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Association between migraine prevalence, treatment with proton-pump inhibitors and CYP2C19 phenotypes in UK Biobank

Claudia Pisanu [a,b], Nike Zoe Welander [a], Gull Rukh [a], Helgi Birgir Schiöth [a,c], Jessica Mwinyi [a,*]

[a] Department of Neuroscience, Uppsala University, Uppsala, Sweden
[b] Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy
[c] Institute for Translational Medicine and Biotechnology, Sechenov First Moscow State Medical University, Moscow, Russia

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ABSTRACT

Proton-pump inhibitors (PPIs) are used to suppress gastric acid secretion in several gastrointestinal conditions. While these drugs are generally well tolerated, their long-term use may be associated with different adverse effects, including migraine. We analyzed the association between treatment with PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole) and migraine prevalence in the UK Biobank cohort through a cross-sectional analysis (using baseline data for 468,280 participants, 16,390 of whom had migraine) and a longitudinal analysis (including 145,007 participants with no migraine at baseline, of whom 3786 had probable migraine without aura [MWOA] and 9981 probable migraine with aura [MWA] or both MWOA and MWA at an average follow-up time of 10.06 years). We also evaluated the modulating role of the metabolizer phenotype of CYP2C19, the major enzyme involved in PPI clearance. Treatment with PPIs was associated with higher migraine prevalence at baseline (odds ratio [OR] = 1.25, $p < 0.0001$). CYP2C19 rapid metabolizer phenotype was associated with lower prevalence of migraine exclusively in participants treated with PPIs (OR = 0.89, $p = 0.029$). In addition, treatment with PPIs was associated with higher incidence of both probable MWOA (OR = 1.24, $p = 0.002$) and MWA (OR = 1.43, $p < 0.0001$) at follow-up. Treatment with PPIs and CYP2C19 poor metabolizer status were associated with higher incidence of probable chronic migraine exclusively in men. Our results suggest a significant association between treatment with PPIs and migraine in this large population-based cohort and support a potential relevant role of gender and CYP2C19 phenotype.

1. Introduction

Proton-pump inhibitors (PPIs) are a group of medications widely used to reduce gastric acid secretion via irreversible inhibition of the H^+/K^+ ATPase enzyme in gastric parietal cells [1]. Besides omeprazole, which was the first PPI to be approved by the Food and Drug Administration (FDA) in 1989, other commonly used PPIs include the first-generation PPIs lansoprazole and pantoprazole, as well as the second-generation PPIs esomeprazole and rabeprazole. While PPIs are generally well tolerated, their use can be associated with different adverse effects. Specifically, headache is a known adverse effect of PPIs [2] and can cause poor adherence to therapy or discontinuation [3]. The molecular mechanisms underlying the induction of headache by PPIs are scarcely known. In addition, it is not clear whether the use of PPIs is only associated with a higher prevalence of tension-type headaches or also with a higher prevalence of migraine.

Migraine is one of the most common neurological disorders worldwide and a major cause of disability [4]. Due to its substantial functional impairment as well as prevalent comorbidities [5,6], migraine ranks as the leading cause of years lived with disability in people younger than 50 years [7]. This heterogeneous disorder is characterized by recurrent headache attacks of unilateral location, pulsating quality and moderate or severe intensity, with associated symptoms such as nausea, vomiting, photophobia or phonophobia [8]. Migraine without aura (MWOA) is the most common form of migraine and is characterized by severe headache attacks lasting 4–72 h with associated gastrointestinal and autonomic symptoms [9]. About one third of patients experience transient focal neurological symptoms before or during the headache attack (migraine with aura [MWA]). Migraine management includes both pharmacological and non-pharmacological treatments [10–12]. While it is known that migraine has a genetic component [13] and that activation of trigeminovascular pain pathways plays an important role in its

* Correspondence to: Department of Neuroscience, Functional Pharmacology, BMC, Uppsala University, Husargatan 3, 751 24 Uppsala, Sweden.
E-mail address: jessica.mwinyi@neuro.uu.se (J. Mwinyi).

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development, its pathogenesis as well as the potential role of drugs as migraine inducers are not completely known.

A recent population-based study conducted in Taiwan, using data from the Taiwan National Health Insurance Database, showed a higher prevalence of headache, but not migraine, in participants using PPIs (odds ratio [OR] = 1.20, 95% confidence interval [CI] = 1.07–1.35) [14]. When analyses were focused on specific PPIs, only omeprazole and lansoprazole were associated with a higher prevalence of headache. Interestingly, the risk for PPI-induced headache was found to be higher in women compared with men [14]. In contrast with this study, a recent analysis of the FDA Adverse Event Reporting System demonstrated a higher propensity for migraine in patients treated with PPIs (OR = 2.19, 95% CI = 1.29–3.72) [15]. In this study, the role of gender was not investigated. It is thus not clear whether gender differences might modulate the observed association.

