Clinical Epidemiology

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ORIGINAL RESEARCH

Lifestyle factors among proton pump inhibitor users and nonusers: a cross-sectional study in a population-based setting

This article was published in the following Dove Press journal:
Clinical Epidemiology
3 December 2013
Number of times this article has been viewed

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Purpose: Lifestyle factors may influence observed associations between proton pump inhibitor (PPI) usage and health outcomes. The aim of the study reported here was to examine characteristics and differences in lifestyle among PPI users and nonusers.

Methods: This cross-sectional study utilized data from a 2006 population-based health survey of 21,637 persons in the Central Danish Region. All persons using prescribed PPIs were identified through linkage to a population-based prescription database. Biometric measures and prevalence of smoking, excessive alcohol consumption, diet, and physical exercise were analyzed, comparing PPI users with nonusers.

Results: Among 10,129 (46.8%) male and 11,508 (53.2%) female survey respondents, 1,356 (13.4%) males and 1,691 (14.7%) females reported ever use of PPIs. PPI users were more obese (16.7%) than nonusers (13.1%), with an age- and sex-standardized prevalence ratio (PR) of 1.3 (95% confidence interval [CI]: 1.2–1.4). The prevalence of smokers was also higher in the PPI group (26.2% vs 22.3% [PR =1.2, 95% CI: 1.1–1.3]), as was the prevalence of ex-smokers (41.0% vs 32.0% [PR =1.2, 95% CI: 1.1–1.2]). Unhealthy diet was slightly more common among PPI users than among nonusers (15.4% vs 13.0%), with a PR of 1.2 (95% CI: 1.1–1.3). Physical exercise level and alcohol consumption were similar in the two groups. Hospital-diagnosed comorbidity was observed in 35% of PPI users (a Charlson Comorbidity Index score of 1 or more) compared with only 15% among nonusers.

Conclusion: PPI users are more obese, smoke more, and have significantly more comorbidities than PPI nonusers. These data are important when evaluating unmeasured confounding in observational studies of PPI effects.

Keywords: PPI, obesity, smoking, reflux, population-based, gastroesophageal reflux

Introduction

After the introduction of proton pump inhibitors (PPIs) more than two decades ago, many studies have documented their beneficial effect in inhibiting gastric acid production.[1–5] PPIs are now the drugs of choice for treating gastroesophageal reflux disease (GERD), which occurs in 42% of Westerners on a monthly basis, as well as for treating peptic ulcer disease, *Helicobacter pylori* infection, and Zollinger–Ellison syndrome.[6–9] Their treatment effects have been well described, and PPIs are now among the most prescribed drugs in the world.[10–16]

As PPIs are considered generally safe drugs to use, a large percentage of patients is prescribed PPIs without a proper medical indication.[17,18] However, some observational database studies have suggested an increased risk of adverse events associated with PPI use, including cancer, osteoporosis, fractures, diarrhea, cardiovascular

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events, and pneumonia.[19–25] Most studies have not been able to adjust for potential differences in health status and lifestyle distinguishing PPI users from nonusers, which may lead to biased associations. Thus, many studies have found an association between unhealthy traits, such as increased body mass index (BMI) scores,[26–34] alcohol consumption,[28,34,35] and smoking,[33,34,36,37] and the risk of GERD, which is an important medical indication for PPI therapy. However, PPI use might be associated with increased health consciousness (frequent consultations with physicians, healthier lifestyle, etc) as is the case for the use of some other prophylactic drugs (eg, statins).

To the best of our knowledge, no study has provided data on health status and lifestyle among PPI users and nonusers in the general population. Such data are needed to evaluate uncontrolled confounding from lifestyle factors in observational PPI studies. Using data from a population-based health survey of 21,637 persons, linked to a nationwide Danish prescription database, we examined BMI, smoking habits, alcohol consumption, physical exercise habits, comorbidity, and diet in relation to PPI use.

Materials and methods

Setting

Denmark has 5.6 million inhabitants and the country provides tax-financed universal access to free health services through the Danish National Health Service. Prescribed medications, including PPIs, are partially reimbursed. The National Health Service is coordinated across five administrative regions. The Central Danish Region is the second largest of these, with 1.25 million mixed rural and urban inhabitants.

