Regular use of proton pump inhibitor and risk of rheumatoid arthritis in women: a prospective cohort study

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ABSTRACT

Background Proton pump inhibitors (PPIs) have a significant impact on gut microbiome, which in turn, may increase the risk of rheumatoid arthritis (RA).

Aim To evaluate regular use of PPIs and risk of RA.

Methods This is a prospective analysis of the US nurses who reported PPI use data, and were free of RA from the Nurses' Health Study (NHS 2002-2014) and NHS II (2003-2015). The exposure was regular use of PPI in the past 2 years, which was repeatedly evaluated in biennial surveys. RA was confirmed by the 1987 or 2010 American College of Rheumatology criteria. We estimated the hazard ratios (HRs) and confidence interval (CIs) with time-dependent Cox regression adjusting for potential confounders.

Results We documented 421 cases of RA over 1,753,879 person-years of follow-up. Regular PPI users had a 44% higher risk of RA as compared with non-regular users (adjusted HR=1.44; 95%CI, 1.10 to 1.89). The risk of RA increased with the total duration of PPI use (*P*-trend = 0.008). Compared with non-regular users, the adjusted HRs were 1.22 (95%CI, 0.93 to 1.62) for women with >0 to 4 years' use and 1.73 (95%CI, 1.14 to 2.61) for > 4 years' use.

Conclusions Regular use of PPI was associated with increased risk of RA in women, with a higher risk observed in individuals with a longer duration of PPI use. Due to the observational study design, large prospective trials are still required to confirm our finding.

Keywords: Proton pump inhibitors; rheumatoid arthritis; cohort; Nurses' Health Studies

INTRODUCTION

Proton pump inhibitors (PPIs) are among the top 10 most commonly prescribed medications worldwide,[1] used for a variety of acid-related disorders such as gastroesophageal reflux disease, peptic ulcer disease, and non-ulcer dyspepsia.[2] Despite the irreplaceable role of PPI in clinical practice, long-term use of PPIs has been linked with a series of health problems including chronic kidney disease, bone fractures, dementia, vitamin and mineral deficiencies.[2, 3] Recent studies have observed a large impact of PPIs on the gut microbiome,[4, 5] as a possible result of gastric acid suppression on lower gastrointestinal tract environment. On a population level, PPIs may have an even more pronounced effect on gut microbiome than other commonly used drugs such as antibiotics, leading to warnings of PPI over-use and calls for further investigation into the sequelae of long-term PPI consumption.[4]

Rheumatoid arthritis (RA) is a chronic autoimmune joint disease, which has been implicated in cartilage and bone damage.[6] In 2014, the prevalence of RA in the U.S. ranged from 0.53% to 0.55%, leading to a conservative estimate of 1.28-1.36 million patients in this country.[7] The etiopathogenic mechanisms of RA remain obscure, though possibly involving a combination of infectious, environmental, hormonal, and genetic risk factors.[8] Since gut microbiota plays a fundamental role on the maturation and function of the host immune system,[9] research interests have recently been directed at its effects on the pathogenesis of RA.[10, 11] In experimental murine models, commensal bacteria can drive autoimmune arthritis by inducing a Th17 response in the intestine.[10, 12] Results in humans also suggested that dysbiosis could promote RA progression, and the inflammation that caused by certain

intestinal microbes like *P. copri*, may contribute to the persistence of arthritis.[10] Two resent epidemiological studies also showed that exposure to antibiotics, another class of medicine with a major impact on gut microbiome, was a significant risk factor for RA.[13, 14]

Mechanically, long-term use of PPIs may be associated with RA through intestinal dysbiosis, however epidemiological evidence remains unclear. In 2013, a retrospective claims-based cohort study evaluated the association of PPI use with the risk of community-acquired pneumonia. In this study, the risk of RA was also evaluated in the falsification analyses and a positive association with PPI use was observed.[15] This study was limited by potential misclassification of exposures and outcomes, and inadequate control for potential confounders.[15] The Nurses' Health Study (NHS), and NHS II are two large ongoing prospective cohorts which have collected a comprehensive range of data on socio-demographic factors, medications use, lifestyle factors, and health conditions such as rheumatologic diseases. These cohorts offer us an opportunity to investigate RA risk factors with adjustment for a wide array of confounding factors or effect modifiers. Using NHS and NHS II datasets, we performed this study to evaluate the association between PPI use and subsequent RA risk among women.

METHODS

Study population

The NHS originally enrolled 121,700 female nurses from 11 U.S. states aged 30 to 55 years in 1976. The NHS II, established in 1989, included 116,430 younger female registered nurses who were between the ages of 25 to 42 years from 14 states in the U.S.. The participants have

received a biennial questionnaire since baseline to collect data on demographics, health-related behaviors, medical history, and newly diagnosed diseases, with a follow-up completion rate of over 90% for each questionnaire cycle. The recruitment and data collection in NHS and NHS II have been reported in detail previously.[16] In the present study, we included women who reported PPI use data and excluded those with a self-report of RA. We also excluded systemic lupus erythematosus (SLE) which is another rheumatic autoimmune disease evaluated in nurse health studies. The NHS and NHS II were approved by the Human Research Committee at the Brigham and Women's Hospital, Boston, MA. The study protocol was approved by the institutional review board (IRB) of the Brigham and Women's Hospital, and the IRB allowed participants' completion of questionnaires to be considered as implied consent.

