ORIGINAL ARTICLE

Proton pump inhibitors are associated with incident type 2 diabetes mellitus in a prospective population-based cohort study

Petra Czarniak[1] 🔘 | Fariba Ahmadizar[2] | Jeff Hughes[1] | Richard Parsons[1] | Maryam Kavousi[2] | Mohammad Ikram[2] | Bruno H. Stricker[2]

[1]Curtin Medical School, Curtin University, Perth, Western Australia, Australia

[2]Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands

Correspondence
Petra Czarniak, Curtin Medical School, Curtin University, Perth, Western Australia, GPO Box U1987. Perth. Western Australia 6845.
Email: p.czarniak@curtin.edu.au

Bruno H. Stricker, Department of Epidemiology, Erasmus Medical Centre, Rotterdam. The Netherlands, PO Box 2040, 3000 CA Rotterdam, The Netherlands.
Email: b.stricker@erasmusmc.nl

Aim: To investigate the association between proton pump inhibitors (PPIs) and risk of incident diabetes in a follow-up study and to investigate its potential mechanisms.

Methods: A total of 9531 individuals without type 2 diabetes (T2DM) at baseline were included from the Rotterdam Study, a prospective population-based cohort of 14 926 individuals aged 45 years or older. During the study period (1 April 1997 to 1 January 2012) all incident cases of T2DM were enrolled. We used multivariable linear regression analysis to investigate the associations of baseline PPI use and various serum biomarkers (eg, serum magnesium, insulin-like growth factor 1) which might modify the association. Thereafter, we excluded prevalent PPI users and performed a Cox proportional hazard regression analysis to explore the time-varying effect of incident PPI use on T2DM during follow-up.

Results: Baseline use of a PPI was associated with increased serum levels of fasting insulin (0.091 pmoL/L, 95% confidence interval [CI] 0.049, 0.133), homeostasis model assessment-insulin resistance (0.100, 95% CI 0.056, 0.145) and C-reactive protein (0.29 mg/L, 95% CI 0.198, 0.384), but decreased levels of magnesium (−0.009 mmol/L, 95% CI −0.014, −0.004) and IGF-1 (−0.805 nmoL/L, 95% CI −1.015, −0.595). After adjustment for risk factors such as physical activity and body mass index/waist-to-hip ratio, current use of PPI was associated with an increased risk of incident T2DM (hazard ratio [HR] 1.69, 95% CI 1.36-2.10). The effect was dose-dependent with the highest risk (HR 1.88, 95% CI 1.29-2.75) in those on more than one defined daily dose.

Conclusion: New users of PPIs during follow-up had a significantly higher dose-dependent risk of incident diabetes. We suggest vigilance regarding their potential adverse effect on glucose homeostasis.

KEYWORDS
C-reactive protein, hypomagnesemia, insulin resistance, insulin-like growth factor, proton pump inhibitors, serum insulin, type 2 diabetes

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1 | INTRODUCTION

The global prevalence of type 2 diabetes (T2DM) in 2015 of approximately 5.5% is predicted to rise to almost 11% by 2045.[1] The worldwide focus on T2DM prevention has highlighted the need to understand the pathophysiological changes leading to diabetes. However, the aetiology of T2DM is complex and involves multiple genetic and nongenetic factors, including drugs with an effect on glucose levels.[2,3]

Proton pump inhibitors (PPIs) are commonly used medications in the treatment of acid-related disorders including peptic ulcer disease, gastro-oesophageal reflux disease (GORD), and Zollinger-Ellison syndrome.[4,5] These medications suppress H^+/K-ATPase present in parietal cells of the gastric mucosa and inhibit gastric acid secretion until replacement pumps can be synthesized.[6] Human studies have shown that insulin secretion is increased in moderate hypergastrinemia.[7] In line with this, a retrospective cohort study within a healthcare database showed a significantly reduced risk of developing T2DM of 20% in patients with upper gastrointestinal disease using PPIs.[8] However, more recent studies suggested that PPIs may increase the risk of T2DM. A randomized controlled trial with a median follow-up of 3 years showed a 15% nonsignificantly increased risk of T2DM associated with pantoprazole,[9] and a recently published analysis in three prospective cohort studies with interview data showed a significant risk increase of T2DM of 24% in regular PPI users.[10] If confirmed, several potential underlying mechanisms might explain this association, such as PPI-induced hypomagnesemia, changes to the gut microbiome, insulin-like growth factor 1 (IGF-1) or pregnane X receptor activation (Figure 1).