Study population

The Danish Health Survey Hvordan har du det? [How are you?] based on self-reported questionnaires, is performed every fourth year.[38] The How Are You? database contains participants' responses regarding lifestyle, diet, self-rated health, biometric measures, and diseases. Between January and March 2006, 31,500 persons living in the Central Danish Region were invited to participate. Eligible participants were Danish citizens, aged 25–79 years, identified using the nationwide Civil Registration System. A total of 21,637 persons (63% of those invited) agreed to participate and completed a detailed questionnaire.[38]

Lifestyle factors

BMI was calculated as self-reported weight in kilograms, divided by self-reported height in meters squared. Scores were categorized according to World Health Organization criteria, as underweight (BMI <18.5), normal weight (BMI =18.5–24.99), overweight (BMI =25.00–29.99) and obesity (BMI ≥ 30). Based on information about predominant type of diet (fat content and type, consumption of vegetables, fruits, bread, etc), respondents were divided into "healthy diet," "moderately healthy diet", and "unhealthy diet" groups. We defined "alcohol consumption" as either above or below the recommended maximum of 21 and 14 drinks weekly for men and women, respectively.[39] "Smoking status" was categorized as "never," "former," or "current" (daily or occasional). Physical exercise was evaluated on the basis of a number of questions regarding the respondent's level of weekly activity (at least 30 minutes of strenuous workout, daily activity in terms of walking or cycling, or other work- or leisure-related physical activities). Responses were classified as regular physical exercise (yes/no).

PPI use

In all Danish medical registries, individuals are identified by means of their Civil Registration Number. This number is a unique identifier, assigned at birth, and stored in the Civil Registration System along with date of birth, residency status, dates of immigration/emigration, and death (if applicable).[40] These identifiers allow unambiguous linkage of individual-level data among medical registries.

The population-based National Prescription Registry records all prescriptions filled nationwide, linking the Civil Registration Number to prescription data, and includes type and quantity of drug dispensed according to the Anatomical Therapeutic Chemical Classification System.[41] We used this system to identify all participants in the How Are You? survey who had received and filled a prescription for a PPI at any time before and up to 100 days after completing the survey questionnaire. PPI users were further divided into current PPI users (at least one recorded prescription for PPIs filled within 100 days before and up to 100 days after the survey date), and former PPI users (one or more PPI prescriptions filled more than 100 days before the survey date).

Comorbidity and indications for PPI

In Denmark, all *International Classification of Diseases* (ICD10)[42] hospital diagnoses and procedures are recorded, using patients' Civil Registration Numbers, in the Danish National Registry of Patients, which covers both inpatient stays and hospital clinic outpatient visits.[43] We used the Charlson Comorbidity Index (CCI) to calculate a comorbidity score for each survey respondent. The CCI covers 19 major disease categories, weighted according to their prognostic impact on

patient survival.[44] We used the Danish National Registry of Patients to search for all ICD10 codes from 1977 onwards, then grouped PPI users and nonusers according to four levels of comorbidity: score 0 (no recorded comorbidity), 1 and 2 (moderate comorbidity), and ≥3 (severe comorbidity).[42] The distribution of comorbidity scores is shown in Table 1. We assessed respondents' medical history of the following medical indications for PPI use separately: esophagitis (K20), gastroesophageal reflux (K21), esophageal erosion or ulcer (K22.1A–K22.1B), gastric ulcer (K25), duodenal ulcer (K26), gastro-duodenal ulcer (K27), and gastro-duodenitis (K29).

Statistical analysis

We estimated the prevalence of demographic variables, comorbidities, and lifestyle factors according to ever use or nonuse of PPIs. We then calculated prevalence ratios (PRs) for lifestyle factors, comparing PPI users and nonusers directly age- and sex-standardized to the cohort of all participants. All ratios were reported with a 95% confidence interval (CI). We repeated the analyses for current PPI users and former PPI users. We also calculated standardized PRs for lifestyle factors, comparing PPI users and nonusers within the subgroups of participants who all had a medical history of esophagitis, gastroesophageal reflux, or peptic ulcer. Statistical analyses were performed using SAS software (v 9.2; SAS Institute Inc., Cary, NC, USA). The Danish Registry Board approved the study (record number 2009-41-3866).

