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STATIN ADHERENCE AND RISK OF ACCIDENTS: A CAUTIONARY TALE

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Abstract

Background—Bias in studies of preventive medications can occur when healthier patients are more likely to initiate and adhere to therapy than less healthy patients. We sought evidence of this bias by examining associations between statin exposure and various outcomes that should not be causally affected by statin exposure, such as workplace and motor vehicle accidents.

Methods and Results—We conducted a prospective cohort study of statin patients using data from British Columbia (BC), Canada, a multi-ethnic society with a population of 4.3 million people. Study subjects were 141,086 patients who initiated statins for primary prevention. We examined the association between adherence and multiple outcomes such as accidents and screening procedures using multivariable-adjusted Cox proportional hazards models.

The study population was 49% female and had an average age of 61. The results from our multivariable-adjusted models showed that more adherent patients were less likely to have accidents than less adherent patients. This effect was greatest for motor vehicle accidents (hazard ratio [HR] 0.75; 95% confidence interval [CI], 0.72 – 0.79) and workplace accidents (HR 0.77; 95% CI, 0.74 – 0.81). More adherent patients had a greater likelihood of using screening services (HR 1.17; 95%

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Conflict of Interest Disclosures

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CI, 1.15 – 1.20) and a lower likelihood of developing other diseases likely to be unrelated to a biological affect of a statin (HR 0.87; 95% CI 0.86 – 0.89).

Conclusions—Our study contributes compelling evidence that patients who adhere to statins are systematically more health seeking than comparable patients who do not remain adherent. Caution is warranted when interpreting analyses that attribute surprising protective effects to preventive medications.

Keywords

confounding bias; healthy user effect; adherence bias; pharmacoepidemiology; epidemiological methods; statins

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Observational post-marketing studies of medications are conducted to evaluate the safety and effectiveness of drugs used in actual clinical settings. These studies are essential since randomized clinical trials (RCT) often exclude populations most likely to use a drug, such as the elderly, and do not account for the complexity of using medications without the support and supervision of a clinical trial. One of the principal limitations of observational studies is confounding bias, i.e., systematic differences in prognosis between a group of patients using a medication and the comparator group of patients (1).

The healthy user effect is a hypothetical source of confounding bias that is thought to affect observational studies of drugs, diets, screening procedures, and other health-related behaviors (2,3,4). This bias presumes that patients who initiate and adhere to preventive therapies are more likely to engage in behaviors consistent with a healthy lifestyle than are patients who do not initiate or adhere to such treatments. Aspects of a healthy lifestyle could include diet, exercise, moderation of alcohol, and avoidance of risky behaviors. These characteristics, which are unmeasured in typical pharmacoepidemiologic databases, may be associated with morbidity and mortality outcomes in observational studies. Thus failure to adjust for them can lead to bias in studies of preventive therapies.

The healthy user bias has been suggested as an explanation for the discrepancy between several experimental and observational studies, including studies of the effects of long-term use of estrogen therapy (5,6,7,8) and Vitamin E (9). It has also been discussed as a potential source of bias in observational studies of the effectiveness of influenza vaccines in the elderly (2) and the association between use of HMG CoA reductase inhibitors (statins) and reduced risk of hip fracture (10), Alzheimer's disease (11), sepsis (12), cancer (13) and mortality (14). This bias has also been observed in RCTs where adherence to placebo was found to be associated with decreased mortality (15). Though long suspected as a source of bias, there is a paucity of empirical data on the healthy user effect.

We sought evidence of the healthy adherer bias in a diverse population of patients taking statins in the province of British Columbia (BC), Canada, a multi-ethnic society with comprehensive databases for prescription drugs, medical services and hospital admissions for most of its population of 4.3 million people. We hypothesized that patients who were adherent to statins would be at decreased risk of accidental events such as motor vehicle and workplace accidents, burns, falls, and other diseases because they were more actively concerned about their health and well-being than otherwise comparable non-adherent patients. Evidence of this bias across a broad number of outcomes was needed as compelling evidence since alternative hypotheses could be use to counter any single association.

