






Regular use of proton pump inhibitors and risk of type 2 diabetes: results from three prospective cohort studies

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Received 16 July 2020
Revised 6 August 2020
Accepted 9 August 2020
Published Online First
28 September 2020

ABSTRACT

Objective The association between the regular use of proton pump inhibitors (PPIs) and the risk of type 2 diabetes remains unclear, although a recent randomised controlled trial showed a trend towards increased risk. This study was undertaken to evaluate the regular use of PPIs and risk of type 2 diabetes.

Method This is a prospective analysis of 204 689 participants free of diabetes in the Nurses' Health Study (NHS), NHS II and Health Professionals Follow-up Study (HPFS). Type 2 diabetes was confirmed using American Diabetes Association (ADA) diagnostic criteria. We evaluated hazard ratios (HRs) adjusting for demographic factors, lifestyle habits, the presence of comorbidities, use of other medications and clinical indications.

Results We documented 10 105 incident cases of diabetes over 2 127 471 person-years of follow-up. Regular PPI users had a 24% higher risk of diabetes than non-users (HR 1.24, 95% CI 1.17 to 1.31). The risk of diabetes increased with duration of PPI use. Fully adjusted HRs were 1.05 (95% CI 0.93 to 1.19) for participants who used PPIs for >0–2 years and 1.26 (95% CI 1.18 to 1.35) for participants who used PPIs for >2 years compared with non-users.

Conclusions Regular use of PPIs was associated with a higher risk of type 2 diabetes and the risk increased with longer duration of use. Physicians should therefore exercise caution when prescribing PPIs, particularly for long-term use.

Significance of this study

What is already known about this subject?

- ▶ Despite the irreplaceable role of proton pump inhibitors (PPIs) in clinical practice, long-term use of PPIs has been linked to a series of health problems such as bone fracture and enteric infections.
- ▶ PPIs have a major impact on gut microbiome which, in turn, may increase the risk of type 2 diabetes, but epidemiological evidence remains unclear.

What are the new findings?

- ▶ In this prospective analysis of 204 689 participants free of diabetes from three ongoing US cohorts, regular use of PPIs was associated with a 24% increased risk of diabetes even after adjusting for putative risk factors and indications for use, with a higher risk observed in individuals with a longer duration of PPI use.

How might it impact on clinical practice in the foreseeable future?

- ▶ Physicians should be aware of the potential risk of type 2 diabetes when prescribing PPIs, particularly for long-term treatment.
- ▶ Screening for abnormal blood glucose and type 2 diabetes may be required for regular PPI users, particularly for high-risk populations.

INTRODUCTION

Proton pump inhibitors (PPIs) are among the top 10 most commonly used medications worldwide.¹ PPIs are routinely recommended for acid-related disorders such as gastro-oesophageal reflux disease, peptic ulcer disease and non-ulcer dyspepsia.² It is generally accepted that short-term use of PPIs for valid indications is safe. However, long-term use of PPIs has been linked to various adverse effects such as bone fractures, chronic kidney disease, enteric infections and gastric cancer.^{2–5} Recent studies have shown that PPIs can affect gut microbial communities by shifting the native gastrointestinal tract milieu.^{6,7} At 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 overuse of PPIs and calls for further investigation into the sequelae of long-term PPI consumption.⁶

Type 2 diabetes has become a global epidemic with a worldwide prevalence of 8.5% in 2014.⁸ The aetiology of type 2 diabetes is complex, involving multiple genetic, behavioural and environmental factors.⁹ In recent years, researchers have turned their attention to the role of human gut microbiota, which is essential for expanding the repertoire of host metabolic processes, in the development of diabetes.^{10–11} Accumulating studies support a causal role for alterations in the gut microbiota in the pathogenesis of metabolic diseases.^{12–13}

Given the pronounced effect of PPIs on the gut microbiome, its use may be associated with an



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To cite: Yuan J, He Q, Nguyen LH, et al. *Gut* 2021;**70**:1070–1077.

increased risk of type 2 diabetes. Nevertheless, the epidemiological evidence remains unclear. In previous observational studies^{4 14} the prevalence of diabetes in PPI users was much higher than in non-users. A recent randomised controlled trial including over 17 000 participants found that PPIs were likely to have a modest, although not statistically significant, increased risk of diabetes compared with placebo (OR 1.15; 95% CI 0.89 to 1.50).¹⁵ Despite the large sample size and rigorous protocol, this trial was limited by a short follow-up time and insufficient statistical power.^{16 17} A secondary analysis based on the observed frequency of diabetes suggested that the smallest OR that could be detected in the trial was 1.20.¹⁵

Given the widespread use of PPIs and the high prevalence of diabetes, investigation of their association could have a major impact on clinical and public health practice. We therefore conducted this prospective study to evaluate the association between PPI use and the subsequent risk of type 2 diabetes based on the Nurses' Health Study (NHS), NHS II and Health Professionals Follow-up Study (HPFS) datasets.

