vs non-kidney stone	Recurrent kidney stones vs first kidney stone

	OR (95% CI)	*P* value	*P* for interaction	OR (95% CI)	*P* value	*P* for interaction
Age			0.439			0.419
< 50 years	1.05(0.98, 1.11)	0.150		1.11(0.98, 1.27)	0.104	
≥ 50 years	1.04(1.01,1.07)	0.004		1.07(1.00,1.14)	0.053	
Sex			0.856			0.623
Female	1.06(1.02,1.10)	0.004		1.08(0.99,1.18)	0.099	
Male	1.02(0.98,1.07)	0.258		1.06(0.98,1.14)	0.156	
Race			0.365			0.282
Non-Hispanic White	1.04(1.01,1.07)	0.005		1.11(1.01, 1.22)	0.037	
Other	1.02(0.98,1.06)	0.422		1.07(1.00,1.13)	0.038	
BMI			0.684			0.922
< 25 kg/m^2	1.06(0.98,1.14)	0.134		1.04(0.90, 1.22)	0.569	
≥ 25 kg/m^2	1.04(1.01,1.06)	0.013		1.07(1.01,1.15)	0.029	

Abbreviations: OR, odds ratio; CI, confidence interval; PPIs, proton pump inhibitors; BMI, body mass index.

*Values are numerical values or weighted OR (95% CI).

Adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, gout, thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake, albumin-adjusted calcium, and eGFR, if not already stratified.

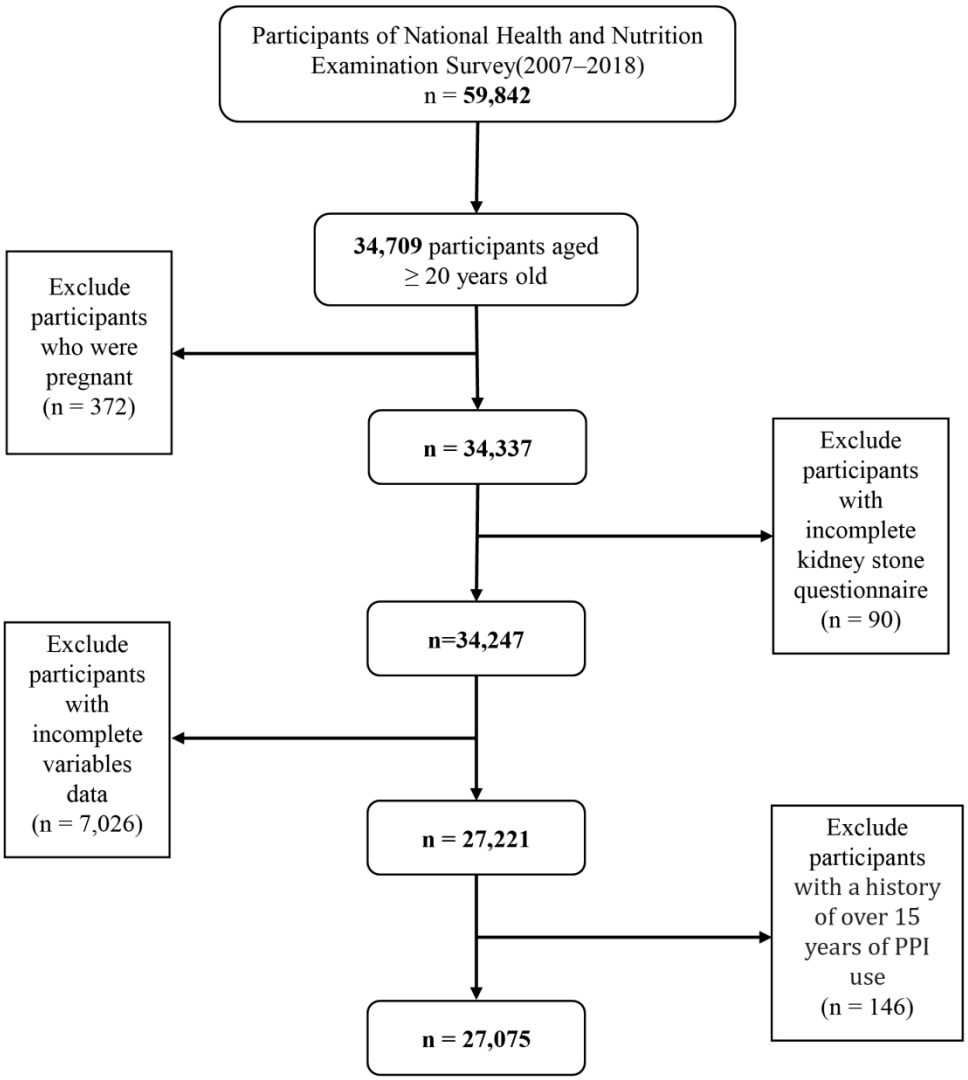

Fig. 1 Study flowchart. Of 59,842 participants in the 2007–2018 National Health and Nutrition Examination Survey (NHANES), 27,075 remained after fulfilling inclusion and exclusion criteria.