Given these controversial results and some inherent limitations of these studies regarding nonavailability of both interview and pharmacy data on drug exposure, potential confounders, and important biomarkers such as serum magnesium, fasting glucose and insulin, we investigated whether incident use of PPIs during follow-up in a prospective population-based cohort study of middle-aged and elderly people without diabetes at baseline was associated with incident T2DM. Furthermore, to explore the biological mechanism, we studied the associations between baseline use of PPI and serum biomarkers including fasting serum glucose and insulin levels, homeostasis model assessment-insulin resistance (HOMA-IR), serum magnesium, serum IGF-1 and serum C-reactive protein (CRP).

2 | METHODS

2.1 | Study setting

This study is embedded within the framework of the Rotterdam Study (RS), a prospective population-based study in three cohorts of predominantly Caucasian background with altogether 14 926 individuals ≥45 years of age living in the well-defined Ommoord district of Rotterdam, the Netherlands. The participants were all extensively examined at study entry, ie, in baseline and subsequent follow-up

What is already known about this subject

- Previous studies reported that gastrin promotes beta-cell proliferation in rodents.
- Proton pump inhibitors (PPIs) can lead to hypergastrinaemia, and some studies reported improved glycaemic control in patients with diabetes on PPI.
- Counterintuitively, studies in people without diabetes suggest an association between PPI and onset of diabetes, but results were contradictory.

What this study adds

- Incident use of PPI was associated with a significantly increased risk of incident diabetes.
- The effect was dependent on dosage and duration of PPI use.
- Whilst the mechanism of glycaemic dysregulation associated with PPI use requires further investigation, low magnesium and glucagon-like peptide-1 are potential contributors.

visits that take place every 3-6 years. They were interviewed at home and then underwent an extensive set of examinations, eg, echocardiogram, echocardiography, computed tomography-scanning and magnetic resonance imaging with an emphasis on imaging (of heart, blood vessels, eyes, skeleton and later brain) and on collecting biospecimens that enabled further in-depth molecular and genetic analyses. The participants in the Rotterdam Study are followed for a variety of diseases that are frequent in the elderly, which include coronary heart disease, heart failure and stroke, and dementia, but also several other chronic diseases such as diabetes and cancer. All physician visits, hospitalizations and pharmacy data are captured.

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus Medical Centre (Erasmus MC) (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalog number NTR6831. Participants provided written informed consent to participate in the study. The complete design and rationale behind the Rotterdam Study are described in a separate publication.[11] The study was also approved by the Curtin University Human Research Ethics Committee (Approval number: HRE2017-0095).

In this study, the following examination rounds were considered as a baseline for our analysis: (1) the third examination of the first cohort (held between 1997 and 1999, which followed a total of 7983
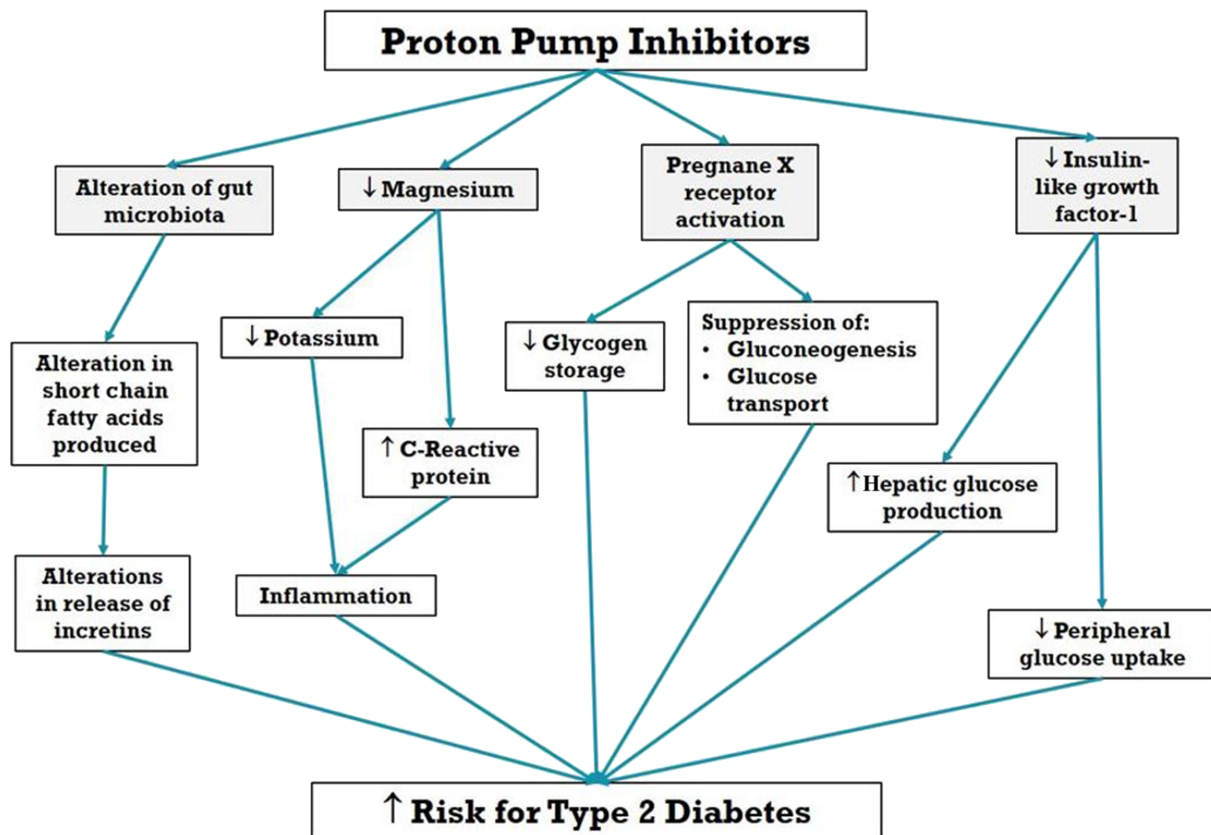
FIGURE 1 Mechanisms by which proton pump inhibitors may contribute to the development of type 2 diabetes (T2DM)