Assessment of PPI/H2 receptor antagonist (H2RA) use

In the 2000, 2002 questionnaire in NHS, and the 2001,2003 questionnaire in NHS II, participants were asked whether, over the previous two years, they had regularly used "Prilosec or Prevacid". In the biennial surveys after 2002 for NHS and after 2003 for NHS II, participants were asked whether, over the previous two years, they had regularly used "Prilosec, Prevacid (lansoprazole), Protonix, Nexium, or Aciphex." In the 2000 questionnaire in NHS, and the 2001 questionnaire in NHS II, participants were asked whether, over the previous two years, they "had regularly used cimetidine or other H2RAs (e.g. Zantac, Pepcid, etc)." In the biennial surveys after 2000 for NHS and after 2001 for NHS II, the participants were asked whether they "had regularly used any H2RAs (e.g. Zantac,cimetidine, Pepcid,

Axid, etc.)". Data about the dose, brand or type of PPI were not collected.

Ascertainment of RA

The ascertainment of RA was reported in previous studies.[17, 18] In brief, we identified RA cases by sending a connective tissue disease screening questionnaire [19] to those who self-reported a diagnosis of RA. For those who screened positive, we checked the medical records to confirm the diagnosis and collect symptom/diagnosis dates and serological status. Two board-certified rheumatologists reviewed the medical records to confirm RA according to the 1987or 2010 American College of Rheumatology classification criteria.[20, 21] Seropositive RA was defined by the presence of either rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP) antibodies, and seronegative RA by the absence of a positive test. The end of follow-up was June 1, 2014 for the NHS and June 1, 2015 for the NHS II.

Assessment of covariates

We selected covariates that may confound the association based on review of previous literature.[8, 22] In the baseline and biennial follow-up questionnaires, we obtained updated information on age, ethnicity, family history of RA, body mass index (BMI), smoking, alcohol intake, menopausal status and postmenopausal hormone use, parity, breastfeeding, comorbidities (hypertension, diabetes, hypercholesterolemia, cancer, gastric or duodenal ulcer, and gastroesophageal reflux disease), and drugs that are likely related to PPI and RA (H2RAs, non-steroidal anti-inflammatory drugs (NSAIDs), and steroids). We calculated the 2010 Alternative Healthy Eating Index (AHEI-2010) to assess overall diet quality. Physical activity was measured by weekly expenditure of metabolic equivalents (METs) which has

been validated in a previous study. [23]

Statistical analysis

We calculated person-years from the date of return of the baseline questionnaire to the date of diagnosis of RA, death, or the end of follow-up, whichever came first. We evaluated the hazard ratios (HRs) and 95% confidence intervals (CIs) with multivariable time-dependent Cox proportional hazards models accounting for potential time-varying effects in the exposure and covariates. We tested the assumption of proportional hazards by evaluating the interaction between age and main exposure in the age, period-stratified model. PPI use data was collected since 2000 in NHS and 2001 in NHS II and the baseline was 2002 for NHS and 2003 for NHS II. We lagged the exposure for two years to reduce the potential influence that subclinical RA symptoms may be related to PPI use and allow a time window for RA risk development. The time-dependent Cox models lagged the exposure by testing the associations between exposure of each biennial surveys (e.g. 2000) with the RA observed two years later (e.g. 2002-2004). Because the number of events, particularly for seronegative RA cases, was low in each individual cohort, we pooled the effect of NHS and NHS II with a one-step method [24] (directly evaluate the effect based on individual data of the two cohorts) to achieve adequate model convergence. The Cox-regression models were stratified by age, period, and study to control the potential influence.

We coded the participants with missing covariate data to the reference group or median value group when the missing rate was low (<1%). When the rate of missing data was ≥ 1%, a separate missing response category was created. In the basic model, we stratified the analyses

jointly by age (in months), the year that the questionnaire was returned, and cohort (NHS and NHS II). In the multivariable-adjusted model 1, we adjusted for race, history of RA in a first-degree relative, BMI, menopausal status and postmenopausal hormone use, number of parity, breastfeeding. Because PPIs were often prescribed along with other drugs, we also included regular use of NSAIDs, steroids in model 1 to control the potential confounding effects. To control the potential confounding from comorbidities, we additionally adjusted for hypertension, diabetes, hypercholesterolemia, cancer, gastric or duodenal ulcer, and gastroesophageal reflux disease in the multivariable-adjusted model 2. In the multivariable-adjusted model 3, we additionally controlled for lifestyle factors, including pack of cigarettes per years, days with alcohol drinking per week, physical activity, and overall diet quality.

To test whether the association between PPI use and RA might be due to its effect on gastric acid suppression, we evaluated regular use of H2RA, a less potent acid suppressor with similar indications as PPI, and risk of RA. If acid suppression plays a role in RA development, it's expected that H2RA would have less or no effect on RA risk.[25] To verify if the association between PPI and RA was confounded by unknown factors, we used falsification analyses by testing implausible associations (basal cell skin cancer, squamous cell skin cancer, and cervical cancer).[26] If PPI also showed associations with these implausible endpoints, its' association with RA may be confounded by unknown factors.