PPIs are extensively metabolized into inactive metabolites by cytochrome P450 enzymes, with CYP2C19 playing a major role in the transformation. Variation in CYP2C19 activity has been linked to PPI exposure, with this effect suggested to be particularly relevant for first-generation PPIs. Because of this, CYP2C19 genetic variation may contribute to the interindividual variability observed in clinical response and adverse effects during treatment with these drugs [16,17]. The *CYP2C19* gene is highly polymorphic with 37 described alleles [16], some of which have been associated with decreased or no function (e.g. *CYP2C19*2* and *CYP2C19*3*) or increased function (*CYP2C19*17*). The Clinical Pharmacogenetics Implementation Consortium (CPIC) recently defined predicted CYP2C19 phenotypes (e.g. poor metabolizers, intermediate, normal, rapid or ultrarapid metabolizers) based on inherited alleles, as well as guidelines for PPI dosing according to the observed phenotype [16]. Besides being involved in the metabolism of different classes of drugs, the CYP2C19 enzyme catalyzes biotransformation of endogenous substrates such as polyunsaturated fatty acids [18] and steroid hormones [19] that play important roles in brain development and plasticity [20,21]. While the CYP2C19 enzyme seems to be expressed in the brain only in the fetus, it has been speculated that its action on endogenous compounds involved in brain development might exert consequences on brain function in adult life [22,23]. Indeed, preclinical studies suggest *CYP2C19* variation to be associated with decreased hippocampal volume and increased stress and anxiety [24]. Results in humans are still controversial, with some studies reporting fewer depressive symptoms in CYP2C19 poor metabolizers compared with non-poor metabolizers [25,26] and other studies reporting no significant association [27]. To our knowledge, the association between CYP2C19 phenotypes and migraine prevalence has not been investigated.

The aim of this study was to evaluate the role of treatment with PPIs, CYP2C19 phenotypes as well as the interplay between these two factors in the prevalence of migraine in the UK Biobank cohort. Due to reduced clearance of PPIs, we hypothesized participants with poor or intermediate CYP2C19 metabolizer phenotypes to be particularly susceptible to this potential adverse effect. In addition, we sought to elucidate possible gender differences underlying this association.

2. Material and methods

2.1. UK Biobank

Data were obtained from UK Biobank, a large population-based cohort including more than 500,000 individuals from the UK, aged between 40 and 69 years at the time of recruitment. Baseline assessments were conducted between 2006 and 2010 at several centers across England, Scotland and Wales. Participants underwent physical and clinical assessments, completed comprehensive questionnaires on socio-demographic, lifestyle and health-related factors, and provided biological samples and electronic signed consent [28]. Genome-wide genotyping was conducted on DNA extracted from blood samples using the Applied Biosystems UK BiLEVE Axiom Array by Affymetrix (now part of Thermo Fisher Scientific) and the Applied Biosystems UK Biobank Axiom Array. Quality control and imputation have been described elsewhere [29]. UK Biobank study has been ethically approved by the North-West Multicenter Research Ethics Committee (UK). The present study has been conducted using the UK Biobank Resource under Application Number 57519. Our use of UK Biobank data has been approved by the Regional Ethics Committee of Uppsala (now the Swedish Ethical Review Authority, 2017/198).

2.2. Variables and measures

We included 468,280 UK Biobank participants for whom both clinical and genetic data at the baseline assessment were available. Migraine cases (n = 16,390) were defined as participants with self-reported migraine (data field 20002 code 1265) and/or a diagnosis code for migraine in accordance with ICD-10 criteria (ICD-10: G43). Controls included 451,890 participants without self-reported migraine or headache (data field 20002 code 1436) or ICD-10 diagnoses of migraine or headache (ICD-10: G44). For each participant, the following variables were used for the analyses: gender, age, body mass index (BMI), treatment with PPIs (including omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole), medical comorbidities with conditions that might require treatment with PPIs (either self-reported or diagnosed in accordance with ICD-10 criteria) and treatment with potentially confounding medications. A complete list of medical comorbidities as well as medications included in the analyses is reported in Supplementary Table 1.