METHODS

Drug Coverage in British Columbia

All residents of British Columbia can enroll in the provincial drug plan. The drug plan includes an income-based deductible of up to 3% of income, a 25% or 30% coinsurance for prescription costs above the deductible, and an out-of-pocket ceiling of 4% of income after which the province covers all eligible costs. Residents receiving social income assistance do not pay for prescription drugs, and any resident may hold supplemental drug insurance either privately or through their employer.

Data Sources and Study Population

Prescriptions for statins were obtained from the British Columbia PharmaNet database that included records of all prescriptions dispensed at community pharmacies regardless of drug plan enrollment status. Drugs dispensed in hospitals were not included in the database but should account for less than 1% of statin prescriptions. Underreporting and misclassification should be low because all community pharmacies used the PharmaNet system, which also performed data quality checks when the claims were transmitted. Prescriptions were linked by encrypted personal health numbers (PHN) to Ministry of Health databases for physician services and hospitalizations. These databases included diagnostic codes (International classification of diseases [ICD] 9th revision [physician services], 10th revision [hospitalizations]), procedure codes, and dates of service activity. The universal aspect of the Canadian health care system means that all hospital admissions and most insured physician visits were captured.

The source population included all residents of BC (3.9 million in 1997 and 4.3 million 2005) who were not residents of a nursing home. We identified patients from the PharmaNet database who used a statin between January 1, 1997 and March 31, 2004. The statins included in our analysis were atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin. New statin patients were identified as those who did not receive a statin in at least the previous 365 days. We defined the first date of a statin prescription as the index date. Patients who started a statin during the study period, discontinued and then started again more than year later were only analyzed during their first episode of care.

Patients with a history of coronary events or diabetes, because of their traumatic experiences and greater risk of future coronary events, have more compelling reasons to adhere to treatment than patients whose only indication for treatment is an elevated blood lipid value. We sought to eliminate the role of these confounders in our study by restricting the cohort to primary prevention patients without a recorded history of diabetes. Therefore, we excluded patients who received a statin for secondary prevention or had diabetes (ICD-9 250). Secondary prevention patients were those who, during the 365 days prior to the index date, had a recorded diagnosis in a hospital admission or physician service record of myocardial infarction (MI) (ICD-9 410 or 412), angina pectoris (ICD-9 413), ischemic heart disease (ICD-9 411 or 414), a recorded procedure of coronary artery bypass graft, angioplasty, stenting, intracoronary or systemic thrombolysis, angiography, or a prescription for nitroglycerin. We also excluded nursing home residents, patients who were not eligible for medical services coverage according to the provincial patient eligibility registry, and patients who received cerivastatin.

Exposure Assessment

Adherence to therapy was ascertained in the first year baseline period after statin initiation. Patients dispensed more than 120 days supply of statin medication in that year were categorized as ‘More Adherent’. Patients dispensed 120 days or less supply in the first year were categorized as ‘Less Adherent’. The typical number of days supply in a statin prescription was

60 days, and the provincial drug plan did not pay for more than 100 days of medication in a single prescription. Therefore, 'More Adherent' patients needed to receive at least 2 prescriptions to qualify for that category, but most patients in the 'More Adherent' category received 3 or more prescriptions.

Covariates

We obtained baseline demographics, health service use, and health status information from BC Ministry of Health eligibility file, Medical Services Plan database (physician visits), hospitalization database and PharmaNet database during the year prior to the first statin prescription. Covariates were defined during the baseline period and included age, sex, number of days spent in hospital, number of physician visits, and presence of various medical conditions as ascertained from inpatient and outpatient records.

Study Outcomes

We evaluated a spectrum of events after the 1-year baseline period to assess the healthy adherer bias. The outcomes were grouped into four broad categories: accident events, screening events, other events not expected to be associated with statin exposure, and other events where a possible association with statin exposure could be expected. We included inpatient and outpatient events as well as primary and secondary diagnoses. Myocardial infarction, the prevention of which is the main purpose of statin treatment, was included in the latter category to provide a relative reference for comparison. Events and corresponding diagnostic codes and procedure codes are listed in Table 1. We only studied the first occurrence of an event in outcomes that could recur.