To verify potential interaction effects, we undertook subgroup analysis according to cohort, age, BMI, family history of RA, menopausal status, breastfeeding time for their children, smoking, and regular use of NSAIDs. Additionally, we performed a number of sensitivity

analyses to check the robustness of the primary results. First, we lagged the exposure for even longer time (4 years) to further address potential reverse causation. Second, we pooled the effect of NHS and NHS II with a two-step method (evaluating the effect within each cohort and then pooling effect with inverse variance weighted random effect meta-analyses).[24] Third, to investigate the potential bias from healthcare utilization (i.e. the participants with better healthcare utilization are likely to have a better access to PPIs and lower chance to be undiagnosed if they had RA), we adjusted physical examination in the previous 2 years (yes or no) as a surrogate indicator. Fourth, we adjusted any use of antibiotics (yes or no) to investigate the effects of other medications that may have major influence on gut microbiota. Antibiotic use could also be considered as a surrogate indicator for infections that might be linked with RA. Forth, we used different methods for missing data (multiple imputation and complete case analysis). Six, to investigate potential time-varying confounding in the primary model, we analyzed the association with marginal structural model.[27, 28] Last, to reduce the variability of underlying diseases requiring PPIs therapy, we restricted the analysis in women with gastroesophageal reflux disease, which is the most common indication for PPIs. We performed the analyses using SAS software, version 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

This study included 173 241 women from NHS (n = 78 327) and NHS II (n = 94 914) (Figure 1). Compared with participants who did not use PPIs, regular users tended to be less physically active, had a higher BMI and rate of hypertension, hypercholesterolemia, diabetes,

gastric or duodenal ulcer, gastroesophageal reflux disease, and were more likely to use NSAIDs and steroids (Table 1). Some of these factors, such as BMI and physical activity, were known risk factors for RA. Whether other RA risk factors, such as infection history, were balanced between groups is unclear and we could not adjust in multivariable analysis, because these data were not available.

Over 1 753 879 person-years of follow-up, we observed 421 cases of RA (NHS: 202, NHS II: 219). Of which, 275 were seropositive RA and 146 were seronegative RA. The absolute risk of all RA among PPI regular users of was 0.41 events per 1000 person-years, compared with 0.21 events per 1000 person years among non-regular users. After adjustment for potential confounders and lagging PPI use for 2 years, regular PPI user was associated with 44% increased risk of all RA as compared with non-regular users (HR=1.44; 95%CI, 1.10 to 1.89) (Table 2). We also observed a association between regular PPI use and seropositive RA (HR=1.50; 95%CI, 1.07 to 2.11). For seronegative RA, there was no sufficient evidence of increased risk in PPI users (HR=1.34; 95%CI, 0.86 to 2.10) after adjusting for confounders.

We observed that the risk of all RA increased with the duration of regular PPI use (*P*-trend = 0.008) (Table 3). Compared with non-regular users, the fully adjusted HRs of all RA were 1.22 (95%CI, 0.93 to 1.62) for women with >0 to 4 years' use of PPIs, and 1.73 (95%CI, 1.14 to 2.61) for women with > 4 years' use. We observed similar results in the multivariable analyses for seropositive RA (*P*-trend =0.008). When compared with current PPI users, the individuals stopping PPIs for > 0 to 2 years (HR=0.59; 95%CI, 0.37 to 0.95) and for > 2 years (HR=0.70; 95%CI, 0.53 to 0.94) had lower risk of all RA (Table 4).

In the analysis for H2RA with same method for PPIs, we did not find sufficient evidence of associations between regular H2RA use and risk of all RA (HR=0.75; 95%CI, 0.48 to 1.16), seropositive RA (HR=0.71; 95%CI, 0.40 to 1.25), and seronegative RA (HR=0.83; 95%CI, 0.42 to 1.66) (see supplementary table S1). We also observed no associations between both duration of H2RA use, time stopping H2RAs with RA risk (supplementary table S2&S3). In the falsification analyses for implausible associations, regular PPI use, as expected, was not associated with increased risk of squamous cell skin cancer (HR=0.99; 95%CI, 0.85 to 1.15), basal cell skin cancer (adjusted HR=1.15; 95%CI, 0.77 to 2.15), and cervical cancer (HR=0.96; 95%CI, 0.73to 1.26) (supplementary table S4).

In the subgroup analyses, we did not find sufficient evidence of interaction effects among pre-specified factors such as study (P=0.42) and age (P=0.33) (see supplementary table S5). In the sensitivity analysis by lagging the exposure for a time window of 4 years, we still observed an increased risk among regular PPI users (HR=1.47; 95%CI, 1.10 to 1.96) (see supplementary table S6). The results were generally unchanged in the sensitivity analyses by two-step pooling method, additionally adjusting for physical examination in the previous 2 years, and adjusting for use of antibiotics. When limited to analyses in women with gastroesophageal reflux disease, we observed an even stronger association (HR=1.52; 95%CI, 1.09 to 2.12).

DISCUSSION

In this prospective study of 173 241 women with over 1.7 million person-years of follow-up, we observed that regular PPI use was associated with increased risk of overall RA and

seropositive RA. Our results also showed that the risk of RA increased with the duration of PPI use, while stopping PPIs was associated with reduced risk as compared with current users. These associations were largely unchanged in a series of sensitivity analyses. By contrast, we did not observe an increased risk of RA among women who used H2RAs, which are less potent acid suppressors than PPI.