METHODS

Study population

The NHS, NHS II and HPFS are three large ongoing prospective cohorts of health professionals in the USA. The NHS enrolled 121 700 female nurses aged 30–55 years in 1976, NHS II included 116 430 younger female registered nurses aged 25–42 years in 1989 and HPFS, established in 1986, included 51 529 male healthcare professionals (dentists, pharmacists, optometrists, osteopath physicians, podiatrists, veterinarians) aged 40–75 years. At baseline and every 2 years thereafter, the participants updated information on their demographic details, health-related behaviours, medical history and newly diagnosed diseases, with a response rate of over 90% in each questionnaire cycle. The recruitment and data collection in the three cohorts have been reported in detail elsewhere.^{18–20} In the current analysis we included participants who reported information about our exposure of interest (PPI usage) and excluded those with a self-report of diabetes. The NHS, NHS II were approved by the Human Research Committee at the Brigham and Women's Hospital, and the HPFS was approved by the Human Subjects Committee by the Harvard T H Chan School of Public Health, Boston, Massachusetts, USA. The return of the questionnaires was considered implied consent. The end of follow-up was 2014 for NHS, 2017 for NHS II and 2016 for HPFS when the latest ascertainment of diabetes was performed.

Assessment of PPI use

Beginning in the year 2000 for the NHS, 2001 for NHS II and 2004 for the HPFS and for every subsequent 2-year period thereafter, participants were asked whether they had used PPIs regularly in the past 2 years. The questionnaires provided examples of brand names for reference. 'Regular use' for medications was routinely defined as '2+ times/week'. We did not specifically collect the data about the dose, brand or type of PPIs and schedule of medication intake. The detailed questions regarding PPI use can be found elsewhere.²¹

Ascertainment of type 2 diabetes

The participants were asked if they had ever been diagnosed with diabetes on biennial questionnaires. To confirm the diagnosis, we mailed a supplementary questionnaire to the participants reporting physician-diagnosed type 2 diabetes to collect detailed data about the date of diagnosis, symptoms, diagnostic tests

and hypoglycaemic agents. Confirmed diabetes should meet at least one of the following criteria in accordance with the American Diabetes Association diagnostic criteria: (1) one or more classic symptoms (excessive thirst, polyuria, weight loss, hunger, pruritus or coma) plus fasting plasma glucose (PG) 126 mg/dL (7.0 mmol/L) or random PG 200 mg/dL (11.1 mmol/L); (2) at least two elevated PG levels on different occasions (fasting PG 140 mg/dL and/or random PG 200 mg/dL and/or PG 200 mg/dL at 2 hours on oral glucose tolerance testing) in the absence of symptoms; or (3) treatment with hypoglycaemic medication (insulin or oral hypoglycaemic agent). The validity of self-reported type 2 diabetes diagnosis has been confirmed through medical record reviews in two separate studies, which showed a correct rate of over 97%.^{22 23}

Assessment of covariates

In the biennial questionnaires we obtained updated information on age, ethnicity, family history of diabetes, body weight, smoking habits, alcohol drinking, multivitamin use, menopausal status and postmenopausal hormone use, parity, breastfeeding, concomitant comorbidities (hypertension, hypercholesterolaemia, cancer, gastric or duodenal ulcer, gastro-oesophageal reflux disease and upper gastrointestinal tract bleeding) and drugs (H2 receptor antagonists (H2RAs), non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and steroids). Overall diet quality was evaluated by the 2010 Alternative Healthy Eating Index (AHEI-2010). We assessed the physical activity by weekly expenditure of metabolic equivalents (METs), which has been validated in a previous study.²⁴

Patient and public involvement

No patients were involved in setting the research question or outcome measures, or in the design and implementation of the study.

