

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-075136
Article Type:	Original research
Date Submitted by the Author:	27-Apr-2023
Complete List of Authors:	liu, wen; Chinese Academy of Medical Sciences & Peking Union Medical College, Wang, Jia; The Affiliated Hospital of Qingdao University, Department of Gastroenterology Wang, Miao; Beijing Hospital, Department of Urology Wang, Miaomiao; Beijing Hospital, Department of Urology Liu, Ming; Beijing Hospital, Department of Urology
Keywords:	Risk Factors, Urolithiasis < UROLOGY, Adverse events < THERAPEUTICS

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Wen Liu^{1,2†}, Jia Wang^{3†}, Miao Wang¹, Miaomiao Wang^{1,2}, and Ming Liu^{1,2*}

1 Department of Urology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China.

2 Graduate School of Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China.

3 Department of Gastroenterology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China.

† Both authors contributed equally to this work

* Correspondence: Ming Liu, Department of Urology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, No.1 DaHua Road, Dong Dan, Beijing, 100730, China.

E-mail: liumingbjh@126.com

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%

1
2
3
4 31 increase in the incidence of recurrent kidney stones for each additional year of PPI use ($P < 0.001$).
5
6 32 Furthermore, these associations remained significant even after conducting propensity score
7
8 33 matching analysis on a subset of PPI users and non-users (all $P \leq 0.001$). Subgroup analyses showed
9
10 34 that the effects of PPI use on kidney stones differed by age, sex, race, and BMI.

11 35 **Conclusions** This study indicated that long-term use of PPI was associated with a higher risk of
12
13 36 both incident and recurrent kidney stones.

14
15 37 **Keywords:** NHANES; urolithiasis; proton pump inhibitors; risk factors; drug effects
16
17 38

19 39 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

20
21 40 The NHANES dataset comprises a representative sample of the national population to ensure that
22
23 41 our findings can be extrapolated to the broader population.

24
25 42 This is the first study to explore the positive relationship between PPI use and recurrent kidney
26
27 43 stones in patients with history of nephrolithiasis.

28
29 44 Multiple potential confounders were adjusted and PSM design was performed to ensure the
30
31 45 reliability of the results.

32
33 46 It is difficult to draw causal conclusions from such cross-sectional analyses.

34
35 47 NHANES may did not record information regarding the time and type of kidney stones and the
36
37 48 dosage and type of PPI use.
38
39 49

40 50 **Introduction**

41
42 51 Kidney stone is a common disease in US, with a high prevalence of 12% of men and 10% of
43
44 52 women, and caused high cost and morbidity(1, 2). Some drugs may affect the risk of kidney
45
46 53 stones by altering active compounds crystallizing in urine or substances impairing urine
47
48 54 composition(3-5).

49
50 55 Proton pump inhibitors (PPIs) are commonly prescribed medications worldwide for the
51
52 56 treatment of gastric acid-related diseases such as gastroesophageal reflux disease (GERD), H.
53
54 57 pylori infection, and gastric ulcers(6). However, the escalating prevalence of PPI overuse,
55
56 58 especially for long-term therapy, has become a concerning issue(6, 7). Long-term PPI intake is
57
58 59 associated with a reduction in intestinal absorption of essential vitamins and minerals and
59
60 60 increased susceptibility to infections, chronic kidney disease, and dementia(7). Given that PPI can

1
2
3
4 61 inhibit gastric acid secretion, thereby affecting the intestinal absorption of essential minerals and
5
6 62 altering the levels of calcium, magnesium, and citrate(8, 9), several studies have investigated the
7
8 63 impact of PPI use on the risk of kidney stones(10-12). For instance, Sui et al. found that PPI use
9
10 64 might elevate the risk of kidney stones by lowering the levels of urinary citrate and magnesium,
11
12 65 which could compromise their inhibitory effect on kidney stone formation(11). However, it should
13
14 66 be noted that all participants in their study were GERD patients. Similarly, Simonov et al.
15
16 67 identified a correlation between PPI use and kidney stones primarily based on a sample of young
17
18 68 individuals and males(10), thereby limiting the generalizability of their findings to not only the
19
20 69 general population but also specific patient groups, such as recurrent stone formers(13).

21 70 This study aimed to investigate the potential association between PPI use and kidney stones
22
23 71 by analyzing National Health and Nutrition Examination Survey (NHANES) data from 2007 to
24
25 72 2018. Our hypothesis was that PPI use increases the risk of both kidney stone formation and
26
27 73 recurrence.

28 29 74 **Materials and methods**

30 31 75 **Study Population and Design**

32
33 76 The NHANES is an ongoing cross-sectional survey that employs a sophisticated multistage
34
35 77 sample methodology to investigate the health and nutritional status of the non-institutionalized
36
37 78 population in US. The protocol was approved by the National Center for Health Statistics (NCHS)
38
39 79 Ethics Review Board, and informed consent was obtained from all participants. Additional
40
41 80 information regarding data collection can be accessed on the NHANES website(14).

42
43 81 Six NHANES cycles were used in the study from 2007 to 2018. Initially, 34,709 participants
44
45 82 aged 20 years and older were included. However, some participants were excluded: 372 participants
46
47 83 who were pregnant, 90 participants with incomplete kidney stone questionnaire, and 7,026
48
49 84 participants with incomplete variables. In addition, given the limited number of participants who
50
51 85 had taken PPI for more than 15 years, the standard errors for model estimates increased
52
53 86 substantially(15), thus 146 participants were excluded. Finally, 27,075 participants were included
54
55 87 in the analysis, consisting of 13,711 females and 13,364 males. Fig. 1 illustrates the filtering process
56
57 88 used in this study.

58 59 89 **Assessment of Outcomes**

60 90 The primary outcome was the response to the question, "Have you ever had kidney stones?"

1
2
3
4 91 (NHANES 2007–2018). Participants who responded “yes” were defined as kidney stone formers.
5
6 92 The secondary outcome was the response to the question, “How many times have you passed a
7
8 93 kidney stone?” (NHANES 2007–2014). Participants who reported passing at least two stones were
9
10 94 classified as recurrent stone formers.

11 95 **Medication Use**

12
13 96 The independent variables in this study were whether participants had taken PPI and the
14
15 97 duration of their PPI use. Information on the types and duration of acid suppressant medication was
16
17 98 obtained through prescription medication questionnaires. The types of PPI in this study included
18
19 99 omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole. For participants using PPI,
20
21 100 the duration of use was equal to the years since initiating therapy. Participants who did not use PPI
22
23 101 had a duration of use recorded as zero. Data on specific dosages or previously discontinued
24
25 102 prescription medications were unavailable.

26 27 103 **Ascertainment of Covariates**

28
29 104 The study collected three types of detailed information about covariates through standardized
30
31 105 personal interviews. The first group included demographic factors including age, sex, race,
32
33 106 education level, smoking status, and alcohol consumption. The second group consisted of factors
34
35 107 that impact the body's metabolism level, including body mass index (BMI), mean arterial pressure,
36
37 108 HbA1c, triglyceride levels, history of cardiovascular disease (CVD), thiazide use, loop diuretic use,
38
39 109 and histamine-2 receptor antagonists (H2RA) use. The third group focused on risk factors related to
40
41 110 kidney stone formation, including sedentary time, total water intake, albumin-adjusted calcium
42
43 111 levels, estimated glomerular filtration rate (eGFR), and history of gout. History of CVD (including
44
45 112 congestive heart failure, coronary heart disease, myocardial infarction, and stroke) was defined if
46
47 113 participants self-reported a history of these conditions. Gout was defined as a self-reported diagnosis
48
49 114 of gout, and/or the use of anti-gout medication.

50 115 **Statistical Analyses**

51
52 116 All statistical analyses considered NHANES survey design characteristics with sampling
53
54 117 weights. Descriptive statistics were used to evaluate the demographic and clinic characteristics of
55
56 118 the study population. The variance inflation factor (VIF) was utilized to evaluate multicollinearity
57
58 119 among covariates and between covariates and kidney stones. A VIF value over 10 indicates
59
60 120 multicollinearity, but none was observed in this study (Supplementary Table 1) (16). To explore the

1
2
3
4 121 relationship between PPI use and kidney stones, we performed four weighted logistics regression
5 122 models and controlled for the aforementioned explanatory variables by modeling PPI as continuous
6 123 variables based on the time of use. To evaluate the potential non-linear relationship between the
7 124 time of PPI use and kidney stones, restricted cubic splines were used with three knots at the 5th,
8 125 50th, and 95th centiles. Subgroup analyses were also performed to explore whether the relationship
9 126 between the time of PPI use and kidney stones differed by age, sex, race, and BMI, and potential
10 127 effect modifiers were tested using the Wald test for multiplicative interactions. Additionally, a 1:1
11 128 propensity score matching (PSM) analysis was performed to balance population differences
12 129 between PPI users and non-users while adjusting for all confounding variables. We conducted a
13 130 meta-analysis using the 'meta' package, which allowed us to combine data from relevant studies and
14 131 estimate an overall effect size for the association between PPI use and kidney stones. All statistical
15 132 tests were two-sided, and P-values < 0.05 (two-sided) were considered statistically significant. R
16 133 4.2.2 software was used for modeling.

134 **Results**

135 **Population Characteristics**

136 This study included 27,075 participants aged 20 years and older from the NHANES database
137 (2007–2018), representing 203,076,872 adults. And table 1 presents their demographic and clinic
138 characteristics based on PPI use. The mean age of all participants was 47.46 ± 0.26 (standard
139 error) years, with roughly equal representation of females (51.13%) and males (48.87%). PPI
140 users were more likely to be older, females, non-Hispanic white, obese, have lower education
141 level, alcohol consumption, total water intake, eGFR, higher sedentary time, mean arterial
142 pressure, HbA1c, triglycerides, albumin-adjusted calcium. PPI users were taking more thiazide,
143 loop diuretics, and H2RAs medications compared to non-users. Furthermore, CVD, gout and
144 kidney stone diseases were more common in PPI users (all $P < 0.05$).

145 **Multivariate Logistics Regression Analysis**

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

1
2
3
4 151 (model 3), PPI use still maintained a significantly positive association with incident kidney stones
5
6 152 ($OR = 1.31$, $95\%CI = 1.07-1.60$), and for each additional year of PPI use, the incidence of kidney
7
8 153 stones increased by 4%. Additionally, we also explored the association between PPI use and
9
10 154 recurrent kidney stones. In the crude model, PPI use showed a significantly positive association
11
12 155 with recurrent kidney stones ($OR = 1.49$, $95\%CI = 1.05-2.09$), and for each additional year of PPI
13
14 156 use, the incidence of recurrent kidney stones increased by 7%. In the fully adjusted model (model
15
16 157 3), PPI use still maintained a significantly positive association with recurrent kidney stones ($OR =$
17
18 158 1.49 , $95\%CI = 1.04-2.13$). The incidence of recurrent kidney stones increased by 7% for each
19
20 159 additional year of PPI use.

21 160 **Dose-response Relationships Between the Time of PPI Use and Kidney Stones**

22
23 161 According to the restricted cubic spline analyses, a significantly positive relationship was
24
25 162 observed between the duration of PPI use and incident kidney stones (P for overall < 0.001 , P for
26
27 163 non-linearity = 0.651) (Fig. 2A) and recurrent kidney stones (P for overall = 0.001, P for non-
28
29 164 linearity = 0.484) (Fig. 2B).

30 165 **Subgroup Analyses**

31
32
33 166 Moreover, subgroup analyses were performed to assess whether the relationship between the
34
35 167 duration of PPI use and kidney stones were influenced by age, sex, race, and BMI (Table 3). After
36
37 168 adjusting for all covariates, it was found that the duration of PPI use was significantly associated
38
39 169 with incident kidney stones in participants aged 50 years or older, females, non-Hispanic White,
40
41 170 and those with a BMI of 25 kg/m² or higher. On the other hand, a significant positive association
42
43 171 between time of PPI use and recurrent kidney stones was observed only in participants non-Hispanic
44
45 172 White, and those with a BMI of 25 kg/m² or higher (all P for interaction > 0.05).

46 173 **Sensitivity Analyses**

47
48
49 174 A 1:1 matched cohort analysis was conducted through PSM to minimize potential bias, given
50
51 175 the significant difference in PPI use and non-use group (Table 1). This approach confirmed 4864
52
53 176 participants in the matched cohort. The descriptive statistics results showed that no significant
54
55 177 differences observed in most variables between the PPI non-user and PPI user groups
56
57 178 (Supplementary Table 2). In the fully adjusted model, the dose-response curve still displayed a
58
59 179 positive association between the duration of PPI use and kidney stones ($OR = 1.05$, $95\%CI = 1.02-$
60
180 1.08 , P for overall < 0.001 , P for non-linearity = 0.956) (Supplementary Fig. 1A) and recurrent

1
2
3
4 181 kidney stones ($OR = 1.10$, $95\%CI = 1.02-1.18$, P for overall = 0.001, P for non-linearity = 0.488)
5
6 182 (Supplementary Fig. 1B).

7 183 **Discussion**

8
9 184 In this large cross-sectional study based on NHANES data from 2007 to 2018, we found that
10
11 185 PPI use was significantly associated with an increased risk of incident kidney stones. The duration
12
13 186 of PPI use demonstrated a dose-response association with incident kidney stones. Furthermore, our
14
15 187 study uncovered a novel association between long-term PPI use and recurrent kidney stones in
16
17 188 patients with a history of kidney stones, demonstrating a significant linear correlation. Additionally,
18
19 189 subgroup analysis found that the effects of age, sex, race, and BMI varied in their influence on the
20
21 190 relationship between PPI use and incident kidney stones.

22
23 191 Several studies have shown that PPI use could increase the risk of kidney stones, with a dose-
24
25 192 response relationship(10-12). A retrospective study conducted on the Women's Veterans Cohort,
26
27 193 which included 465,891 individuals, revealed that PPI use was linked to a 1.25-fold higher risk of
28
29 194 kidney stones ($95\% CI = 1.19-1.33$) (Supplementary Fig. 2)(10). It should be noted that this study
30
31 195 included mainly young individuals (with a median age of 32 years) and was predominantly males
32
33 196 (86%), thus having a certain degree of selection bias(13). Another study by Sui et al. also found a
34
35 197 positive association between PPI use and kidney stones in patients with GERD, with a 1.46-fold
36
37 198 increased risk ($95\%CI = 1.38-1.55$), which could help in assessing the potential risk of kidney
38
39 199 stones associated with PPI exposure (Supplementary Fig. 2)(11). Nevertheless, both studies were
40
41 200 limited to specific populations, limiting the generalizability of their findings to the general
42
43 201 population. In contrast, a nationwide population cohort from Korea, without selection bias, also
44
45 202 showed a positive association between PPI use and kidney stones, displaying a dose-response
46
47 203 relationship(12). Similarly, the current study, based on data from the NHANES database
48
49 204 representing over 203 million individuals, found that PPI use was significantly associated with not
50
51 205 only a higher risk of incident kidney stones, but also recurrent kidney stones. Furthermore, the risk
52
53 206 of developing kidney stones was found to be higher in individuals who used PPI for a longer
54
55 207 duration, highlighting the importance of monitoring this potential side effects of long-term PPI
56
57 208 treatment, especially for patients with a history of kidney stones.

58 209 The mechanisms underlying the impact of PPI on kidney stone formation remain unclear.
59
60 210 Studies have suggested that PPI can elevate gastric pH, leading to a decrease in magnesium

1
2
3
4 211 absorption and urinary magnesium levels(9). Magnesium has been known to inhibit the formation
5
6 212 of calcium oxalate crystals in urine(17, 18). A meta-analysis of nine observational studies found a
7
8 213 significant increased risk of hypomagnesemia among patients using PPI(19). It should be noted that
9
10 214 magnesium absorption occurs through both active and passive mechanisms, and alterations in pH
11
12 215 do not affect passive absorption(19). Therefore, PPI use does not always result in hypomagnesemia,
13
14 216 but patients with impaired gastrointestinal absorptive capacity may have an increased risk of
15
16 217 developing hypomagnesemia. On the other hand, research has shown that citrate can inhibit the
17
18 218 crystallization of calcium salts in urine, and a deficiency of citrate can increase the risk of stone
19
20 219 formation(20, 21). A study of 301 nephrolithiasis patients with 24-hour urine data found that PPI
21
22 220 exposure significantly reduced urinary citrate excretion, but did not affect urinary magnesium, pH,
23
24 221 or other urinary minerals(8). Similarly, another study on GERD patients reported a significant
25
26 222 correlation between PPI use and lower levels of urinary citrate and magnesium(11). Therefore, given
27
28 223 the association between PPI use and hypomagnesemia and hypocitraturia, it may monitor the levels
29
30 224 of urinary magnesium and citrate when using PPI.