Table 1 Demographic factors and comorbidities associated with ever use of proton pump inhibitors among 21,637 persons aged 25–79 years who participated in the Hvordan har du det? [How are you?][38] survey study in the Central Danish Region, 2006

Characteristic	Ever use, n=3,047 (14.1%)	Never use, n=18,590 (85.9%)
Age, years		
Under 40	464 (15.2%)	4,667 (25.1%)
40–49	549 (18.0%)	4,303 (23.2%)
50–59	702 (23.0%)	4,283 (23.0%)
60–69	779 (25.6%)	3,485 (18.8%)
70+	553 (18.0%)	1,852 (10.0%)
Sex		
Female	1,691 (55.5%)	9,817 (52.8%)
Male	1,356 (45.5%)	8,773 (47.2%)
Charlson comorbidity index score		
0	1,982 (65.1%)	15,831 (85.2%)
1	523 (17.2%)	1,504 (8.1%)
2	309 (10.1%)	910 (4.9%)
3+	233 (7.7%)	345 (1.9%)
Hospital history of reflux, esophagitis, or ulcer diagnosis		
No	2,567 (84.3%)	18,433 (99.16%)
Yes	480 (15.8%)	157 (0.84%)

Note: Missing values are not shown.

Results

Among survey respondents, 1,356 (13.4%) males and 1,691 (14.7%) females reported PPI use. Table 1 describes PPI use by age, sex, and comorbidity level. Compared with nonusers, PPI users were older (median age =57 vs 50 years) and slightly more were female. Among PPI users, 35% had a CCI score of 1 or more, compared with only 15% among nonusers.

Among the 637 (3%) persons in the survey cohort who had previous hospital-diagnosed esophagitis, gastroesophageal reflux, or peptic ulcer, 75% (480 persons) were in the PPI-exposed group. This corresponds to prevalence rates of 16% for these medical indications among PPI users and 1% among nonusers (Table 1).

While approximately 1%–3% of survey response answers were missing for the various lifestyle questions, the proportion of missing answers was very similar for PPI users and nonusers. One exception was data on alcohol consumption data, which were missing for 8.3% of the PPI users and 13.2% of the nonusers (Table 2).

BMI

In the cohort as a whole, 7,724 persons (35.7%) reported overweight (BMI =25–30) and 2,951 (13.4%) reported obesity (BMI >30). In general, more males (44%–47%) were overweight than females (27%–29%) among both PPI users and nonusers, whereas in the obese category no major difference was seen between sexes. More PPI users were obese than nonusers (16.7% vs 13.1%, Table 2). After standardizing for differences in sex and age, PPI users had an unaltered higher prevalence of obesity (standardized prevalence =16.6% [95% CI: 15.2%–18.0%]) than nonusers (standardized prevalence =13.2% [95% CI: 12.7%–13.7%]), corresponding to a standardized PR of 1.3 (95% CI: 1.2–1.4). No major differences were seen in the other weight categories.

Diet and exercise

We observed an increased standardized PR (1.2 [95% CI: 1.1–1.3]) for unhealthy diets among PPI users compared with nonusers. Among both PPI users and nonusers, only one-third undertook regular exercise. The standardized PR for exercise among PPI users was 0.9 (95% CI: 0.9–1.0).

Smoking and alcohol

The number of current smokers (25.1% vs 22.4%) and previous smokers (41.0% vs 32.0%) was higher among PPI users than nonusers. The corresponding PRs among PPI users were 1.2 (95% CI: 1.1–1.3) for current smoking and

Table 2 Prevalence and standardized prevalence ratios (PRs) for various lifestyle factors among ever users of proton pump inhibitors (PPIs) compared with never users of PPIs

Characteristic	Crude prevalence, ever PPI use, n=3,047	Crude prevalence, never PPI use, n=18,590	Standardized PR,* ever vs never use of PPIs (95% CI)
BMI			
Underweight	47 (1.5%)	265 (1.4%)	1.0 (0.7–1.4)
Normal weight	1,280 (42.0%)	8,862 (47.7%)	0.9 (0.8–0.9)
Overweight	1,137 (37.3%)	6,587 (35.4%)	1.1 (1.0–1.1)
Obese	508 (16.7%)	2,443 (13.1%)	1.3 (1.2–1.4)
Missing	75 (2.5%)	433 (2.3%)	–
Diet			
Healthy	632 (20.7%)	3,901 (21.0%)	0.9 (0.9–1.0)
Moderately healthy	1,872 (61.4%)	11,852 (63.6%)	1.0 (0.9–1.0)
Unhealthy	446 (14.6%)	2,434 (13.1%)	1.2 (1.1–1.3)
Missing	97 (3.2%)	403 (2.2%)	–
Exercise			
Regular	1,221 (40.1%)	8,468 (45.6%)	0.9 (0.9–1.0)
Not regular	1,746 (57.3%)	9,740 (52.4%)	1.1 (1.0–1.1)
Missing	80 (2.6%)	382 (2.0%)	–
Tobacco smoking			
Current smoker	764 (25.1%)	4,169 (22.4%)	1.2 (1.1–1.3)
Former smoker	1,250 (41.0%)	5,949 (32.0%)	1.2 (1.1–1.2)
Never smoker	989 (32.5%)	8,307 (44.7%)	0.8 (0.7–0.8)
Missing	44 (1.4%)	165 (0.9%)	–
Alcohol intake			
>14/>21 weekly drinks for women/men	16.9 (16.9%)	3,080 (16.6%)	1.0 (0.9–1.1)
≤14/≤21 weekly drinks for women/men	2,129 (69.9%)	13,974 (75.2%)	1.0 (0.9–1.0)
Missing	402 (13.2%)	1,536 (8.3%)	–