Statistical analysis

We calculated follow-up time in person-years from the date of return of the baseline questionnaire to the date of diagnosis of type 2 diabetes, death, loss to follow-up or the end of follow-up, whichever came first. The baseline was 2002 for NHS, 2003 for NHS II and 2006 for HPFS. We estimated the HR of PPI use on diabetes with a multivariable time-dependent Cox proportional hazards model accounting for potential time-varying effects in the exposure and covariates. In time-varying Cox regression, the exposure and covariates in each circle were linked to the events that identified in the next circle. The estimates of each circle were combined to get the overall results. We tested the proportional hazards assumption by evaluating interactions between age and main exposures in time-varying Cox regression models. To address potential reverse causation where symptoms of subclinical diabetes may be related to PPI use, we lagged the exposure for one biennial survey cycle. In the lagged analysis we set a 2-year interval between the time of exposure and outcome assessment, which could strengthen the temporality and allow a time window for diabetes risk development. To present any possible association in a clinically translatable way, we calculated the number needed to harm (NNH) based on a previously described method.²⁵ We performed the analysis separately in each cohort and combined the estimates with inverse variance-weighted, random effect meta-analyses. We tested the heterogeneity in the meta-analyses using the Cochrane Q statistic and the I² statistic.

In the basic model we stratified the analyses jointly by age (in months) and the year that the questionnaire was returned. In the multivariable-adjusted model 1, we adjusted for race, family history of diabetes, body mass index (BMI), number of pack-years of smoking, alcohol intake per day, physical activity, overall diet quality, total calorie intake, multivitamin use, history of hypertension, hypercholesterolaemia, cancer, menopausal status and postmenopausal hormone use in women, number of parity in women, breastfeeding in women, any use of antibiotics, regular NSAID use and any use of steroids. To address the possible confounding effect of clinical indications for PPI use, we additionally controlled for gastro-oesophageal reflux disease, gastric or duodenal ulcer, upper gastrointestinal tract bleeding and regular use of H2RAs in the multivariable-adjusted model 2.

To investigate potential effect modifiers, we conducted stratified analyses according to sex, age, BMI, family history of diabetes, smoking status, alcohol intake, dietary quality, physical activity, history of hypertension, hypercholesterolaemia and regular use of NSAIDs. Because PPIs and H2RAs have similar clinical indications, we evaluated the effects of regular use of H2RAs on subsequent diabetes risk with the same methods for the analysis of PPIs. We performed a number of sensitivity analyses to check the robustness of the primary results. First, we lagged the exposure for an even longer time (4 years). Second, to investigate the potential bias from healthcare utilisation (ie, the participants with better healthcare utilisation are likely to have better access to PPIs and a higher chance to be diagnosed if they had diabetes), we adjusted the physical examination in the previous 2 years (yes or no) and the number of commonly used medicines as surrogate indicators. Third, we directly estimated the effect of PPI use in all the participants including NHS, NHS II and HPFS instead of pooling the effect of NHS, NHS II and HPFS with a two-step method. Fourth, we additionally controlled statins, beta-blockers, thiazide diuretics and antipsychotics for potential influence. Last, to reduce the variability of underlying clinical indications for PPIs, we limited the analysis to participants with gastro-oesophageal reflux disease, and other major indications for PPIs (gastric or duodenal ulcer and upper gastrointestinal tract bleeding). To test the potential influence of unmeasured confounders, we calculated the E-value, which is defined as the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the treatment and the outcome to fully explain away a specific treatment–outcome association, conditional on the measured covariates.²⁶ A large E-value suggested that considerable unmeasured confounding would be needed to explain away an effect estimate. We performed the analyses using SAS software, Version 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

This study included 176 050 women from NHS (n=80 500) and NHS II (n=95 550), and 28 639 men from HPFS (see flowchart of participant selection in online supplementary figure S1). At baseline, regular PPI users (n=13 528) tended to be less physically active, had a higher rate of hypertension and hypercholesterolaemia, and were more likely to use NSAIDs and steroids than non-PPI users (n=191 161, table 1). As expected, PPI users had considerably higher rates of gastric or duodenal ulcer, gastro-oesophageal reflux disease and upper gastrointestinal tract bleeding.

Over a total of 2 127 471 person-years of follow-up (median follow-up time 12 years in NHS and NHS II, 9.8 years in HPFS), we documented 10 105 incident diabetes diagnoses (4726 in

NHS, 4631 in NHS II and 748 in HPFS). The absolute risk of diabetes among regular PPI users was 7.44/1000 person-years compared with 4.32/1000 person-years among non-users (table 2). After lagging PPI use for 2 years and stratification by age and study period, regular PPI users had a 74% higher risk in diabetes compared with non-users (HR 1.74, 95% CI 1.37 to 2.20). This association was attenuated somewhat, but remained significant after multivariable adjustment for demographic factors, lifestyle habits, the presence of comorbidities, use of other medications and clinical indications for PPI use (HR 1.24, 95% CI 1.17 to 1.31). In our analysis of the individual cohorts we did not see a statistically significant effect in HPFS (HR 1.12, 95% CI 0.91 to 1.38), which may be due to the small number of cases. For ease of interpretation, we calculated NNHs based on the fully adjusted pooled HR and incidence rate of type 2 diabetes in non-PPI users (figure 1). Every 318.9 (95% CI 285.2 to 385.0), 170.8 (95% CI 209.7 to 150.8) and 77.3 (95% CI 97.0 to 66.8) regular PPI users may result in one case of diabetes over 1, 2 and 5 years, respectively.