participants aged ≥55 years, RS-I), (2) the first examination of the second cohort (held between 2000 and 2001, which followed a total of 3011 participants aged ≥ 55 years, RS-II) and (3) the first examination of the third cohort (held between 2006 and 2008, which followed a total of 3932 participants aged ≥45 years, RS-III). From 10 696 participants eligible for this study, we excluded participants with prevalent T2DM at baseline (n = 1165). For the association between PPIs and incident T2DM, we also excluded participants with the prevalent use of PPIs at baseline (n = 656).

2.2 | Study designs

We performed two analyses. First, we performed a cross-sectional analysis to study the association between prevalent PPI use at baseline and biomarkers as defined below. Second, we completed a longitudinal study in individuals without a history of PPI use at baseline to examine the association of incident PPI use with incident T2DM. In this follow-up analysis, PPI use was analyzed as a time-varying exposure. In this design, PPI exposure preceding the first incident case of T2DM was compared to PPI exposure preceding the same day of follow-up in each participant without T2DM in the remainder of the cohort. This meant that each participant, cases as well as noncases, had the same day of follow-up as an index date (date of incident

T2DM) which served as a reference to assess exposure on that date. The details of this method have been published previously.[12]

2.3 | Measurement of exposure

Drug exposure was monitored continuously from 1 January 1991 through linkage with pharmacy records of all pharmacies in the study district. Dispensing data on PPI use, including dispensing date, Anatomical Therapeutic Chemical (ATC) code, prescribed daily dose and the amount prescribed was obtained from all pharmacies in the study district. The prescription duration was calculated as the number of dispensed tablets, divided by the prescribed daily number and a participant was considered as exposed to PPI if the index date fell within the prescription duration period. For all individuals, their PPI use at each index date was classified into one of the following categories: "current use", "past use", or "never use". A person was classified as a current user if their follow-up date for that stratum occurred within a prescription episode of PPIs. If a participant had previously used PPIs during follow-up but was not a current user at the index date, they were classified as a "past user". They were classified as a "never user" if they had not taken a PPI during the study period at any time before the index date. The cumulative duration of PPI during the study period was classified into four groups: no use, 1-90 days, 91-730 days

and >730 days. The dose of PPI on the index date was classified as no use, low (<1 defined daily dose [DDD]), moderate (1 DDD) or high (>1 DDD) dose, as defined by the World Health Organization.[13]

2.4 | Measurement of outcomes

2.4.1 | Baseline biomarkers

All biochemical variables were assessed in serum samples taken after overnight fasting. Serum fasting glucose (mmol/L) concentration was measured using the glucose hexokinase method within 1 week after sampling and insulin concentration (pmol/L) by metric assay (Biosource Diagnostics, Camarillo, CA, USA). Serum fasting glucose (mmol/L) and serum fasting insulin (pmol/l) levels were measured at the Erasmus MC research center. To measure insulin resistance, we calculated the HOMA-IR index by the following formula: (fasting serum insulin (mU/L) $\times$ fasting serum glucose (mmol/L))/22.5.[14] Serum magnesium (mmol/L) was measured by the Department of Clinical Chemistry of the Erasmus MC using a Roche/Hitachi Cobas c501 analyzer. Serum IGF-I (nmol/L) was measured with a commercially available noncompetitive two-site immunoradiometric assay.[15] CRP (mg/L) was measured by sensitive immunologic methods using an in-house enzyme immunoassay (n = 516 subjects; Dako, Glostrup, Denmark) or a nephelometric method (n = 160; Dade-Behring, Marburg, Germany), with high agreement of these two methods.[16]

