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The effect of medications which cause inflammation of the gastro-oesophageal tract on cancer risk: A nested case-control study of routine Scottish data

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Abbreviations: PCCIUR: Primary Care Clinical Information Unit Research; OR: odds ratio; CI: confidence interval; MICE: multiple imputation with chained equations

Novelty and Impact: This is the first study to investigate the impact of tetracyclines and spironolactone use on gastro-oesophageal cancer risk. Our findings should provide considerable reassurance to the many GPs and patients prescribing or taking these medications. Previous evidence around the effect of bisphosphonates on gastro-oesophageal cancer risk is mixed. Our work provides further evidence of no association, and could suggest that previous findings of positive associations might have been impaired by ascertainment bias.

Abstract (Structured)

Purpose: Bisphosphonate, tetracycline and spironolactone use has been shown to increase gastro-oesophageal inflammation, an accepted risk factor for cancer. We explore whether use of these medications is associated with an increased risk of gastro-oesophageal cancer.

Methods: A nested case-control study was conducted using the Primary Care Clinical Information Unit Research (PCCIUR) database from Scotland. Cases with oesophageal or gastric cancer between 1999 and 2011 were matched to up to five controls based on age, gender, year of diagnosis and general practice. Medication use was ascertained using electronic prescribing records. Conditional logistic regression was used to calculate odds ratios (ORs) for the association between medication use and cancer risk after adjustment for comorbidities and other medication use.

Results: A similar proportion of gastro-oesophageal cancer cases received bisphosphonates (3.9% vs. 3.5%), tetracycline (6.0% vs. 6.0%) and spironolactone (1.4% vs. 1.1%) compared with the controls. The adjusted ORs for the association between gastro-oesophageal cancer and bisphosphonates, tetracycline and spironolactone were 1.05 (95% CI: 0.85, 1.31), 0.99 (95% CI: 0.84, 1.17) and 1.04 (95% CI: 0.73, 1.49). Further analysis revealed bisphosphonates were associated with increased oesophageal cancer risk (1.34, 95% CI: 1.03, 1.74) but reduced gastric cancer risk (0.71, 95% CI: 0.49, 1.03), although there was no obvious dose-response relationship.

Conclusions: There is little evidence that that the use of bisphosphonate, tetracycline or spironolactone is associated with increased risk of gastro-oesophageal cancer. Our findings should reassure GPs and patients that these widely-used medications are safe with respect to gastro-oesophageal cancer risk.

Abstract (Unstructured)

Bisphosphonate, tetracycline and spironolactone use has been shown to increase gastro-oesophageal inflammation, an accepted risk factor for cancer. However, evidence on the effect of these medications on gastro-oesophageal cancer risk are mixed or missing entirely. Therefore, we conducted a nested case-control study using the Primary Care Clinical Information Unit Research (PCCIUR) database from Scotland. Cases with oesophageal or gastric cancer between 1999 and 2011 were matched to up to five controls based on age, gender, year of diagnosis and general practice. Medication use was ascertained using electronic prescribing records. Conditional logistic regression was used to calculate odds ratios (ORs) for the association between medication use and cancer risk after adjustment for comorbidities and other medication use.

A similar proportion of gastro-oesophageal cancer cases received bisphosphonates (3.9% vs. 3.5%), tetracycline (6.0% vs. 6.0%) and spironolactone (1.4% vs. 1.1%) compared with the controls. The adjusted ORs for the association between gastro-oesophageal cancer and bisphosphonates, tetracycline and spironolactone were 1.05 (95% CI: 0.85, 1.31), 0.99 (95% CI: 0.84, 1.17) and 1.04 (95% CI: 0.73, 1.49). Further analysis revealed bisphosphonates were associated with increased oesophageal cancer risk (1.34, 95% CI: 1.03, 1.74) but reduced gastric cancer risk (0.71, 95% CI: 0.49, 1.03), although there was no obvious dose-response relationship. Overall, there is little evidence that that the use of bisphosphonate, tetracycline or spironolactone is associated with increased risk of gastro-oesophageal cancer. Our findings should reassure GPs and patients that these widely-used medications are safe with respect to gastro-oesophageal cancer risk.