The risk of diabetes was associated with the duration of PPI use (figure 2). Compared with non-users, the fully adjusted HRs were 1.05 (95% CI 0.93 to 1.19) for participants who used PPIs for >0–2 years and 1.26 (95% CI 1.18 to 1.35) for participants who used PPIs for >2 years. In addition, stopping PPI use was likely to be associated with a lower risk of diabetes. Compared with current PPI users, the adjusted HR was 0.83 (95% CI 0.70 to 0.98) for participants who stopped PPI use within 2 years and 0.81 (95% CI 0.76 to 0.86) for those who PPIs > 2 years (online supplementary table S1).

Given the shared clinical indications for PPIs and H2RAs, we also evaluated the effects of regular use of H2RAs on subsequent diabetes risk. Regular H2RA users also had a higher risk of diabetes (adjusted HR 1.14, 95% CI 1.07 to 1.23) (online supplementary table S2). In addition, longer duration of H2RA use was associated with a higher risk of diabetes, and longer time since stopping H2RAs was associated with a lower risk (online supplementary table S2). These results were consistent between H2RAs and PPIs, although the estimated effects among H2RA users were less profound.

In subgroup analyses, the estimates for risk of diabetes among PPI users did not differ by sex, age, family history of diabetes, smoking status, alcohol intake, dietary quality, physical activity, hyperlipidaemia and regular use of NSAIDs (figure 3). However, the risk of diabetes with PPI use seemed to be higher among participants with lower BMI or normal blood pressure (p-interactions <0.05). Our main results were robust in several sensitivity analyses by lagging the exposure for even 4 years, adjusting for physical examination in the previous 2 years as an additional covariate, and limiting our analysis only to participants with major indications for PPI. When we directly estimated PPI use and diabetes risk in all participants we observed an even stronger association (HR 1.32, 95% CI 1.25 to 1.39) (online supplementary table S3). In the analysis for unmeasured confounders, we obtained an E-value of 1.8 for the primary estimate and 1.6 for the lower confidence limit. As we have controlled for major confounders, there is unlikely to be an unmeasured confounder showing HRs with both PPI use and diabetes risk over 1.6.

DISCUSSION

In this analysis of three large prospective cohorts we found that regular PPI use was associated with a 24% higher risk of type 2 diabetes. The risk of diabetes was likely to increase with the duration of PPI use and to decrease with the time stopping PPIs.

Table 1 Age-adjusted baseline characteristics by use of PPIs in the Nurses' Health Study (NHS), the Nurses' Health Study II (NHS II) and the Health Professionals Follow-up Study (HPFS)

	NHS		NHS II		HPFS	
	Non-regular PPI user	Regular PPI user	Non-regular PPI user	Regular PPI user	Non-regular PPI user	Regular PPI user
No of participants	75 872	4628	90 816	4734	24 473	4166
Mean (SD) age, years	68.11 (7.07)	68.69 (7.11)	48.68 (4.64)	49.67 (4.44)	71.30 (8.63)	72.79 (8.59)
White race, %	97	98	96	97	91	92
Family history of diabetes, %	19	23	26	32	13	15
Mean (SD) body mass index, kg/m ²	26.36 (5.04)	27.82 (5.39)	26.51 (5.97)	29.35 (7.15)	25.08 (5.49)	25.68 (4.71)
Never smoker, %	71	69	74	72	72	70
Median (IQR) physical activity, MET hours/week	13.4 (31.3)	7.9 (17.5)	17.7 (42.6)	8.7 (19.6)	39.4 (70.5)	32.9 (59.5)
Median (IQR) alcohol intake per day, g	1.3 (6.5)	1.2 (3.6)	2.1 (3.4)	2.1 (3.2)	12.26 (14.56)	11.94 (14.73)
Mean (SD) total calories	1688 (496)	1693 (506)	1816 (471)	1823 (491)	2009 (568)	2002 (581)
Mean (SD) Alternate Health Eating Index	50.78 (10.6)	49.9 (10.6)	51.6 (10.3)	50.37 (10.49)	56.06 (10.07)	55.39 (10.25)
Median (IQR) breastfeeding time, months	3 (4)	2 (4)	6 (4)	5 (4)		
Parity						
Nulliparity, %	5	6	17	19	NA	NA
1–2 children, %	37	38	54	57	NA	NA
≥3 children, %	58	56	29	23	NA	NA
Menopausal status and postmenopausal hormone use						
Premenopausal, %	0.5	0.3	52	43	NA	NA
Postmenopausal and never use, %	21	15	8	6	NA	NA
Postmenopausal and past use, %	31	33	5	7	NA	NA
Postmenopausal and current use, %	33	39	21	32	NA	NA
Hypertension, %	38	51	14	26	36	45
Hypercholesterolaemia, %	38	52	17	29	34	42
Cancer, %	9	10	3	3	14	16
Gastro-oesophageal reflux disease, %	27	78	25	75	20	73
Gastric or duodenal ulcer, %	2	12	1	7	2	6
Upper gastrointestinal tract bleeding, %	2	4	0.5	2	2	4
Multivitamin use, %	59	63	57	59	62	71
Regular use of NSAIDs, %	65	76	49	64	61	69
Any use of antibiotics, %	84	89	86	91	61	63
Any use of statin drugs, %	19	31	5	13	33	45
Any use of steroids, %	2	6	1	5	1	2

HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent; NHS, Nurses' Health Study; NSAID, non-steroidal anti-inflammatory drug; PPIs, proton pump inhibitors.

The association was likely to be stronger among participants with lower BMI or normal blood pressure. Additional analyses showed that H2RAs, a less potent acid suppressor, was also associated with diabetes but the association was less marked, lending further biological plausibility to the interplay between acid suppression and the aetiopathogenesis of type 2 diabetes. These associations were independent of traditional diabetes risk factors as well as major clinical indications for PPI use.

Comparison with other studies

A number of studies have suggested that long-term use of PPIs is associated with various adverse effects such as pneumonia,¹⁴ fracture,²¹ chronic kidney disease²⁷ and gastric cancer.^{4,5} A retrospective cohort study including 388 098 patients showed that patients with upper gastrointestinal disease receiving PPIs had a 20% decreased risk of diabetes over a 5-year follow-up period.²⁸ However, many important confounders including smoking, alcohol drinking and BMI were not adjusted for in that study, leading to concerns about the validity of the findings.²⁸ A recent randomised controlled trial evaluated the safety of pantoprazole over a median follow-up of 3 years in 17 598 participants. When compared with placebo, pantoprazole was likely to have

a moderate although not statistically significant increased risk of diabetes (OR 1.15, 95% CI 0.89 to 1.50).¹⁵ This study is by far the largest trial evaluating the safety of PPIs; however, the statistical power remains insufficient with a minimum detectable OR of 1.20.¹⁵ The trial was also limited by a short follow-up time frame, potential selection bias and a number of conflicts of interests.^{16,17} The magnitude of the effect in this trial is smaller than our estimates (HR 1.24). An explanation for this difference is that 80% of the participants in the trial were male, who were likely to have a weaker association between PPIs and diabetes (estimated HRs in our study: men, 1.12; women, 1.26). Other possible explanations included different follow-up time, the presence of residual confounders and other biases inherent to observational studies.

PPIs may also lead to other medical conditions such as obesity,²⁹ metabolic syndrome³⁰ and chronic liver disease³¹ that are closely related to diabetes. A recent retrospective cohort study of 333 353 children indicated that the use of PPIs and H2RAs within the first 2 years of life was associated with childhood obesity.³² In adults with gastro-oesophageal reflux disease, long-term treatment with PPIs was associated with an increased risk in undesired weight gain.^{33,34} Also, in a cohort of 301 patients with

Table 2 Risk of type 2 diabetes according to regular use of proton pump inhibitors (PPIs)

		HR (95% CI)		
	Cases/person-years	Age and period-stratified model	Multivariable adjusted model 1 *	Multivariable adjusted model 2†
NHS				
Non-regular PPI user	3864/758043	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Regular PPI user	862/123249	1.63 (1.51 to 1.76)	1.27 (1.18 to 1.37)	1.22 (1.12 to 1.33)
NHS II				
Non-regular PPI user	3457/866393	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Regular PPI user	1174/135042	2.16 (2.01 to 2.33)	1.36 (1.26 to 1.47)	1.27 (1.17 to 1.38)
HPFS				
Non-regular PPI user	607/210398	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Regular PPI user	141/34346	1.44 (1.20 to 1.74)	1.22 (1.01 to 1.47)	1.12 (0.91 to 1.38)
Pooled				
Non-regular PPI user	7928/1834834	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Regular PPI user	2177/292637	1.74 (1.37 to 2.20)	1.31 (1.24 to 1.38)	1.24 (1.17 to 1.31)

*Multivariable adjusted model 1: additionally adjusted for race (white or other), family history of diabetes (yes or no), BMI (continuous), pack-years of smoking (0, 10–20, 20+, missing), alcohol intake per day (0, 0–2, 2–5, >5 g), physical activity (in quintiles), overall diet quality (AHEI score <30, 30.1–60, or >60), total calories (in quintiles), multivitamin use (yes or no), hypertension (yes or no), hypercholesterolaemia (yes or no), cancer (yes or no), 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), any use of antibiotics (yes or no), regular use of non-steroidal anti-inflammatory drugs (yes or no), and any use of steroids (yes or no).