Statistical Analysis

Patients became eligible for follow-up if they survived the 1-year baseline period, had at least one prescription and one physician visit in both the first 6 months and second 6 months of the baseline year, and did not enter a nursing facility during that period. Patients contributed person-time beginning at the end of the baseline period and were followed until the earliest of March 31, 2007, death, or in each analysis, the occurrence of the event.

The relationship between statin adherence and each outcome was examined using both unadjusted and multivariable adjusted Cox proportional hazards models. The first Cox model made no statistical adjustments for any covariates. The second model was stratified on age (<40 years, >=75 years, and 5 year age groups for ages >=40 and <75) and sex, and included the following covariates: number of drugs, physician visits, days in hospital during the baseline period, history during the baseline period of chronic obstructive pulmonary disease, peripheral vascular disease, liver disease, rheumatoid arthritis, osteoarthritis, atrial fibrillation, cancer, and Romano comorbidity score, which is meant to adjust for confounding by concomitant illnesses by assigning weights to a patient's ICD-9 diagnoses and summing those weights into a single score (16). All data analysis was performed in SAS V9.1.3.

RESULTS

We identified 247,348 patients who initiated a statin other than cerivastatin during the study period. We omitted 30,742 patients who lost eligibility during the baseline period (365 days after starting a statin) through de-enrollment or lack of system use during the year, 1,409 patients who were admitted to a nursing home prior to start of follow-up, 30,935 patients with evidence of existing coronary artery disease, 43,083 with diabetes, and 93 patients who were dispensed more than 300 days supply of statin medication in one prescription. We were left with a final cohort of 141,086 patients whose characteristics during the baseline period are given in Table 2. The cohort was 49% female and had an average age of 61. During the 12-

month baseline period, cohort members used 5 medications on average and 9% experienced an acute care hospitalization. In a small number of patients we observed a history of cancer (4%), osteoarthritis (8%), liver disease (0.3%), and peripheral vascular disease (3%). Follow-up times after the one-year baseline period varied for each patient and outcome studied. The average follow-time for all outcomes was 4.9 years. The lowest average follow-up time was 3.3 years for PSA tests in men, and the largest was 5.2 years for Sexually transmitted diseases (both sexes).

The results of our Cox proportional hazards regressions are summarized in Table 3. In the full model, stratifying on age and gender and adjusting for co-morbid conditions, we found that patients defined as 'More Adherent' to statins were less likely than 'Less Adherent' statin patients to have accidents in all of the types that we measured: burns (hazard ratio [HR]=0.88, 95% confidence interval [CI] 0.79–0.97), falls (HR=0.90, 95% CI 0.83–0.98), fractures (HR=0.92, 95% CI 0.88–0.96), motor vehicle accidents (HR=0.75, 95% CI 0.72–0.79), open wounds (HR=0.91, 95% CI 0.88–0.95), poisoning (HR=0.86, 95% CI 0.78–0.94) and workplace accidents (HR=0.77, 95% CI 0.74–0.81).

In our adjusted Cox models, patients in the 'More Adherent' category were more like to receive eye examinations (HR=1.08, 95% CI 1.05–1.12), fecal occult blood testing (HR=1.21, 95% CI 1.18–1.24), bone mineral density testing (HR=1.10, 95% CI 1.06–1.14), and prostate specific antigen testing (HR=1.07, 95% CI 1.04–1.10) during the subsequent follow-up period. There was no association or only borderline association between statin adherence and undergoing mammography (HR=1.05, 95% CI 1.00–1.10), Pap test (HR=1.03, 95% CI 0.99–1.07), or sigmoidoscopy HR=1.07, 95% CI 0.98–1.16).

Among the other events we analyzed, 15 of 20 showed a statistically significant (Type I α=0.05) association with statin adherence in our multivariable Cox model. All five of the remaining events had non-significant point estimates below 1.0. Of the 15 associations that were significant, 14 showed a reduced risk of the event in 'More Adherent' patients (Table 3). The exception was an increased association with malignant melanoma (HR=1.23, 95% CI 1.05–1.43).