Introduction

Oesophageal and gastric cancer are among the most common cancers in the world with around 456,000 and 952,000 new cases diagnosed annually.[1] Prognosis is extremely poor, even in OECD countries such as the UK, where around 55% of patients die within one year of diagnosis.[2] Those who survive suffer marked reduction in their quality of life during treatment and recovery.[3-5] Inflammation is a well-established risk factor for cancer and various mechanisms have been proposed to explain this connection.[6, 7] Several studies have demonstrated that patients with reflux oesophagitis have much higher oesophageal cancer risk[8], most likely through the Barrett's pathway.[9, 10] It is also well recognised that chronic gastric inflammation, for example due to *H. pylori* infection, may progress to atrophy (e.g. ulceration), metaplasia, dysplasia, and gastric cancer.[11, 12]

Bisphosphonates, tetracyclines and spironolactone are widely used medications with main indications of osteoporosis, infections/acne/rosacea and hypertension/cardiac failure, respectively. During 2015, approximately 8.2, 3.2 and 2.5 million were prescribed by English general practitioners.[13] Long-term usage of these medications is common; for example the anti-fracture effects of some bisphosphonates are only realised after 36 months[14] and tetracycline treatment for acne can last indefinitely.[15] Each of these medications has been associated with increased risk of gastro-oesophageal inflammation. Specifically, bisphosphonates have been shown in case reports to cause severe esophagitis including inflammation and thickening of the oesophageal wall[16, 17] Tetracyclines have also been shown to cause oesophagitis[18, 19] with prospective studies finding an increased risk of oesophageal injury and ulceration[20], and case reports demonstrating tetracycline induced lesions.[21] Similarly, spironolactone has been associated with inflammation of the stomach including increased risk of gastric ulcers[22], possibly due to impaired mucosal healing. [22, 23] Despite the widespread and prolonged use of these medications, epidemiological studies have focussed solely on bisphosphonates and gastro-oesophageal cancer risk[24], and have yet to investigate the risk associated with tetracyclines and spironolactone use.

Therefore, in a case-control study nested within a population-based primary care cohort from Scotland, we investigated whether bisphosphonates, tetracyclines or spironolactone were associated with an increased risk of gastro-oesophageal cancer.

Methods

Data

We conducted a nested case-control study using the Primary Care Clinical Information Unit Research (PCCIUR) database.[25] Between 1993 and 2011, the PCCIUR collected computerised medical records from approximately 15% of the Scottish general practice population, and includes details on patient demographics (e.g. age, deprivation), primary care encounters, clinical diagnoses and prescriptions. Access to the PCCIUR data was approved by the Research Applications and Data Management Team, University of Aberdeen. Ethical approval for this study was supplied by the Queen's University Belfast, School of Medicine Ethics Committee (reference number: 15.43).

Cases and controls

Our primary outcome was gastro-oesophageal cancer since classifying tumours arising close to the oesophagogastric junction is difficult, and guidance on this process evolved throughout the study period.[26, 27] However, separate site-specific estimates for oesophageal and gastric cancer were also presented. Cases were defined as patients with a first-time oesophageal (Read code: B10..) or gastric (Read code: B11..) cancer diagnosis after 1st January 1999 and before 30th April 2011. Up to five controls were randomly selected for each case matched on age, gender, year of diagnosis and general practice. The index date was defined as the diagnosis date of the case in each matched group. The start of the exposure period was the latest of 1st January 1996 (as prescriptions before this were less likely to be generated electronically) or the date of general practice registration. Additionally, the exposure period was truncated to ensure it was identical across the matched groups.[28] Cases and controls with an earlier cancer diagnosis (other than non-melanoma skin cancer), and those with less than three years of exposure prior to index date, were excluded from the matching process.