†Multivariable adjusted model 2: additionally adjusted for gastro-oesophageal reflux disease (yes or no), gastric or duodenal ulcer (yes or no), upper gastrointestinal tract bleeding (yes or no) and regular use of histamine-2 receptor antagonists (yes or no).

HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study.

newly diagnosed coeliac disease, exposure to PPIs added further risk of incident metabolic syndrome and hepatic steatosis.³⁵ In a cohort of 4830 patients with a diagnosis of chronic alcohol abuse, active PPI users had a significantly higher risk of developing chronic liver disease than previous users (adjusted HR 1.37, 95% CI 1.00 to 1.88) or never-users (adjusted HR 1.52, 95% CI 1.21 to 1.91).³⁶ These studies added additional evidence for the link between PPIs and diabetes.

Our results suggested that participants with lower BMI or normal blood pressure seemed to be at a greater risk for diabetes in association with PPI use. Previous studies that evaluated the association between diabetes risk and statin use showed a similar pattern.^{37,38} A cohort study of 161 808 postmenopausal women suggested that the risk of diabetes with statin use was higher among women with a BMI <25 than in those with BMI ≥30.³⁷ Another cohort study including over 2 000 000 participants reported that the increased risk of diabetes with statin use was

smaller among participants with hypertension. An explanation for this is that the participants with hypertension or obesity have already been at very high risk of diabetes, so the effects of relatively weak risk factors tended to be weaker. Additionally, participants with hypertension or obesity may receive more advice about lifestyle modifications and drug usage, and they are more likely to comply with this advice. These changes in lifestyle behaviour could reduce the risk of diabetes. More research is required to explain these interactions.

Possible mechanisms

The mechanism underlying the association between PPI use and diabetes is still unclear. Increasing evidence suggests that gut microbiota may mediate this association. Previous studies have shown that PPI use is associated with reduced diversity of gut

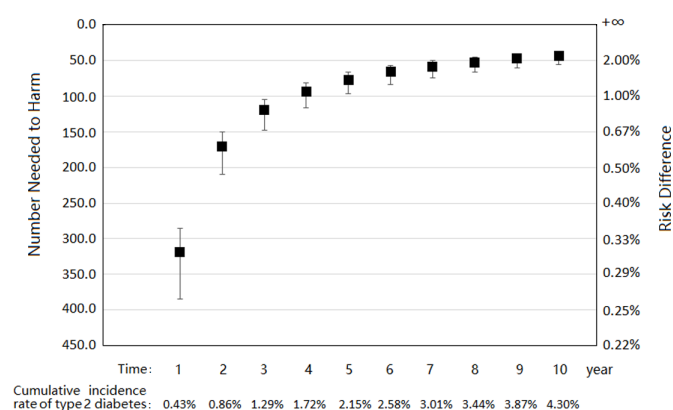


Figure 1 Estimated number needed to harm for regular users of proton pump inhibitors (PPIs) use and risk of type 2 diabetes. The estimated number needed to harm was based on the fully adjusted HR of regular PPI use versus non-use (1.24, 95% CI 1.17 to 1.31) and diabetes rate in the non-user group (4.3 cases/1000 person-years), with the method described by Altman *et al.*²⁵

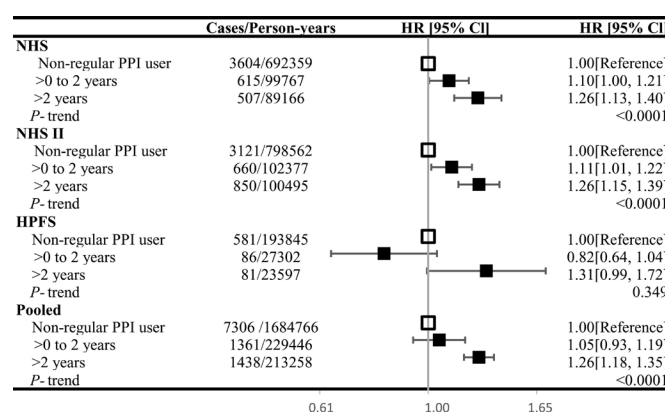


Figure 2 Risk of type 2 diabetes according to the overall duration of use of proton pump inhibitors (PPIs). Participants who reported regular use of PPIs in one circle were grouped as PPI use duration of >0–2 years and those who reported regular use of PPIs in two or more consecutive circles were grouped as PPI use duration >2 years. Estimated effects were based on the fully adjusted model (see footnote in table 2). NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study.