31 225 PPIs are commonly prescribed for acid-related disorders, and patients with these conditions
32
33 226 may be at higher risk for kidney stone formation(22). In this study, we employed the PSM analysis
34
35 227 to minimize potential differences between PPI users and non-users, yet still identified a significant
36
37 228 association between PPI use and incident and recurrent kidney stones. Subgroup analyses further
38
39 229 revealed that certain patient groups, including the elderly, females, non-Hispanic Whites, and those
40
41 230 with a BMI of 25 kg/m² or higher, exhibited a stronger positive association between PPI use and
42
43 231 incident kidney stones, highlighting the importance of considering potential side effects of PPI use
44
45 232 in these populations. While it is undeniable that PPI therapy has improved the quality of life for
46
47 233 many patients with acid-related disorders(23), a growing body of literature suggested a relationship
48
49 234 between long-term PPI use and adverse events(24). Caution should be exercised when discontinuing
50
51 235 PPI use for evidence-based indications(25), but global concerns over long-term PPI overuse should
52
53 236 not be overlooked(6, 7), especially in individuals with a history of kidney stones and high-risk
54
55 237 factors, such as the elderly, females, non-Hispanic Whites, and those with a BMI of 25 kg/m² or
56
57 238 higher, in order to reduce unnecessary use.

58 239 This study has several strengths. Firstly, the NHANES dataset comprises a representative
59
60 240 sample of the national population, and we utilize NHANES-provided weights to ensure that our

1
2
3
4 241 findings can be extrapolated to the broader population. Secondly, this is the first study to explore
5
6 242 the positive relationship between PPI use and recurrent kidney stones in patients with history of
7
8 243 nephrolithiasis. Furthermore, multiple potential confounders were adjusted and PSM design was
9
10 244 performed to ensure the reliability of the results. However, this study also has several limitations.
11
12 245 Firstly, it is difficult to draw causal conclusions from such cross-sectional analyses. Although we
13
14 246 adjusted for three types of detailed covariate information, there may still be unmeasured potential
15
16 247 factors that could affect the association between PPI and nephrolithiasis. Secondly, the
17
18 248 questionnaire survey may have been prone to recall bias and reporting bias, which could affect the
19
20 249 accuracy of the data collected. Thirdly, NHANES may have missed some asymptomatic kidney
21
22 250 stones without physical examination and did not record information regarding the time and type of
23
24 251 kidney stones. Finally, the lack of information about the dosage and type of PPI use may limit the
25
26 252 interpretability of the results.

27 253 **Conclusions**

28
29 254 In conclusion, our study demonstrated a significant relationship between PPI use and incident
30
31 255 kidney stones, as well as an increased risk of recurrent kidney stones in patients with a history of
32
33 256 nephrolithiasis. To mitigate this potential adverse effect, caution should be exercised regarding
34
35 257 unnecessary long-term use of PPI.

36
37 258

38 39 259 **Acknowledgments**

40
41 260 We appreciate the American Centers for Disease Control and Prevention for conducting the survey and
42
43 261 making it available online freely, and all the participants for providing these data.

44 45 262 **Contributors**

46
47 263 W-L: conceptualization, methodology, data analysis, manuscript writing; J-W: methodology, data
48
49 264 collection, data analysis, manuscript writing; M-W: methodology, data collection, data analysis; MM-
50
51 265 W: data analysis, manuscript writing, supervision; M-L: conceptualization, supervision, manuscript
52
53 266 editing, funding acquisition.

54 55 267 **Funding**

56
57 268 This work was supported by the National Key Research and Development Program of China
58
59 269 [2022YFC3602900] and National High Level Hospital Clinical Research Funding [BJ-2022-115].

60 270 **Competing interests**

1
2
3
4 271 None declared

5 272 **Patient and public involvement**

7 273 Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination
8
9 274 plans of this research.

11 275 **Patient consent for publication**

13 276 Not applicable.

15 277 **Ethical statement**

17 278 The studies involving human participants were reviewed and approved by the Ethics Review Board of
18
19 279 the NCHS (Protocol #98-12). The patients/participants provided their written informed consent to
20
21 280 participate in this study.

23 281 **Data availability statement**

25 282 Publicly available datasets were analyzed in this study. This data can be downloaded here:

27 283 <https://www.cdc.gov/nchs/nhanes/> (NHANES 2005-2006 and 2007-2008).
28
29 284

31 285 **References**

33 286 1. Saigal CS, Joyce G, Timilsina AR. Direct and indirect costs of nephrolithiasis in an employed
34
35 287 population: opportunity for disease management? *Kidney Int.* 2005;68(4):1808-14.

37 288 2. Abufaraj M, Xu T, Cao C, Waldhoer T, Seitz C, D'Andrea D, et al. Prevalence and Trends in Kidney
38
39 289 Stone Among Adults in the USA: Analyses of National Health and Nutrition Examination Survey 2007-
40
41 290 2018 Data. *Eur Urol Focus.* 2021;7(6):1468-75.

43 291 3. Dauw CA, Yi Y, Bierlein MJ, Yan P, Alruwaily AF, Ghani KR, et al. Factors Associated With Preventive
44
45 292 Pharmacological Therapy Adherence Among Patients With Kidney Stones. *Urology.* 2016;93:45-9.

47 293 4. Daudon M, Frochet V, Bazin D, Jungers P. Drug-Induced Kidney Stones and Crystalline
48
49 294 Nephropathy: Pathophysiology, Prevention and Treatment. *Drugs.* 2018;78(2):163-201.

51 295 5. Cohen AJ, Adamsky MA, Nottingham CU, Pruitt J, Lapin B, Wang CH, et al. Impact of Statin Intake
52
53 296 on Kidney Stone Formation. *Urology.* 2019;124:57-61.

54 297 6. Savarino V, Marabotto E, Zentilin P, Furnari M, Bodini G, De Maria C, et al. Proton pump inhibitors:
55
56 298 use and misuse in the clinical setting. *Expert Rev Clin Pharmacol.* 2018;11(11):1123-34.

58 299 7. Eusebi LH, Rabitti S, Artesiani ML, Gelli D, Montagnani M, Zagari RM, et al. Proton pump inhibitors:
59
60 300 Risks of long-term use. *J Gastroenterol Hepatol.* 2017;32(7):1295-302.

- 1
2
3
4 301 8. Patel PM, Kandabarow AM, Aiwerioghene E, Blanco-Martinez E, Hart S, Leehey DJ, et al. Proton-
5
6 302 pump inhibitors associated with decreased urinary citrate excretion. *Int Urol Nephrol*. 2021;53(4):679-
7
8 303 83.
- 9
10 304 9. Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and
11
12 305 effects on absorption of calcium, vitamin B12, iron, and magnesium. *Curr Gastroenterol Rep*.
13
14 306 2010;12(6):448-57.
- 15
16 307 10. Simonov M, Abel EA, Skanderson M, Masoud A, Hauser RG, Brandt CA, et al. Use of Proton Pump
17
18 308 Inhibitors Increases Risk of Incident Kidney Stones. *Clin Gastroenterol Hepatol*. 2021;19(1):72-9.e21.
- 19
20 309 11. Sui W, Miller NL, Gould ER, Zhang KC, Koyama T, Hsi RS. Proton pump inhibitors use and risk of
21
22 310 incident nephrolithiasis. *Urolithiasis*. 2022;50(4):401-9.
- 23
24 311 12. Kim SY, Yoo DM, Bang WJ, Choi HG. Association between Urolithiasis and History Proton Pump
25
26 312 Inhibitor Medication: A Nested Case-Control Study. *J Clin Med*. 2022;11(19).
- 27
28 313 13. Pella E, Chalkidou M, Sarafidis P. Proton Pump Inhibitors, Histamine-2 Receptor Antagonists, and
29
30 314 the Risk of Kidney Stones: Negligible or Not? *Clin Gastroenterol Hepatol*. 2021;19(3):624-5.
- 31
32 315 14. NHANES Questionnaires, Datasets, and Related Documentation. Available from:
33
34 316 <https://www.cdc.gov/nchs/nhanes/Default.aspx>: [Accessed April 14, 2023 pp.].
- 35
36 317 15. Chang SL, Harshman LC, Presti JC, Jr. Impact of common medications on serum total prostate-
37
38 318 specific antigen levels: analysis of the National Health and Nutrition Examination Survey. *J Clin Oncol*.
39
40 319 2010;28(25):3951-7.
- 41
42 320 16. Charidimou A, Martinez-Ramirez S, Reijmer YD, Oliveira-Filho J, Lauer A, Roongpiboonsopit D, et
43
44 321 al. Total Magnetic Resonance Imaging Burden of Small Vessel Disease in Cerebral Amyloid Angiopathy:
45
46 322 An Imaging-Pathologic Study of Concept Validation. *JAMA Neurol*. 2016;73(8):994-1001.
- 47
48 323 17. Schwartz BF, Bruce J, Leslie S, Stoller ML. Rethinking the role of urinary magnesium in calcium
49
50 324 urolithiasis. *J Endourol*. 2001;15(3):233-5.
- 51
52 325 18. Johansson G, Backman U, Danielson BG, Fellström B, Ljunghall S, Wikström B. Effects of
53
54 326 magnesium hydroxide in renal stone disease. *J Am Coll Nutr*. 1982;1(2):179-85.
- 55
56 327 19. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Srivali N, Edmonds PJ, Ungprasert
57
58 328 P, et al. Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of
59
60 329 observational studies. *Ren Fail*. 2015;37(7):1237-41.

- 1
2
3
4 330 20. Goldberg H, Grass L, Vogl R, Rapoport A, Oreopoulos DG. Urine citrate and renal stone disease.
5 331 *Cmaj*. 1989;141(3):217-21.
6
7 332 21. Pak CY. Citrate and renal calculi: an update. *Miner Electrolyte Metab*. 1994;20(6):371-7.
8
9 333 22. Bapir R, Bhatti KH, Eliwa A, García-Perdomo HA, Gherabi N, Hennessey D, et al. Risk of urinary
10 334 stone formation associated to proton pump inhibitors: A systematic review and metanalysis. *Arch Ital*
11 335 *Urol Androl*. 2022;94(4):507-14.
12
13 336 23. Moayyedi P, Armstrong D, Hunt RH, Lei Y, Bukoski M, White RJ. The gain in quality-adjusted life
14 337 months by switching to esomeprazole in those with continued reflux symptoms in primary care:
15 338 EncompASS--a cluster-randomized trial. *Am J Gastroenterol*. 2010;105(11):2341-6.
16
17 339 24. Elias E, Targownik LE. The Clinician's Guide to Proton Pump Inhibitor Related Adverse Events.
18 340 *Drugs*. 2019;79(7):715-31.
19
20 341 25. Boghossian TA, Rashid FJ, Thompson W, Welch V, Moayyedi P, Rojas-Fernandez C, et al.
21 342 Deprescribing versus continuation of chronic proton pump inhibitor use in adults. *Cochrane Database*
22 343 *Syst Rev*. 2017;3(3):Cd011969.

23
24
25
26
27
28
29
30
31
32
33 345 **Fig. 1** Study flowchart. Of 59,842 participants in the 2007–2018 National Health and Nutrition
34 346 Examination Survey (NHANES), 27,075 remained after fulfilling inclusion and exclusion criteria.

35
36 347 **Fig. 2** Dose-response relationships between time of PPIs and kidney stones. (A) Time of PPIs
37 348 use and kidney stones; (B) Time of PPIs use and recurrent kidney stones.

38
39 349 Abbreviations: OR, odds ratio; PPIs, proton pump inhibitors. Adjusted for age, sex, race, education
40 350 level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of
41 351 CVD, gout, thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake,
42 352 albumin-adjusted calcium, and eGFR. The shaded part represents the 95% CI.

43
44
45
46
47 353 **Supplementary Fig. 1** Dose-response relationships between time of PPIs use and kidney stones
48 354 after PSM. (A) Time of PPIs use and kidney stones; (B) Time of PPIs use and recurrent kidney
49 355 stones.

50
51
52
53
54 356 Abbreviations: OR, odds ratio; PPIs, proton pump inhibitors; PSM, propensity score matching.
55 357 Adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial
56 358 pressure, HbA1c, triglycerides, history of CVD, gout, thiazide use, loop diuretics use, and H2RAs
57 359 use, sedentary time, total water intake, albumin-adjusted calcium, and eGFR. The shaded part

360 represents the 95% CI.

361 **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/m ²), 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

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

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

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

367 ‡BMI was calculated by dividing weight in kilograms (kg) by height in meters squared (m²). Participants were classified as
 368 normal weight (BMI < 25 kg/m²), and overweight/obese (BMI ≥ 25 kg/m²).

369

370

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)

371 Abbreviations: *OR*, odds ratio; *CI*, confidence interval; PPIs, proton pump inhibitors.372 *Values are numerical values or weighted *OR* (95% *CI*).

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

374 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.

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

377

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		
	<i>OR</i> (95% <i>CI</i>)	<i>P</i> value	<i>P</i> for interaction	<i>OR</i> (95% <i>CI</i>)	<i>P</i> value	<i>P</i> 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	

378 Abbreviations: *OR*, odds ratio; *CI*, confidence interval; PPIs, proton pump inhibitors; BMI, Body mass index.379 *Values are numerical values or weighted *OR* (95% *CI*).380 Adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides,
381 history of CVD, gout, thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake, albumin-adjusted
382 calcium, and eGFR, if not already stratified.