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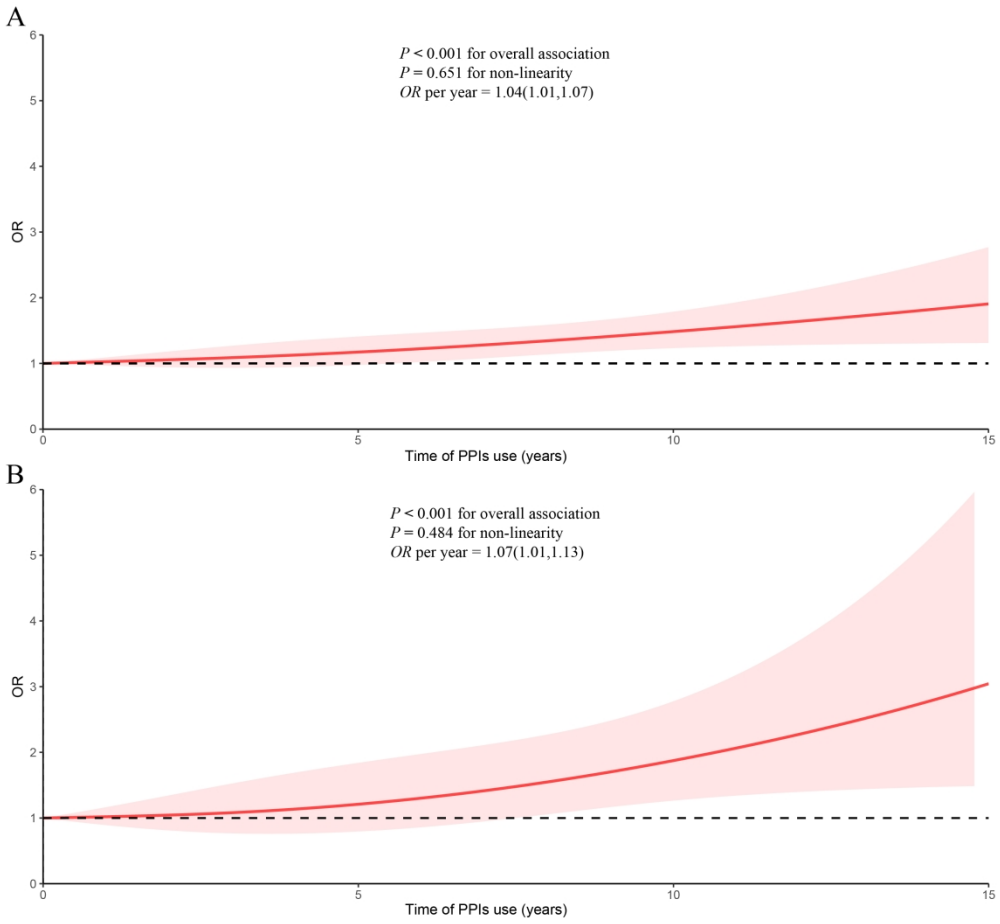

Fig. 2 Dose-response relationships between time of PPIs use and kidney stones. (A) Time of PPIs use and kidney stones; (B) Time of PPIs use and recurrent kidney stones.
Abbreviations: OR, odds ratio; PPIs, proton pump inhibitors. Adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, gout, thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake, albumin-adjusted calcium, and eGFR. The shaded part represents the 95% CI.