Note: *Standardized to the distribution of age and gender in the total study population.
Abbreviations: BMI, body mass index; CI, confidence interval.

1.2 (95% CI: 1.1–1.2) for previous smoking (Tables 2 and 3). There was little difference in overall alcohol consumption between the two groups, with 16.6% (95% CI: 16.0%–17.1%) of PPI users and 16.9% (95% CI: 15.3%–18.9%) of nonusers exceeding recommended weekly alcohol consumption, yielding a standardized PR of 1.0 (95% CI: 0.9–1.1).

Sub-analyses for current versus former PPI use and medical indications for PPIs

In general, we observed similar lifestyle associations with PPI use among current and former PPI users (Table 3).

When we restricted our analyses to persons with a hospital history of medical indication for PPI use (esophagitis, gastroesophageal reflux, or peptic ulcer), the associations between PPI use and an increased BMI were similarly strong, as in the overall cohort. Thus, standardized PRs among PPI users were 1.4 (95% CI: 0.8–2.2) for obesity and 1.4 (95% CI: 1.0 – 1.9) for overweight. In contrast, the PRs for current and former smoking associated with PPI use in the medical indication sub-cohort were lower than in the overall cohort – that is, close to 1.0. PRs for the other lifestyle factors were similar to those for the overall cohort.

Discussion

This study of more than 20,000 participants in a population-based survey found that the prevalence of obesity, smoking, comorbidity, and, to a lesser degree, unhealthy diet was higher among PPI users than among persons who never used PPIs. To our knowledge, this is the first population-based study evaluating lifestyle characteristics in PPI users compared with nonusers, based on population comparisons after controlling for age and sex differences.

Our finding that more than one-third of PPI users were either overweight or obese, with PPI users more obese than nonusers is in accordance with earlier research showing that high BMI is a major risk factor for gastroesophageal reflux, which in turn is the main indication for prescribing PPIs.[26–34] Further, when we restricted our analysis to persons with a hospital-diagnosed indication for PPI use, we still found that PPI users were more obese than nonusers. In a recent study of 726 PPI users in the UK, the proportion of overweight or obese patients was 67.5%.[45] Similarly, a recent report based on Nurses' Health Study data found PPI users to have both a higher BMI and be less physically active than PPI nonusers.[25] In contrast, a study of PPI use and risk of hip

Table 3 Prevalence and standardized prevalence ratios (PRs) for various lifestyle factors among current and former proton pump inhibitor (PPI) users compared with never users of PPIs