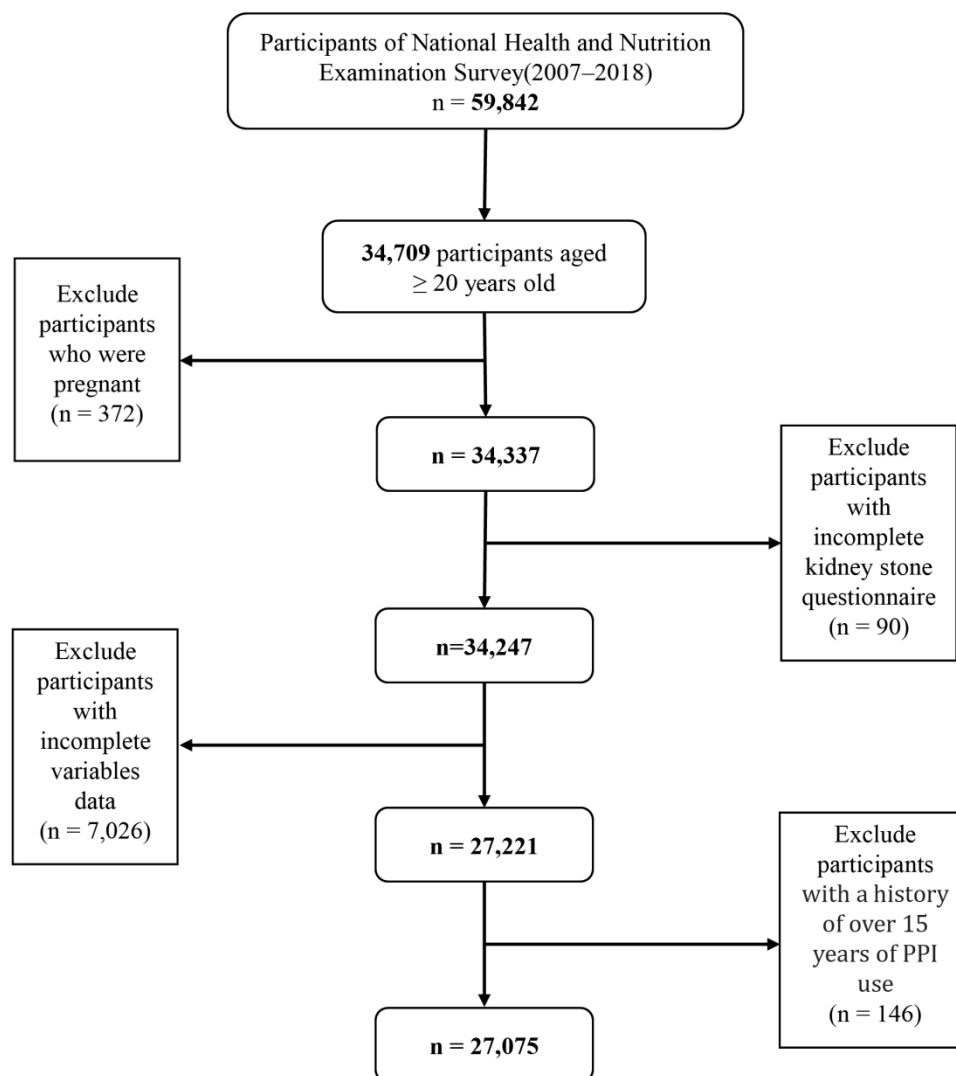
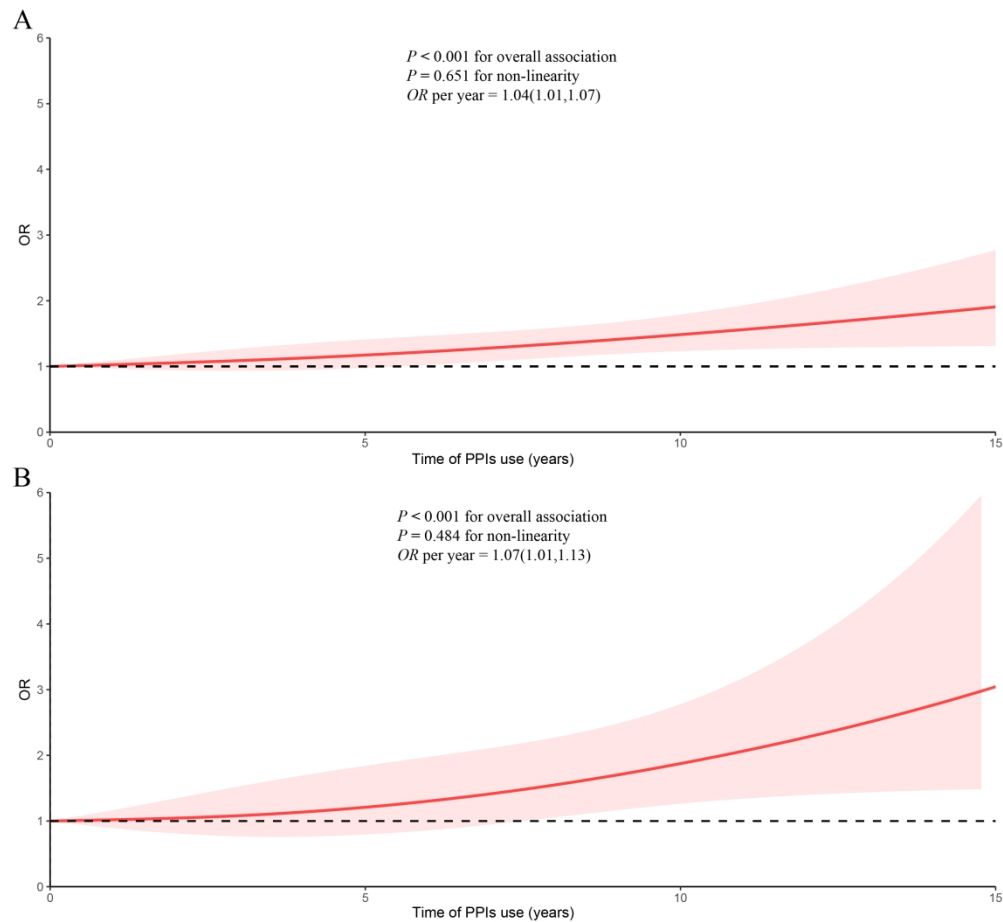


Fig. 1 Study flowchart. Of 59,842 participants in the 2007–2018 National Health and Nutrition Examination Survey (NHANES), 27,075 remained after fulfilling inclusion and exclusion criteria.

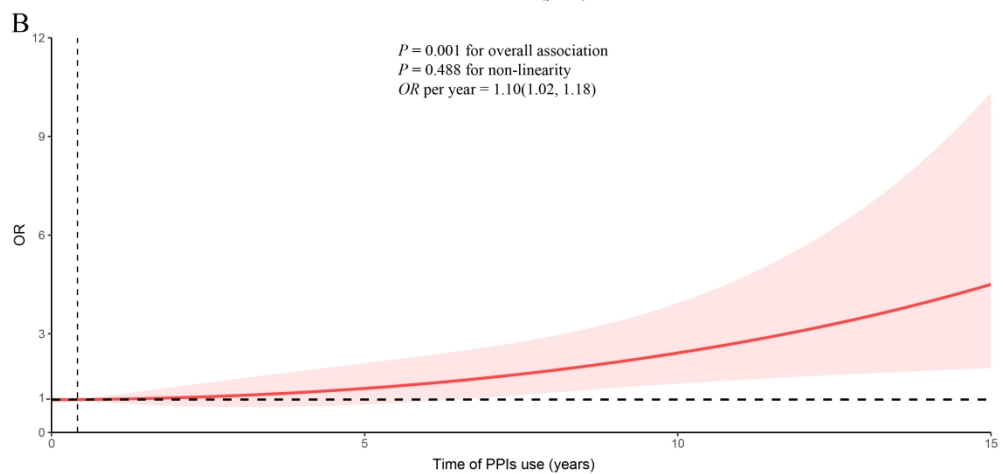
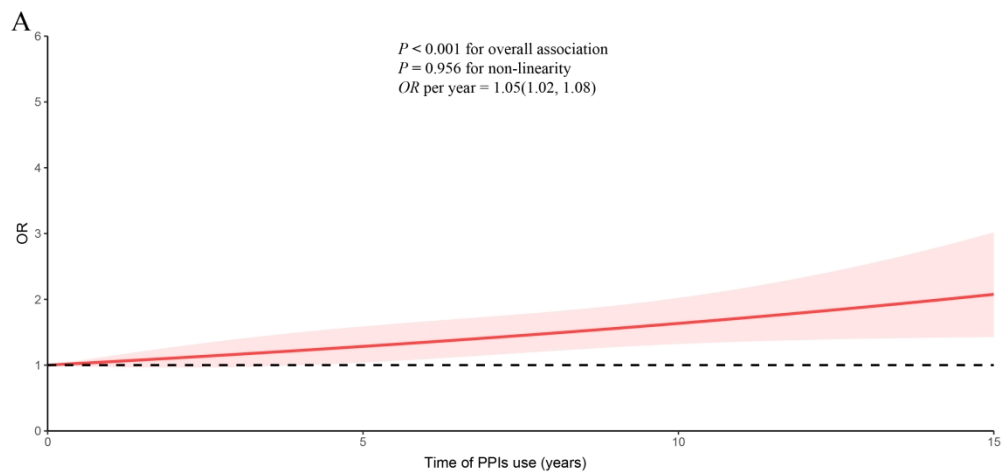
169x190mm (300 x 300 DPI)



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

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

42
43 263x243mm (300 x 300 DPI)
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



263x246mm (300 x 300 DPI)

Study	HR/OR	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%

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

1 2 3

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/m ²), n (%) [‡]	4013(82.25)	2029(82.53)	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 (m²). Participants were classified as normal weight (BMI < 25 kg/m²), and overweight/obese (BMI \geq 25 kg/m²).

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	<i>Describe any efforts to address potential sources of bias</i>	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.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-075136.R1
Article Type:	Original research
Date Submitted by the Author:	24-Aug-2023
Complete List of Authors:	liu, wen; Chinese Academy of Medical Sciences & Peking Union Medical College, Wang, Jia; The Affiliated Hospital of Qingdao University, Department of Gastroenterology Wang, Miao; Beijing Hospital, Department of Urology Wang, Miaomiao; Beijing Hospital, Department of Urology Liu, Ming; Beijing Hospital, Department of Urology
Primary Subject Heading:	Urology
Secondary Subject Heading:	Gastroenterology and hepatology, Public health
Keywords:	Risk Factors, Urolithiasis < UROLOGY, Adverse events < THERAPEUTICS

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 1 **Association of Proton Pump Inhibitor Use with the risk of kidney stones in**
5
6 2 **NHANES population: A cross-sectional study**

7 3 **Wen Liu^{1,2†}, Jia Wang^{3†}, Miao Wang¹, Miaomiao Wang^{1,2}, and Ming Liu^{1,2*}**

9 4 1 Department of Urology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric
11 5 Medicine, Chinese Academy of Medical Sciences, Beijing, China.

13 6 2 Graduate School of Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing,
15 7 China.

17 8 3 Department of Gastroenterology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong,
19 9 China.

21 10 † Both authors contributed equally to this work

23 11 * Correspondence: Ming Liu, Department of Urology, Beijing Hospital, National Center of
25 12 Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, No.1 DaHua
27 13 Road, Dong Dan, Beijing, 100730, China.

29 14 E-mail: liumingbjh@126.com

31 15
32 16 **Abstract**

34 17 **Objective** Several studies have suggested a potential link between proton pump inhibitors (PPIs)
36 18 use and the risk of kidney stones, attributed to alterations in urine mineral levels. Our study aimed
38 19 to investigate the association between PPI use and kidney stones in US adults.

40 20 **Design** Cross-sectional study.

42 21 **Setting** National Health and Nutrition Examination Survey (NHANES) (2007–2018).

44 22 **Participants** A total of 27,075 individuals with complete information for PPI use and history of
46 23 kidney stones were included in this study.

48 24 **Outcomes and analyses** Nonlinear analysis, logistic regression analysis, and subgroup analysis
50 25 were conducted to estimate the relationship between PPI use and the occurrence and recurrence of
52 26 kidney stones, after adjusting for potential confounding factors.

54 27 **Results** Multivariable logistic regression analysis revealed a significant association between PPI
56 28 use and kidney stones (odds ratio [OR] 1.31, 95%CI 1.07–1.60), with a 4% increase in the
58 29 prevalence of kidney stones for each additional year of PPI use ($P < 0.001$). Similarly, PPI use was
60 30 significantly associated with recurrent kidney stones (OR 1.49, 95%CI 1.04–2.13), with a 7%

1
2
3
4 31 increase in the recurrence of kidney stones for each additional year of PPI use ($P < 0.001$).
5
6 32 Furthermore, these associations remained significant even after conducting propensity score
7
8 33 matching analysis on a subset of PPI users and non-users (all $P \leq 0.001$). Subgroup analyses showed
9
10 34 that the effects of PPI use on kidney stones differed by age, sex, race, and BMI.

11 35 **Conclusions** This study indicated that long-term use of PPI was associated with a higher risk of
12
13 36 both the presence and recurrence of kidney stones.

14
15 37 **Keywords:** NHANES; urolithiasis; proton pump inhibitors; risk factors; drug effects
16
17 38

19 39 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

20
21 40 The NHANES dataset comprises a representative sample of the national population to ensure that
22
23 41 our findings can be extrapolated to the broader population.

24
25 42 This study explores the positive relationship between PPI use and recurrent kidney stones in
26
27 43 patients with history of nephrolithiasis.

28
29 44 Multiple potential confounders were adjusted and PSM design was performed to ensure the
30
31 45 reliability of the results.

32
33 46 It is difficult to draw causal conclusions from such cross-sectional analyses.

34
35 47 NHANES may did not record information regarding the time and type of kidney stones and the
36
37 48 dosage and type of PPI use.

40 49 41 50 **Introduction**

42
43 51 Kidney stone is a common disease in US, with a high prevalence of 12% of men and 10% of
44
45 52 women, and caused high cost and morbidity(1, 2). Some drugs may affect the risk of kidney
46
47 53 stones by altering active compounds crystallizing in urine or substances impairing urine
48
49 54 composition(3-5).

50
51 55 Proton pump inhibitors (PPIs) are commonly prescribed medications worldwide for the
52
53 56 treatment of gastric acid-related diseases such as gastroesophageal reflux disease (GERD), H.
54
55 57 pylori infection, and gastric ulcers(6). However, the escalating prevalence of PPI overuse,
56
57 58 especially for long-term therapy, has become a concerning issue(6, 7). Long-term PPI intake is
58
59 59 associated with a reduction in intestinal absorption of essential vitamins and minerals and
60
60 60 increased susceptibility to infections, chronic kidney disease, and dementia(7). Given that PPI can

1
2
3
4 61 inhibit gastric acid secretion, thereby affecting the intestinal absorption of essential minerals and
5
6 62 altering the levels of calcium, magnesium, and citrate(8, 9), several studies have investigated the
7
8 63 impact of PPI use on the risk of kidney stones(10-12). For instance, Sui et al. found that PPI use
9
10 64 might elevate the risk of kidney stones by lowering the levels of urinary citrate and magnesium,
11
12 65 which could compromise their inhibitory effect on kidney stone formation(11). However, it should
13
14 66 be noted that all participants in their study were GERD patients. Similarly, Simonov et al.
15
16 67 identified a correlation between PPI use and kidney stones primarily based on a sample of young
17
18 68 individuals and males(10), thereby limiting the generalizability of their findings to not only the
19
20 69 general population but also specific patient groups, such as recurrent stone formers(13).

21 70 This study aimed to investigate the potential association between PPI use and kidney stones
22
23 71 by analyzing National Health and Nutrition Examination Survey (NHANES) data from 2007 to
24
25 72 2018. Our hypothesis was that PPI use increases the risk of both kidney stone formation and
26
27 73 recurrence.

28 29 74 **Methods**

30 31 75 **Study Population and Design**

32
33 76 The NHANES is an ongoing cross-sectional survey that employs a sophisticated multistage
34
35 77 sample methodology to investigate the health and nutritional status of the non-institutionalized
36
37 78 population in US. Demographic characteristics, clinical history, and self-reported dietary were
38
39 79 collected from participants using a structured household interview. Physical examinations,
40
41 80 including anthropometric measurements and blood samples, were collected within a mobile
42
43 81 examination center. The protocol was approved by the National Center for Health Statistics (NCHS)
44
45 82 Ethics Review Board, and informed consent was obtained from all participants. Additional
46
47 83 information regarding data collection can be accessed on the NHANES website(14).

48
49 84 Six NHANES cycles were used in the study from 2007 to 2018. Initially, 34,709 participants
50
51 85 aged 20 years and older were included. However, some participants were excluded: 372 participants
52
53 86 who were pregnant, 90 participants with incomplete kidney stone questionnaire, and 7,026
54
55 87 participants with incomplete variables. In addition, given the limited number of participants who
56
57 88 had taken PPI for more than 15 years, the standard errors for model estimates increased
58
59 89 substantially(15), thus 146 participants were excluded. Finally, 27,075 participants were included
60
90 90 in the analysis, consisting of 13,711 females and 13,364 males. Fig. 1 illustrates the filtering process

1
2
3
4 91 used in this study.

5 92 **Assessment of Outcomes**

6
7 93 The primary outcome was the response to the question, “Have you ever had kidney stones?”
8
9 94 (NHANES 2007–2018). Participants who responded “yes” were defined as kidney stone formers.
10
11 95 The secondary outcome was the response to the question, “How many times have you passed a
12
13 96 kidney stone?” (NHANES 2007–2014). Participants who reported passing at least two stones were
14
15 97 classified as recurrent stone formers.

16
17 98 **Medication Use**

18
19 99 The independent variables in this study were whether participants had taken PPI and the
20
21 100 duration of their PPI use. Information on the types and duration of acid suppressant medication was
22
23 101 obtained through prescription medication questionnaires. The types of PPI in this study included
24
25 102 omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole. For participants using PPI,
26
27 103 the duration of use was equal to the years since initiating therapy. Participants who did not use PPI
28
29 104 had a duration of use recorded as zero. Data on specific dosages or previously discontinued
30
31 105 prescription medications were unavailable.

32
33 106 **Ascertainment of Covariates**

34
35 107 The study collected three types of detailed information about covariates through standardized
36
37 108 personal interviews. The first group included demographic factors including age, sex, race,
38
39 109 education level, smoking status, and alcohol consumption. The second group consisted of factors
40
41 110 that impact the body's metabolism level, including body mass index (BMI), mean arterial pressure,
42
43 111 HbA1c, triglyceride levels, history of cardiovascular disease (CVD), thiazide use, loop diuretic use,
44
45 112 and histamine-2 receptor antagonists (H2RA) use. The third group focused on risk factors related to
46
47 113 kidney stone formation, including sedentary time, total water intake, albumin-adjusted calcium
48
49 114 levels, estimated glomerular filtration rate (eGFR), and history of gout. Education level was
50
51 115 categorized as follows: Grades 0–12, high school graduate/General Equivalency Diploma, and some
52
53 116 college or above. Smokers was defined as smoking at least 100 cigarettes during their lifetime. BMI
54
55 117 was calculated by dividing weight in kilograms (kg) by height in meters squared (m²). History of
56
57 118 CVD (including congestive heart failure, coronary heart disease, myocardial infarction, and stroke)
58
59 119 was defined if participants self-reported a history of these conditions. The Chronic Kidney Disease
60
120 Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR(16). The CKD-EPI

1
2
3
4 121 equation is as follows: $eGFR = 141 \times \min(\text{Scr}/\kappa, 1)^\alpha \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if
5 122 female] 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is
6 123 -0.329 for females and -0.411 for males, min indicates the minimum of Scr/ κ or 1, and max
7 124 indicates the maximum of Scr/ κ or 1. Gout was defined as a self-reported diagnosis of gout, and/or
8 125 the use of anti-gout medication.