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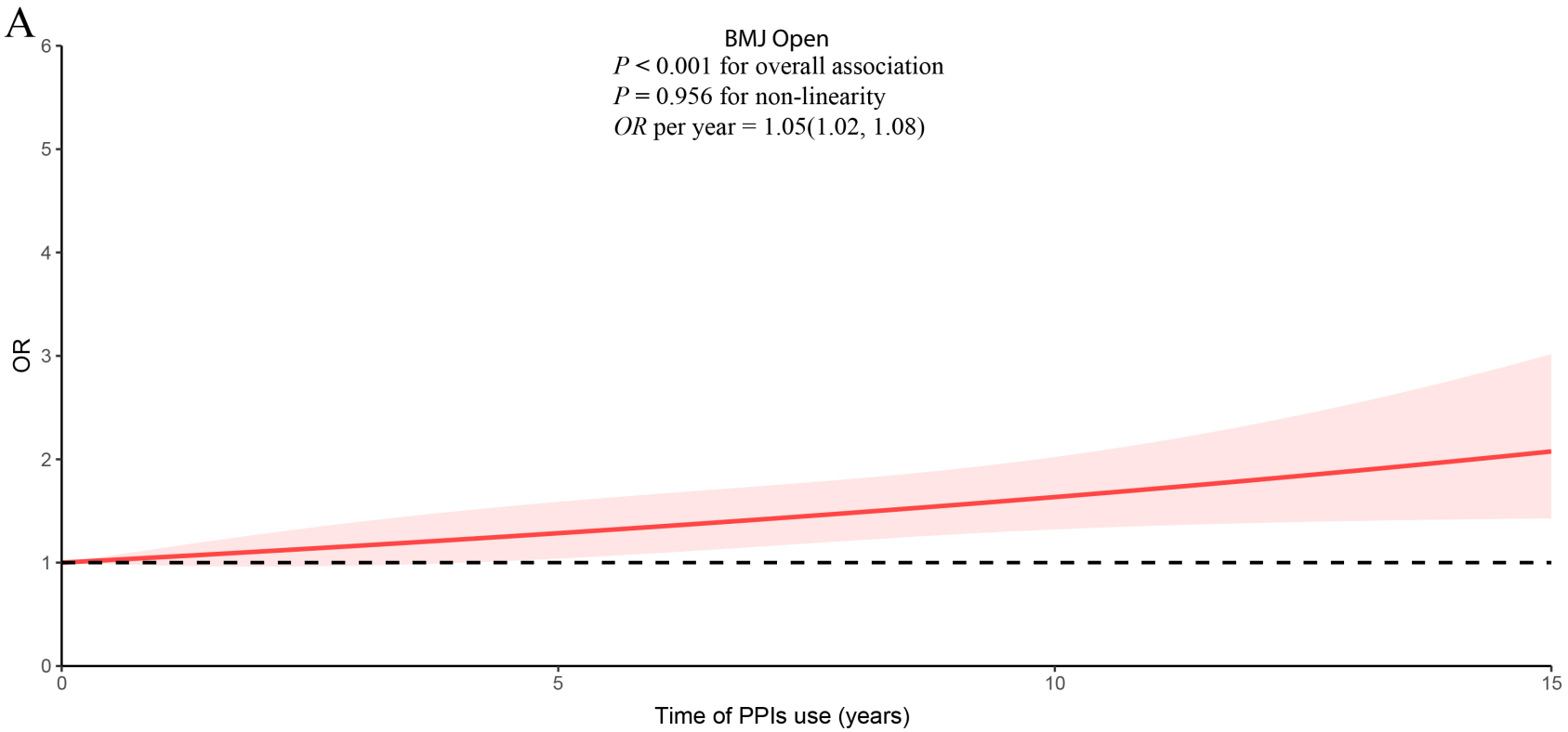