We also used data related to genotypes of four *CYP2C19* variants: rs4244285 (*CYP2C19*2*), rs4986893 (*CYP2C19*3*), rs17884712 (*CYP2C19*9*) and rs12248560 (*CYP2C19*17*). CYP2C19 phenotypes were assigned based on *CYP2C19*2*, *CYP2C19*3*, *CYP2C19*9* and *CYP2C19*17* alleles according to CPIC guidelines [16]. Categories with small frequencies such as ultrarapid metabolizers, likely intermediate metabolizers and likely poor metabolizers were combined with rapid, intermediate and poor metabolizers, respectively.

Among the 468,280 participants included in our study, 157,345 participants completed the UK Biobank 'Experience of Pain' questionnaire, a web-based follow-up questionnaire aimed at investigating the type, severity and duration of chronic pain. Participants who reported that they had experienced headache were asked more detailed questions on its duration, frequency, intensity and accompanying symptoms. This information was used to construct "probable MWOA," "probable MWA" and "probable chronic migraine" variables to analyze the longitudinal association between treatment with PPIs at baseline and development of migraine at follow-up in participants with no migraine diagnosis at baseline (n = 145,007). Diagnoses of probable MWOA and probable MWA were defined in accordance with the International Classification of Headache Disorders (ICHD-3) criteria to the extent possible based on information reported in the UK Biobank Experience of Pain Questionnaire [9]. For probable MWOA, the criteria included unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by routine physical activity and associated symptoms such as nausea/vomiting and photophobia or phonophobia. For probable MWA, the criteria included presence of visual or sensory aura symptoms and aura symptoms spreading gradually over several minutes or more before or near the onset of headaches. Participants were coded as having "probable chronic migraine" if they fulfilled the criteria for either probable MWOA or MWA and reported to have experienced headache on ≥15 days/month in the preceding three months. A total of 13,767 participants were coded with a diagnosis of probable migraine (3786 exclusively with probable MWOA, 9981 with either probable MWA [5375] or both probable MWOA and MWA [4606]) and compared with 131,240 controls. Among participants with probable migraine, 230 were coded with probable chronic migraine and compared with controls. The average time between the baseline visit and assessment with the UK

Biobank Experience of Pain Questionnaire for participants included in our study was 10.06 years (standard deviation: 0.91 years).

2.3. Statistical analysis

The unadjusted association between migraine prevalence and treatment with any PPI, specific PPIs or CYP2C19 phenotypes was tested using Fisher's exact test. The association between migraine prevalence and age or BMI was tested using Mann-Whitney *U* test. Next, we constructed three binary logistic regression models with increasing complexity, all with migraine prevalence as the outcome. In the first model, we tested the association between migraine prevalence, treatment with PPIs (either as a combined category or for specific PPIs) and CYP2C19 phenotypes (coded as dummy variables with normal metabolizers as the reference) adjusting for gender, age and BMI. The second model was additionally adjusted for medical comorbidities listed in Supplementary Table 1, while the third model was additionally adjusted for both medical comorbidities as well as potentially confounding medications listed in Supplementary Table 1. Interaction terms between PPI intake and either gender or CYP2C19 phenotypes were also tested and stratified analyses were conducted in case interaction terms were significant.

For participants without a diagnosis of migraine at baseline and for which the follow-up pain questionnaire was available, we evaluated the longitudinal association between intake of PPIs at baseline and development of migraine at follow-up. We constructed binary logistic regression models using diagnoses of probable MWOA, probable MWA (including participants with diagnosis of both probable MWOA and MWA) or probable chronic migraine as the outcome, using PPI intake at baseline and CYP2C19 phenotypes as predictors, adjusting for gender, age, BMI and time to follow-up. We also constructed models adjusted for medical comorbidities and intake of other medications. A p-value < 0.05 was considered to be significant. Analyses were conducted using SPSS v. 26 (IBM Statistics).

3. Results

3.1. Cross-sectional association between treatment with PPIs and migraine prevalence

Characteristics of the sample are reported in Table 1. As expected, participants with migraine were more likely to be women, were younger and had a slightly lower BMI (Table 1). Participants with migraine were more likely to be under treatment with PPIs compared with controls (13.9% vs. 9.6%, $\chi^2 = 338.45$, $p < 0.0001$). Unadjusted analyses on specific PPIs showed a higher frequency of treatment with omeprazole, lansoprazole, esomeprazole ($p < 0.0001$ for all) and pantoprazole ($p = 0.0002$) but not rabeprazole ($p = 0.07$), possibly due to the limited number of participants treated with this drug (Table 1). Frequencies of the CYP2C19 phenotypes are reported in Table 1 and were not found to be significantly different among participants with migraine and controls ($\chi^2 = 1.83$, $p = 0.61$).