Our results were in line with a previous retrospective claims-based cohort study (26 436 PPI users and 28 054 non-users) from the U.S. [15] The primary objective of this study was to evaluate the association of PPI use with risk of community-acquired pneumonia. The risk of RA was evaluated in the falsification analyses and a positive association with PPI use was observed (PPI group: 85 cases/10,000 persons per year, control group: 68 cases /10,000 persons per year, $p < .001$).[15] The authors considered the association between PPI and RA was implausible and concluded that the observed associations between PPI use and community-acquired pneumonia may be confounded. RA might be used as implausible association in 2013 when this study was carried out, but the association is no longer implausible now. A lot of studies published after 2013 suggested PPIs have a major impact on gut microbiome, which in turn, may increase the risk of rheumatoid arthritis. [4, 5, 10]A comprehensive literature search did not identify any other epidemiological studies investigating this association.

The mechanisms underlying the observed association between PPIs use and RA remain unclear. A possible explanation is that gut microbiota may mediate their association. Strong evidence showed that PPIs could result in intestinal dysbiosis,[4, 5] while intestinal dysbiosis has been linked with autoimmune mechanisms which are involved in the development of RA.[10, 11]

Certain bacteria, such as *Escherichia coli,* maybe involved in the disease process of RA. In a combined analysis of three cohorts of 1815 adult individuals, PPI users showed a significant increase in the abundance of pathogenic species *Escherichia coli.* [4] In a cohort of 246 patients, IgM antibodies to *Escherichia coli* were associated with early RF+ rheumatoid arthritis, suggesting *Escherichia coli* alteration appear to be an early event in the disease course of seropositive RA.[29] Further investigation suggested that RF+ patients were more commonly colonized with phylogenetic Group D *Escherichia coli*, whereas RF− patients were more commonly colonized with phylogenetic Group B2 *Escherichia coli*.[30] How the *Escherichia coli* infection or the antibodies, or both, contribute to the disease process of RA is still unresolved. Furthermore, PPIs may increase RA risk through hampering the transforming growth factor beta (TGF-β) function by alkalization of PH.[31, 32] Increased TGF-β function is one of the key ways to restore joint homeostasis in RA.[33, 34] Future research is still required to investigate the underlying mechanisms.

We analyzed H2RAs with the same methods as PPIs, because H2RAs have similar applications in clinical practice but are much less potent than PPI in terms of gastric acid suppression. Such analysis would be helpful to reduce unmeasured factors that may confound the causal relationship (such as protopathic bias and imbalance in the underlying diseases for acid suppressants use). Our finding that only PPIs were associated with increased RA risk suggested that PPIs may increase RA risk through their effects on gastric acid secretion. This was in line with previous study finding that PPIs were associated with greater risk of *Salmonella, Campylobacter,* and other enteric infections than H2RAs.[35] However, the results should be interpreted with caution because 1) the estimated HRs were not precise as the

number of cases was small in regular H2RA users; 2) such analysis provided additional evidence, but was unable to prove the casual relationship between PPI use and RA.

One concern with our findings could be that the positive association between PPI use and RA was due to reverse causation whereby subclinical RA symptoms may be related to PPI use. In the primary analysis, we lagged the exposure for a time window of two years, allowing the participants with subclinical RA symptoms to progress and be diagnosed with RA. Additional lagging exposure for even longer time showed similar results. In addition, we excluded individuals with RA confirmed by rheumatologists as well as those with self-reported RA. Self-reported RA in this setting has been shown to lack specificity and included participants with subclinical RA symptoms but did not fulfill the RA classification criteria. Last, H2RAs may also be related to subclinical symptoms in the same way as PPIs, but no increased risk was observed in H2RA users. Another concern in pharmacoepidemiological studies is immortal time bias, however, the risk is low in our study since PPI use was determined before the start of follow-up.[36] In addition, the association between PPI and RA maybe interacted by NSAIDs as these two medicines are often prescribed together. In this study, the crude risk ratios of RA by PPI use were similar between regular NSAID users and non-NSAID users (supplementary table S7). Subgroup analysis by NSAIDs also showed no interaction effect (P=0.87).

Strengths and limitations of this study

One of our strengths is that this study was based on two well-established prospective cohorts with large sample sizes and over 12 years of follow-up. Data on exposures and most

covariates data were collected with biennial questionnaires and potential time-varying effects were adjusted. The participants were nurses who were able to provide complete and accurate health information. Additionally, we comprehensively controlled for established RA risk factors, which minimized potential confounding effects. Last, robust sensitivity analyses and the clear dose-response relationship additionally increased our confidence in the results.

This study has limitations. First, as an observational study, this study could not confirm the causal-relationship between PPI use and RA risk. Despite our careful adjustment for potential confounders, residual confounding effects may still exist. Genetic factors, such as major histocompatibility complex (MHC) gene, may confound the effect but we were unable to fully control the influence as these data were not collected. However, we controlled family history of RA and the results were not changed. Second, we did not collect detailed PPI usage data, including dosage, frequency, duration, type or brand, and the reasons for using PPIs, so more specified evaluation of the effects for PPI could not be performed. Third, the association between PPI use and RA may be confounded by the indications for using PPI. In this study, regression analyses adjusting for common indications (gastroesophageal reflux disease, gastric or duodenal ulcer) showed almost no change in the estimated effect. Analyses limiting the participants in women with gastroesophageal reflux disease indicated an even stronger association. Fourth, all the included participant were female nurses who may have different characteristics as general population, such as gender, education, income, and lifestyles. Our findings may not be generalizable to general population. The subgroup analyses by age, BMI, family history of RA, menopausal status, breastfeeding time, and smoking did not found sufficient evidence of effect modification. Fifth, the number of cases may not be enough for

seronegative RA and subgroup analyses. However these analyses were not for the primary objective of this study, and would not influence our conclusion. The number of cases were small so the confidence intervals were wide, which might not be able to provide precise estimates of effects. Sixth, for the lagged analysis, we cannot determine the most appropriate lagging time based on solid evidence as current research about PPI use and RA risk is sparse. In the primary analysis, we lagged the exposure for 2 years, which was widely used in other NHS analyses. Additionally lagging exposure for 4 years showed similar results. Last, pharmacoepidemiologic research based on Nurses Health Studies are also limited by left truncation, interval data, and reliance on self-report.