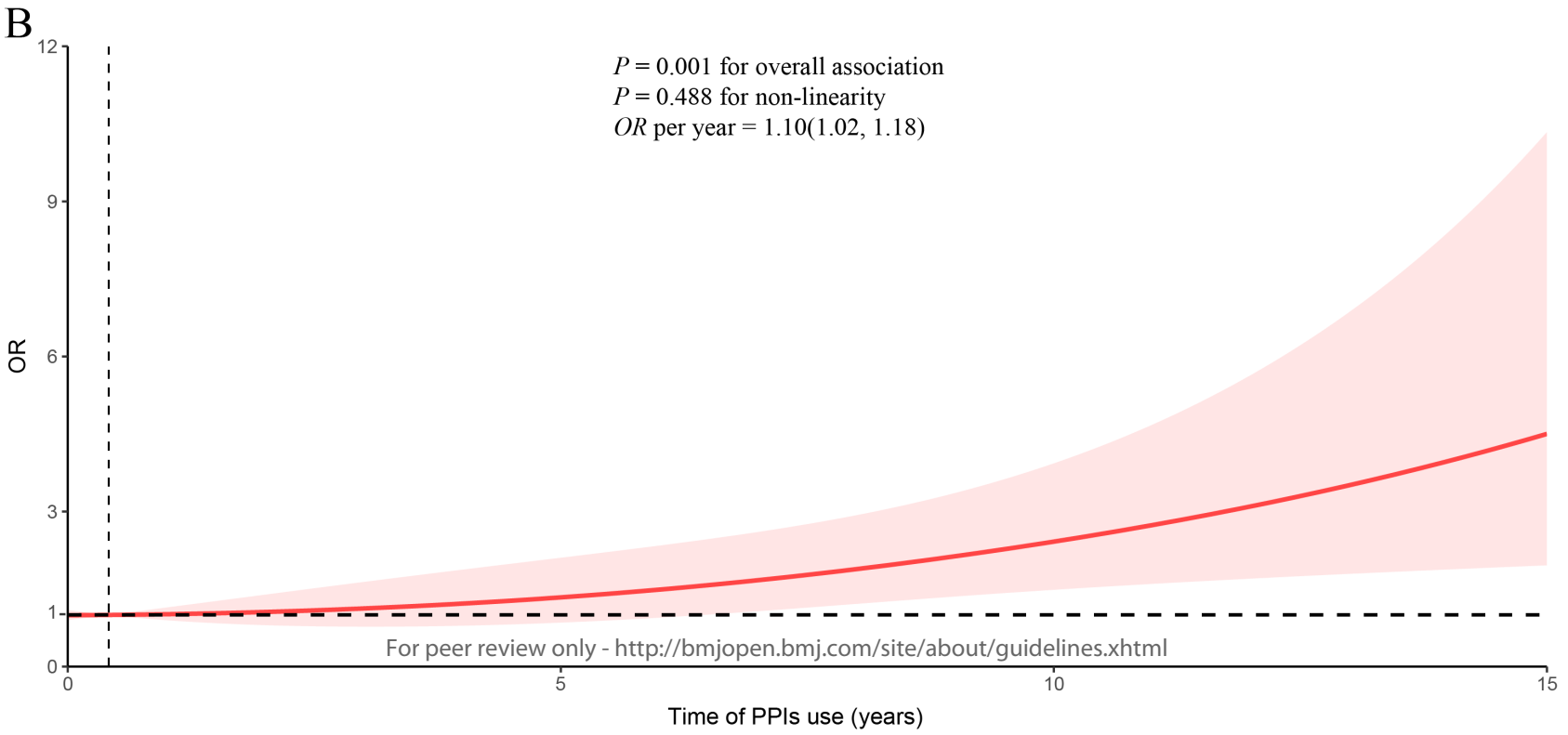

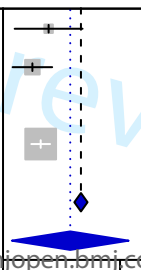

Study	HR/OR	95%CI	Weight (fixed)	Weight (random)
The present study	1.31	[1.07; 1.60]	3.8%	23.7%
Sui et al. 2022	1.19	[1.06; 1.34]	11.2%	25.1%
Kim et al. 2022	2.49	[2.33; 2.66]	35.1%	25.6%
Simonov et al. 2021	1.25	[1.19; 1.33]	49.8%	25.6%
Fixed effect model	**1.59**	**[1.53; 1.65]**	**100.0%**	**--**
Random effects model	**1.49**	**[1.05; 2.10]**	**--**	**100.0%**

Supplementary Table 1. Collinearity analysis

Variables	VIF
Age	3.80
Sex	1.54
Race/ethnicity	1.85
Education	2.50
Smoking	2.08
Alcohol consumption	1.75
BMI	1.26
Sedentary time	1.54
Mean arterial pressure	1.25
Total water intake	1.99
HbA1c	1.81
Triglycerides	1.44
Albumin-adjusted calcium	1.97
eGFR	3.72
CVD	1.77
Thiazide use	1.78
Loop diuretics use	1.56
H2RAs use	1.27

Abbreviations: VIF, variance inflation factor; BMI, body mass index; eGFR, effective glomerular filtration rate; CVD, cardiovascular disease; H2RAs, H2-receptor antagonist.

Supplementary Table 2. Akaike information criterion (AIC) and P-value for non-linearity of restricted cubic splines models across different knots

The occurrence of kidney stones			The recurrence of kidney stones		
Knots	AIC	P for non-linearity	Knots	AIC	P for non-linearity
3	16664.48	0.651	3	2167.76	0.484
4	16664.67	0.071	4	2170.74	0.594
5	16667.34	0.108	5	2169.07	0.146

Supplementary Table 3. Demographic and clinic characteristics according to PPIs use after PSM. NHANES 2007–2018*