Definition of exposure

We identified prescriptions of bisphosphonates, tetracyclines and spironolactone from electronic prescription records. We used the British National Formulary (August 2016 version) to compile a list of proprietary and generic drug names containing these compounds (Appendix 1). We excluded prescriptions before 1st January 1996 and those in the year prior to the index date (to prevent reverse causation). We defined patients as users if they had at least one prescription during the exposure period. To enable the testing of dose-response relationships we calculated the total number of prescriptions received during the exposure period and split patients into lower (less than the median) and higher (more than the median) users. We conducted a separate analysis for

nitrogen-containing bisphosphonates, as these have a mechanism of action distinct from non-nitrogen containing products[29], and alendronate, which has been previously linked to cases of esophageal cancer.[30]

Confounding factors

We identified eleven comorbidities (myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, connective tissue disease, dementia, chronic obstructive pulmonary disease, rheumatoid arthritis, diabetes, renal disease, liver disease) using Read codes recorded by the GP during the exposure period.[31] Use of aspirin and statins within the exposure period were identified from prescription records (Appendix 1) as associations with oesophageal and/or gastric cancer have been identified previously.[32, 33] Lifestyle data including obesity (BMI>30), smoking status (never, ex, current) and alcohol use (none, low [e.g. moderate or light drinker], high [e.g. above recommended limits, chronic alcoholism]) were also recorded in the PCCIUR data using Read codes.

Statistical Analysis

We calculated descriptive statistics and compared the demographics and clinical characteristics of the cases and controls. We used conditional logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for the association between medication use and gastro-oesophageal cancer. The matched design of the study accounted for the effect of age, gender, general practice and year of diagnosis with additional adjustments were made for statin use (yes/no), aspirin use (yes/no) and the presence of each comorbidity (yes/no) using regression.

We performed additional sensitivity analysis to investigate the impact of additionally adjusting for smoking, alcohol consumption and obesity using complete case and multiple imputation with chained equations (MICE) methods. The imputation used ordered logit models with age, gender and deprivation, separately for cases and controls. Briefly, MICE is a simulation-based approach for handling missing data which leads to valid statistical inferences.[34] Sensitivity analyses were also conducted investigating the impact of excluding prescriptions in the two years prior to the index date (as opposed to one in the main analysis) and defining medication users as patients with at least three prescriptions (as opposed to one in the main analysis). Analyses was conducted using Stata version 13.[35]

Results

We identified 3,098 cases of gastro-oesophageal cancer (1,979 oesophageal and 1,119 gastric cancer) (Table 1). An average of 4.8 controls existed for each case with a median exposure period of 5.5 years (min 3.0, max 15.1). There were some potentially important differences between cases and controls. Most notably, a larger proportion of cases had a history of COPD (11.7% vs 8.5%), and were more likely to be current or ex-smokers (64.7% vs 55.3%), drink high levels of alcohol (7.5% vs. 5.3%) and have a BMI under thirty (85.8% vs 79.9%). The proportion of missing data for smoking status and alcohol consumption was 21.5% and 32.0% respectively.

Overall, 3.9% (122/3098) of cases and 3.5% (526/14937) of controls used bisphosphonates suggesting little association between bisphosphonate use and gastro-oesophageal cancer risk (OR_{adj}= 1.05; 95% CI: 0.85, 1.31) (Table 2). There was evidence of a 34% increased risk (OR_{adj}= 1.34; 95% CI: 1.03, 1.74) of oesophageal cancer in bisphosphonate users but a reduction of 29% (OR_{adj}= 0.71; 95% CI: 0.49, 1.03) in gastric cancer. The association between bisphosphonate use and oesophageal or gastric cancer did not appear to follow a dose-response relationship.