126 **Statistical Analyses**

127 All statistical analyses considered NHANES survey design characteristics with sampling
128 weights. Descriptive statistics were used to evaluate the demographic and clinic characteristics of
129 the study population. The variance inflation factor (VIF) was utilized to evaluate multicollinearity
130 among covariates and between covariates and kidney stones. A VIF value over 10 indicates
131 multicollinearity, but none was observed in this study (Supplementary Table 1) (17). To explore the
132 relationship between PPI use and kidney stones, we performed four weighted logistic regression
133 models and controlled for the aforementioned explanatory variables by modeling PPI as continuous
134 variables based on the time of use. To evaluate the potential non-linear relationship between the
135 time of PPI use and kidney stones, restricted cubic splines were used with three knots at the 5th,
136 50th, and 95th centiles. Subgroup analyses were also performed to explore whether the relationship
137 between the time of PPI use and kidney stones differed by age, sex, race, and BMI, and potential
138 effect modifiers were tested using the Wald test for multiplicative interactions. Additionally, a 1:1
139 propensity score matching (PSM) analysis was performed to balance population differences
140 between PPI users and non-users while adjusting for all confounding variables. Previous studies
141 have established links between kidney stones and dietary factors, such as vitamin C intake, caffeine
142 consumption, and the dietary inflammatory index (DII)(18-20). To address potential confounding
143 effects, a sensitivity analysis was conducted using model 3 as the baseline, with additional
144 adjustments made for three variables: vitamin C intake, caffeine intake, and DII. We conducted a
145 meta-analysis using the 'meta' package, which allowed us to combine data from relevant studies and
146 estimate an overall effect size for the association between PPI use and kidney stones. All statistical
147 tests were two-sided, and P-values < 0.05 (two-sided) were considered statistically significant. R
148 4.2.2 software was used for modeling.

149 **Results**

150 **Population Characteristics**

1
2
3
4 151 This study included 27,075 participants aged 20 years and older from the NHANES database
5
6 152 (2007–2018), representing 203,076,872 adults. And table 1 presents their demographic and clinic
7
8 153 characteristics based on PPI use. The mean age of all participants was 47.46 ± 0.26 (standard
9
10 154 error) years, with roughly equal representation of females (51.13%) and males (48.87%). PPI
11
12 155 users were more likely to be older, females, non-Hispanic white, obese, have lower education
13
14 156 level, alcohol consumption, total water intake, eGFR, higher sedentary time, mean arterial
15
16 157 pressure, HbA1c, triglycerides, albumin-adjusted calcium. PPI users were taking more thiazide,
17
18 158 loop diuretics, and H2RAs medications compared to non-users. Furthermore, CVD, gout and
19
20 159 kidney stone diseases were more common in PPI users (all $P < 0.05$).

21 160 **Multivariable Logistic Regression Analyses**

22
23 161 Weighted univariable and multivariable logistic regression models were used to investigate the
24
25 162 independent association between PPI use and the risk of kidney stones, with PPI non-user as the
26
27 163 reference group (Table 2). In the crude model, PPI use showed a significantly positive association
28
29 164 with the prevalence of kidney stones ($OR = 1.86$, $95\%CI = 1.55–2.22$). In the fully adjusted model
30
31 165 (model 3), the association between PPI use and the prevalence of kidney stones remained significant
32
33 166 ($OR = 1.31$, $95\%CI = 1.07–1.60$). When considering PPI use as a continuous variable, the restricted
34
35 167 cubic spline analyses indicated a linear relationship between the duration of PPI use and the
36
37 168 prevalence of kidney stones (P for non-linearity = 0.651) (Fig. 2A). With each additional year of
38
39 169 PPI use, the prevalence of kidney stones increased by 4% (Table 2). Additionally, we explored the
40
41 170 association between PPI use and recurrent kidney stones. In the crude model, PPI use showed a
42
43 171 significantly positive association with the recurrence of kidney stones ($OR = 1.49$, $95\%CI = 1.05–$
44
45 172 2.09). This positive association persisted in the fully adjusted model (model 3) ($OR = 1.49$, $95\%CI$
46
47 173 $= 1.04–2.13$). The duration of PPI use exhibited a linear correlation with the recurrence of kidney
48
49 174 stones (P for non-linearity = 0.484) (Fig. 2B), with a 7% increase for each additional year of PPI
50
51 175 use (Table 2).

52 176 **Subgroup Analyses**

53
54 177 Moreover, subgroup analyses were performed to assess whether the relationship between the
55
56 178 duration of PPI use and kidney stones were influenced by age, sex, race, and BMI (Table 3). After
57
58 179 adjusting for all covariates, it was found that the duration of PPI use was significantly associated
59
60 180 with the prevalence of kidney stones in participants aged 50 years or order, females, non-Hispanic

1
2
3
4 181 White, and those with a BMI of 25 kg/m² or higher. On the other hand, a significant positive
5
6 182 association between time of PPI use and recurrent kidney stones was observed only in participants
7
8 183 non-Hispanic White, and those with a BMI of 25 kg/m² or higher (all *P* for interaction > 0.05).

9 184 **Sensitivity analyses and Meta-analysis**

10
11 185 A 1:1 matched cohort analysis was conducted through PSM to minimize potential bias, given
12
13 186 the significant difference in PPI use and non-use group (Table 1). This approach confirmed 4864
14
15 187 participants in the matched cohort. The descriptive statistics results showed that no significant
16
17 188 differences observed in most variables between the PPI non-user and PPI user groups
18
19 189 (Supplementary Table 2). In the fully adjusted model, the dose–response curve still displayed a
20
21 190 positive association between the duration of PPI use and kidney stones (*OR* = 1.05, 95%*CI* = 1.02–
22
23 191 1.08, *P* for non-linearity = 0.956) (Supplementary Fig. 1A) and recurrent kidney stones (*OR* = 1.10,
24
25 192 95%*CI* = 1.02–1.18, *P* for non-linearity = 0.488) (Supplementary Fig. 1B). Moreover, the results
26
27 193 remained significant after making additional adjustments for vitamin C intake, caffeine
28
29 194 consumption, and DII (Supplementary Table 3). Furthermore, we performed a meta-analysis based
30
31 195 on our findings and previously published research, confirming a positive association between the
32
33 196 PPI use and the risk of kidney stones (*OR* = 1.49, 95%*CI* = 1.05–2.10) (Supplementary Fig. 2)(10–
34
35 197 12).

36 198 **Discussion**

37
38
39 199 In this large cross-sectional study based on NHANES data from 2007 to 2018, we found that
40
41 200 PPI use was associated with an increased risk of kidney stones. The duration of PPI use
42
43 201 demonstrated a dose-response association with kidney stones. Furthermore, our study uncovered a
44
45 202 novel association between long-term PPI use and recurrent kidney stones in patients with a history
46
47 203 of kidney stones, demonstrating a significant linear correlation. Additionally, subgroup analysis
48
49 204 found that the effects of age, sex, race, and BMI varied in their influence on the relationship between
50
51 205 PPI use and the prevalence of kidney stones.

52
53 206 Several studies have shown that PPI use could increase the risk of kidney stones, with a dose-
54
55 207 response relationship(10-12). A retrospective study conducted on the Women's Veterans Cohort,
56
57 208 which included 465,891 individuals, revealed that PPI use was linked to a 1.25-fold higher risk of
58
59 209 kidney stones (95% *CI* = 1.19–1.33)(10). It should be noted that this study included mainly young
60
210 individuals (with a median age of 32 years) and was predominantly males (86%), thus having a

1
2
3
4 211 certain degree of selection bias(13). Another study by Sui et al. also found a positive association
5
6 212 between PPI use and kidney stones in patients with GERD, with a 1.46-fold increased risk (95%CI
7
8 213 = 1.38–1.55), which could help in assessing the potential risk of kidney stones associated with PPI
9
10 214 exposure(11). Nevertheless, both studies were limited to specific populations, limiting the
11
12 215 generalizability of their findings to the general population. In contrast, a nationwide population
13
14 216 cohort from Korea, without selection bias, also showed a positive association between PPI use and
15
16 217 kidney stones, displaying a dose-response relationship(12). Similarly, the current study, based on
17
18 218 data from the NHANES database representing over 203 million individuals, found that PPI use was
19
20 219 significantly associated with not only a higher risk of kidney stones, but also recurrent kidney stones.
21
22 220 The findings from the meta-analysis conducted in this study have confirmed the positive association
23
24 221 between PPI use and the risk of kidney stones. Furthermore, the risk of developing kidney stones
25
26 222 was found to be higher in individuals who used PPI for a longer duration, highlighting the
27
28 223 importance of monitoring this potential side effects of long-term PPI treatment, especially for
29
30 224 patients with a history of kidney stones.

31 225 The mechanisms underlying the impact of PPI on kidney stone formation remain unclear.
32
33 226 Studies have suggested that PPI can elevate gastric pH, leading to a decrease in magnesium
34
35 227 absorption and urinary magnesium levels(9). Magnesium has been known to inhibit the formation
36
37 228 of calcium oxalate crystals in urine(21, 22). A meta-analysis of nine observational studies found a
38
39 229 significant increased risk of hypomagnesemia among patients using PPI(23). It should be noted that
40
41 230 magnesium absorption occurs through both active and passive mechanisms, and alterations in pH
42
43 231 do not affect passive absorption(23). Therefore, PPI use does not always result in hypomagnesemia,
44
45 232 but patients with impaired gastrointestinal absorptive capacity may have an increased risk of
46
47 233 developing hypomagnesemia. On the other hand, research has shown that citrate can inhibit the
48
49 234 crystallization of calcium salts in urine, and a deficiency of citrate can increase the risk of stone
50
51 235 formation(24, 25). A study of 301 nephrolithiasis patients with 24-hour urine data found that PPI
52
53 236 exposure significantly reduced urinary citrate excretion, but did not affect urinary magnesium, pH,
54
55 237 or other urinary minerals(8). Similarly, another study on GERD patients reported a significant
56
57 238 correlation between PPI use and lower levels of urinary citrate and magnesium(11). Therefore, given
58
59 239 the association between PPI use and hypomagnesuria and hypocitraturia, it may monitor the levels
60
240 of urinary magnesium and citrate when using PPI.

1
2
3
4 241 PPIs are commonly prescribed for acid-related disorders, and patients with these conditions
5
6 242 may be at higher risk for kidney stone formation(26). In this study, we employed the PSM analysis
7
8 243 to minimize potential differences between PPI users and non-users, yet still identified a significant
9
10 244 association between PPI use and the occurrence and recurrence of kidney stones. Subgroup analyses
11
12 245 further revealed that certain patient groups, including the elderly, females, non-Hispanic Whites,
13
14 246 and those with a BMI of 25 kg/m² or higher, exhibited a stronger positive association between PPI
15
16 247 use and the prevalence of kidney stones, highlighting the importance of considering potential side
17
18 248 effects of PPI use in these populations. While it is undeniable that PPI therapy has improved the
19
20 249 quality of life for many patients with acid-related disorders(27), a growing body of literature
21
22 250 suggested a relationship between long-term PPI use and adverse events(28). Caution should be
23
24 251 exercised when discontinuing PPI use for evidence-based indications(29), but global concerns over
25
26 252 long-term PPI overuse should not be overlooked(6, 7), especially in individuals with a history of
27
28 253 kidney stones and high-risk factors, such as the elderly, females, non-Hispanic Whites, and those
29
30 254 with a BMI of 25 kg/m² or higher, in order to reduce unnecessary use.

31 255 This study has several strengths. Firstly, the NHANES dataset comprises a representative
32
33 256 sample of the national population, and we utilize NHANES-provided weights to ensure that our
34
35 257 findings can be extrapolated to the broader population. Secondly, this study not only elucidates the
36
37 258 correlation between PPI use and the prevalence of kidney stones but also probes its association with
38
39 259 the recurrence of renal calculi in individuals with a history of nephrolithiasis.. Furthermore, multiple
40
41 260 potential confounders were adjusted and PSM design was performed to ensure the reliability of the
42
43 261 results. However, this study also has several limitations. Firstly, it is difficult to draw causal
44
45 262 conclusions from such cross-sectional analyses. Although we adjusted for three types of detailed
46
47 263 covariate information, there may still be unmeasured potential factors that could affect the
48
49 264 association between PPI and nephrolithiasis. Secondly, the questionnaire survey may have been
50
51 265 prone to recall bias and reporting bias, which could affect the accuracy of the data collected. Thirdly,
52
53 266 NHANES lacks objective diagnostic imaging for the identification of kidney stones, potentially
54
55 267 resulting in the omission of asymptomatic cases. Additionally, the dataset does not provide details
56
57 268 on the timing and specific type of kidney stones. Finally, the lack of information about the dosage
58
59 269 and type of PPI use may limit the interpretability of the results.

60 270 **Conclusions**

1
2
3
4 271 In conclusion, our study revealed a relationship between PPI use and the prevalence of kidney
5
6 272 stones, as well as an increased risk of recurrent kidney stones in patients with a history of
7
8 273 nephrolithiasis. To mitigate this potential adverse effect, caution should be exercised regarding
9
10 274 unnecessary long-term use of PPI.

11 275

12 276 **Acknowledgments**

13
14
15 277 We appreciate the American Centers for Disease Control and Prevention for conducting the survey and
16
17 278 making it available online freely, and all the participants for providing these data.

18 279 **Contributors**

19
20
21 280 W-L: conceptualization, methodology, data analysis, manuscript writing; J-W: methodology, data
22
23 281 collection, data analysis, manuscript writing; M-W: methodology, data collection, data analysis; MM-
24
25 282 W: data analysis, manuscript writing, supervision; M-L: conceptualization, supervision, manuscript
26
27 283 editing, funding acquisition.

28 284 **Funding**

29
30
31 285 This work was supported by the National Key Research and Development Program of China
32
33 286 [2022YFC3602900] and National High Level Hospital Clinical Research Funding [BJ-2022-115].

34 287 **Competing interests**

35
36 288 None declared

37 289 **Patient and public involvement**

38
39 290 None.

40 291 **Patient consent for publication**

41
42 292 Not applicable.

43 293 **Ethical statement**

44
45
46 294 Ethical review and approval for the research involving human participants were obtained from the
47
48 295 Ethics Review Board of the NCHS (Protocol #98-12). The current analysis, which is based on publicly
49
50 296 available data, did not necessitate any further ethics approval. Written informed consent was obtained
51
52 297 from all patients or participants who were part of the study.

53 298 **Data availability statement**

54
55
56 299 Publicly available datasets were analyzed in this study. This data can be downloaded here:
57
58 300 <https://www.cdc.gov/nchs/nhanes/> (NHANES 2005-2006 and 2007-2008).