2.4.2 | Type 2 diabetes diagnosis

We identified incident T2DM by use of general practitioner records, hospital discharge letters, pharmacy dispensing data and serum fasting glucose measurements taken at the study centre visits. During follow-up, study participants visited the research center at 4-year intervals. During these visits, incident T2DM was defined according to WHO guidelines as a fasting serum glucose level of ≥7.0 mmol/L or a nonfasting serum glucose concentration of ≥11.1 mmol/L (when fasting serum samples were not available) or the use of blood glucose-lowering medications. Two physicians independently adjudicated all potential events of T2DM. In case of disagreement, a consensus was achieved by an endocrinologist.[17] We included all cases of incident T2DM between 1 April 1997 and 1 January 2012.

2.4.3 | Covariables

At baseline, information was obtained on individuals' characteristics, medical and medication history, health status and lifestyle factors. Baseline body mass index (BMI) was calculated by dividing body weight in kilograms by the square of height in metres. The waist-to-hip ratio (WHR) was calculated as waist circumference/hip circumference. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or

antihypertensive medication use. Information on smoking habits and current alcohol consumption was obtained during a home interview. Physical activity levels were assessed using a validated adapted version of the Zutphen Physical Activity Questionnaire.[18]

2.4.4 | Statistical analysis

We performed descriptive statistics including the mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables and numbers (percent) for categorical variables to summarize the profile of the participants at the time of their entry into the study. Where needed, skewed variables were log-transformed.

The cross-sectional associations between baseline PPI with biomarkers including glycemic traits, serum magnesium, serum IGF-1 and CRP were investigated using multivariable linear regression analyses. Because of skewness in the distributions of these biomarkers, their natural logarithms were used in the models. Results were reported as the adjusted mean differences associated with PPI use and their 95% confidence intervals (CI). All analyses were adjusted for age and sex (Model 1), and further adjusted for BMI, hypertension, current smoking, alcohol consumption, physical activity and education levels (Model 2).

In the longitudinal study in individuals without T2DM and without a history of PPI use at baseline, we used Cox proportional hazard regression analysis to explore the association of (i) PPI current use (yes/no), (ii) duration of PPI use (three categories) and (iii) dosage of PPI (three categories) with incident T2DM in which PPI use was analysed as a time-varying exposure. In this type of Cox regression, PPI exposure preceding the first incident case of T2DM was compared to PPI exposure preceding the same day of follow-up in each participant without T2DM in the remainder of the cohort. This meant that each participant, cases as well as noncases, had the same day of follow-up as an index date (date of incident T2DM) which served as a reference to assess exposure on that date. Consequently, noncases may serve as a reference for a case of T2DM on multiple time points during follow-up. Details of this method have been published previously.[12] All analyses were adjusted for age, sex and PPI past use (except for the duration of use) (Model 1), and further adjusted for BMI, hypertension, current smoking, alcohol consumption, physical activity and education levels (Model 2). We also included interaction terms in Model 2 to study whether any significant associations were modified by sex, age, serum magnesium, IFG-1 or CRP.

In a series of sensitivity analyses in Model 2, the associations between PPI current use and incident T2DM were further adjusted for baseline measurements of (i) total cholesterol, high-density lipoprotein-cholesterol and lipid-lowering medications, (ii) WHR, (iii) statin use, (iv) serum magnesium, (v) serum IGF-I receptor stimulating activity and (vi) CRP. Furthermore, the analysis was performed after excluding prevalent prediabetes (serum fasting glucose 6.1-6.9 mmol/L). The longitudinal analyses were also repeated using different definitions of PPI current use in which we subtracted 1 year (cumulative PPIs) from the index date in T2DM cases (in noncases 1 year from the same date of follow-up) and the associations with PPI

use until that date were studied. We also studied whether there was an association between the use of histamine-2 (H2) receptor-blockers (used for similar indications as PPIs) and incident T2DM to exclude that an association might be confounded by the indication. Finally, apart from excluding prevalent PPI users at baseline (to exclude immortal time bias), we excluded every study participant with a history of PPI use before baseline, retaining 7383 for our analyses on PPI use (current, past, duration and dose) and incident T2DM.