Characteristic	Crude prevalence, current use of PPIs, n=1,179	Standardized PR,* current vs never use of PPIs (95% CI)	Crude prevalence, former use of PPIs, n=1,868	Standardized PR,* former vs never use of PPIs (95% CI)
BMI				
Underweight	17 (1.4%)	1.1 (0.7–1.9)	30 (1.6%)	0.9 (0.6–1.4)
Normal weight	449 (38.8%)	0.9 (0.8–0.9)	831 (44.9%)	1.0 (0.9–1.0)
Overweight	459 (38.1%)	1.0 (0.9–1.1)	678 (36.3%)	1.0 (0.9–1.1)
Obese	220 (18.7%)	1.4 (1.2–1.7)	288 (15.4%)	1.2 (1.0–1.3)
Exercise				
Regular	438 (37.2%)	0.8 (0.8–0.9)	783 (41.9%)	1.0 (0.9–1.0)
Not regular	713 (60.5%)	1.1 (1.1–1.2)	1,033 (55.3%)	1.0 (1.0–1.1)
Diet				
Healthy	250 (21.2%)	0.9 (0.8–1.1)	382 (20.5%)	1.0 (0.9–1.1)
Moderately healthy	713 (60.5%)	1.0 (0.9–1.0)	1,159 (62.0%)	1.0 (0.9–1.0)
Unhealthy	174 (14.8%)	1.2 (1.0–1.4)	272 (14.6%)	1.1 (1.0–1.3)
Tobacco smoking				
Current smoker	287 (24.3%)	1.1 (1.0–1.2)	477 (25.5%)	1.1 (1.0–1.3)
Former smoker	517 (43.9%)	1.2 (1.1–1.3)	733 (39.2%)	1.1 (1.0–1.2)
Never smoker	355 (30.1%)	0.7 (0.7–0.8)	634 (33.9%)	0.8 (0.7–0.9)
Alcohol intake				
>14/>21 weekly drinks for women/men	215 (18.2%)	1.0 (0.9–1.1)	247 (13.2%)	0.9 (0.8–1.0)
≤14/≤21 weekly drinks for women/men	809 (68.6%)	1.0 (0.9–1.0)	1,320 (70.6%)	1.0 (0.9–1.0)

Notes: *Standardized to age and sex in the total study population. Missing values are not shown.
Abbreviations: BMI, body mass index; CI, confidence interval.

fractures reported no difference in either BMI or smoking habits between PPI users and nonusers.[46] In our study, both current and previous smoking were more prevalent among PPI users than among nonusers. This accords with a number of previous studies of which many reported odds ratios of ~2 for an association between smoking and risk of reflux symptoms.[31,34,36,37,46,47]

We did not observe an association between ever use of PPIs and overall alcohol consumption. Conflicting reports have been published about the association between alcohol consumption and risk of reflux symptoms, and some studies found such an association only for selected types of alcohol.[28,34,37,48,49]

We found no association between physical exercise habits and PPI use. Absence of an association between exercise and reflux symptoms has been found in some questionnaire studies,[49,50] whereas two recent population-based studies found a lower prevalence of GERD symptoms among persons who exercised regularly.[34,37] Some studies have suggested that physical exercise may increase the amount of transient lower esophageal sphincter relaxation, thereby possibly diminishing any positive effect of regular exercise on GERD.[48]

Previous data on dietary habits among PPI users are scarce. Published results have been conflicting concerning unhealthy diet as a possible risk factor for GERD. Some studies found no association between dietary fat intake and GERD,[34,49] whereas other studies are compatible with an association between high intake of dietary fat and reflux symptoms.[51] Further studies are needed to clarify this association.

It is evident from our data that patients prescribed PPIs have substantially more comorbidity than nonusers. Previous studies in reflux patients have reported similar findings,[52,53] and a recent study performed at our institution showed marked comorbidity differences between controls and reflux patients.[54] Thus, comorbidity should be taken into account when designing and interpreting studies involving reflux patients or PPI users.

Strengths and limitations

The main strengths of our study are its comparatively large size, yielding precise risk estimates, and the use of independent population-based and highly valid registries for assessing PPI use and comorbidity, minimizing the possibility of recall and investigator bias as compared with other studies. A study limitation is the response rate of 63% in the survey, so generalizations of our findings should be made with caution. Further, persons who choose to participate in a survey may have a different risk factor profile and better health than those who decline.[55] However, this is likely to apply to both PPI users and nonusers, and thus would not bias the relative estimates we report. Another study limitation is its

cross-sectional design, which makes it uncertain whether PPI use preceded lifestyle changes or vice versa. However, our main objective was to examine lifestyle differences among PPI users and nonusers, rather than to make inferences about the causal mechanisms.

Conclusion

This cross-sectional study among health survey respondents found that persons who use PPIs are more obese, smoke more, tend to follow a less healthy diet, and have more comorbidity than nonusers. These data may be useful when estimating the amount of uncontrolled confounding from lifestyle factors in observational studies of reflux patients and of PPI effects.

Acknowledgment

The authors acknowledge Henrik T Sorensen for his contribution in the planning of this study.

Disclosure

This study was supported by the Institute of Clinical Medicine and Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark. The sponsors played no role in the study design, data collection, data analysis, data interpretation, or writing of the report. Frederik Hvid-Jensen, Rikke B Nielsen, Lars Pedersen, Peter Funch-Jensen, Asbjørn M Drewes, Finn B Larsen, and Reimar W Thomsen declare no conflicts of interest in this work.

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