Characteristics	Total Adults (N = 4,864)	Non-user (N = 2,432)	PPIs user (N = 2,432)	*P* value
Age, years, mean (SE)	59.15(0.35)	59.24(0.42)	59.05(0.47)	0.733
Female, n (%)	2679(56.73)	1303(57.02)	1376(56.43)	0.800
Race (Non-Hispanic White), n (%)	2634(78.13)	1317(78.63)	1317(77.61)	0.460
Education, n (%)				0.760
Grades 0–12	1379(17.54)	682(17.24)	697(17.85)	
High school graduate/GED	1217(26.31)	621(25.95)	596(26.69)	
Some college or above	2268(56.14)	1129(56.80)	1139(55.46)	
Smoking†, n (%)	904(18.71)	462(19.46)	442(17.93)	0.715
Alcohol consumption, n (%)	952(22.76)	493(22.89)	459(22.63)	0.902
BMI, kg/m‡2, mean (SE)	30.64(0.17)	30.41(0.23)	30.89(0.22)	0.113
Weight status (≥ 25 kg/m^2), n (%)‡	4013(82.25)	2029(82.531)	1984(81.948)	0.715
Sedentary time, hours/day, mean (SE)	390.48(4.72)	386.03(6.16)	395.13(5.96)	0.236
Mean arterial pressure, mmHg, mean (SE)	89.92(0.29)	90.25(0.40)	89.59(0.35)	0.194
Total water intake, g, mean (SE)	1058.14(24.20)	1047.33(32.08)	1069.41(30.63)	0.582
HbA1c, %, mean (SE)	5.89(0.02)	5.89(0.03)	5.89(0.03)	0.917
Triglycerides, mmol/L, mean (SE)	1.96(0.03)	1.95(0.03)	1.97(0.04)	0.716
Albumin-adjusted calcium, mmol/L, mean (SE)	2.30(0.00)	2.30(0.00)	2.30(0.00)	0.939
eGFR, mL/min, mean (SE)	81.68(0.45)	82.11(0.63)	81.23(0.61)	0.306
Gout, n (%)	169(2.83)	75(2.44)	94(3.23)	0.216
CVD history, n (%)	989(20.33)	444(14.83)	545(17.44)	0.070
Thiazide user, n (%)	983(17.98)	491(18.20)	492(17.75)	0.776
Loop diuretics user, n (%)	436(7.13)	186(5.97)	250(8.35)	0.016
H2RAs user, n (%)	168(3.11)	75(3.10)	93(3.12)	0.979
Kidney stones, n (%)	658(13.51)	286(11.23)	372(15.88)	0.002

Abbreviations: PPIs, proton pump inhibitors; PSM, propensity score matching; NHANES, National Health and Nutrition Examination Survey; SE, standard error; GED, General Equivalency Diploma; BMI, body mass index; eGFR, effective glomerular filtration rate; CVD, cardiovascular disease; H2RAs, H2-receptor antagonist.

*Means and percentages were adjusted for survey weights of NHANES.

†Smoking was defined as smoking at least 100 cigarettes during their lifetime.

‡BMI was calculated by dividing weight in kilograms (kg) by height in meters squared (m^2). Participants were classified as normal weight (BMI < 25 kg/m^2), and overweight/obese (BMI ≥ 25 kg/m^2).

Supplementary Table 4. Sensitivity analyses of the associations between kidney stones and PPIs use after additional adjustment for vitamin C intake, caffeine intake and dietary inflammation index*

Model (*OR* [95%*CI*])		*P*-value
Kidney stones (N = 2,589) VS Non-kidney stone (N = 24,486) (NHANES 2007–2018)		
PPIs use		0.01
No	1[Reference]	
Yes	1.31(1.07,1.60)	
Time of use (years)	1.04(1.01,1.07)	0.004
Recurrent kidney stones (N = 550) VS first kidney stone (N = 1,138) (NHANES 2007–2014)		
PPIs use		0.03
No	1[Reference]	
Yes	1.49(1.04,2.13)	
Time of use (years)	1.07(1.01,1.13)	0.03

Abbreviations: *OR*, odds ratio; *CI*, confidence interval; PPIs, proton pump inhibitors.

*Values are numerical values or weighted *OR* (95% *CI*).

Model was adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, thiazide use, loop diuretics use, H2RAs use, sedentary time, total water intake, albumin-adjusted calcium, eGFR history of gout, vitamin C intake, caffeine intake and dietary inflammation index.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	3-4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3-4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3-4
Bias	9	*Describe any efforts to address potential sources of bias*	3-4
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3-4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4-5
		(*b*) Describe any methods used to examine subgroups and interactions	4-5
		(*c*) Explain how missing data were addressed	4-5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	4-5
		(*e*) Describe any sensitivity analyses	4-5
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	3, 5
		(c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	5
Outcome data	15*	Report numbers of outcome events or summary measures	6-7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-7
		(*b*) Report category boundaries when continuous variables were categorized	6-7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6-7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	7-9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.