3 | RESULTS

3.1 | Baseline characteristics

We included 9531 participants free of T2DM at baseline (Table 1). The majority of participants were female (5555, 58.3%) and the mean age of the population was 64.8 years. The mean BMI was 27.0 kg/m^2,

TABLE 1 Demographic and baseline characteristics of the study participants

Characteristic	Total population (n = 9531)
Age, years	64.8 (10.0)
Sex, female, n (%)	5555 (58.3)
Baseline glucose, mmol/L, median (IQR)	5.4 (5.0-5.8)
Baseline insulin, pmol/l, median (IQR)	67.0 (46.0-97.0)
[a]HOMA-IR index, median (IQR)	2.3 (1.5-3.4)
Alcohol intake, g/d, median (IQR)	3.7 (0.30-15.7)
BMI, kg/m^2, mean (SD)	27.0 (4.1)
Obese (BMI ≥ 30), n (%)	1707 (18%)
Total cholesterol, mmol/L mean (SD)	5.8 (1.1)
Triglycerides, mmol/L mean (SD)	1.5 (2.4)
HDL-cholesterol, mmol/L, median (IQR)	1.4 (1.1-1.7)
Lipid-lowering medications, n (%)	1714 (18.0)
Physical activity, median, MET hour (IQR)	62.2 (30.8-97.0)
Hypertension, n (%)	5601 (58.8)
Blood-pressure lowering medications, n (%)	3011 (31.6)
Magnesium, mmol/L mean (SD)	0.85 (0.06)
IGF-1, nmol/L, median (IQR)	2.3 (1.0-13.9)
CRP, mg/L, median (IQR)	1.5 (0.6-3.34)
PPI use at baseline date, n (%)	656 (6.9)

Note: Hypertension defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or antihypertensive medication use. Abbreviations: IQR, interquartile range; HOMA-IR, homeostasis model assessment-insulin resistance; SD, standard deviation; BMI, body mass index; HDL, high-density lipoprotein; PPI, proton pump inhibitor; IGF-1, insulin-like growth factor 1.
[a]HOMA-IR index as a surrogate marker for the degree of insulin resistance calculated by the following formula: (fasting serum insulin (mU/l) $\times$ fasting serum glucose (mmol/L))/22.5.

with 62.0% having a BMI ≥25 kg/m^2 and hence classified as overweight/obese. Baseline fasting glucose levels (5.4 [IQR 5.0-5.8] mmol/L), insulin (67.0 [IQR 46.0-97.0] pmol/L) and HOMA-IR (2.3 [IQR 1.5-3.4]) were within normal limits. Of the 9531 participants, 899 were diagnosed with T2DM at some time during a median follow-up of 4.0 years (IQR 2.1-6.0 years). At baseline, PPIs including omeprazole (n = 329), lansoprazole (n = 125), pantoprazole (n = 82), rabeprazole (n = 76) and esomeprazole (n = 44) were used by 656 participants.

3.2 | Association of PPI use with biomarkers

As shown in Table 2, in Model 2 of adjustment, baseline use of a PPI was associated with significantly increased fasting insulin levels (mean difference 0.091 [0.049, 0.133]), HOMA-IR (mean difference 0.100 [0.056, 0.145]) and CRP levels (mean difference 0.29 [0.198, 0.384]). There were also statistically significant associations between the use of PPIs and decreased levels of magnesium (mean difference −0.009 [−0.014, −0.004]) and serum IGF-I receptor stimulating activity levels (mean difference −0.805 [−1.015, −0.595]).

3.3 | Association of PPI use and incident T2DM

Out of 899 patients who developed T2DM, 29.2% were obese. Of these obese persons with T2DM during follow-up, 25.3% were exposed to PPI as against 23.7% in obese participants without T2DM. Our analyses showed that in Model 2 adjustment, current PPI use was associated with an increased risk of incident T2DM (HR 1.69, 95% CI 1.36-2.10). During follow-up, the proportion of current users of PPI on the index date of the total population was 4.8% for omeprazole (HR 1.76, 95% CI 1.39-2.23), 1.7% for pantoprazole (HR 1.98, 95% CI 1.38-2.82), 1.3% for lansoprazole (HR 1.22, 95% CI 0.70-2.11), 2.2% for rabeprazole (HR 1.32, 95% CI 0.92-1.91) and 1.1% for esomeprazole (HR 1.96, 95% CI 1.26-3.02). The associations were lower but remained statistically significant in PPI past users (1.24, 95% CI 1.05-1.45) (Table 3 and Figure 1). As for the cumulative duration of use, the highest risk of incident T2DM was associated with PPI use for a duration longer than 731 days (1.49, 95% CI 1.14-1.95, P value for trend <0.01), which became even stronger after excluding participants with a history of PPI use before baseline (Table 4). There was also a dose-response trend in the association between PPI dose from low dose (1.61, 95% CI 1.05-2.46) to high dose (1.88, 95% CI 1.29-2.75). Sex (P value = 0.23), age (P value = 0.92), serum magnesium (P value = 0.45), IGF-1 (P value = 0.35) and CRP (P value = 0.72) did not modify the associations between PPI use and incident T2DM.