Conclusions

Overall, this prospective cohort study indicated that regular use of PPI was associated with increased risk of RA, with a higher risk observed in individuals with a longer duration of use. As PPIs have been linked with other health problems, such as fractures and gastric cancer,[2, 3] our study once again suggested the importance of carefully evaluating the need for long term, continuous use of PPIs. Further research is required to confirm our findings as well as to investigate the underlying mechanisms.

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AUTHORSHIP

Guarantor of the article: Yihang Pan

Author contributions: JQY and YHP had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; Concept and design: JQY, CHZ, and YLH; Statistical analysis: JQY, JS, and SM; Drafting of the manuscript: JQY, and CHZ; Critical revision of the manuscript for important intellectual content: All authors; Obtained funding: JQY; Administrative, technical, or material support: YHP, and YLH. Supervision: YHP, and YLH. All authors read and approved the final version of the manuscript.

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STATEMENT OF INTERESTS

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SUPPORTING INFORMATION

Additional Supporting Information is available online.

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TABLES

Table 1. Age-adjusted baseline characteristics according to use of proton pump inhibitors in the Nurses' Health Study and the Nurses' Health Study II

	Nurses' Health Study		Nurses' Health Study II	
	Non-regular PPI user	**Regular PPI user**	**Non-regular PPI user**	**Regular PPI user**
Number of participants	74 177	4 150	90 376	4 538
Mean (SD) age, years	67.9(7.0)	68.4(7.1)	48.8 (4.6)	49.7 (4.4)
White, %	97	98	96	97
Family history of rheumatoid arthritis, %	6	8	8	9
Mean (SD) body mass index, kg/m^2	26.7 (5.3)	28.4 (5.7)	26.7 (6.2)	29.8 (7.5)
Median (IQR) breastfeeding time, months	3 (4)	2 (4)	6 (4)	5 (4)
Derived parity, %				
nulliparity	5	6	18	20
1-2 children	37	38	54	57
≥3 children	58	56	28	23
Menopausal status and postmenopausal hormone use				
Premenopausal,%	0	0	55	45
Postmenopausal and never use,%	22	16	8	6
Postmenopausal and past use,%	31	34	5	7
Postmenopausal and current use,%	33	39	20	32
Never smoker, %	71	69	74	72
Median (IQR) days of alcohol drink per week	1 (4)	1 (3)	1 (2)	0 (2)
Mean (SD) physical activity time, MET-hours/week				
<9 MET-hours/week, %	38	54	33	51
9.1 - 27 MET-hours/week, %	44	30	45	31
>27 MET-hours/week, %	18	15	22	18
Mean (SD) Alternate Health Eating Index	56.4 (12.0)	55.1 (11.6)	54.7 (13.2)	52.5 (13.1)
Hypertension, %	41	54	16	29
Hypercholesterolemia, %	41	54	19	33
Diabetes, %	7	10	3	7
Cancer, %	9	10	6	7
Gastroesophageal reflux disease, %	27	80	25	77
Gastric or duodenal ulcer,%	2	11	1	6
Regular use of NSAIDs (including aspirin), %	65	78	50	66
Regular use of steroids, %	2	4	1	4
Any use of antibiotics, %	86	92	87	93

Abbreviations: SD, standard deviation; IQR, interquartile range; MET, metabolic equivalent; NSAIDs, Non-Steroid Anti-Inflammatory Drugs

Table 2. Risk of rheumatoid arthritis according to regular use of proton pump inhibitors

	All rheumatoid arthritis		Seropositive rheumatoid arthritis		Seronegative rheumatoid arthritis	
	Non-regular user	Regular PPI user	Non-regular user	Regular PPI user	Non-regular user	Regular PPI user
No of cases/ Person-years	335/1 544 858	86/209 021	221/1 544 986	54/209 048	114/1 545 052	32/209 068
Hazard Ratio [95% Confidence Interval]						
Age, period, and study-stratified model	1.00	1.87 [1.47, 2.39]	1.00	1.77 [1.30, 2.40]	1.00	2.08 [1.38, 3.12]
Multivariable adjusted model 1†	1.00	1.59 [1.24, 2.04]	1.00	1.55 [1.14, 2.12]	1.00	1.68 [1.11, 2.54]
Multivariable adjusted model 2‡	1.00	1.45 [1.11, 1.89]	1.00	1.51 [1.08, 2.12]	1.00	1.35 [0.86, 2.11]
Multivariable adjusted model 3¶	1.00	1.44 [1.10, 1.89]	1.00	1.50 [1.07, 2.11]	1.00	1.34 [0.86, 2.10]

† Multivariable adjusted model 1: additionally adjusted for history of rheumatoid arthritis in a first-degree relative (yes, or no), BMI, menopausal status and postmenopausal hormone use (premenopausal, postmenopausal (never, past, current menopausal hormone use, or unknown), or missing), number of parity (0, 1-2, 3+ children), breastfeeding (no, 1-2 years, 2+ years, or missing), regularly use of NSAIDs (yes or no), steroids (yes or no), and regular use of H2RAs (yes or no).