The logistic regression model adjusted for gender, age and BMI confirmed the significant association between treatment with PPIs and higher migraine prevalence (Table 2). This association was confirmed in the models adjusted for medical comorbidities and medication intake (Table 2). Although the contribution of CYP2C19 phenotype to the model was not significant, we detected a significant interaction term between treatment with PPIs and CYP2C19 rapid/ultrarapid metabolizer status ($p = 0.046$). Stratified analyses based on treatment with PPIs showed this phenotype to be significantly associated with a lower prevalence of migraine in participants treated with PPIs but not in participants not exposed to these drugs (Supplementary Table 2).

When investigating the association between migraine prevalence

Table 2
Association between migraine prevalence, treatment with PPIs and CYP2C19 phenotypes.

Variable	OR	95% CI	p
Model 1 (adjusted for gender, age and BMI)[1]			
Treatment with PPIs	**1.66**	**1.59–1.74**	**<0.0001**
CYP2C19 Rapid or ultrarapid metabolizers	0.98	0.95–1.02	0.37
CYP2C19 Likely intermediate and intermediate metabolizers	0.99	0.95–1.03	0.64
CYP2C19 Likely poor and poor metabolizers	1.03	0.94–1.14	0.52
Model 2 (adjusted for gender, age, BMI and medical comorbidities)			
Treatment with PPIs	**1.29**	**1.23–1.37**	**<0.0001**
CYP2C19 Rapid or ultrarapid metabolizers	0.98	0.95–1.02	0.35
CYP2C19 Likely intermediate and intermediate metabolizers	0.99	0.95–1.03	0.63
CYP2C19 Likely poor and poor metabolizers	1.03	0.93–1.14	0.55
Model 3 (adjusted for gender, age, BMI, medical comorbidities and medication intake)			
Treatment with PPIs	**1.25**	**1.18–1.32**	**<0.0001**
CYP2C19 Rapid or ultrarapid metabolizers	0.98	0.95–1.02	0.36
CYP2C19 Likely intermediate and intermediate metabolizers	0.99	0.95–1.03	0.66
CYP2C19 Likely poor and poor metabolizers	1.04	0.94–1.15	0.46

The association between migraine prevalence and treatment with PPIs was tested using binary logistic regression models with increasing complexity, all with migraine prevalence as the outcome.

Abbreviations: CI, confidence interval; OR, odds ratio.

[1] Significant interaction term between CYP2C19 rapid metabolizer status and treatment with PPIs ($p = 0.046$). No other interactions terms were significant.

Table 1
Demographic and clinical characteristics of the sample.

	Participants with migraine (n = 16,390)	Controls (n = 451,890)	Statistics	p
Gender, %F	**77.4%**	**53.4%**	**$\chi^2 = 3729.12$**	**<0.0001**
Age (median, IQR)	**56 (13)**	**58 (13)**	**U = 3,336,171,468**	**<0.0001**
BMI (median, IQR)	**26.3 (6.1)**	**26.8 (5.7)**	**U = 3,536,904,143**	**<0.0001**
Treatment with any PPI, %	**13.9%**	**9.6%**	**$\chi^2 = 338.45$**	**<0.0001**
Treatment with omeprazole, %	**9.5%**	**6.4%**	**$\chi^2 = 241.48$**	**<0.0001**
Treatment with lansoprazole, %	**4.7%**	**3.2%**	**$\chi^2 = 102.85$**	**<0.0001**
Treatment with esomeprazole, %	**0.8%**	**0.5%**	**$\chi^2 = 43.57$**	**<0.0001**
Treatment with pantoprazole, %	**0.3%**	**0.2%**	**$\chi^2 = 15.44$**	**0.0002**
Treatment with rabeprazole, %	0.2%	0.1%	$\chi^2 = 3.56$	0.07
CYP2C19 RM and URM, %	29.3%	29.8%	$\chi^2 = 1.83$	0.61
CYP2C19 NM, %	41.2%	41.0%		
CYP2C19 LIM and IM %	26.6%	26.7%		
CYP2C19 LPM and PM %	2.7%	2.6%		

The unadjusted association between migraine prevalence and treatment with any PPI, specific PPIs or CYP2C19 phenotypes was tested using Fisher's exact test. The association between migraine prevalence and age or BMI was tested using Mann-Whitney *U* test.