As shown in Table 4, in a series of sensitivity analyses adding more potential confounders to Model 2, adjustment attenuated the effect estimates but the association of current PPI use and incident T2DM remained statistically significant. When excluding prediabetic cases from the analysis, the association between current PPI use and incident T2DM was even stronger (1.82, 95% CI 1.41-2.34).

TABLE 2 Association of PPI use and incident type 2 diabetes (n = 8875)

		Model 1, hazard ratio (95% CI)	Model 2, hazard ratio (95% CI)
No PPI use		1.00 (reference)	1.00 (reference)
PPI past use		1.29 (1.10-1.51)	1.24 (1.05-1.45)
PPI current use		1.79 (1.45-2.22)	1.69 (1.36-2.10)
PPI duration	No use	1.00 (reference)	1.00 (reference)
	<90 d	1.40 (1.16-1.68)	1.38 (1.14-1.67)
	91-730 d	1.33 (1.05-1.69)	1.20 (0.94-1.53)
	>731 d	1.59 (1.22-2.07)	1.49 (1.14-1.95)
Dose categories**	No use	1.00 (reference)	1.00 (reference)
	<1 DDD	1.69 (1.11-2.58)	1.61 (1.05-2.46)
	=1 DDD	1.77 (1.35-2.33)	1.65 (1.25-2.17)
	>1 DDD	1.93 (1.32-2.82)	1.88 (1.29-2.75)

Note: Model 1 adjusted for age and sex, PPI past use (not for the duration of use) (for association between PPI past use and incident T2DM, the association was adjusted for current PPI use). Model 2 is model 1 additionally adjusted for BMI, hypertension, current smoking, alcohol consumption, physical activity and education levels. Hypertension defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or antihypertensive medication use.
Abbreviations: CI, confidence interval; PPI, proton pump inhibitor; IGF-1, insulin-like growth factor 1.
**P value for trend <.001.
P value for the interactions of:
PPI dose × sex = .23.
PPI dose × *age = .92.
PPI dose × *magnesium = .45.
PPI dose × *IGF-1 = .35.
PPI dose × *CRP-1 = .72.

TABLE 3 Association of PPI use and glycaemic traits, magnesium and IGF-1 at baseline

Baseline PPI use	Model 1, mean difference, 95% CI	Model 2, mean difference, 95% CI
Serum glucose, mmol/L (n = 8841)	0.053 [0.006, 0.10]	0.014 [−0.032, 0.059]
Serum insulin, pmol/L (n = 8656)	0.190 [0.143, 0.246]	0.091 [0.049, 0.133]
HOMA-IR (n = 8603)	0.207 [0.158, 0.257]	0.100 [0.056, 0.145]
Magnesium, mmol/L (n = 8607)	−0.010 [−0.015, −0.005]	−0.009 [−0.014, −0.004]
IGF-1, nmol/L (n = 1220)	−0.83 [−1.04, −0.623]	−0.805 [−1.015, −0.595]
CRP, mg/L (8,548)	0.39 [0.294, 0.488]	0.29 [0.198, 0.384]

Note: Model 1 adjusted for age and sex. Model 2 is Model 1 additionally adjusted for BMI, hypertension, current smoking, alcohol consumption, physical activity and education levels. Hypertension defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or antihypertensive medication use. To achieve a normal distribution, serum insulin, HOMA-IR, IGF-1 and CRP were log-transformed. To interpret the amount of change in the original metric of serum insulin, HOMA-IR, IGF-1 and CRP, we used the exponents of the beta coefficients.
Abbreviations: PPI, proton pump inhibitor; SE, standard error; HOMA-IR, homeostasis model assessment-insulin resistance; IGF-1, insulin-like growth factor 1; CRP, C-reactive protein.

However, the associations of current PPI use and incident T2DM 1 year before the diagnosis of T2DM after subtracting a 1-year lag time did not remain statistically significant. We also studied the association between histamine-2 receptor blockers and incident T2DM, where the association was not significant (0.94, 95% CI 0.57-1.54). When we excluded individuals with a history of PPIs at baseline, all associations of incident PPI use and incident T2DM remained statistically significant and often stronger (Table 4).