DISCUSSION

In a cohort of new statin patients in British Columbia, we found that patients who were more adherent to therapy during a one-year baseline period during which adherence was ascertained, were significantly less likely to be involved in motor vehicle and workplace accidents requiring medical attention than less adherent patients. Adherent patients were also less likely to experience a variety of negative health outcomes unlikely to have be related to a therapeutic effect of statins. Our results are consistent with the hypothesis that patients who are more adherent to drug treatment take better care of themselves by engaging in various behaviors aimed at improving or maintaining health. Some examples of such health-related behaviors include better nutrition, regular exercise, seat belt use, improved dental hygiene, less smoking and moderation of alcohol consumption.

We analyzed 14 types of accident and screening events and found significant differences in event rates between more adherent and less adherent patients for all events except sigmoidoscopy, pap tests and mammography. However, all the accident and screening events, statistically significant and otherwise, were in directions that would be predicted under a healthy adherer bias (a decrease for accidents and an increase for screening). The screening results are consistent with associations between adherence and use preventive services discovered in a frail elderly American population (3). Increased relative use of fecal occult blood tests and bone mineral density tests were similar in BC and in the elderly Medicaid

patients in Pennsylvania (PA). Greater use of mammography and prostate-specific antigen tests in PA could be attributable to the older age of that cohort. In the present study, we observe the healthy adherence phenomenon in a much broader and more representative population and, additionally, we found that patients more adherent to statins were less likely to experience all of the adverse clinical outcomes we evaluated, with the exception of malignant melanoma. The increase in malignant melanoma was is possibly due to screening bias—i.e., more health-seeking patients being more likely to visit a dermatologist and have a skin lesion biopsied.

An apparent reduction in myocardial infarction (MI) in more adherent patients may have been due to a drug effect (17,18,19,20,21) in addition to the adherer bias, but the magnitude of the relative effect (RR 0.72) is not appreciably different than the reduction in motor vehicle accidents (RR 0.75) and workplace accidents (RR 0.77) where a drug effect is unlikely. Relative reductions in emergency hospital admissions and non-elective surgeries could also have been partially due to a drug effect.

We speculate that the observed association between adherence and accident events, screening tests, and the negative health outcomes we studied is due to unmeasured confounding by health-seeking behaviors of healthier patients. However, there are other potential explanations for these findings. Our definition of adherence could not be validated due to privacy constraints. Bias resulting from the definition and its ascertainment would come from patients who were classified as non-adherent but became adherent during follow-up, or adherent patients who became non-adherent. In both cases this misclassification would bias our estimate towards the null. Observational studies have attributed a protective effect of statins on cognitive functioning (22–30). If true, statin adherence could decrease the risk of accidents by improving cognition, but the magnitude of our effect estimates for accidents, especially in workplace accidents (younger patients), lacks plausibility as a drug effect. Other observed associations could be due to confounding by factors other than unmeasured health-related behaviors. For example, the association between statin adherence and reduced risk of fracture could be due to body mass index, a variable unavailable in our database. Heavier patients may have a greater clinical need for a statin yet are at decreased risk for osteoporosis and therefore less likely to experience a fracture. We also did not have reliable income data or information on whether a patient paid out-of-pocket or with private insurance. Income might be a relevant predictor of adherence and disease risk. However, it is worth noting that most screening services are available free of charge to all residents the province's universal system, and our results showing significant increased use of those services in adherent patients provides reassurance that that our findings were not the result of an income effect. While the association between adherence and any individual outcome could be plausibly attributed to a variety of different effects, the results as a whole are consistent with the healthy-adherer hypothesis, and also a recent and large cohort study of 129,000 statin initiators and 600,000 controls that found little evidence to support wide-ranging effects of statins on non-vascular outcomes (31). The principle of Occam's Razor leads us to prefer the most parsimonious explanation, which is that the associations reported in this study are largely due to unmeasured healthy behaviors that are correlated with both adherence and the outcomes.