Abbreviations: F, female; IM, intermediate metabolizers; IQR, interquartile range; LIM, likely intermediate metabolizers; LPM, likely poor metabolizers; NM, normal metabolizers; PM, poor metabolizers; PPI, proton-pump inhibitors, RM, rapid metabolizers; URM, ultrarapid metabolizers.

and specific PPIs, the model adjusted for gender, age, BMI and time to follow-up showed a higher frequency of treatment with all PPIs in participants with migraine compared with controls (Table 3). In the models adjusted for medical comorbidities and medication intake, treatment with all PPIs except rabeprazole was associated with a higher prevalence of migraine (Table 3). We detected a significant interaction between CYP2C19 rapid/ultrarapid metabolizer status and treatment with omeprazole ($p = 0.038$) and between CYP2C19 intermediate metabolizer status and treatment with rabeprazole ($p = 0.022$). Analyses stratified based on treatment with PPIs for which the interaction terms were found to be significant showed the CYP2C19 rapid/ultrarapid metabolizer status to be associated with a lower prevalence of migraine in participants treated with omeprazole but not in participants not treated with this drug (Supplementary Table 3). In addition, we observed CYP2C19 intermediate metabolizer status to be associated with a higher prevalence of migraine in participants treated with rabeprazole but not in participants not treated with this drug (Supplementary Table 4).

3.2. Longitudinal association between treatment with PPIs at baseline and migraine incidence at follow-up

In participants with no migraine diagnosis at baseline, we investigated the association between PPI intake at baseline and development of migraine at follow-up using data from the UK Biobank Experience of Pain Questionnaire. We found PPI exposure at baseline to be significantly associated with a higher incidence of probable migraine and probable chronic migraine at follow-up in unadjusted analyses (Table 4) or in analyses adjusted for gender, age, BMI and time to follow-up (Table 5). For probable MWOA and MWA the association remained significant after adjustment for medical comorbidities or treatment with other medications (Supplementary Table 5). For probable chronic migraine, the association was no longer significant after adjustment for confounding medications (Supplementary Table 6). However, in the model with probable chronic migraine as the outcome, we detected a significant interaction between treatment with PPIs and gender ($p = 0.032$). Therefore, we conducted stratified analyses that revealed that treatment with PPIs was associated with a higher incidence of probable chronic migraine at follow-up only in men (Supplementary Table 7). In addition, poor metabolizer status was significantly associated with a higher incidence of migraine exclusively in men (Supplementary Table 7).

When investigating the follow-up associations for treatment with specific PPIs and adjusting for gender, age, BMI and time to follow-up, treatment with omeprazole and rabeprazole was associated with a higher incidence of probable MWOA. In addition, treatment with these drugs or with lansoprazole was associated with a higher incidence of probable MWA and chronic migraine (Table 6). These analyses remained significant after adjustment for medical comorbidities and medication intake (Supplementary Table 8). For probable chronic migraine, a significant association was only found for rabeprazole when adjusting for medical comorbidities and medication intake (Supplementary Table 9). In the model with probable chronic migraine as the outcome, we detected a significant interaction between treatment with lansoprazole and gender ($p = 0.013$). Stratified analyses showed treatment with lansoprazole to be associate with higher incidence of migraine in men but not in women (Supplementary Table 10). In addition, the CYP2C19 poor metabolizer status was associated with a higher incidence of migraine only in men (Supplementary Table 10).

Table 3
Association between migraine prevalence, treatment with specific PPIs and CYP2C19 phenotypes.