‡ Multivariable adjusted model 2: additionally adjusted for race hypertension (yes or no), diabetes (yes or no), hypercholesterolemia (yes or no), cancer (yes or no), gastroesophageal reflux disease(yes or no), gastric or duodenal ulcer (yes or no).

¶ Multivariable adjusted model 3: additionally adjusted for pack of cigarettes per years (0, 10-20, 20+, missing), days with alcohol drinking per week (0, 1-3, over 3days), physical activity (<9, 9.1- 27, or >27 MET-h/week), overall diet quality (AHEI score <30, 30.1-60, or >60)

Table 3. Risk of rheumatoid arthritis according to the duration of use of proton pump inhibitors

	Cases/Person-years	Hazard Ratio [95% Cl]	*P*-trend
All rheumatoid arthritis			
Non-regular user	311/1 443 450	1.00	
>0 to 4 years	76/238 172	1.22 [0.93, 1.62]	0.008
>4 years	34/72 258	1.73 [1.14, 2.61]	
Seropositive Rheumatoid arthritis			
Non-regular user	206/1 443 567		
>0 to 4 years	46/238 202	1.22 [0.86, 1.74]	0.008
>4 years	23/72 266	2.06 [1.24, 3.42]	
Seronegative rheumatoid arthritis			
Non-regular user	105/1 443 630		
>0 to 4 years	30/238 211	1.22 [0.77, 1.92]	0.390
>4 years	11/72 279	1.30 [0.64, 2.64]	

Abbreviation: CI, Confidence Interval.
Estimated effects were based on the fully adjusted model (see the footnote in table 2).

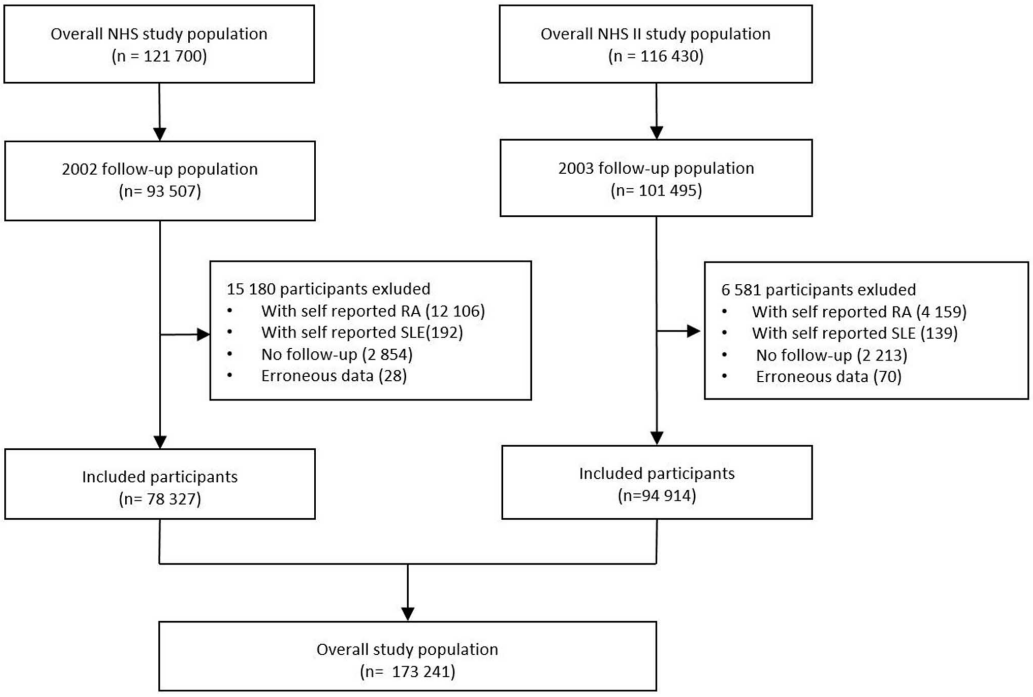
Table 4. Risk of rheumatoid arthritis according to time since stopping use of proton pump inhibitors

Time since stopping PPIs	Cases/Person-years	Hazard Ratio [95% CI]	*P*-trend
All rheumatoid arthritis			
Current user	86/209 021	1.00	
>0 to 2 years	88/381 602	0.59 [0.37, 0.95]	0.02
>2 years	247/1 163 256	0.70 [0.53, 0.94]	
Seropositive Rheumatoid arthritis			
Current user	54/209 048	1.00	
>0 to 2 years	53/381 644	0.53 [0.29, 0.99]	0.04
>2 years	168/1 163 342	0.69 [0.48, 0.98]	
Seronegative rheumatoid arthritis			
Current user	32/209 068	1.00	
>0 to 2 years	35/381 644	0.70 [0.34, 1.46]	0.25
>2 years	79/1 163 407	0.73 [0.45, 1.18]	

Abbreviation: CI, Confidence Interval.
Estimated effects were based on the fully adjusted model (see the footnote in table 2).

FIGURES

Figure 1. Flowchart of participant selection.