301

302 **References**

- 303 1. Saigal CS, Joyce G, Timilsina AR. Direct and indirect costs of nephrolithiasis in an employed
304 population: opportunity for disease management? *Kidney Int.* 2005;68(4):1808-14.
- 305 2. Abufaraj M, Xu T, Cao C, Waldhoer T, Seitz C, D'Andrea D, et al. Prevalence and Trends in Kidney
306 Stone Among Adults in the USA: Analyses of National Health and Nutrition Examination Survey 2007-
307 2018 Data. *Eur Urol Focus.* 2021;7(6):1468-75.
- 308 3. Dauw CA, Yi Y, Bierlein MJ, Yan P, Alruwaily AF, Ghani KR, et al. Factors Associated With Preventive
309 Pharmacological Therapy Adherence Among Patients With Kidney Stones. *Urology.* 2016;93:45-9.
- 310 4. Daudon M, Frochot V, Bazin D, Jungers P. Drug-Induced Kidney Stones and Crystalline
311 Nephropathy: Pathophysiology, Prevention and Treatment. *Drugs.* 2018;78(2):163-201.
- 312 5. Cohen AJ, Adamsky MA, Nottingham CU, Pruitt J, Lapin B, Wang CH, et al. Impact of Statin Intake
313 on Kidney Stone Formation. *Urology.* 2019;124:57-61.
- 314 6. Savarino V, Marabotto E, Zentilin P, Furnari M, Bodini G, De Maria C, et al. Proton pump inhibitors:
315 use and misuse in the clinical setting. *Expert Rev Clin Pharmacol.* 2018;11(11):1123-34.
- 316 7. Eusebi LH, Rabitti S, Artesiani ML, Gelli D, Montagnani M, Zagari RM, et al. Proton pump inhibitors:
317 Risks of long-term use. *J Gastroenterol Hepatol.* 2017;32(7):1295-302.
- 318 8. Patel PM, Kandabarow AM, Aiwerioghene E, Blanco-Martinez E, Hart S, Leehey DJ, et al. Proton-
319 pump inhibitors associated with decreased urinary citrate excretion. *Int Urol Nephrol.* 2021;53(4):679-
320 83.
- 321 9. Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and
322 effects on absorption of calcium, vitamin B12, iron, and magnesium. *Curr Gastroenterol Rep.*
323 2010;12(6):448-57.
- 324 10. Simonov M, Abel EA, Skanderson M, Masoud A, Hauser RG, Brandt CA, et al. Use of Proton Pump
325 Inhibitors Increases Risk of Incident Kidney Stones. *Clin Gastroenterol Hepatol.* 2021;19(1):72-9.e21.
- 326 11. Sui W, Miller NL, Gould ER, Zhang KC, Koyama T, Hsi RS. Proton pump inhibitors use and risk of
327 incident nephrolithiasis. *Urolithiasis.* 2022;50(4):401-9.
- 328 12. Kim SY, Yoo DM, Bang WJ, Choi HG. Association between Urolithiasis and History Proton Pump
329 Inhibitor Medication: A Nested Case-Control Study. *J Clin Med.* 2022;11(19).
- 330 13. Pella E, Chalkidou M, Sarafidis P. Proton Pump Inhibitors, Histamine-2 Receptor Antagonists, and
331 the Risk of Kidney Stones: Negligible or Not? *Clin Gastroenterol Hepatol.* 2021;19(3):624-5.
- 332 [dataset] 14. NHANES Questionnaires, Datasets, and Related Documentation. Available from:
333 <https://wwwn.cdc.gov/nchs/nhanes/Default.aspx>: [Accessed April 14, 2023 pp.].
- 334 15. Chang SL, Harshman LC, Presti JC, Jr. Impact of common medications on serum total prostate-
335 specific antigen levels: analysis of the National Health and Nutrition Examination Survey. *J Clin Oncol.*
336 2010;28(25):3951-7.
- 337 16. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to
338 estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-12.
- 339 17. Charidimou A, Martinez-Ramirez S, Reijmer YD, Oliveira-Filho J, Lauer A, Roongpiboonsopit D, et
340 al. Total Magnetic Resonance Imaging Burden of Small Vessel Disease in Cerebral Amyloid Angiopathy:
341 An Imaging-Pathologic Study of Concept Validation. *JAMA Neurol.* 2016;73(8):994-1001.
- 342 18. Ferraro PM, Curhan GC, Gambaro G, Taylor EN. Total, Dietary, and Supplemental Vitamin C Intake

- 1
2
3 343 and Risk of Incident Kidney Stones. *Am J Kidney Dis.* 2016;67(3):400-7.
- 4 344 19. Geng J, Qiu Y, Kang Z, Li Y, Li J, Liao R, et al. The association between caffeine intake and risk of
5 345 kidney stones: A population-based study. *Front Nutr.* 2022;9:935820.
- 6 346 20. Liu N, Feng Y, Li J, Ma X, Ma F. Relationship between the dietary inflammatory index and kidney
7 347 stone prevalence. *World J Urol.* 2022;40(6):1545-52.
- 8 348 21. Schwartz BF, Bruce J, Leslie S, Stoller ML. Rethinking the role of urinary magnesium in calcium
9 349 urolithiasis. *J Endourol.* 2001;15(3):233-5.
- 10 350 22. Johansson G, Backman U, Danielson BG, Fellström B, Ljunghall S, Wikström B. Effects of
11 351 magnesium hydroxide in renal stone disease. *J Am Coll Nutr.* 1982;1(2):179-85.
- 12 352 23. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Srivali N, Edmonds PJ, Ungprasert
13 353 P, et al. Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of
14 354 observational studies. *Ren Fail.* 2015;37(7):1237-41.
- 15 355 24. Goldberg H, Grass L, Vogl R, Rapoport A, Oreopoulos DG. Urine citrate and renal stone disease.
16 356 *Cmaj.* 1989;141(3):217-21.
- 17 357 25. Pak CY. Citrate and renal calculi: an update. *Miner Electrolyte Metab.* 1994;20(6):371-7.
- 18 358 26. Bapir R, Bhatti KH, Eliwa A, García-Perdomo HA, Gherabi N, Hennessey D, et al. Risk of urinary
19 359 stone formation associated to proton pump inhibitors: A systematic review and metanalysis. *Arch Ital*
20 360 *Urol Androl.* 2022;94(4):507-14.
- 21 361 27. Moayyedi P, Armstrong D, Hunt RH, Lei Y, Bukoski M, White RJ. The gain in quality-adjusted life
22 362 months by switching to esomeprazole in those with continued reflux symptoms in primary care:
23 363 EncompASS--a cluster-randomized trial. *Am J Gastroenterol.* 2010;105(11):2341-6.
- 24 364 28. Elias E, Targownik LE. The Clinician's Guide to Proton Pump Inhibitor Related Adverse Events.
25 365 *Drugs.* 2019;79(7):715-31.
- 26 366 29. Boghossian TA, Rashid FJ, Thompson W, Welch V, Moayyedi P, Rojas-Fernandez C, et al.
27 367 Deprescribing versus continuation of chronic proton pump inhibitor use in adults. *Cochrane Database*
28 368 *Syst Rev.* 2017;3(3):Cd011969.

29 369
30
31
32
33
34
35
36
37
38
39 370 **Fig. 1** Study flowchart. Of 59,842 participants in the 2007–2018 National Health and Nutrition
40 371 Examination Survey (NHANES), 27,075 remained after fulfilling inclusion and exclusion criteria.

41 372 **Fig. 2** Dose-response relationships between time of PPIs use and kidney stones. (A) Time of PPIs
42 373 use and kidney stones; (B) Time of PPIs use and recurrent kidney stones.

43 374 Abbreviations: OR, odds ratio; PPIs, proton pump inhibitors. Adjusted for age, sex, race, education
44 375 level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of
45 376 CVD, gout, thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake,
46 377 albumin-adjusted calcium, and eGFR. The shaded part represents the 95% CI.

47 378 **Supplementary Fig. 1** Dose-response relationships between time of PPIs use and kidney stones
48 379 after PSM. (A) Time of PPIs use and kidney stones; (B) Time of PPIs use and recurrent kidney
49 380 stones.

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

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

387

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/m ²), 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

388 Abbreviations: NHANES, National Health and Nutrition Examination Survey; PPIs, proton pump inhibitors; SE, standard error;
 389 GED, General Equivalency Diploma; BMI, body mass index; eGFR, effective glomerular filtration rate; CVD, cardiovascular
 390 disease; H2RAs, H2-receptor antagonist.
 391 *Means and percentages were adjusted for survey weights of NHANES.
 392 †Smoking was defined as smoking at least 100 cigarettes during their lifetime.
 393 ‡BMI was calculated by dividing weight in kilograms (kg) by height in meters squared (m²). Participants were classified as
 394 normal weight (BMI < 25 kg/m²), and overweight/obese (BMI ≥ 25 kg/m²).
 395

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)

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

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

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

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

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

402

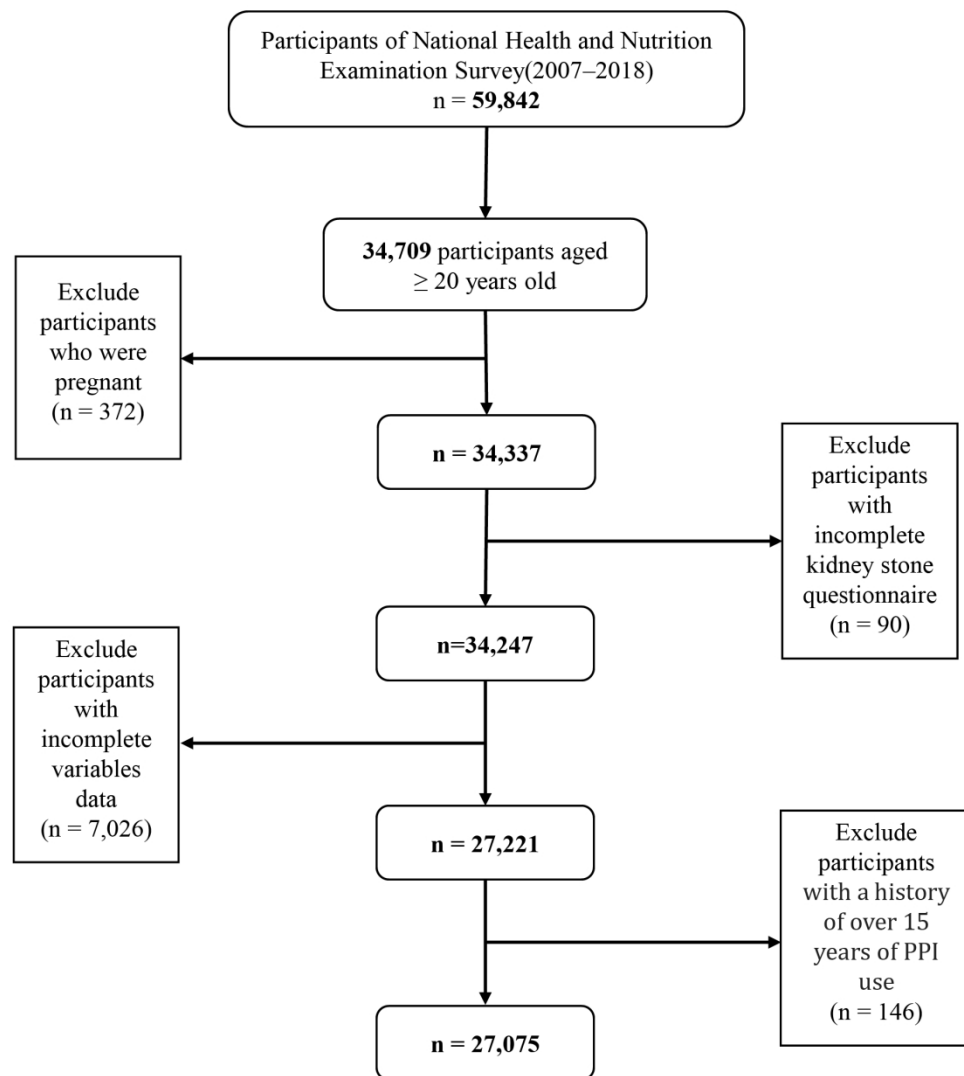
Table 3. OR (95% CI) for kidney stones across time of PPIs use stratified by selected factors*

	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	

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

1
2
3 404 *Values are numerical values or weighted *OR* (95% *CI*).
4 405 Adjusted for age, sex, race, education level, smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides,
5 406 history of CVD, gout, thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake, albumin-adjusted
6 407 calcium, and eGFR, if not already stratified.
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only



42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

169x190mm (300 x 300 DPI)

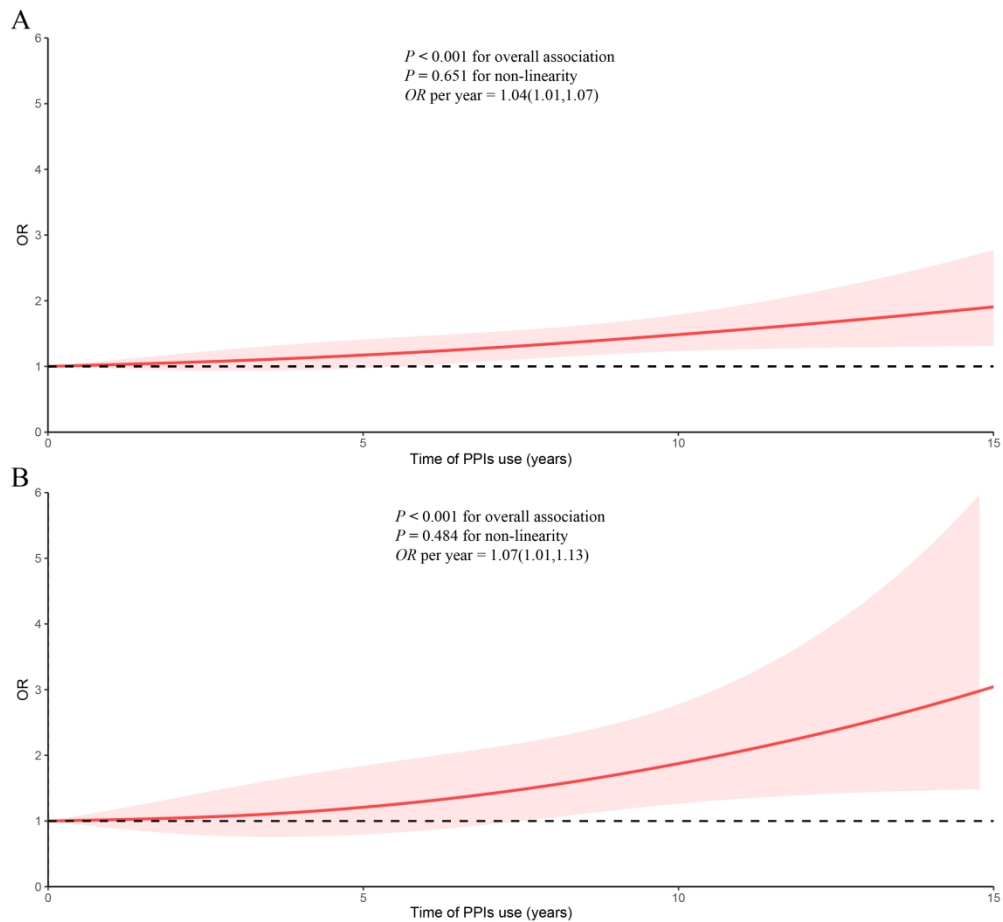
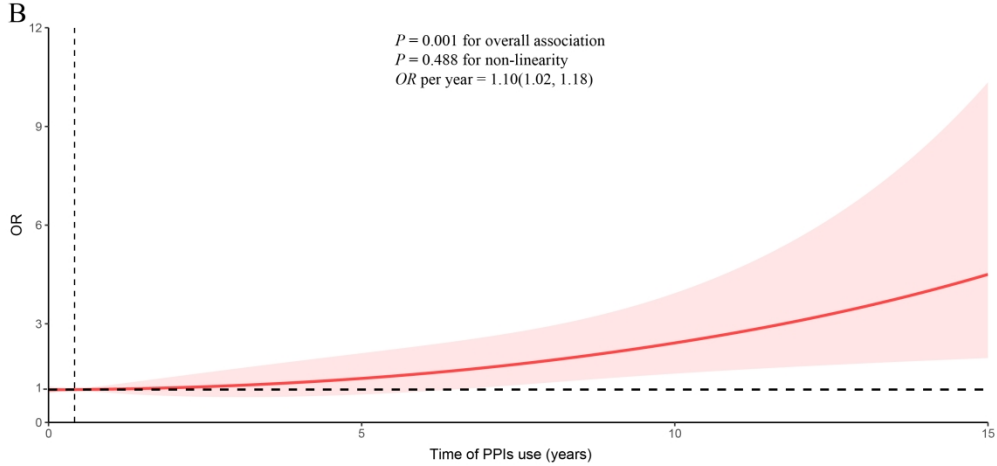
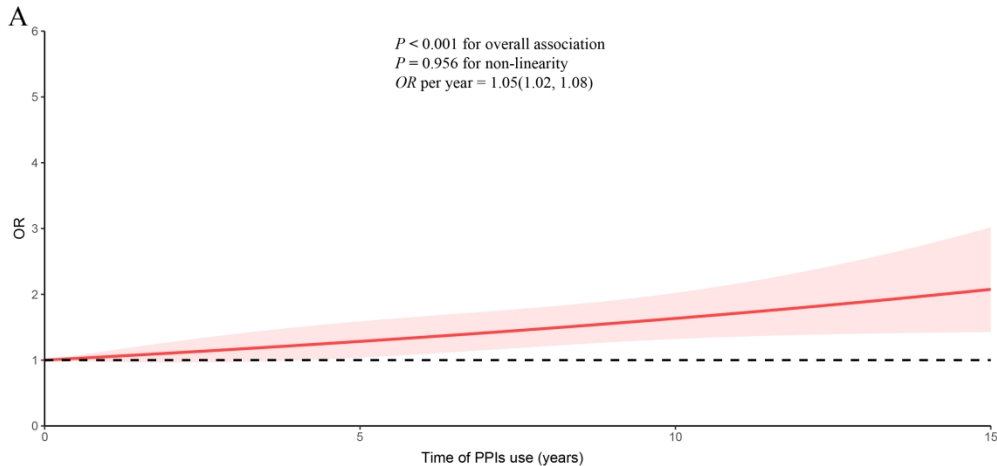








Fig. 2 Dose-response relationships between time of PPIs use and kidney stones. (A) Time of PPIs use and kidney stones; (B) Time of PPIs use and recurrent kidney stones. Abbreviations: OR, odds ratio; PPIs, proton pump inhibitors. Adjusted for age, sex, race, education level, smoking, alcohol consumption, 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.