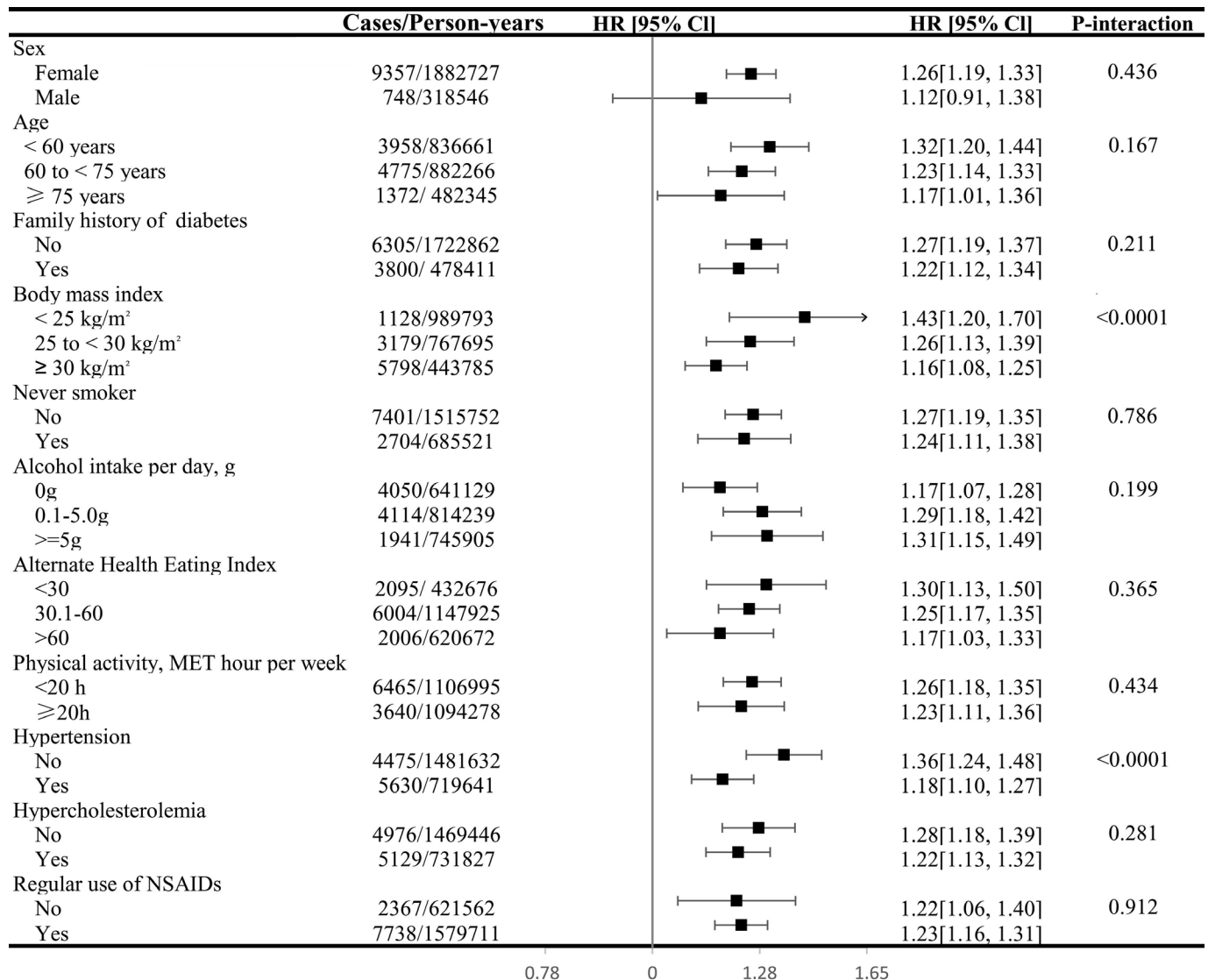


Figure 3 Subgroup analyses of regular use of proton pump inhibitors and risk of type 2 diabetes. Estimated effects were based on the fully adjusted model (see footnote in table 2).

microbiome and consistent changes in the microbiota phenotype.³⁹ For example, both PPI use and diabetes are associated with an increase in the abundance of *Blautia* and *Lactobacillus* and a decrease in the genus *Bifidobacterium*.^{39,40} Observational studies have also suggested that other medicines with a major impact on gut microbiota, such as antibiotics, are associated with an increased risk of diabetes.⁴¹⁻⁴³ In addition, as mentioned previously, PPI use could result in weight gain,^{33,34} metabolic syndrome³⁵ and chronic liver disease,^{35,36} which in turn may increase the risk of type 2 diabetes.²⁹⁻³¹ Furthermore, PPIs may raise the plasma asymmetric dimethylarginine level,⁴⁴ which has been associated with insulin resistance and diabetes.⁴⁵ Further research is warranted to investigate the underlying mechanisms.