Tetracycline was used by 6.0% (186/3098) of cases and 6.0% (894/14937) of controls; there was no evidence of association with gastro-oesophageal cancer risk (OR_{adj}= 0.99; 95% CI: 0.84, 1.17). Similarly, little associations were observed between tetracycline use and oesophageal (OR_{adj}= 1.01; 95% CI: 0.82, 1.25) and gastric cancer (OR_{adj}= 0.96; 95% CI: 0.73, 1.28).

Overall, 1.4% (43/3098) of cases and 1.1% (159/14937) of controls used spironolactone but there were small associations with gastro-oesophageal cancer risk after adjustment for confounders (OR_{adj}= 1.04; 95%: 0.73, 1.49). Again, there was little evidence of higher risk for oesophageal or gastric cancer alone, with adjusted odds ratios of 1.04 (95% CI: 0.68, 1.61) and 1.05 (95% CI: 0.55, 2.00) respectively.

In general, our conclusions were little altered in sensitivity analyses (Table 3). Similar associations were observed when excluding prescriptions in the two years prior to diagnosis rather than one (to reduce the risk of reverse causality), and when the exposure definition of ‘ever use’ was based upon three or more prescriptions rather than one. Additionally adjusting for lifestyle factors (smoking, alcohol consumption, and obesity), either in a complete case analysis or when using MICE, resulted in similar estimates to the main analysis. We also found slightly larger, although still moderate, associations when restricting our analysis to nitrogen-containing bisphosphonates (OR_{adj}= 1.15; 95%

CI: 0.90, 1.46), or alendronate alone (OR_{adj}= 1.13; 95% CI: 0.87, 1.46), compared to the main analysis which combined all bisphosphonates.

Discussion

In this study of oesophageal and gastric cancer cases and controls in a community-based population, we found little evidence of an association between gastro-oesophageal cancer risk and the use of bisphosphonates, tetracyclines or spironolactone. Although there was some evidence that bisphosphonates increased the risk of oesophageal cancer, there was no obvious dose-response relationship and these increases were largely offset by a reduction in gastric cancer risk.

Strengths and limitations

The main strength of our study lies in the high-quality and nationally representative data on which it is based.[36] It is the first study to investigate the effect of tetracycline and spironolactone on gastro-oesophageal cancer risk and has found no evidence of an increased incidence, which is important and reassuring given the large numbers of patients who use these medications often for prolonged periods of time. We used prescribing data collected as part of routine clinical care, in many cases, several years before the onset of oesophageal or gastric cancer which accurately reflects GP prescribing practices and negates the risk of recall bias. Although a weakness of this approach is that we do not know if patients used their prescribed medications, the main conclusions were similar when restricting our analysis to patients who received multiple repeat prescriptions (>12) where non-compliance is likely to be less of an issue. Additionally, GP records do not contain data on over-the-counter medications which may have impaired our ability to accurately adjust for aspirin use (due to exposure misclassification).

Our study is observational and hence open to confounding; although we have controlled for several of the key determinants of cancer risk through the matched design and analysis (e.g. age, comorbidities and general practice) some other risk factors, including ethnicity and nutrition, were not available. This could be a particular concern in the bisphosphonate analysis, as patients with osteoporosis may be more likely to report upper gastrointestinal disorders, even prior to bisphosphonate initiation.[37] Our analysis is based on GP diagnosed cancer. Although a recent CPRD study found that over 95% of gastro-oesophageal cancers are captured within GP records[38], a higher proportion of oesophageal cancers were recorded in the Scottish Cancer Registry[39] than the PCCIUR data, which could suggest some misclassification of cancer site in our study. This potential issue would not affect our primary analysis which combined oesophageal and gastric cancers. Finally, histological data were not available to allow a separate analysis of squamous cell carcinoma and adenocarcinoma, the two most common forms of oesophageal cancer.

Comparisons with other research

To our knowledge, this is the first study to investigate the impact of tetracyclines and spironolactone use on gastro-oesophageal cancer risk.