263x243mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



263x246mm (300 x 300 DPI)

Study	HR/OR	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%

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

1 2 3

1
2
3
4
5
6
7
8
9
10
11

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/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, 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 (m²). Participants were classified as normal weight (BMI < 25 kg/m²), and overweight/obese (BMI \geq 25 kg/m²).

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 (<i>OR</i> [95% <i>CI</i>])	<i>P</i> -value
Kidney stones (N = 2,589) VS Non-kidney stone (N = 24,486) (NHANES 2007–2018)		
PPIs use		
No	1[Reference]	0.01
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		
No	1[Reference]	0.03
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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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	<i>Describe any efforts to address potential sources of bias</i>	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.

BMJ Open

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)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-075136.R2
Article Type:	Original research
Date Submitted by the Author:	26-Sep-2023
Complete List of Authors:	liu, wen; Chinese Academy of Medical Sciences & Peking Union Medical College, Wang, Jia; The Affiliated Hospital of Qingdao University, Department of Gastroenterology Wang, Miao; Beijing Hospital, Department of Urology Wang, Miaomiao; Beijing Hospital, Department of Urology Liu, Ming; Beijing Hospital, Department of Urology
Primary Subject Heading:	Urology
Secondary Subject Heading:	Gastroenterology and hepatology, Public health
Keywords:	Risk Factors, Urolithiasis < UROLOGY, Adverse events < THERAPEUTICS

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 1 **Association of proton pump inhibitor use with risk of kidney stones: an analysis**
5 2 **of cross-sectional data from the US National Health and Nutrition Examination**
6 3 **Survey (2007–2018)**
7
8
9
10 4

11 5 **Wen Liu^{1,2†}, Jia Wang^{3†}, Miao Wang¹, Miaomiao Wang^{1,2}, and Ming Liu^{1,2*}**
12
13 6

14
15 7 1 Department of Urology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric
16 8 Medicine, Chinese Academy of Medical Sciences, Beijing, China.

17
18
19 9 2 Graduate School of Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing,
20 10 China.

21
22
23 11 3 Department of Gastroenterology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong,
24 12 China.

25
26
27 13 †Both authors contributed equally to this work.

28
29 14 *Correspondence to:

30
31 15 Ming Liu, Department of Urology, Beijing Hospital, National Center of Gerontology, Institute of
32 16 Geriatric Medicine, Chinese Academy of Medical Sciences, No.1 DaHua Road, Dong Dan, Beijing,
33 17 100730, China.

34
35
36 18 E-mail: liumingbjh@126.com
37
38
39 19

40 20 **Abstract**

41
42 21 **Objective** Several studies have suggested a potential link between use of proton pump inhibitors
43 22 (PPIs) and the risk of kidney stones, attributed to alterations in urine mineral levels. Our study aimed
44 23 to investigate the association between PPI use and kidney stones in US adults.

45
46
47 24 **Design** Cross-sectional study.

48
49
50 25 **Setting** National Health and Nutrition Examination Survey (NHANES) (2007–2018).

51
52 26 **Participants** 27,075 individuals with complete information for PPI use and history of kidney stones
53 27 were included in this study.

54
55
56 28 **Outcomes and analyses** Nonlinear analysis, logistic regression analysis, and subgroup analysis
57 29 were conducted to estimate the relationship between PPI use and the occurrence and recurrence of
58 30 kidney stones, after adjusting for potential confounding factors.
59
60

1
2
3
4 31 **Results** Multivariable logistic regression analysis revealed a significant association between PPI
5
6 32 use and kidney stones (odds ratio [OR] 1.31, 95%CI 1.07–1.60), with a 4% increase in the
7
8 33 prevalence of kidney stones for each additional year of PPI use ($P < 0.001$). Similarly, PPI use was
9
10 34 significantly associated with recurrent kidney stones (OR 1.49, 95%CI 1.04–2.13), with a 7%
11
12 35 increase in the recurrence of kidney stones for each additional year of PPI use ($P < 0.001$).
13
14 36 Furthermore, these associations remained significant even after conducting propensity score
15
16 37 matching analysis on a subset of PPI users and non-users (all $P \leq 0.001$). Subgroup analyses showed
17
18 38 that the effects of PPI use on kidney stones differed by age, sex, race, and BMI.

19 39 **Conclusions** This study indicated that long-term use of PPI was associated with a higher risk of
20
21 40 both the presence and recurrence of kidney stones.
22

23
24
25 41 **Keywords:** NHANES; urolithiasis; proton pump inhibitors; risk factors; drug effects
26
27 42
28 43

29 44 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 30
31 45 • The NHANES dataset comprises a representative sample of the national population to
32
33 46 ensure that our findings can be extrapolated to the broader population.
34
35 47 • Multiple potential confounders were adjusted for and a propensity score matching
36
37 48 analysis was performed to ensure the reliability of the results.
38
39 49 • It is difficult to draw causal conclusions from cross-sectional analyses.
40
41 50 • NHANES did not record information regarding the time and type of kidney stones or the
42
43 51 dosage and type of proton pump inhibitor use.
44
45 52

46 53 **Introduction**

47
48 54 Kidney stones are a common disease in US, with a prevalence of 12% in men and 10% in women,
49
50 55 and have a substantial impact in terms of cost and morbidity(1, 2). Some drugs may affect the risk
51
52 56 of kidney stones by altering active compounds crystallizing in urine or substances impairing urine
53
54 57 composition(3-5).

55
56 58 Proton pump inhibitors (PPIs) are commonly prescribed medications worldwide for the
57
58 59 treatment of gastric acid-related diseases such as gastroesophageal reflux disease (GERD), H.
59
60 60 pylori infection, and gastric ulcers(6). However, the escalating prevalence of PPI overuse,

1
2
3
4 61 especially for long-term therapy, has become a concerning issue(6, 7). Long-term PPI intake is
5
6 62 associated with a reduction in intestinal absorption of essential vitamins and minerals and
7
8 63 increased susceptibility to infections, chronic kidney disease, and dementia(7). Given that PPI can
9
10 64 inhibit gastric acid secretion, thereby affecting the intestinal absorption of essential minerals and
11
12 65 altering the levels of calcium, magnesium, and citrate(8, 9), several studies have investigated the
13
14 66 impact of PPI use on the risk of kidney stones(10-12). For instance, Sui et al. found that PPI use
15
16 67 might elevate the risk of kidney stones by lowering the levels of urinary citrate and magnesium,
17
18 68 which could compromise their inhibitory effect on kidney stone formation(11). However, it should
19
20 69 be noted that all participants in their study were GERD patients. Similarly, Simonov et al.
21
22 70 identified a correlation between PPI use and kidney stones primarily based on a sample of young
23
24 71 individuals and males(10), thereby limiting the generalizability of their findings to not only the
25
26 72 general population but also specific patient groups, such as recurrent stone formers(13).

27
28 73 This study aimed to investigate the potential association between PPI use and kidney stones
29
30 74 by analyzing National Health and Nutrition Examination Survey (NHANES) data from 2007 to
31
32 75 2018. Our hypothesis was that PPI use increases the risk of both kidney stone formation and
33
34 76 recurrence.

35 77 **Methods**

36 78 **Study design and population**

37
38 79 The NHANES is an ongoing cross-sectional survey that employs a sophisticated multistage sample
39
40 80 methodology to investigate the health and nutritional status of the non-institutionalized population
41
42 81 in US. Demographic characteristics, clinical history, and self-reported dietary were collected from
43
44 82 participants using a structured household interview. Physical examinations, including
45
46 83 anthropometric measurements and blood samples, were collected within a mobile examination
47
48 84 center. The protocol was approved by the National Center for Health Statistics (NCHS) Ethics
49
50 85 Review Board, and informed consent was obtained from all participants. Additional information
51
52 86 regarding data collection can be accessed on the NHANES website(14).

53
54 87 Six NHANES cycles were used in the study from 2007 to 2018. Initially, 34,709 participants
55
56 88 aged 20 years and older were included. However, some participants were excluded: 372 participants
57
58 89 who were pregnant, 90 participants with incomplete kidney stone questionnaire, and 7,026
59
60 90 participants with incomplete variables. In addition, given the limited number of participants who

1
2
3
4 91 had taken PPI for more than 15 years, the standard errors for model estimates increased
5
6 92 substantially(15), thus 146 participants were excluded. Finally, 27,075 participants were included
7
8 93 in the analysis, consisting of 13,711 females and 13,364 males. Fig. 1 illustrates the filtering process
9
10 94 used in this study.

11 95 **Outcome assessment**

12
13 96 The primary outcome was the response to the question, “Have you ever had kidney stones?”
14
15 97 (NHANES 2007–2018). Participants who responded “yes” were defined as kidney stone formers.
16
17 98 The secondary outcome was the response to the question, “How many times have you passed a
18
19 99 kidney stone?” (NHANES 2007–2014). Participants who reported passing at least two stones were
20
21 100 classified as recurrent stone formers.

23 101 **Medication use**

24
25 102 The independent variables in this study were whether participants had taken PPI and the duration of
26
27 103 their PPI use. Information on the types and duration of acid suppressant medication was obtained
28
29 104 through prescription medication questionnaires. The types of PPI in this study included omeprazole,
30
31 105 esomeprazole, lansoprazole, pantoprazole, and rabeprazole. For participants using PPI, the duration
32
33 106 of use was equal to the years since initiating therapy. Participants who did not use PPI had a duration
34
35 107 of use recorded as zero. Data on specific dosages or previously discontinued prescription
36
37 108 medications were unavailable.

39 109 **Covariates**

40
41 110 The study collected three types of detailed information about covariates through standardized
42
43 111 personal interviews. The first group included demographic factors including age, sex, race,
44
45 112 education level, smoking status, and alcohol consumption. The second group consisted of factors
46
47 113 that impact the body's metabolism level, including body mass index (BMI), mean arterial pressure,
48
49 114 HbA1c, triglyceride levels, history of cardiovascular disease (CVD), thiazide use, loop diuretic use,
50
51 115 and histamine-2 receptor antagonists (H2RA) use. The third group focused on risk factors related to
52
53 116 kidney stone formation, including sedentary time, total water intake, albumin-adjusted calcium
54
55 117 levels, estimated glomerular filtration rate (eGFR), and history of gout. Education level was
56
57 118 categorized as follows: Grades 0–12, high school graduate/General Equivalency Diploma, and some
58
59 119 college or above. Smokers was defined as smoking at least 100 cigarettes during their lifetime. BMI
60
120 was calculated by dividing weight in kilograms (kg) by height in meters squared (m²). History of

1
2
3
4 121 CVD (including congestive heart failure, coronary heart disease, myocardial infarction, and stroke)
5
6 122 was defined if participants self-reported a history of these conditions. The Chronic Kidney Disease
7
8 123 Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR(16). The CKD-EPI
9
10 124 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
11
12 125 female] 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is
13
14 126 -0.329 for females and -0.411 for males, min indicates the minimum of Scr/ κ or 1, and max
15
16 127 indicates the maximum of Scr/ κ or 1. Gout was defined as a self-reported diagnosis of gout, and/or
17
18 128 the use of anti-gout medication.

19 129 **Statistical analyses**

20
21 130 All statistical analyses considered NHANES survey design characteristics with sampling weights.
22
23 131 Descriptive statistics were used to evaluate the demographic and clinic characteristics of the study
24
25 132 population. The variance inflation factor (VIF) was utilized to evaluate multicollinearity among
26
27 133 covariates and between covariates and kidney stones. A VIF value over 10 indicates
28
29 134 multicollinearity, but none was observed in this study (Supplementary Table 1) (17). To explore the
30
31 135 relationship between PPI use and kidney stones, we performed four weighted logistic regression
32
33 136 models and controlled for the aforementioned explanatory variables by modeling PPI as continuous
34
35 137 variables based on the time of use. We utilized restricted cubic splines to explore the potential non-
36
37 138 linear link between PPI use duration and kidney stones. Assessing model fit, we employed the
38
39 139 Akaike Information Criterion (AIC). Our knot selection process prioritized the model with the
40
41 140 lowest AIC value, leading us to choose a model with three knots located at the 5th, 50th, and 95th
42
43 141 centiles, as detailed in Supplementary Table 2. Subgroup analyses were also performed to explore
44
45 142 whether the relationship between the time of PPI use and kidney stones differed by age, sex, race,
46
47 143 and BMI, and potential effect modifiers were tested using the Wald test for multiplicative
48
49 144 interactions. Additionally, a 1:1 propensity score matching (PSM) analysis was performed to
50
51 145 balance population differences between PPI users and non-users while adjusting for all confounding
52
53 146 variables. Previous studies have established links between kidney stones and dietary factors, such
54
55 147 as vitamin C intake, caffeine consumption, and the dietary inflammatory index (DII)(18-20). To
56
57 148 address potential confounding effects, a sensitivity analysis was conducted using model 3 as the
58
59 149 baseline, with additional adjustments made for three variables: vitamin C intake, caffeine intake,
60
150 150 and DII. We conducted a meta-analysis using the 'meta' package, which allowed us to combine data

1
2
3
4 151 from relevant studies and estimate an overall effect size for the association between PPI use and
5
6 152 kidney stones. All statistical tests were two-sided, and P-values < 0.05 (two-sided) were considered
7
8 153 statistically significant. R 4.2.2 software was used for modeling.

9 154 **Patient and public involvement**

11 155 None.

13 156 **Results**

15 157 **Population characteristics**

17 158 This analysis included 27,075 participants aged 20 years and older from the NHANES database
18
19 159 (2007–2018), representing 203,076,872 adults. And table 1 presents their demographic and
20
21 160 clinical characteristics based on PPI use. The mean age of all participants was 47.46 ± 0.26
22
23 161 (standard error) years, with roughly equal representation of females (51.13%) and males (48.87%).
24
25 162 PPI users were more likely to be older, females, non-Hispanic white, obese, have lower education
26
27 163 level, alcohol consumption, total water intake, eGFR, higher sedentary time, mean arterial
28
29 164 pressure, HbA1c, triglycerides, albumin-adjusted calcium. PPI users were taking more thiazide,
30
31 165 loop diuretics, and H2RAs medications compared to non-users. Furthermore, CVD, gout and
32
33 166 kidney stone diseases were more common in PPI users (all $P < 0.05$).

35 167 **Multivariable logistic regression analyses**

36
37 168 Weighted univariable and multivariable logistic regression models were used to investigate the
38
39 169 independent association between PPI use and the risk of kidney stones, with PPI non-user as the
40
41 170 reference group (Table 2). In the crude model, PPI use showed a significantly positive association
42
43 171 with the prevalence of kidney stones ($OR = 1.86$, $95\%CI = 1.55–2.22$). In the fully adjusted model
44
45 172 (model 3), the association between PPI use and the prevalence of kidney stones remained significant
46
47 173 ($OR = 1.31$, $95\%CI = 1.07–1.60$). When considering PPI use as a continuous variable, the restricted
48
49 174 cubic spline analyses indicated a linear relationship between the duration of PPI use and the
50
51 175 prevalence of kidney stones (P for non-linearity = 0.651) (Fig. 2A). With each additional year of
52
53 176 PPI use, the prevalence of kidney stones increased by 4% (Table 2). Additionally, we explored the
54
55 177 association between PPI use and recurrent kidney stones. In the crude model, PPI use showed a
56
57 178 significantly positive association with the recurrence of kidney stones ($OR = 1.49$, $95\%CI = 1.05–$
58
59 179 2.09). This positive association persisted in the fully adjusted model (model 3) ($OR = 1.49$, $95\%CI$
60
180 $= 1.04–2.13$). The duration of PPI use exhibited a linear correlation with the recurrence of kidney

1
2
3
4 181 stones (P for non-linearity = 0.484) (Fig. 2B), with a 7% increase for each additional year of PPI
5
6 182 use (Table 2).