Our study contributes new evidence of a healthy adherer association between statin treatment and numerous other health outcomes and accidental events which are not known to be a pharmacologic effect of statin treatment. These data provide a compelling reason to expect that the healthy adherer effect may be a confounder in studies of statins and health outcomes. Patients who are adherent to one medication are probably more likely to adhere to others, and our results could extend to other chronic preventive medications and health-related behaviors in general. Furthermore, the direction of healthy user bias can be anticipated. When the effect is inversely associated with the outcome then the apparent hazard ratio will be less than the true estimate. When it is positively associated with an outcome the apparent hazard ratio will

be greater than the true estimate. Therefore, a healthy adherer effect that is unaccounted for in the design or analysis of a study will make null effects appear protective, exaggerate protective effects, and attenuate harmful effects or even make them appear protective.

Our study proposes the idea that the healthy adherer effect might be detectable by examining the association between adherence to treatment and the downstream occurrence of events that should not be affected by the treatment. The British Columbia databases included medical encounters related to motor vehicle and workplace accidents. Databases in other jurisdictions may not contain those data but should contain data for other accidents such as burns, falls, fractures and open wounds. Data for screening procedures should also be ubiquitous in administrative databases. Further work in the area is clearly needed to gain a better understanding of the healthy adherer effect and to develop methods to adjust for it in observational studies. Choices in study design and analytical methods could potentially be used to control for the bias. Some possibilities are a new user design which uses an active comparator, controlling for past adherence to treatments, and instrumental variable analysis. Until this phenomenon is better understood, however, the results from our research suggest that caution is warranted when interpreting any observational analyses that report moderate protective effects to preventive medications, preventive screening, or other "healthy" behaviors known to be associated with adherence.

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Approvals:

The study received ethics approval from the University of British Columbia (UBC CREB Number H02-70020). The BC Ministry of Health approved data access.

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Table 1

Outcome Definitions

Outcome	Definition
Asthma/COPD hospitalization	DAD[a] ICD-9[b] codes: 491, 492, 493, 496 and Entry Code = Emergency
Asthma/COPD outpatient visit	MSP[c] ICD-9 codes: 491, 492, 493, 496
Bacterial Infection	ICD-9 codes: 041
Bone Mineral Density Test[e]	MSP fee item: 8688, 8689, 8696
Burns	ICD-9 codes: 940 – 949
DVT and Pulmonary Embolism	ICD-9 codes: 453.40, 453.41, 451, 415.1
Dental Problems	ICD-9 codes: 521, 522, 523, 525
Diverticulitis	ICD-9 codes: 562
Drug Dependency	ICD-9 codes: 304
Emergency Room Admission	DAD Entry Code = Emergency
Eye Exams	MSP fee item: 2015
Falls	ICD-9 codes: E88
Fecal Occult Blood Test	MSP fee item: 9234, 15110, 36509
Food-borne Bacterial Infection	ICD-9 codes: 003, 004, 005, 006, 007, 008, 009, 988
Fractures	ICD-9 codes: 800 – 829
Gall Stones	ICD-9 codes: 574
GI Bleed	ICD-9 codes: 531, 532, 533, 534, 578
Gout	ICD-9 codes: 274
Kidney Stones	ICD-9 codes: 592
Lung Cancer	ICD-9 codes:162
Malignant Melanoma	ICD-9 codes:172
Migraine	ICD-9 codes: 346
Motor Vehicle Accidents	MSP claim type = Insurance Corporation of British Columbia
Myocardial Infarction	DAD first 2 diagnosis codes: 410
Non-elective Surgery	DAD Admit Category = Urgent
Open Wound	ICD-9 codes:870 −897
PAP Test[e]	MSP fee item: 14560
Poisoning	ICD-9 codes: 960 – 987, 989
Prostate Specific Antigen Test[f]	MSP fee item: 9234, 15110, 36509
Screening Mammography[e]	MSP fee item: 8611
Sigmoidoscopy	MSP fee item: 716
Skin Infection	ICD-9 codes: 681, 682
Sexually Transmitted Disease	ICD-9 codes: 042, 054.1, 090–099
Workers Compensation Board Claim	MSP claim type = W (WCB)

[a] DAD: Discharge Abstract Database contains summary 'abstract' information from every hospital discharge or day surgery case in BC hospitals, and hospitalizations of BC residents in other Canadian provinces.