Several studies have previously examined the effect of bisphosphonates on gastro-oesophageal cancer risk. In agreement with our findings, two UK-based studies which combined the oesophageal and gastric cancer sites together in a single analysis found no significant association[40, 41] with bisphosphonate use, while another Danish study reported a 37% decrease in risk.[42] Although a recent meta-analysis reported no significant association between bisphosphonate use and oesophageal cancer risk[24], several individual studies have observed an association. For example, one UK-based study reported a 30% increased risk of oesophageal cancer among bisphosphonate users, which was similar to the 34% effect size estimated in our study.[43, 44] Our finding of reduced gastric cancer incidence among bisphosphonate users was replicated by several other studies[43-45], including one which found a 39% reduction in the risk of gastric cancer[42], although a recent meta-analysis reported no overall effect.[24] Several studies investigating the effect of bisphosphonate use on cancer incidence, separately for both the oesophageal and gastric sites, reported a similar pattern to our study (i.e. increased risk of oesophageal cancer which was largely offset by a decreased risk of gastric cancer).[43-45]

Implications

Bisphosphonate, tetracycline and spironolactone are widely used and effective treatments for a range of indications including osteoporosis, infections/acne/rosacea and hypertension/cardiac failure respectively. Our study suggests that any inflammation caused by these medications does not substantially increase the risk of gastro-oesophageal cancer, and GPs or patients should not be unduly concerned about cancer risk when prescribing or taking these treatments.

It is unclear why bisphosphonate users had an increased risk of oesophageal cancer in our study. Firstly, these results could represent a true causal association; bisphosphonates are well known to cause dyspepsia and other inflammatory changes (e.g. oesophagitis, mucosal abnormalities)[46] which could form an important part of the upper-gastrointestinal cancer pathway.[30] Perhaps more likely, particularly given our concurrent finding of lower gastric cancer risk among bisphosphonate users, is that these associations are at least partly driven by a form of ascertainment bias. One Danish study

reported that, due to higher rates of gastrointestinal side effects, patients receiving bisphosphonates were more than twice as likely to undergo upper endoscopy (4.1% vs. 1.7%).[42] This could lead to earlier detection of oesophageal cancer and more accurate classification of some oesophageal tumours proximal to the oesophagogastric junction in bisphosphonate users, which would have otherwise been incorrectly recorded as gastric in origin.[42]

Conclusions

Overall, our study provided little evidence that the use of bisphosphonate, tetracyclines or spironolactone are associated with increased risk of gastro-oesophageal cancer. These findings should reassure GPs and patients that these widely-used medications are safe with respect to gastro-oesophageal cancer risk.

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Tables and Figures

Table 1: Characteristics of controls and cases with oesophageal or gastric cancer

	Cases	Controls
Count	3,098	14,937
Median Exposure Years (Min, Max)	5.5 (3.0, 15.1)	5.5 (3.0, 15.1)
Year of Diagnosis		
1999-2003	1,063 (34.3%)	5,151 (34.5%)
2004-2007	1,404 (45.3%)	6,741 (45.1%)
2008-2011	631 (20.4%)	3,045 (20.4%)
Mean Age (SD)	69.6 (11.3)	69.1 (11.2)
0-39	26 (0.8%)	133 (0.9%)
40-59	563 (18.2%)	2,807 (18.8%)
60-79	1,886 (60.9%)	9,269 (62.1%)
80+	623 (20.1%)	2,728 (18.3%)
Sex		
Female	1,095 (35.3%)	5,287 (35.4%)
Male	2,003 (64.7%)	9,650 (64.6%)
Smoking status		
Non-smoker	931 (35.3%)	5,147 (44.7%)
Ex-smoker	898 (34.0%)	3,656 (31.8%)
Current smoker	811 (30.7%)	2,708 (23.5%)
Missing	458	3,426
Alcohol Consumption		
No	551 (24.4%)	2,338 (23.3%)
Low	1,534 (68.1%)	7,145 (71.3%)
High	169 (7.5%)	532 (5.3%)
Missing	844	4,922
Obesity		
Not Obese	2,658 (85.8%)	11,932 (79.9%)
Obese	440 (14.2%)	3,005 (20.1%)
Deprivation Quintile		
1 (Least Deprived)	375 (12.3%)	1,776 (12.0%)
2	555 (18.1%)	2,657 (18.0%)
3	648 (21.2%)	3,137 (21.3%)
4	748 (24.4%)	3,637 (24.6%)
5 (Most Deprived)	734 (24.0%)	3,549 (24.1%)
Missing	38	181
Common Comorbidities[a]		
Connective Tissue Disease	1,377 (44.4%)	6,752 (45.2%)
Diabetes	328 (10.6%)	1,422 (9.5%)
COPD	361 (11.7%)	1,267 (8.5%)
CVD	283 (9.1%)	1,214 (8.1%)
MI	272 (8.8%)	1,181 (7.9%)
Other Drug Use		
Aspirin	915 (29.5%)	4,217 (28.2%)
Statin	753 (24.3%)	3,367 (22.5%)