4 | DISCUSSION

In this prospective population-based cohort study in middle-aged and elderly people without diabetes at baseline, incident use of PPI was associated with a significantly increased risk of incident diabetes during follow-up, after adjustment for known risk factors such as physical activity, BMI or WHR. The effect was dose-dependent in current users of PPI, duration-dependent and declined in past users. Interestingly, users of PPI at baseline (who were excluded from the follow-up

TABLE 4 Sensitivity analyses for the association between PPI use and incident type 2 diabetes (n = 8875)

	Hazard ratio (95% CI)
Model 2 plus total cholesterol, HDL-cholesterol and lipid-lowering medication	1.62 (1.31-2.02)
Model 2 plus statin at baseline	1.65 (1.33-2.05)
Model 2 plus CRP at baseline	1.68 (1.35-2.08)
Model 2 plus magnesium at baseline	1.70 (1.37-2.10)
Model 2 plus IGF-1 at baseline	1.69 (1.36-2.10)
Model 2 plus WHR at baseline	1.71 (1.37-2.14)
Model 2 excluding prevalent prediabetes cases at baseline	1.82 (1.41-2.34)
Current PPI use, until 365 days before the index date	1.17 (0.92-1.50)
H2 blockers and incident T2D	0.94 (0.57-1.54)
Association PPI use and incident type 2 diabetes after excluding PPI past users at baseline (model 2), n = 7383	
Current PPI use	1.90 (1.49-2.42)
Past PPI use	1.18 (0.97-1.45)
PPI duration	
<90 days	1.32 (1.07-1.63)
91-730 days	1.26 (0.95-1.67)
>731 days	1.68 (1.23-2.31)
PPI dose	
<1 DDD	1.64 (1.00-2.68)
=1 DDD	1.97 (1.45-2.68)
>1 DDD	2.00 (1.28-2.12)

Note: Model 1 adjusted for age and sex, PPI past use. Model 2 is Model 1 additionally adjusted for BMI, hypertension, current smoking, alcohol consumption, physical activity and education levels. Hypertension defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or antihypertensive medication use.
Abbreviations: CI, confidence interval; PPI, proton pump inhibitor; IGF-1, insulin-like growth factor 1; H2 blockers, histamine-2 receptor blockers; WHR, waist to hip ratio.

analyses) had significantly higher serum fasting insulin levels, insulin resistance and CRP but lower serum levels of magnesium and IGF-1. Adjusting for these baseline biomarkers during follow-up in incident users did not impact the association of PPI use with incident T2DM. Although there were slight differences in risk estimates and significance between the individual PPIs omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole, these differences were not materially different and probably partly explained by different sample sizes.

These findings are in line with an earlier analysis in three cohorts in the United States[10] but the risk in the current study is higher. One explanation might be that the use of PPI in these cohorts came from repeated 2-year interviews, which may have led to nondifferential misclassification of PPI use with an underestimation of the true risk. Although exposure during repeated interviews may serve as a proxy

indicator of continuous use, drug dispensing is a more reliable data source.[19]

Several potential underlying mechanisms may be involved in the contribution of PPIs to the development of T2DM, including PPI-induced hypomagnesemia, changes to the gut microbiome, IGF-1 or pregnane X receptor activation (Figure 1). First, an inverse relationship has been reported between dietary magnesium intake and risk of developing T2DM,[20-22] which is in line with the results of our study where low baseline magnesium was associated with T2DM during follow-up (data not shown). Hypomagnesaemia has been reported to be associated with increased insulin resistance[23-25] and possibly reduced insulin secretion.[26] In our study, PPI at baseline was associated with low serum magnesium, and also in a recent meta-analysis of observational studies researchers reported a significant association between PPI use and hypomagnesemia.[27-29] In a study investigating the extent to which magnesium intake is related to systemic inflammation and metabolic syndrome, researchers reported that magnesium intake was inversely associated with plasma CRP concentrations.[30] They also reported low magnesium intake was inversely associated with the prevalence of metabolic syndrome. CRP is a measure of systemic inflammation, which is thought to be a common mechanism underlying the development of metabolic-related disorders such as T2DM. Although in our study PPI-associated T2DM was independent of baseline serum magnesium, it is still possible that individuals starting with PPI during follow-up developed hypomagnesemia, and that PPI-lowered serum magnesium was an intermediate step in the causal pathway.