Variable	OR	95% CI	p
Model 1 (adjusted for gender, age and BMI)[1]			
Omeprazole	**1.54**	**1.46–1.63**	**<0.0001**
Lansoprazole	**1.54**	**1.42–1.66**	**<0.0001**
Esomeprazole	**1.66**	**1.39–1.99**	**<0.0001**
Pantoprazole	**1.83**	**1.35–2.49**	**0.0001**
Rabeprazole	**1.56**	**1.10–2.22**	**0.013**
CYP2C19 Rapid and ultrarapid metabolizers	0.98	0.95–1.02	0.37
CYP2C19 Likely intermediate and intermediate metabolizers	0.99	0.95–1.03	0.64
CYP2C19 Likely poor and poor metabolizers	1.04	0.94–1.14	0.49
Model 2 (adjusted for gender, age, BMI and medical comorbidities)			
Omeprazole	**1.25**	**1.18–1.33**	**<0.0001**
Lansoprazole	**1.25**	**1.15–1.35**	**<0.0001**
Esomeprazole	**1.33**	**1.11–1.60**	**0.002**
Pantoprazole	**1.45**	**1.06–1.97**	**0.018**
Rabeprazole	1.25	0.87–1.77	0.23
CYP2C19 Rapid and ultrarapid metabolizers	0.98	0.95–1.02	0.35
CYP2C19 Likely intermediate and intermediate metabolizers	0.99	0.95–1.03	0.64
CYP2C19 Likely poor and poor metabolizers	1.03	0.93–1.14	0.54
Model 3 (adjusted for gender, age, BMI, medical comorbidities and medication intake)			
Omeprazole	**1.21**	**1.14–1.28**	**<0.0001**
Lansoprazole	**1.22**	**1.13–1.32**	**<0.0001**
Esomeprazole	**1.39**	**1.16–1.67**	**0.0004**
Pantoprazole	**1.49**	**1.09–2.03**	**0.012**
Rabeprazole	1.19	0.84–1.71	0.34
CYP2C19 Rapid and ultrarapid metabolizers	0.98	0.95–1.02	0.36
CYP2C19 Likely intermediate and intermediate metabolizers	0.99	0.95–1.03	0.67
CYP2C19 Likely poor and poor metabolizers	1.04	0.94–1.15	0.46

The association between migraine prevalence and treatment with specific PPIs was tested using binary logistic regression models with increasing complexity, all with migraine prevalence as the outcome.

Abbreviations: CI, confidence interval; OR, odds ratio.

[1] Significant interaction term between CYP2C19 rapid metabolizer status and treatment with omeprazole ($p = 0.038$) and between intermediate metabolizer status and treatment with rabeprazole ($p = 0.022$). No other interactions terms were significant.

4. Discussion

We observed a higher prevalence of migraine among participants treated with PPIs in the UK Biobank cohort. In addition, in participants with no migraine diagnosis at baseline, treatment with PPIs was associated with a higher incidence of probable MWOA and MWA at follow-up based on data from the UK Biobank Experience of Pain Questionnaire. These results were confirmed after adjustment for gastrointestinal medical comorbidities frequently treated with PPIs, some of which have been recently shown to be significantly associated with higher migraine prevalence [30], as well as for several classes of potentially confounding drugs. Our finding of a strong association between treatment with PPIs and higher incidence of both migraine subtypes complement and extend results from a previous study conducted using the FDA Adverse Event Reporting System, which showed higher propensity for different PPI-induced adverse effects, including migraine [15]. This study was however burdened by limitations that characterize pharmacovigilance databases such as lack of information on factors that may influence the

Table 4
Unadjusted association between treatment with PPIs at baseline and incidence of probable migraine without aura, migraine with aura or chronic migraine at follow-up.

	No PPI intake at baseline	PPI intake at baseline	χ^2	p
Probable migraine without aura, %	2.7%	3.6%	20.75	<0.0001
Probable migraine with aura, %	6.7%	11.2%	289.17	<0.0001
Probable chronic migraine, %	0.2%	0.5%	46.55	<0.0001

The unadjusted association between treatment with PPIs at baseline and incidence of probable migraine at follow-up was tested using Fisher's exact test.

Table 5
Association between treatment with PPIs and incidence of probable migraine without aura, migraine with aura or chronic migraine at follow-up.

Outcome: probable migraine without aura	OR	95% CI	p
Treatment with PPIs	**1.43**	**1.27–1.61**	**<0.0001**
CYP2C19 Rapid and ultrarapid metabolizers	1.00	0.93–1.08	0.94
CYP2C19 Likely intermediate and intermediate metabolizers	0.99	0.92–1.08	0.84
CYP2C19 Likely poor and poor metabolizers	0.93	0.75–1.16	0.53
Outcome: probable migraine with aura			
Treatment with PPIs	**1.78**	**1.66–1.90**	**<0.0001**
CYP2C19 Rapid and ultrarapid metabolizers	1.01	0.96–1.06	0.63
CYP2C19 Likely intermediate and intermediate metabolizers	1.02	0.97–1.07	0.52
CYP2C19 Likely poor and poor metabolizers	1.13	0.99–1.28	0.07
***Outcome: probable chronic migraine*[2]**			
Treatment with PPIs	**3.31**	**2.34–4.69**	**<0.0001**
CYP2C19 Rapid and ultrarapid metabolizers	1.18	0.88–1.60	0.27
CYP2C19 Likely intermediate and intermediate metabolizers	0.94	0.67–1.31	0.70
CYP2C19 Likely poor and poor metabolizers	1.09	0.47–2.48	0.85

The association between treatment with PPIs at baseline and incidence of probable migraine at follow-up was tested using binary logistic regression models, adjusting for gender, age, BMI and time to follow-up.
[1] No significant interaction terms between PPI intake and either gender or CYP2C19 phenotypes.
Abbreviations: CI, confidence interval; OR, odds ratio.
[2] Significant interaction term between PPI intake and gender (p = 0.032).