[a] For brevity only the 5 most common comorbidities are listed. The full analysis included myocardial infarction (MI), heart failure, peripheral vascular disease, cerebrovascular disease (CVD), connective tissue disease, dementia, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, diabetes, renal disease and liver disease

Table 2: Combined analysis of drug use risk with oesophageal and gastric cancer risk

	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]
Gastro-oesophageal combined				
Bisphosphonates				
Never	2,976 (96.1%)	14,411 (96.5%)	Ref	Ref
Ever	122 (3.9%)	526 (3.5%)	1.09 (0.88,1.34)	1.05 (0.85,1.31)
Lower Usage (1-18 prescriptions)	64 (2.1%)	249 (1.7%)	1.22 (0.92,1.61)	1.16 (0.87,1.55)
Higher Usage (19+)	58 (1.9%)	277 (1.9%)	0.97 (0.72,1.31)	0.95 (0.71,1.29)
Tetracycline				
Never	2,912 (94.0%)	14,043 (94.0%)	Ref	Ref
Ever	186 (6.0%)	894 (6.0%)	1.01 (0.86,1.20)	0.99 (0.84,1.17)
Lower Usage (1)	104 (3.4%)	542 (3.6%)	0.93 (0.75,1.16)	0.92 (0.74,1.14)
Higher Usage (2+)	82 (2.6%)	352 (2.4%)	1.14 (0.89,1.45)	1.10 (0.86,1.42)
Spironolactone				
Never	3,055 (98.6%)	14,778 (98.9%)	Ref	Ref
Ever	43 (1.4%)	159 (1.1%)	1.24 (0.88,1.75)	1.04 (0.73,1.49)
Lower Usage (1-10)	21 (0.7%)	77 (0.5%)	1.26 (0.77,2.05)	1.10 (0.67,1.81)
Higher Usage (11+)	22 (0.7%)	82 (0.5%)	1.23 (0.76,1.98)	0.99 (0.60,1.62)
Oesophageal				
Bisphosphonates				
Never	1,895 (95.8%)	9,254 (97.0%)	Ref	Ref
Ever	84 (4.2%)	289 (3.0%)	1.40 (1.08,1.81)	1.34 (1.03,1.74)
Lower Usage (1-18)	47 (2.4%)	127 (1.3%)	1.78 (1.25,2.51)	1.70 (1.20,2.43)
Higher Usage (19+)	37 (1.9%)	162 (1.7%)	1.09 (0.75,1.58)	1.04 (0.71,1.52)
Tetracycline				
Never	1,858 (93.9%)	8,976 (94.1%)	Ref	Ref
Ever	121 (6.1%)	567 (5.9%)	1.04 (0.85,1.29)	1.01 (0.82,1.25)
Lower Usage (1)	66 (3.3%)	341 (3.6%)	0.95 (0.72,1.24)	0.93 (0.70,1.22)
Higher Usage (2+)	55 (2.8%)	226 (2.4%)	1.19 (0.88,1.61)	1.14 (0.83,1.55)
Spironolactone				
Never	1,949 (98.5%)	9,436 (98.9%)	Ref	Ref
Ever	30 (1.5%)	107 (1.1%)	1.27 (0.84,1.92)	1.04 (0.68,1.61)
Lower Usage (1-10)	13 (0.7%)	55 (0.6%)	1.05 (0.57,1.95)	0.94 (0.50,1.75)
Higher Usage (11+)	17 (0.9%)	52 (0.5%)	1.50 (0.86,2.61)	1.15 (0.64,2.06)
Gastric				
Bisphosphonates				
Never	1,081 (96.6%)	5,157 (95.6%)	Ref	Ref
Ever	38 (3.4%)	237 (4.4%)	0.72 (0.50,1.04)	0.71 (0.49,1.03)
Lower Usage (1-18)	17 (1.5%)	122 (2.3%)	0.65 (0.39,1.08)	0.62 (0.37,1.04)
Higher Usage (19+)	21 (1.9%)	115 (2.1%)	0.80 (0.49,1.29)	0.80 (0.49,1.31)
Tetracycline				
Never	1,054 (94.2%)	5,067 (93.9%)	Ref	Ref
Ever	65 (5.8%)	327 (6.1%)	0.96 (0.72,1.27)	0.96 (0.73,1.28)
Lower Usage (1)	38 (3.4%)	201 (3.7%)	0.90 (0.63,1.29)	0.92 (0.64,1.31)
Higher Usage (2+)	27 (2.4%)	126 (2.3%)	1.04 (0.68,1.59)	1.04 (0.68,1.59)
Spironolactone				
Never	1,106 (98.8%)	5,342 (99.0%)	Ref	Ref
Ever	13 (1.2%)	52 (1.0%)	1.18 (0.63,2.21)	1.05 (0.55,2.00)
Lower Usage (1-10)	8 (0.7%)	22 (0.4%)	1.78 (0.78,4.08)	1.53 (0.66,3.57)
Higher Usage (11+)	5 (0.4%)	30 (0.6%)	0.75 (0.29,1.98)	0.71 (0.27,1.87)