Second, in our study PPIs were associated with a lower IGF-1, a hormone with structural homology to insulin, which is produced primarily by the liver on stimulation by growth hormone.[31] It has a positive impact on glucose homeostasis by improving insulin sensitivity by decreasing hepatic glucose production and increasing peripheral glucose uptake.[31] Low IGF-1 levels have been found in obesity, metabolic syndrome and diabetes.[32] In a recent cross-sectional study investigating the effects of PPIs on IGF-1 in 938 older people, PPI use was independently and negatively associated with IGF-1 levels.[32] Both low and high IGF-I levels are related to impaired glucose tolerance and a higher risk of T2DM.[33]

A third mechanism might involve the gut microbiota. PPIs have been reported to influence the composition of the gut microbiota, producing small intestine bacterial overgrowth or dysbiosis.[34] Gut microbiota breaks down indigestible carbohydrates to various metabolites, the most abundant of which are the short-chain fatty acids acetate, butyrate and propionate.[35] They exert systemic anti-inflammatory effects by producing immunosuppressive cytokines and immunoglobulin A.[36] They also promote the secretion of glucagon-like peptide-1 (GLP-1), an incretin hormone released by L-cells, which results in a reduction in appetite, delayed gastric emptying, glucose-dependent insulin secretion and inhibition of glucagon secretion. The release of enteroendocrine cell hormones such as GLP-1 may be influenced by the gut microbiome.[35] Hence depending on the composition of the host microbiome, this may influence GLP-1 release and therefore glucose homeostasis and risk of developing T2DM.

A fourth mechanism might follow activation of pregnane X receptor (PXR), a ligand-activated nuclear receptor that has been reported to be associated with the regulation of hepatic glucose metabolism.[37] PXR is activated by various chemicals known to induce CYP3A4 gene expression, including PPIs.[38] Despite PXR activation suppressing gluconeogenesis, it has been reported to impair glucose tolerance, possibly by downregulation of the hepatic glucose transporter 2.[37] Due to its detrimental role in the regulation of glucose metabolism, activation of PXR may contribute to the development of T2DM.[37]

Alternatively, there might be a role for gastrin, which is supposed to improve glucose control. Gastrin may stimulate beta-cell proliferation and function.[33,39] Indeed, users of PPI had significantly higher fasting insulin in our study. We postulate that long-term gastrin release may exhaust this mechanism and consequently increase the risk of T2DM.

There were several strengths associated with this study. The most important strengths were the availability of data on important biomarkers such as serum magnesium and IGF-1, PPI dose and duration of treatment, and the long follow-up in community-dwelling middle-aged and elderly people free of T2DM at baseline. As this was a population-based study that gathered data prospectively, there is a reduced likelihood of information and selection bias. Moreover, we studied people without a history of PPI use at baseline, which means that a "healthy user effect" or misclassification of a duration of exposure cannot explain our results. However, there is a potential limitation to consider as well, ie, risk of diagnostic bias if people who regularly consult their doctor for a prescription of PPI might more readily obtain a diagnosis of T2DM. This is unlikely, however, for three reasons. First, the case finding was mainly based on a prospective regular investigation of study participants at 4-year intervals irrespective of drug use and specialist-based diagnoses of T2DM in between. Second, a lag time of 1 year subtracted from diagnosis of T2DM still showed an increased risk in PPI users, albeit lower and no longer significant for current use but still for duration of use. Third, there was no association whatsoever with the use of H2-blockers, which are used for the same indications as PPI. Unfortunately, we did not have repeated data on magnesium level, IGF-1 and gut microbiota, which could have yielded important information on the mechanism.

In conclusion, PPI use is associated with the onset of T2DM, and its risk increases with daily dose and duration of use. This risk increase seems higher than previously reported. Given the very large-scale use of PPI, including the over-the-counter availability in many countries and the increasing prevalence of diabetes, the large-scale and free availability of PPI might have to be reconsidered. Also, our findings underline the need to be vigilant regarding metabolic adverse effects. In high-risk individuals (eg, obese, prediabetic) using PPI therapy regularly or for prolonged periods, glucose monitoring may be justified.

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COMPETING INTERESTS

No potential conflicts of interest relevant to this article were reported.

CONTRIBUTORS

P.C. and J.H. developed the study concept and design, with contributions from B.S. B.S. provided the data. J.H., R.P., P.C., B.S. and F.A. established the data analysis plan. Data analysis was performed by R.P., F.A. and B.S. P.C. drafted the initial manuscript, which was revised and approved by J.H., F.A. and B.S. All authors contributed to, critically revised and approved the final version of the manuscript. All authors assume responsibility for its content. B.S. is the guarantor of this work. B.S. had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

The datasets analysed during the current study are not publicly available as they are embedded within the framework of the Rotterdam Study.

ORCID

Petra Czarniak (iD) https://orcid.org/0000-0001-7212-0667

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