Limitations and strengths of the study

One of the strengths of our study is that it was based on three well-established prospective cohorts with large sample sizes, a sufficient number of events and over 12 years of follow-up. These cohorts are well known for their contributions to uncovering risk factors for type 2 diabetes.⁴⁶ In addition, most established diabetes risk factors were repeatedly collected and

adjusted in time-varying regression analyses, which minimised potential confounding effects. Third, the participants were healthcare professionals who were able to provide complete and accurate health information. Last, robust sensitivity analyses and the dose-response relationship additionally increased our confidence in the findings.

This study has limitations. First, as an observational study, we could not completely rule out residual confounding effects. However, in the sensitivity analysis for unmeasured confounders we obtained an E-value of 1.8 for the primary estimate and 1.6 for the lower confidence limit, suggesting the effects were unlikely to be fully explained by unmeasured confounding. Second, detailed data on PPI use including dosage, frequency, brand and indications were not collected in the NHS, NHS II and HPPS studies so we could not conduct further analysis for these factors. Third, the association between PPI use and diabetes may be confounded by the indications for using PPIs. However, adjusting for common indications (eg, gastro-oesophageal reflux disease, gastric or duodenal ulcer) and restriction of participants in those with these indications showed no major change in the estimated effect. Fourth, all the participants are health

professionals, who may have different characteristics from the general population. Therefore, the study findings may not apply to the general population. Fifth, the timing of onset of exposure was not collected, which may lead to misclassification of participants. However, it would only misclassify PPI users (ever or occasional users) to the non-user group which, in turn, would reduce the estimated effect. Sixth, pharmacoepidemiological studies are often influenced by immortal time bias and latency bias.⁴⁷ Immortal time bias is often introduced by misclassifying exposure.⁴⁷ We applied time-varying analysis and specified the PPI use status at different periods for individual participants. Such analysis largely reduced potential misclassification of exposure. Latency bias is introduced by not incorporating latency in the exposure definition.⁴⁷ We lagged the exposure for 2 years in the primary analysis. Sensitivity analysis by lagging the exposure for 4 years showed similar results. Thus, the risk of these biases was low in this study. Seventh, the study outcome was self-reported which may result in misclassification. However, the influence on our conclusion would be minor because (1) the report of PPI use is expected to be non-differential to diabetes diagnosis as the participants were unlikely to know there was an association between PPI use and the risk of diabetes; and (2) all of the participants were health professionals who know the symptoms and diagnosis of diabetes very well. Last, our results may be limited by left truncation, interval data and reliance on self-report.

CONCLUSIONS

Overall, this prospective analysis of over 0.2 million participants indicated that regular PPI use was likely to be associated with an increased risk of type 2 diabetes, particularly for those with prolonged use. Owing to its wide usage, the overall number of diabetes cases associated with PPI use could be considerable. Given the potential risk of diabetes and other adverse effects such as enteric infections, clinicians should carefully balance the benefits and harms in prescribing PPIs, particularly for long-term continuous use. For patients who have to receive long-term PPI treatment, screening for abnormal blood glucose and type 2 diabetes is recommended. Future evaluations including well-designed cohort studies, randomised controlled trials and meta-analyses are required to confirm our conclusion. We also recommend additional basic scientific research to investigate the underlying mechanisms.

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Acknowledgements The authors would like to thank Professor Jae Hee Kang and Professor Francine Grodstein (Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA) for their help in sharing data and comments on data analysis.

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Funding This work was supported by the Startup Fund for the 100 Top Talents Program, SYSU (392012), the National Heart, Lung, and Blood Institute grants (CA176726, CA186107, and CA167552) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grants (DK082486, DK58845 and DK112940).

Competing interests None declared.

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

Patient consent for publication Not required.

Ethics approval This study was approved by the institutional review board at the Brigham and Women's Hospital.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party (nhsaccess@channing.harvard.edu) and are not publicly available. Requests for access to data, questionnaires, and statistical code may be made by contacting the corresponding author at zhchangh@mail.sysu.edu.cn.

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