[b] Adjusted for statin and aspirin use, and the presence of myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, connective tissue disease, dementia, chronic obstructive pulmonary disease, rheumatoid arthritis, diabetes, renal disease and liver disease. Additionally conditioned on age, general practice and year of diagnosis

Table 3: Sensitivity analysis

	Cases	Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[c]
Bisphosphonates				
2- year exposure lag				
Never	3,001 (96.9%)	14,520 (97.2%)	Ref	Ref
Ever	97 (3.1%)	417 (2.8%)	1.09 (0.86,1.37)	1.04 (0.82,1.33)
Ever use ≥3 prescriptions				
Never	2,988 (96.4%)	14,442 (96.7%)	Ref	Ref
Ever	110 (3.6%)	495 (3.3%)	1.05 (0.84,1.30)	1.01 (0.81,1.26)
MI[d] lifestyle adjusted				
Never	2,976 (96.1%)	14,411 (96.5%)	Ref	Ref
Ever	122 (3.9%)	526 (3.5%)	1.09 (0.88,1.34)	1.03 (0.83,1.28)
Lifestyle complete case				
Never	2,123 (96.0%)	9,218 (96.2%)	Ref	Ref
Ever	88 (4.0%)	369 (3.8%)	1.00 (0.77,1.29)	0.93 (0.71,1.21)
Nitrogen containing bisphosphonates				
Never	3,001 (96.9%)	14,551 (97.4%)	Ref	Ref
Ever	97 (3.1%)	386 (2.6%)	1.18 (0.93,1.50)	1.15 (0.90,1.46)
Alendronate only				
Never	3,015 (97.3%)	14,603 (97.8%)	Ref	Ref
Ever	83 (2.7%)	334 (2.2%)	1.17 (0.91,1.51)	1.13 (0.87,1.46)
Tetracycline				
2- year exposure lag				
Never	2,933 (94.7%)	14,200 (95.1%)	Ref	Ref
Ever	165 (5.3%)	737 (4.9%)	1.10 (0.92,1.31)	1.07 (0.89,1.28)
Ever use ≥3 prescriptions				
Never	3,049 (98.4%)	14,718 (98.5%)	Ref	Ref
Ever	49 (1.6%)	219 (1.5%)	1.10 (0.80,1.50)	1.05 (0.76,1.45)
MI lifestyle adjusted				
Never	2,912 (94.0%)	14,043 (94.0%)	Ref	Ref
Ever	186 (6.0%)	894 (6.0%)	1.01 (0.86,1.20)	1.02 (0.86,1.20)
Lifestyle complete case				
Never	2,067 (93.5%)	8,914 (93.0%)	Ref	Ref
Ever	144 (6.5%)	673 (7.0%)	0.93 (0.76,1.13)	0.92 (0.75,1.13)
Spironolactone				
2- year exposure lag				
Never	3,069 (99.1%)	14,805 (99.1%)	Ref	Ref
Ever	29 (0.9%)	132 (0.9%)	1.02 (0.68,1.53)	0.82 (0.54,1.26)