7 183 **Subgroup analyses**

8
9 184 Moreover, subgroup analyses were performed to assess whether the relationship between the
10
11 185 duration of PPI use and kidney stones were influenced by age, sex, race, and BMI (Table 3). After
12
13 186 adjusting for all covariates, it was found that the duration of PPI use was significantly associated
14
15 187 with the prevalence of kidney stones in participants aged 50 years or older, females, non-Hispanic
16
17 188 White, and those with a BMI of 25 kg/m² or higher. On the other hand, a significant positive
18
19 189 association between time of PPI use and recurrent kidney stones was observed only in participants
20
21 190 non-Hispanic White, and those with a BMI of 25 kg/m² or higher (all P for interaction > 0.05).

22 191 **Sensitivity analyses and meta-analysis**

23
24 192 A 1:1 matched cohort analysis was conducted through PSM to minimize potential bias, given the
25
26 193 significant difference in PPI use and non-use group (Table 1). This approach confirmed 4864
27
28 194 participants in the matched cohort. The descriptive statistics results showed that no significant
29
30 195 differences observed in most variables between the PPI non-user and PPI user groups
31
32 196 (Supplementary Table 3). In the fully adjusted model, the dose-response curve still displayed a
33
34 197 positive association between the duration of PPI use and kidney stones ($OR = 1.05$, $95\%CI = 1.02-$
35
36 198 1.08 , P for non-linearity = 0.956) (Supplementary Fig. 1A) and recurrent kidney stones ($OR = 1.10$,
37
38 199 $95\%CI = 1.02-1.18$, P for non-linearity = 0.488) (Supplementary Fig. 1B). Moreover, the results
39
40 200 remained significant after making additional adjustments for vitamin C intake, caffeine
41
42 201 consumption, and DII (Supplementary Table 4). Furthermore, we performed a meta-analysis based
43
44 202 on our findings and previously published research, confirming a positive association between the
45
46 203 PPI use and the risk of kidney stones ($OR = 1.49$, $95\%CI = 1.05-2.10$) (Supplementary Fig. 2)(10-
47
48 204 12).

49 205 **Discussion**

50
51 206 In this large cross-sectional study based on NHANES data from 2007 to 2018, we found that PPI
52
53 207 use was associated with an increased risk of kidney stones. The duration of PPI use demonstrated a
54
55 208 dose-response association with kidney stones. Furthermore, our study uncovered a novel association
56
57 209 between long-term PPI use and recurrent kidney stones in patients with a history of kidney stones,
58
59 210 demonstrating a significant linear correlation. Additionally, subgroup analysis found that the effects

1
2
3
4 211 of age, sex, race, and BMI varied in their influence on the relationship between PPI use and the
5
6 212 prevalence of kidney stones.

7
8 213 Several studies have shown that PPI use could increase the risk of kidney stones, with a dose-
9
10 214 response relationship(10-12). A retrospective study conducted on the Women's Veterans Cohort,
11
12 215 which included 465,891 individuals, revealed that PPI use was linked to a 1.25-fold higher risk of
13
14 216 kidney stones (95% CI = 1.19–1.33)(10). It should be noted that this study included mainly young
15
16 217 individuals (with a median age of 32 years) and was predominantly males (86%), thus having a
17
18 218 certain degree of selection bias(13). Another study by Sui et al. also found a positive association
19
20 219 between PPI use and kidney stones in patients with GERD, with a 1.46-fold increased risk (95%CI
21
22 220 = 1.38–1.55), which could help in assessing the potential risk of kidney stones associated with PPI
23
24 221 exposure(11). Nevertheless, both studies were limited to specific populations, limiting the
25
26 222 generalizability of their findings to the general population. In contrast, a nationwide population
27
28 223 cohort from Korea, without selection bias, also showed a positive association between PPI use and
29
30 224 kidney stones, displaying a dose-response relationship(12). Similarly, the current study, based on
31
32 225 data from the NHANES database representing over 203 million individuals, found that PPI use was
33
34 226 significantly associated with not only a higher risk of kidney stones, but also recurrent kidney stones.
35
36 227 The findings from the meta-analysis conducted in this study have confirmed the positive association
37
38 228 between PPI use and the risk of kidney stones. Furthermore, the risk of developing kidney stones
39
40 229 was found to be higher in individuals who used PPI for a longer duration, highlighting the
41
42 230 importance of monitoring this potential side effects of long-term PPI treatment, especially for
43
44 231 patients with a history of kidney stones.

45
46 232 The mechanisms underlying the impact of PPI on kidney stone formation remain unclear.
47
48 233 Studies have suggested that PPI can elevate gastric pH, leading to a decrease in magnesium
49
50 234 absorption and urinary magnesium levels(9). Magnesium has been known to inhibit the formation
51
52 235 of calcium oxalate crystals in urine(21, 22). A meta-analysis of nine observational studies found a
53
54 236 significant increased risk of hypomagnesemia among patients using PPI(23). It should be noted that
55
56 237 magnesium absorption occurs through both active and passive mechanisms, and alterations in pH
57
58 238 do not affect passive absorption(23). Therefore, PPI use does not always result in hypomagnesemia,
59
60 239 but patients with impaired gastrointestinal absorptive capacity may have an increased risk of
240
241 240 developing hypomagnesemia. On the other hand, research has shown that citrate can inhibit the

1
2
3
4 241 crystallization of calcium salts in urine, and a deficiency of citrate can increase the risk of stone
5
6 242 formation(24, 25). A study of 301 nephrolithiasis patients with 24-hour urine data found that PPI
7
8 243 exposure significantly reduced urinary citrate excretion, but did not affect urinary magnesium, pH,
9
10 244 or other urinary minerals(8). Similarly, another study on GERD patients reported a significant
11
12 245 correlation between PPI use and lower levels of urinary citrate and magnesium(11). Therefore, given
13
14 246 the association of PPI use with hypomagnesuria and hypocitraturia, it may monitor the levels of
15
16 247 urinary magnesium and citrate when using PPI.

17
18 248 PPIs are commonly prescribed for acid-related disorders, and patients with these conditions
19
20 249 may be at higher risk for kidney stone formation(26). In this study, we employed the PSM analysis
21
22 250 to minimize potential differences between PPI users and non-users, yet still identified a significant
23
24 251 association between PPI use and the occurrence and recurrence of kidney stones. Subgroup analyses
25
26 252 further revealed that certain patient groups, including the elderly, females, non-Hispanic Whites,
27
28 253 and those with a BMI of 25 kg/m² or higher, exhibited a stronger positive association between PPI
29
30 254 use and the prevalence of kidney stones, highlighting the importance of considering potential side
31
32 255 effects of PPI use in these populations. While it is undeniable that PPI therapy has improved the
33
34 256 quality of life for many patients with acid-related disorders(27), a growing body of literature
35
36 257 suggested a relationship between long-term PPI use and adverse events(28). Caution should be
37
38 258 exercised when discontinuing PPI use for evidence-based indications(29), but global concerns over
39
40 259 long-term PPI overuse should not be overlooked(6, 7), especially in individuals with a history of
41
42 260 kidney stones and high-risk factors, such as the elderly, females, non-Hispanic Whites, and those
43
44 261 with a BMI of 25 kg/m² or higher, in order to reduce unnecessary use.

45
46 262 This study has several strengths. Firstly, the NHANES dataset comprises a representative
47
48 263 sample of the national population, and we utilize NHANES-provided weights to ensure that our
49
50 264 findings can be extrapolated to the broader population. Secondly, this study not only elucidates the
51
52 265 correlation between PPI use and the prevalence of kidney stones but also probes its association with
53
54 266 the recurrence of renal calculi in individuals with a history of nephrolithiasis. Furthermore, multiple
55
56 267 potential confounders were adjusted and PSM design was performed to ensure the reliability of the
57
58 268 results. However, this study also has several limitations. Firstly, it is difficult to draw causal
59
60 269 conclusions from such cross-sectional analyses. Although we adjusted for three types of detailed
270
covariate information, there may still be unmeasured potential factors that could affect the

1
2
3
4 271 association between PPI and nephrolithiasis. Secondly, the questionnaire survey may have been
5
6 272 prone to recall bias and reporting bias, which could affect the accuracy of the data collected. Thirdly,
7
8 273 NHANES lacks objective diagnostic imaging for the identification of kidney stones, potentially
9
10 274 resulting in the omission of asymptomatic cases. Additionally, the dataset does not provide details
11
12 275 on the timing and specific type of kidney stones. Finally, the lack of information about the dosage
13
14 276 and type of PPI use may limit the interpretability of the results.

15 277 **Conclusions**

16
17 278 In conclusion, our study revealed a relationship between PPI use and the prevalence of kidney stones,
18
19 279 as well as an increased risk of recurrent kidney stones in patients with a history of nephrolithiasis.
20
21 280 To mitigate this potential adverse effect, caution should be exercised regarding unnecessary long-
22
23 281 term use of PPI.

24 25 26 27 283 **Acknowledgements**

28
29 284 We appreciate the American Centers for Disease Control and Prevention for conducting the survey and
30
31 285 making it available online freely, and all the participants for providing these data.

32 33 286 **Contributors**

34
35 287 W-L: conceptualization, methodology, data analysis, manuscript writing; J-W: methodology, data
36
37 288 collection, data analysis, manuscript writing; M-W: methodology, data collection, data analysis; MM-
38
39 289 W: data analysis, manuscript writing, supervision; M-L: conceptualization, supervision, manuscript
40
41 290 editing, funding acquisition.

42 43 291 **Funding**

44
45 292 This work was supported by the National Key Research and Development Program of China
46
47 293 [2022YFC3602900] and National High Level Hospital Clinical Research Funding [BJ-2022-115].

48 49 294 **Competing interests**

50
51 295 None declared.

52 53 296 **Patient consent for publication**

54
55 297 Not applicable.

56 57 298 **Ethics statement**

58
59 299 Ethical review and approval for the original research involving human participants were obtained from
60
300 the Ethics Review Board of the NCHS (Protocol #98-12). Written informed consent was obtained from

1
2
3
4 301 all patients or participants who were part of the study. The current analysis, which is based on publicly
5
6 302 available data, did not require any further ethics approval.

7
8 303 **Data availability statement**

9
10 304 Publicly available datasets were analyzed in this study. Data are available from
11
12 305 <https://www.cdc.gov/nchs/nhanes/> (NHANES 2005-2006 and 2007-2008).

13
14 306

15
16 307 **References**

- 17 308 1. Saigal CS, Joyce G, Timilsina AR. Direct and indirect costs of nephrolithiasis in an employed
18 309 population: opportunity for disease management? *Kidney Int.* 2005;68(4):1808-14.
- 19 310 2. Abufaraj M, Xu T, Cao C, Waldhoer T, Seitz C, D'Andrea D, et al. Prevalence and Trends in Kidney
20 311 Stone Among Adults in the USA: Analyses of National Health and Nutrition Examination Survey 2007-
21 312 2018 Data. *Eur Urol Focus.* 2021;7(6):1468-75.
- 22 313 3. Dauw CA, Yi Y, Bierlein MJ, Yan P, Alruwaily AF, Ghani KR, et al. Factors Associated With Preventive
23 314 Pharmacological Therapy Adherence Among Patients With Kidney Stones. *Urology.* 2016;93:45-9.
- 24 315 4. Daudon M, Frochot V, Bazin D, Jungers P. Drug-Induced Kidney Stones and Crystalline
25 316 Nephropathy: Pathophysiology, Prevention and Treatment. *Drugs.* 2018;78(2):163-201.
- 26 317 5. Cohen AJ, Adamsky MA, Nottingham CU, Pruitt J, Lapin B, Wang CH, et al. Impact of Statin Intake
27 318 on Kidney Stone Formation. *Urology.* 2019;124:57-61.
- 28 319 6. Savarino V, Marabotto E, Zentilin P, Furnari M, Bodini G, De Maria C, et al. Proton pump inhibitors:
29 320 use and misuse in the clinical setting. *Expert Rev Clin Pharmacol.* 2018;11(11):1123-34.
- 30 321 7. Eusebi LH, Rabitti S, Artesiani ML, Gelli D, Montagnani M, Zagari RM, et al. Proton pump inhibitors:
31 322 Risks of long-term use. *J Gastroenterol Hepatol.* 2017;32(7):1295-302.
- 32 323 8. Patel PM, Kandabarow AM, Aiwerioghene E, Blanco-Martinez E, Hart S, Leehey DJ, et al. Proton-
33 324 pump inhibitors associated with decreased urinary citrate excretion. *Int Urol Nephrol.* 2021;53(4):679-
34 325 83.
- 35 326 9. Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and
36 327 effects on absorption of calcium, vitamin B12, iron, and magnesium. *Curr Gastroenterol Rep.*
37 328 2010;12(6):448-57.
- 38 329 10. Simonov M, Abel EA, Skanderson M, Masoud A, Hauser RG, Brandt CA, et al. Use of Proton Pump
39 330 Inhibitors Increases Risk of Incident Kidney Stones. *Clin Gastroenterol Hepatol.* 2021;19(1):72-9.e21.
- 40 331 11. Sui W, Miller NL, Gould ER, Zhang KC, Koyama T, Hsi RS. Proton pump inhibitors use and risk of
41 332 incident nephrolithiasis. *Urolithiasis.* 2022;50(4):401-9.
- 42 333 12. Kim SY, Yoo DM, Bang WJ, Choi HG. Association between Urolithiasis and History Proton Pump
43 334 Inhibitor Medication: A Nested Case-Control Study. *J Clin Med.* 2022;11(19).
- 44 335 13. Pella E, Chalkidou M, Sarafidis P. Proton Pump Inhibitors, Histamine-2 Receptor Antagonists, and
45 336 the Risk of Kidney Stones: Negligible or Not? *Clin Gastroenterol Hepatol.* 2021;19(3):624-5.
- 46 337 [dataset] 14. NHANES Questionnaires, Datasets, and Related Documentation. Available from:
47 338 <https://www.cdc.gov/nchs/nhanes/Default.aspx>: [Accessed April 14, 2023 pp.].
- 48 339 15. Chang SL, Harshman LC, Presti JC, Jr. Impact of common medications on serum total prostate-
49 340 specific antigen levels: analysis of the National Health and Nutrition Examination Survey. *J Clin Oncol.*
50 341 2010;28(25):3951-7.

- 1
2
3 342 16. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to
4 343 estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-12.
5 344 17. Charidimou A, Martinez-Ramirez S, Reijmer YD, Oliveira-Filho J, Lauer A, Roongpiboonsopit D, et
6 345 al. Total Magnetic Resonance Imaging Burden of Small Vessel Disease in Cerebral Amyloid Angiopathy:
7 346 An Imaging-Pathologic Study of Concept Validation. *JAMA Neurol.* 2016;73(8):994-1001.
8 347 18. Ferraro PM, Curhan GC, Gambaro G, Taylor EN. Total, Dietary, and Supplemental Vitamin C Intake
9 348 and Risk of Incident Kidney Stones. *Am J Kidney Dis.* 2016;67(3):400-7.
10 349 19. Geng J, Qiu Y, Kang Z, Li Y, Li J, Liao R, et al. The association between caffeine intake and risk of
11 350 kidney stones: A population-based study. *Front Nutr.* 2022;9:935820.
12 351 20. Liu N, Feng Y, Li J, Ma X, Ma F. Relationship between the dietary inflammatory index and kidney
13 352 stone prevalence. *World J Urol.* 2022;40(6):1545-52.
14 353 21. Schwartz BF, Bruce J, Leslie S, Stoller ML. Rethinking the role of urinary magnesium in calcium
15 354 urolithiasis. *J Endourol.* 2001;15(3):233-5.
16 355 22. Johansson G, Backman U, Danielson BG, Fellström B, Ljunghall S, Wikström B. Effects of
17 356 magnesium hydroxide in renal stone disease. *J Am Coll Nutr.* 1982;1(2):179-85.
18 357 23. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Srivali N, Edmonds PJ, Ungprasert
19 358 P, et al. Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of
20 359 observational studies. *Ren Fail.* 2015;37(7):1237-41.
21 360 24. Goldberg H, Grass L, Vogl R, Rapoport A, Oreopoulos DG. Urine citrate and renal stone disease.
22 361 *Cmaj.* 1989;141(3):217-21.
23 362 25. Pak CY. Citrate and renal calculi: an update. *Miner Electrolyte Metab.* 1994;20(6):371-7.
24 363 26. Bapir R, Bhatti KH, Eliwa A, García-Perdomo HA, Gherabi N, Hennessey D, et al. Risk of urinary
25 364 stone formation associated to proton pump inhibitors: A systematic review and metanalysis. *Arch Ital*
26 365 *Urol Androl.* 2022;94(4):507-14.
27 366 27. Moayyedi P, Armstrong D, Hunt RH, Lei Y, Bukoski M, White RJ. The gain in quality-adjusted life
28 367 months by switching to esomeprazole in those with continued reflux symptoms in primary care:
29 368 EnCOMPASS--a cluster-randomized trial. *Am J Gastroenterol.* 2010;105(11):2341-6.
30 369 28. Elias E, Targownik LE. The Clinician's Guide to Proton Pump Inhibitor Related Adverse Events.
31 370 *Drugs.* 2019;79(7):715-31.
32 371 29. Boghossian TA, Rashid FJ, Thompson W, Welch V, Moayyedi P, Rojas-Fernandez C, et al.
33 372 Deprescribing versus continuation of chronic proton pump inhibitor use in adults. *Cochrane Database*
34 373 *Syst Rev.* 2017;3(3):Cd011969.