Supporting Information

Table S1. Risk of rheumatoid arthritis according to regular use of H2 receptor antagonists

	All rheumatoid arthritis		Seropositive rheumatoid arthritis		Seronegative rheumatoid arthritis	
	Non-regular user	**Regular H2RA user**	**Non-regular user**	**Regular H2RA user**	**Non-regular user**	**Regular H2RA user**
No of cases/ Person-years	399/1 659 568	22/94 310	262/1 659 713	13/94 322	137/1 659 800	9/94 319
Hazard Ratio [95% Confidence Interval]						
Age, period, and study-stratified model	1.00	0.92 [0.60, 1.41]	1.00	0.82 [0.47, 1.44]	1.00	1.10 [0.56, 2.17]
Multivariable adjusted model 1†	1.00	0.81 [0.52, 1.24]	1.00	0.73 [0.42, 1.28]	1.00	0.97 [0.49, 1.91]
Multivariable adjusted model 2‡	1.00	0.75 [0.48, 1.16]	1.00	0.71 [0.40, 1.25]	1.00	0.83 [0.42, 1.66]
Multivariable adjusted model 3¶	1.00	0.75 [0.48, 1.16]	1.00	0.71 [0.40, 1.25]	1.00	0.83 [0.42, 1.66]

† Multivariable adjusted model 1: additionally adjusted for race (white, or non-white), history of rheumatoid arthritis in a first-degree relative (yes, or no), BMI, menopausal status and postmenopausal hormone use (premenopausal, postmenopausal (never, past, current menopausal hormone use, or unknown), or missing), number of parity (0, 1-2, 3+ children), breastfeeding (no, 1-2 years, 2+ years, or missing), gastroesophageal reflux disease(yes or no), regularly use of NSAIDs (yes or no), steroids (yes or no), regular use of PPIs (yes or no).

‡ Multivariable adjusted model 2: additionally adjusted for race hypertension (yes or no), diabetes (yes or no), hypercholesterolemia (yes or no), cancer (yes or no), gastric or duodenal ulcer(yes or no).

¶ Multivariable adjusted model 3: additionally adjusted for pack of cigarettes per years (0, 10-20, 20+, missing), days with alcohol drinking per week (0, 1-3, over 3days), physical activity (<9, 9.1-27, or >27 MET-h/week), overall diet quality (AHEI score <30, 30.1-60, or >60).

Table S2. Risk of rheumatoid arthritis according to the duration of regular use of H2 receptor antagonists

Duration of regular H2 receptor antagonist use	Cases/Person-years	Hazard Ratio [95% CI]	*P*-trend
All rheumatoid arthritis			
Non-regular user	359/1 554 472	1.00	
1 to 4 years	55/175 499	1.02 [0.75, 1.38]	0.84
>4 years	7/23 908	0.85 [0.39, 1.83]	
Seropositive Rheumatoid arthritis			
Non-regular user	236/1 554 601	1.00	
1 to 4 years	37/175 519	1.10 [0.75, 1.60]	0.64
>4 years	2/23 914	0.39 [0.10, 1.61]	
Seronegative rheumatoid arthritis			
Non-regular user	123/1 554 684	1.00	
1 to 4 years	18/175 526	0.89 [0.53, 1.52]	0.74
>4 years	5/23 909	1.61 [0.63, 4.16]	

Abbreviation: CI, Confidence Interval.
Estimated effects were based on the fully adjusted model (see the footnote in supplemental table 1).

Table S3. Risk of rheumatoid arthritis according to time since stopping use of H2 receptor antagonists

Time since stopping H2 receptor antagonists	Cases/Person-years	Hazard Ratio [95% CI]	*P*-trend
All rheumatoid arthritis			
Current user	24/95 691	1.00	0.10
>0 to 2 years	90/372 424	0.89 [0.50, 1.58]	
>2 years	307/1 285 764	1.40 [0.89, 2.21]	
Seropositive Rheumatoid arthritis			
Current user	14/95 705	1.00	0.19
>0 to 2 years	57/372 465	1.10 [0.53, 2.31]	
>2 years	204/1 285 866	1.42 [0.79, 2.53]	
Seronegative rheumatoid arthritis			
Current user	10/95 700	1.00	0.36
>0 to 2 years	33/372 470	0.67 [0.27, 1.61]	
>2 years	103/1 285 948	1.38 [0.65, 2.92]	

Abbreviation: CI, Confidence Interval.

Estimated effects were based on the fully adjusted model (see the footnote in supplemental table 1).

Table S4. Falsification analysis of PPI use and risk of squamous cell skin cancer, basal cell skin cancer, and cervical cancer.

	Squamous cell skin cancer		Basal cell skin cancer		Cervical cancer	
	Non-regular user	Regular H2RA user	Non-regular user	Regular H2RA user	Non-regular user	Regular H2RA user
No of cases/ Person-years	1525/1385508	231/187819	204/1306331	19/174841	461/1434462	74/196764
Hazard Ratio [95% Confidence Interval]						
Age, period, and study-stratified model	1.00	1.06[0.92, 1.22]	1.00	1.24[0.77, 2.00]	1.00	1.10[0.85, 1.41]
Multivariable adjusted model 1†	1.00	1.06[0.92, 1.23]	1.00	1.22[0.75, 1.98]	1.00	1.05[0.81, 1.35]
Multivariable adjusted model 2‡	1.00	0.97[0.84, 1.13]	1.00	1.31[0.78, 2.18]	1.00	0.97[0.74, 1.28]
Multivariable adjusted model 3¶	1.00	0.99[0.85, 1.15]	1.00	1.29[0.77, 2.15]	1.00	0.96[0.73, 1.26]

† Multivariable adjusted model 1: additionally adjusted for history of rheumatoid arthritis in a first-degree relative (yes, or no), BMI, menopausal status and postmenopausal hormone use (premenopausal, postmenopausal (never, past, current menopausal hormone use, or unknown), or missing), number of parity (0, 1-2, 3+ children), breastfeeding (no, 1-2 years, 2+ years, or missing), regularly use of NSAIDs (yes or no), steroids (yes or no), and regular use of H2RAs (yes or no).