[b] International Classification of Disease Coding System, ninth revision.

[c] MSP: The Medical Services Plan insures medically required services provided by physicians and supplementary health care practitioners, laboratory services and diagnostic procedures.

[e] Restricted to female patients

[f] Restricted to male patients

Table 2

Characteristics Assessed During a 1-year Baseline Period

Characteristics	More Adherent[†]	Less Adherent[†]	Difference
N	114 612	26 474	
Age, mean (SD)	61.3 (11.6)	58.5 (12.7)	2.8
Female, % (no.)	47.9 (54 901)	51 (13 502)	−3.1
Median no. of physician visits in prior year (IQR[‡])	10 (6, 17)	11 (6, 20)	1.0
Median no. of different physicians in prior year (IQR[‡])	4 (2, 6)	4 (2, 6)	0
Median no. of distinct medications in prior year (IQR[‡])	4 (2, 6)	4 (2, 7)	0
Median no. of total hospitalizations within the previous 5 years (IQR[‡])	0 (0, 2)	0 (0, 2)	0
Median Romano score (IQR[‡])[§]	0 (0, 0)	0 (0, 0)	0
Acute care hospitalized % (no.)	8.7 (9 925)	8.6 (2 272)	0.1
History of COPD % (no)	4.9 (5 560)	6.5 (1 727)	−1.6
History of atrial fibrillation % (no.)	1.2 (1 333)	0.9 (229)	0.3
History of PVD % (no.)	2.8 (3 156)	2.2 (581)	0.6
History of liver disease % (no.)	0.3 (303)	0.4 (107)	−0.1
History of cancer % (no.)	3.7 (4 272)	3.4 (902)	0.3
History of rheumatoid arthritis % (no.)	1.4 (1 625)	1.8 (474)	−0.4
History of osteoarthritis % (no.)	7.5 (8 593)	8.5 (2 242)	−1.0

[†]Patients dispensed >120 days of medication within 1 year of initiation on a statin were classified as 'More Adherent'. Patients dispensed ≤120 days were classified as 'Less Adherent'.

[‡]Inter-Quartile Range.

[§]The majority of Romano scores were zero because the cohort was comprised of primary prevention patients

Table 3

Association Between Adherence to Statin Therapy and Risk of Health-Related Events

Outcome	More Adherent Event Rate (/ 100 py)	Less Adherent Event Rate (/ 100 py)	Unadjusted Hazard Ratio	95% Confidence Limits for Hazard Ratio	Adjusted Hazard Ratio	95% Confidence Limits for Hazard Ratio
Accident Events:						
Both Sexes (n=141,086)						
Burn	0.28	0.36	0.78	(0.71 – 0.87)	0.88	(0.79 – 0.97)
Fall	0.53	0.54	0.98	(0.90 – 1.06)	0.90	(0.83 – 0.98)
Fracture	2.20	2.38	0.93	(0.89 – 0.96)	0.92	(0.88 – 0.96)
Motor vehicle accident	1.48	2.25	0.66	(0.63 – 0.69)	0.75	(0.72 – 0.79)
Open wound	2.44	2.74	0.89	(0.86 – 0.92)	0.91	(0.88 – 0.95)
Poisoning	0.32	0.41	0.78	(0.71 – 0.86)	0.86	(0.78 – 0.94)
Workplace accident	1.31	2.13	0.62	(0.59 – 0.65)	0.77	(0.74 – 0.81)
All (first occurrence)	**7.38**	**9.39**	**0.79**	**(0.77 – 0.81)**	**0.85**	**(0.83 – 0.87)**
Screening Events:						
Both Sexes (n=141,086)						
Eye examination	3.58	2.93	1.21	(1.17 – 1.26)	1.08	(1.05 – 1.12)
Fecal occult blood test	8.06	6.14	1.31	(1.27 – 1.34)	1.21	(1.18 – 1.24)
Sigmoidoscopy	0.53	0.49	1.09	(1.00 – 1.18)	1.07	(0.98 – 1.16)
All (first occurrence)	**12.01**	**9.28**	**1.28**	**(1.25 – 1.31)**	**1.17**	**(1.15 – 1.20)**
Females (n=68,403)						
Bone mineral density test	6.74	5.96	1.13	(1.09 – 1.17)	1.10	(1.06 – 1.14)
Pap test	5.27	6.06	0.87	(0.84 – 0.91)	1.03	(0.99 – 1.07)
Screening mammography	3.35	3.32	1.01	(0.96 – 1.06)	1.05	(1.00 – 1.10)
All (first occurrence)	**6.43**	**6.76**	**0.95**	**(0.93 – 0.98)**	**1.07**	**(1.04 – 1.10)**
Males (n=72,683)						
Prostate-specific antigen test	15.63	12.91	1.20	(1.16 – 1.23)	1.07	(1.04 – 1.10)
Other events, possible association expected						
Both Sexes (n=141,086)						
Emergency hospital admission	5.59	5.96	0.94	(0.91 – 0.96)	0.87	(0.85 – 0.89)
Lung cancer	0.39	0.38	1.04	(0.94 – 1.14)	0.92	(0.83 – 1.01)
Myocardial infarction	0.50	0.61	0.82	(0.75 – 0.88)	0.72	(0.67 – 0.78)
Non-elective surgery	6.45	6.70	0.96	(0.94 – 0.99)	0.90	(0.88 – 0.92)