374

375 **FIGURE TITLE/LEGENDS**376 **Figure 1.** Study flowchart

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

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

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

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

60

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.

385

386 SUPPLEMENTARY FIGURE TITLE/LEGENDS

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

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

390 Abbreviations: OR, odds ratio; PPIs, proton pump inhibitors; PSM, propensity score matching.

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

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

396

397 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/m ²), 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

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

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

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

403 ‡BMI was calculated by dividing weight in kilograms (kg) by height in meters squared (m²). Participants were classified as
 404 normal weight (BMI < 25 kg/m²), and overweight/obese (BMI ≥ 25 kg/m²).

405

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)

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

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

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

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

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

412

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	

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

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

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

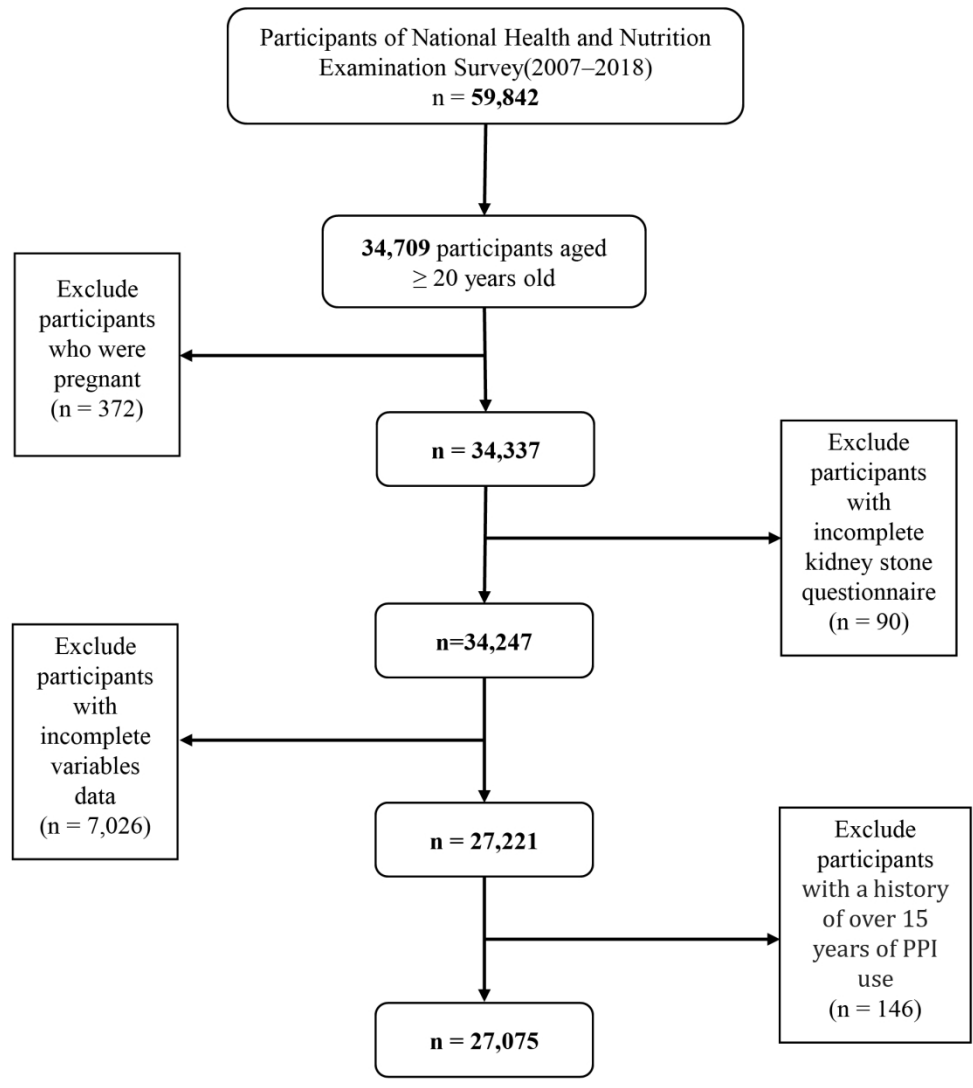
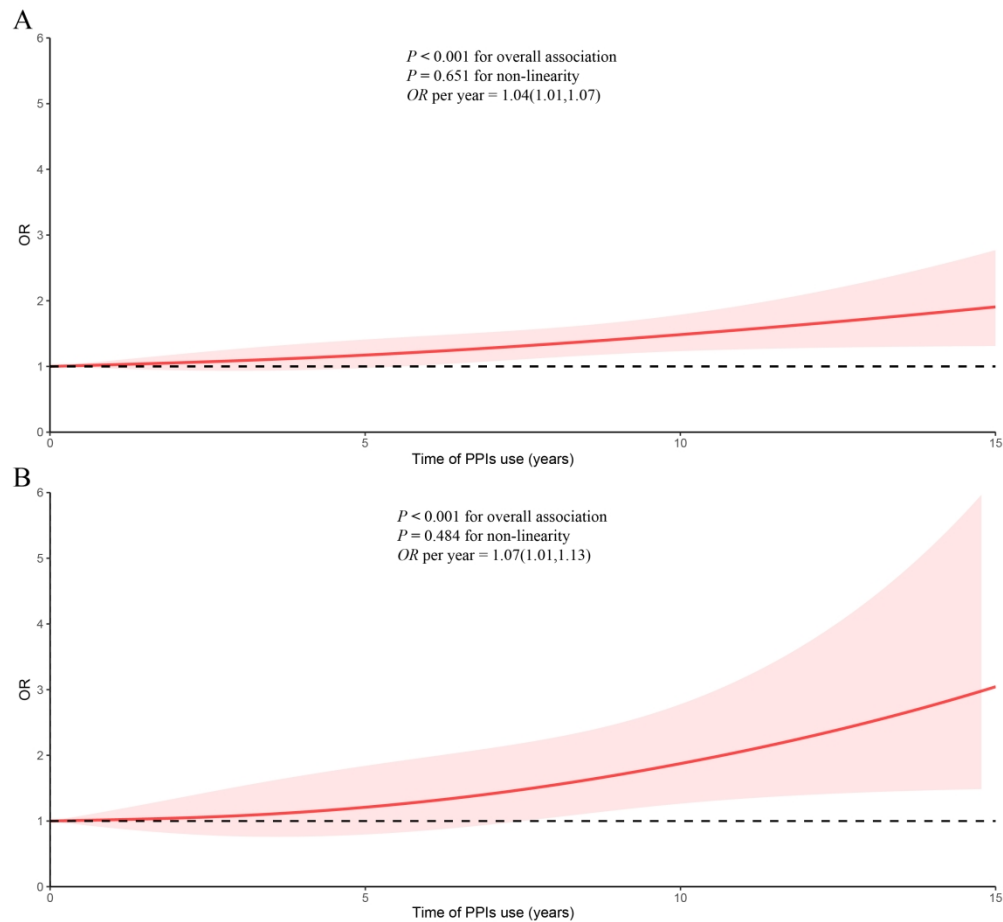


Fig. 1 Study flowchart. Of 59,842 participants in the 2007–2018 National Health and Nutrition Examination Survey (NHANES), 27,075 remained after fulfilling inclusion and exclusion criteria.

169x190mm (300 x 300 DPI)

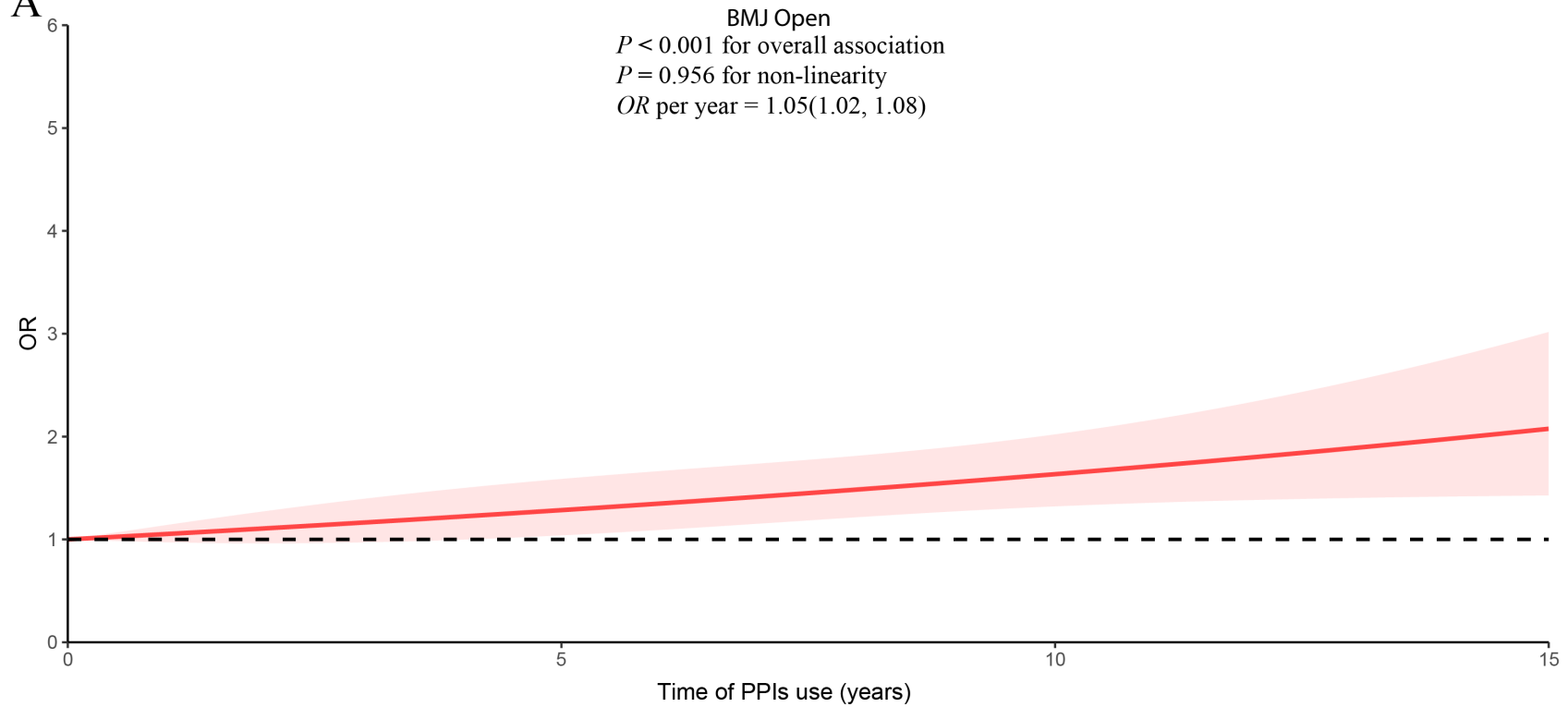


36 Fig. 2 Dose-response relationships between time of PPIs use and kidney stones. (A) Time of PPIs use and
 37 kidney stones; (B) Time of PPIs use and recurrent kidney stones.

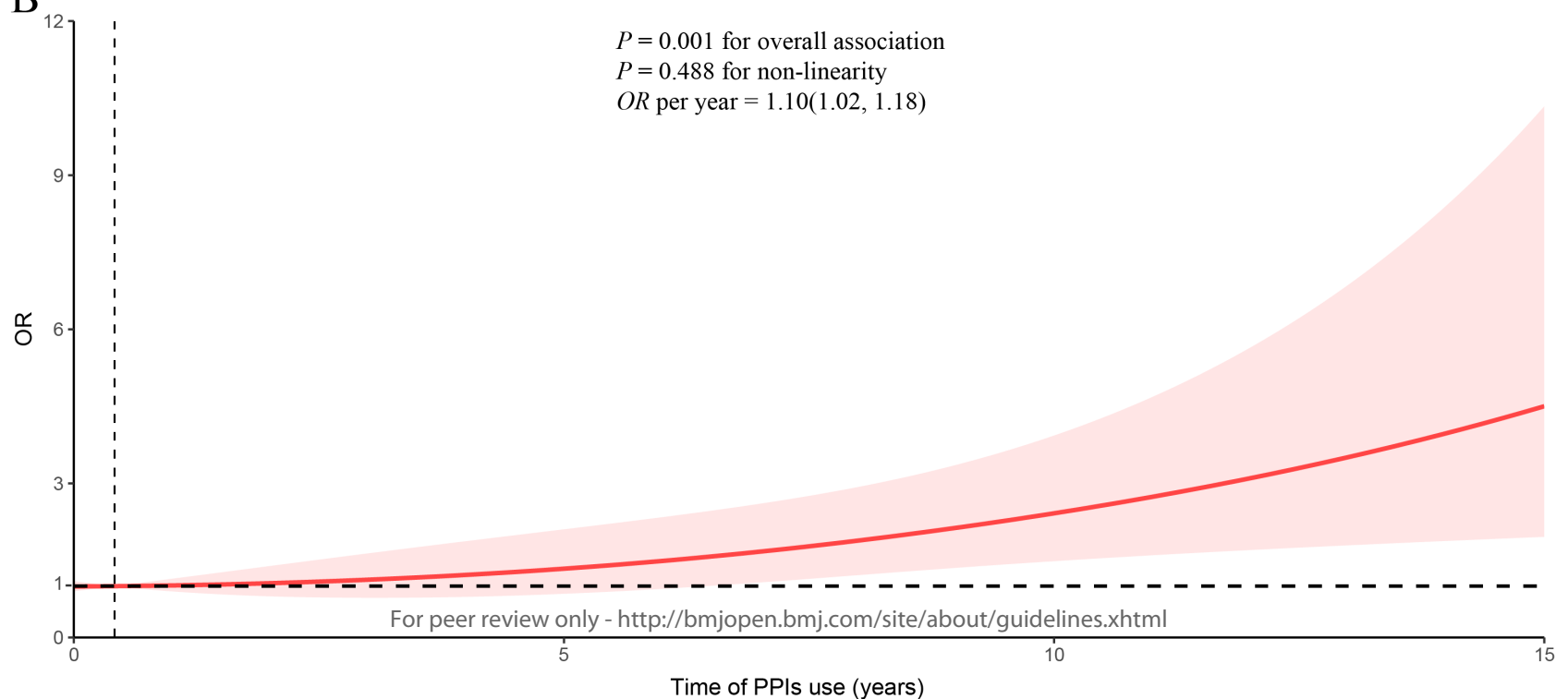
38 Abbreviations: OR, odds ratio; PPIs, proton pump inhibitors. Adjusted for age, sex, race, education level,
 39 smoking, alcohol consumption, BMI, mean arterial pressure, HbA1c, triglycerides, history of CVD, gout,
 40 thiazide use, loop diuretics use, and H2RAs use, sedentary time, total water intake,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

42
43 263x243mm (300 x 300 DPI)







A



B



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

Study	HR/OR	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%

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

1 2 3

1
2
3
4
5
6
7
8
9
10
11

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

For peer review only

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 (m²). Participants were classified as normal weight (BMI < 25 kg/m²), and overweight/obese (BMI \geq 25 kg/m²).

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 (<i>OR</i> [95% <i>CI</i>])	<i>P</i> -value
Kidney stones (N = 2,589) VS Non-kidney stone (N = 24,486) (NHANES 2007–2018)		
PPIs use		
No	1[Reference]	0.01
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		
No	1[Reference]	0.03
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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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	<i>Describe any efforts to address potential sources of bias</i>	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.