Ever use ≥3 prescriptions				
Never	3,061 (98.8%)	14,802 (99.1%)	Ref	Ref
Ever	37 (1.2%)	135 (0.9%)	1.26 (0.87,1.83)	1.05 (0.72,1.54)
MI lifestyle adjusted				
Never	3,055 (98.6%)	14,778 (98.9%)	Ref	Ref
Ever	43 (1.4%)	159 (1.1%)	1.24 (0.88,1.75)	1.09 (0.76,1.57)
Lifestyle complete case				
Never	2,175 (98.4%)	9,478 (98.9%)	Ref	Ref
Ever	36 (1.6%)	109 (1.1%)	1.25 (0.83,1.89)	1.10 (0.72,1.69)

[c] Adjusted for statin and aspirin use, and the presence of myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, connective tissue disease, dementia, chronic obstructive pulmonary disease, rheumatoid arthritis, diabetes, renal disease and liver disease. Additionally conditioned on age, general practice and year of diagnosis

[d] Multiple imputation with chained equations for smoking, alcohol consumption and obesity with age, gender and deprivation used in the imputation, separately for cases and controls, using chained ordered logit models

Appendices

Appendix 1: List of generic and proprietary drug names for each exposure and confounder medication

Substance Name	Drug Name
Aspirin	Asasantin, Aspirin, Caprin, Co-codaprin, Micropirin, Migramax, Nu-Seals
Bisphosphonates	Aclasta, Actonel, Alendronic acid, Aredia, Binosto, Bondronat, Bonefos, Bonviva, Clasteon, Clodronate, Didronel, Didronel PMO, Fosamax, Fosavance, Iasibon, Ibrandronic acid, Loron, Pamidronate, Risedronate, Zoledronic acid, Zometa
Spironolactone	Aldactide, Aldactone, Co-flumactone, Lasilactone, Spironolactone
Statin	Atorvastatin, Cholib, Crestor, Dorisin, Fluvastatin, Inegy, Lescol, Lipitor, Lipostat, Luvinsta, Pinmactil, Pravastatin, Rosuvastatin, Simvador, Simvastatin, Stefluvin, Zocor
Tetracycline	Acnamino, Aknemin, Democlocyline, Doxycycline, Doxylar, Efracea, Lymecycline, Minocin, Minocycline, Oxymycin, Oxytetracycline, Sebomin, Tetracycline, Tetralysal, Tigecycline, Tygacil, Vibramycin-D