Outcome	More Adherent Event Rate (/ 100 py)	Less Adherent Event Rate (/ 100 py)	Unadjusted Hazard Ratio	95% Confidence Limits for Hazard Ratio	Adjusted Hazard Ratio	95% Confidence Limits for Hazard Ratio
All (first occurrence)	**6.81**	**7.12**	**0.96**	**(0.94 – 0.99)**	**0.90**	**(0.87 – 0.92)**
Other events, no association expected						
Both Sexes (n=141,086)						
Asthma/COPD hospitalization	0.38	0.42	0.91	(0.83 – 0.99)	0.87	(0.79 – 0.95)
Asthma/COPD outpatient visit	3.29	4.02	0.82	(0.80 – 0.85)	0.87	(0.85 – 0.90)
Bacterial infection	0.43	0.46	0.93	(0.85 – 1.01)	0.91	(0.83 – 0.99)
Deep Vein Thrombosis or other clot	0.58	0.56	1.03	(0.95 – 1.11)	0.98	(0.91 – 1.07)
Dental problem	0.71	1.02	0.69	(0.65 – 0.74)	0.76	(0.72 – 0.81)
Diverticulitis	1.34	1.28	1.04	(0.99 – 1.10)	0.98	(0.93 – 1.03)
Drug dependency	0.17	0.29	0.59	(0.53 – 0.67)	0.73	(0.65 – 0.83)
Food-borne bacterial infection	1.77	2.18	0.81	(0.78 – 0.85)	0.85	(0.82 – 0.89)
Gall stone	0.63	0.78	0.81	(0.75 – 0.86)	0.81	(0.76 – 0.87)
Gastrointestinal bleed	1.71	1.86	0.92	(0.88 – 0.96)	0.90	(0.86 – 0.94)
Gout	1.35	1.44	0.94	(0.89 – 0.99)	0.89	(0.85 – 0.94)
Kidney stone	0.51	0.55	0.93	(0.85 – 1.00)	0.96	(0.89 – 1.04)
Malignant melanoma	0.19	0.14	1.35	(1.16 – 1.58)	1.23	(1.05 – 1.43)
Migraine	0.81	1.20	0.67	(0.63 – 0.71)	0.82	(0.78 – 0.87)
Sexually Transmitted Disease	0.13	0.16	0.82	(0.71 – 0.95)	0.93	(0.80 – 1.09)
Skin infection	3.08	3.41	0.90	(0.87 – 0.93)	0.93	(0.90 – 0.96)
All (first occurrence)	**14.58**	**17.47**	**0.85**	**(0.83 – 0.86)**	**0.87**	**(0.86 – 0.89)**

*The analysis is stratified on age and sex. Multivariable adjustments are made for all the other covariates given in Table 2. Subjects were censored by end of follow-up and death.