Table 6
Association between treatment with specific PPIs and incidence of probable migraine without aura, migraine with aura or chronic migraine at follow-up.

Variable	OR	95% CI	p
***Outcome: probable migraine without aura*[1]**			
Omeprazole	**1.41**	**1.22–1.62**	**<0.0001**
Lansoprazole	1.23	1.00–1.52	0.051
Esomeprazole	1.03	0.59–1.80	0.93
Pantoprazole	0.82	0.30–2.22	0.70
Rabeprazole	**2.73**	**1.37–5.43**	**0.004**
CYP2C19 Rapid and ultrarapid metabolizers	1.00	0.93–1.08	0.95
CYP2C19 Likely intermediate and intermediate metabolizers	0.99	0.92–1.08	0.85
CYP2C19 Likely poor and poor metabolizers	0.93	0.75–1.16	0.53
***Outcome: probable migraine with aura*[1]**			
Omeprazole	**1.60**	**1.47–1.73**	**<0.0001**
Lansoprazole	**1.74**	**1.56–1.94**	**<0.0001**
Esomeprazole	1.21	0.88–1.66	0.24
Pantoprazole	0.79	0.43–1.47	0.46
Rabeprazole	**2.66**	**1.73–4.09**	**<0.0001**
CYP2C19 Rapid and ultrarapid metabolizers	1.01	0.96–1.06	0.63
CYP2C19 Likely intermediate and intermediate metabolizers	1.02	0.97–1.07	0.51
CYP2C19 Likely poor and poor metabolizers	1.13	0.99–1.29	0.06
***Outcome: probable chronic migraine*[2]**			
Omeprazole	**2.48**	**1.63–3.76**	**<0.0001**
Lansoprazole	**2.40**	**1.37–4.2**	**0.002**
Esomeprazole	0.00	0.00-NA	0.99
Pantoprazole	0.00	0.00-NA	1.00
Rabeprazole	**7.48**	**1.82–30.75**	**0.005**
CYP2C19 Rapid and ultrarapid metabolizers	1.18	0.87–1.6	0.28
CYP2C19 Likely intermediate and intermediate metabolizers	0.94	0.67–1.32	0.73
CYP2C19 Likely poor and poor metabolizers	1.10	0.48–2.51	0.82

The association between treatment with specific PPIs at baseline and incidence of probable migraine at follow-up was tested using binary logistic regression models, adjusting for gender, age, BMI and time to follow-up.
[1] No significant interaction terms between intake of specific PPIs and either gender or CYP2C19 phenotypes.
[2] Significant interaction term between lansoprazole intake and gender (p = 0.013). No other interactions terms were significant. Abbreviations: CI, confidence interval; NA, not available OR, odds ratio.

volume of reported adverse reactions as well as under-reporting, which allowed to analyze a low number of migraine adverse reaction reports in patients treated with PPIs (n = 168) [15].

We hypothesized this putative adverse effect to be more prevalent in participants with genetic variations in the gene encoding the CYP2C19 enzyme, which plays a major role in PPI metabolism. Indeed, in the cross-sectional analyses we found the rapid/ultrarapid metabolizer phenotype to be significantly associated with a lower prevalence of migraine only in participants treated with PPIs. This finding is in accordance with the hypothesis that patients with increased PPI clearance and decreased plasma concentrations might be less exposed to this adverse effect. When conducting analyses on specific PPIs, we observed the rapid/ultrarapid metabolizer phenotype to be significantly associated with lower prevalence of migraine in participants treated with omeprazole, in line with the major role played by CYP2C19 in the clearance of first-generation PPIs [16]. On the other hand, we also observed the CYP2C19 intermediate metabolizer status to be associated with a higher prevalence of migraine in participants treated with rabeprazole. This suggests that CYP2C19 might contribute to modulating the association between PPIs and migraine also in patients treated with PPIs primarily cleared by nonenzymatic mechanisms such as rabeprazole [17]. In addition to being involved in the metabolism of several drugs, this enzyme can act on endogenous compounds that play a major role in brain development, thus possibly exerting consequences on brain function in adult life [22,23]. Due to this, its potential association with neurological and psychiatric phenotypes is gaining increasing attention [24]. However, we did not observe significant differences in migraine prevalence based on CYP2C19 phenotype in participants not treated with PPIs. This result is in line with previous observations of a lack of significant associations between genetic variants located in this gene and migraine prevalence in, e.g., genome-wide association studies [31]. While our results do not support a major role of genetic variation of CYP2C19 in migraine prevalence in participants not treated with PPIs, its modulatory role in the association between treatment with these drugs and migraine is worthy of further investigation.