‡ Multivariable adjusted model 2: additionally adjusted for race hypertension (yes or no), diabetes (yes or no), hypercholesterolemia (yes or no), gastroesophageal reflux disease(yes or no), gastric or duodenal ulcer (yes or no).

¶ Multivariable adjusted model 3: additionally adjusted for pack of cigarettes per years (0, 10-20, 20+, missing), days with alcohol drinking per week (0, 1-3, over 3days), physical activity (<9, 9.1- 27, or >27 MET-h/week), overall diet quality (AHEI score <30, 30.1-60, or >60)

Table S5. Subgroup analyses of regular use of proton pump inhibitors and risk of all rheumatoid arthritis

	Cases/ Person-years	Hazard Ratio [95% CI]		*P*-interaction
		Non-regular user	Regular PPI user	
Cohort				
Nurses' Health Study	202/771 104	1.00	1.24 [0.84, 1.83]	0.42
Nurses' Health Study II	219/982 775	1.00	1.78 [1.22, 2.59]	
Age				
< 55 years	120/579 973	1.00	1.17 [0.65, 2.11]	0.33
55 to < 75 years	245/912 137	1.00	1.58 [1.12, 2.21]	
≥ 75 years	56/261 769	1.00	1.65 [0.83, 3.28]	
Family history of rheumatoid arthritis				
Yes	352/1 611 170	1.00	1.38 [1.03, 1.85]	0.96
No	69/142 709	1.00	2.23 [1.07, 4.64]	
Body mass index				
< 30 kg/m^2	291/1 325 218	1.00	1.57 [1.13, 2.19]	0.15
≥ 30 kg/m^2	130/428 661	1.00	1.31 [0.82, 2.09]	
Never smoker				
Yes	310/1 259 887	1.00	1.43 [1.04, 1.96]	0.97
No	111/493 992	1.00	1.50 [0.88, 2.55]	
Menopausal status				
Premenopausal	65/359 208	1.00	1.70 [0.78, 3.70]	0.55
Postmenopausal	347/1 349 726	1.00	1.45 [1.09, 1.95]	
Breastfeeding				
<1 year	251/980 908	1.00	1.50 [1.07, 2.11]	0.83
≥1 year	136/595 034	1.00	1.55 [0.95, 2.53]	
NSAIDs use				
Yes	355/466 397	1.00	1.53[1.15, 2.04]	0.87
No	66/1 287 481	1.00	1.29[0.48, 3.50]	

Abbreviation: CI, Confidence Interval.
Estimated effects were based on the fully adjusted model (see footnote in table 2).

Table S6. Sensitivity analyses of proton pump inhibitors the risk of all rheumatoid arthritis

	No of cases/ Person-years	Non-regular user	Regular PPI user
Lagging the exposure for 4 years and allow a time window for rheumatoid arthritis risk.			
Hazard Ratio [95% Confidence Interval]	337/1425806	1.00	1.47 [1.10, 1.96]
Pooling the effect with effect of NHS and NHS II with a two-step method			
Hazard Ratio [95% Confidence Interval]	421/1753879	1.00	1.49 [1.04, 2.13]
Additionally adjusting for physical examination in the previous 2 years (yes or no)			
Hazard Ratio [95% Confidence Interval]	421/1753879	1.00	1.44 [1.10, 1.89]
Additionally adjusting for any use of antibiotics (yes or no)			
Hazard Ratio [95% Confidence Interval]	421/1753879	1.00	1.44 [1.09, 1.88]
Multiple imputation for missing covariate data			
Hazard Ratio [95% Confidence Interval]	421/1753879	1.00	1.45 [1.10, 1.90]
Complete case analysis			
Hazard Ratio [95% Confidence Interval]	363/1534588	1.00	1.47 [1.10, 1.95]
Marginal structural models			
Hazard Ratio [95% Confidence Interval]	421/1753879	1.00	1.40 [1.06, 1.83]
Limiting the participants in in women with gastroesophageal reflux disease			
Hazard Ratio [95% Confidence Interval]	168/514512	1.00	1.52 [1.09, 2.12]

Estimated effects were based on the fully adjusted model (see the footnote in supplemental table 1).

Table S7. The case and participant numbers by PPI and NSAID use.

	NSAID+		NSAID-	
	PPI+	**PPI-**	**PPI+**	**PPI-**
N	6247	93932	2441	70621
Case	78	277	8	58
%	1.249%	0.295%	0.328%	0.082%
Risk Ratio	4.23		3.99	

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
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	7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) If applicable, explain how loss to follow-up was addressed	8-9
		(*e*) Describe any sensitivity analyses	8-9
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	10
		(b) Give reasons for non-participation at each stage	figure 1
		(c) Consider use of a flow diagram	figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	table 2-4
Outcome data	15*	Report numbers of outcome events or summary measures over time	table 2-4
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	table 2-4
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

1

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
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	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
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	17-18

*Give information separately for exposed and unexposed groups.

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 http://www.strobe-statement.org.