We observed significant gender differences in the longitudinal association between treatment with PPIs at baseline and development of probable chronic migraine at follow-up. Specifically, baseline treatment with PPIs as well as the CYP2C19 poor metabolizer phenotype were associated with higher incidence of probable chronic migraine in men but not in women (Supplementary Table 7). Analyses on specific PPIs confirmed this association for the first-generation PPI lansoprazole (Supplementary Table 10). We can therefore speculate that men might be particularly exposed to this putative adverse effect of PPIs, especially in the case of treatment with lansoprazole. The interpretation of these results is not straightforward. Expression of CYP2C19 has been suggested to be lower in women [32] or not different in women compared with men [33], thus suggesting that women might instead be more or equally exposed to adverse effects associated with reduced PPI clearance. In addition, these results are limited by the small number of participants with a diagnosis of probable chronic migraine in our data (Table 4). The observation that the poor metabolizer status might be associated with a higher incidence of chronic migraine in participants treated with PPIs highlights the importance of assessing CYP2C19 phenotypes and adopting appropriate dosage adjustments in participants with extreme phenotypes, in accordance with CPIC guidelines [16].

When considering the contribution of different PPIs to the observed association, we found migraine to be significantly associated with treatment with all PPIs in cross-sectional analyses except rabeprazole. This difference might be explained by the limited number of participants treated with this drug (Table 1), which in any case showed the same direction of effect as other PPIs. Previous studies had shown a higher incidence of headache in patients treated with omeprazole, lansoprazole or pantoprazole [34], or with esomeprazole and lansoprazole but not omeprazole, pantoprazole or rabeprazole [14]. Conversely, in longitudinal analyses we observed a significant association between exposure

to omeprazole, lansoprazole and rabeprazole and diagnosis of probable migraine at follow-up. While it cannot be excluded that differences in bioavailability or metabolism might modulate the association with migraine risk among various PPIs, we suggest that all commonly used PPIs might be associated with higher migraine prevalence.

To our knowledge, this is the first study to specifically investigate the association between treatment with PPIs, CYP2C19 metabolic phenotypes and migraine prevalence in a large cohort. Strengths of this study include: 1) the large number of participants with genetic and clinical information, that allowed to adjust analyses for different comorbidities and potentially confounding medications, 2) the availability of follow-up data to explore the longitudinal association between PPI exposure and development of probable migraine as well as migraine subtypes. Nonetheless, our results need to be interpreted in light of some limitations. In the cross-sectional analyses, it was not possible to infer causality in the observed association between migraine prevalence and treatment with PPIs. In addition, the lack of information on migraine subtype or severity in the baseline assessment of UK Biobank did not enable us to investigate the role of these variables in our analyses. We partially addressed this limitation by conducting longitudinal analyses in a subsample of participants with probable migraine at follow-up based on the UK Biobank Experience of Pain Questionnaire. However, information reported in this questionnaire only allowed us to assess part of the ICHD-3 criteria, leading to "probable" diagnoses. In addition, our dataset did not contain detailed information on intensity and duration of headache attacks, which might be relevant when analyzing the impact of adverse effects of PPI treatment. Finally, information on medication use was self-reported and no information on treatment adherence was available. Therefore, further studies will be needed to confirm and extend our results.

In conclusion, we observed a higher prevalence of migraine in participants treated with PPIs in UK Biobank. Men and participants with CYP2C19 phenotypes associated with decreased clearance of PPIs might be at greater risk of this adverse effect.

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CRediT authorship contribution statement

Claudia Pisanu: Conceptualization, Formal analysis, Writing – original draft. **Nike Zoe Welander:** Conceptualization, Data curation, Writing – review & editing. **Gull Rukh:** Data curation, Writing – review & editing. **Helgi Birgir Schiöth:** Supervision, Writing – review & editing. **Jessica Mwinyi:** Conceptualization, Supervision, Writing – review & editing.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jece.2021.106332.

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