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Statins and Male Sexual Health: A Retrospective Cohort Analysis

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Abstract

Introduction—Conflicting reports exist regarding the role of statins in male gonadal and sexual function. Some studies report a beneficial effect, particularly for erectile dysfunction (ED), through statins' anti-inflammatory and cardiovascular protective properties. Others suggest that statins might be associated with sexual dysfunction through negative effects on hormone levels.

Aim—To compare the risk of gonadal or sexual dysfunction in statin-users versus non-users in a single payer healthcare system.

Methods—A retrospective cohort study of all male patients (30–85 years) enrolled in Tricare San Antonio market. Using 79 baseline characteristics, we created a propensity score-matched cohort of statin-users and non-users. The study duration was divided into a baseline period (October 1,

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2003 to September 30, 2005), to describe patient baseline characteristics, and a follow-up period (October 1, 2005 to March 1, 2012) to determine patient outcomes. Statin-users were defined as those prescribed a statin for 3 months between October 1, 2004 and September 30, 2005.

Main Outcome Measures—Outcomes were identified as the occurrence of benign prostatic hypertrophy (BPH), ED, infertility, testicular dysfunction, or psychosexual dysfunction during the follow-up period as identified by inpatient or outpatient *International Classification of Diseases, 9th Revision, Clinical Modification* codes. Logistic regression was used to determine the association of statin use with patient outcomes.

Results—Of 20,731 patients who met study criteria, we propensity score-matched 3,302 statinusers with 3,302 non-users. Statin use in men was not significantly associated with an increased or decreased risk of BPH (OR 1.08; 95% CI 0.97-1.19), ED (OR 1.01; 95% CI 0.90-1.13), infertility (OR 1.22; 95% CI 0.66-2.29), testicular dysfunction (OR 0.91; 95% CI 0.73-1.14), or psychosexual dysfunction (OR 1.03; 95% CI 0.94-1.14).

Conclusions—Statin use was not associated with increased risk of being diagnosed with gonadal or sexual dysfunction in men. Further studies using larger sample may be needed.

Keywords

benign prostatic hypertrophy; erectile dysfunction; male infertility; testicular dysfunction; psychosexual dysfunction; statin

Introduction

Men sexual health has emerged as a major public health concern in the United States (U.S.), particularly as the population ages and develops co-existing medical conditions. Sexual dysfunction is increasingly common among U.S. men. It is estimated that erectile dysfunction (ED) affects 18 million men in the U.S.¹ Furthermore, BPH affects more than half of men age 60 years and older and can result in reduced sexual function.^{2,3} Finally, these conditions may have a significant negative impact on quality of life and result in substantial health care costs.³⁻⁶

Prior studies have demonstrated an association between hyperlipidemia and increased risk of sexual dysfunction, mediated through endothelial dysfunction and inflammation.⁷ ED frequently precedes cardiovascular disease and may serve as an early maker of disease progression.⁸ Lipidlowering drugs, such as HMG-CoA reductase inhibitors (i.e. statins), have been hypothesized to reduce sexual dysfunction in men; however, results are conflicting. Several studies have associated statins with sexual and gonadal dysfunction, including ED, lower testosterone levels, and decreased libido.⁹⁻¹¹ On the other hand, statins ameliorate endothelial dysfunction and increase nitric oxide bioavailability, which can improve ED.¹²⁻¹⁴ Furthermore, the antiinflammatory properties of statins may result in a decreased risk for the development of BPH; however, few studies have evaluated this association.¹⁵

In light of the limited and conflicting evidence regarding statins and gonadal and sexual function, the objective of this study is to examine the risks of gonadal and sexual

dysfunction among statin-users and non-users in a large cohort of patients from a single-payer health system.

Methods

Study design

The study was approved by the Brooke Army Medical Center Institutional Review Board, San Antonio, Texas. The study population and database characteristics have been published elsewhere.¹⁶ In short, this was a retrospective cohort study of patients enrolled in the San Antonio Tricare catchment area. We collected longitudinal data using the Military Health System Management Analysis and Reporting Tool (M2) from October 1, 2003 through June 1, 2012. The M2 application is used for administrative monitoring, outcome tracking, and correlational research.¹⁷⁻²⁰ This system is comprised of outpatient medical records, inpatient medical records, benefits claims for health care delivered outside the military health system, laboratory data, and pharmacy data. The laboratory data include all tests performed within the military health care system and results of those tests. Pharmacy data include all pertinent patient demographics and medication dosing information regardless of point-of-care location.

The study was divided into two sequential time periods: an initial period from October 1, 2003 to September 30, 2005 to establish the baseline patient characteristics, and a follow-up period from October 1, 2005 to March 1, 2012 to assess patient outcomes.

Patient population

Patients were included in this study if they: (1) were enrolled in Tricare Prime/Plus during fiscal year (FY) 2010 in the San Antonio catchment area, (2) were 30 to 85 years old, (3) had at least one outpatient visit during both the baseline (FY 2003 to 2005) and follow-up (FY 2006 to March 1, 2012) periods, and (4) received at least one prescription medication during the baseline period.

Three groups of patients were excluded from the study. The first group included trauma and burn patients as identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes. We excluded this group because patient outcomes may be attributed to the severity of trauma or burn rather than the statin. Burn patients were identified using ICD-9-CM codes identified by the Agency for Healthcare Research and Quality Clinical Classifications Software (AHRQ-CCS), category 240.²¹ We also excluded patients who began a statin after the end of the baseline period, to allow for equal duration of follow-up for statin-users and non-users. Finally, we excluded transient statin-users who received statin medications for less than 90 days.

Treatment groups

The exposure variable was the use of a statin during FY 2005 (October 1, 2004 to September, 30, 2005) for 90 days or longer as identified from pharmacy data. Based on this exposure variable, we divided our cohort into two groups: 1) statin-users: patients who received and filled a statin medication for at least 90 days in FY 2005; and 2) non-users:

patients who did not receive a statin anytime during the study period from October 1, 2003 to March 1, 2012.

Patient outcomes

An outcome event was defined as any occurrence of an ICD-9-CM code during any inpatient or outpatient health care encounter during the study follow-up period. The outcomes were defined as follows:

1. BPH: included all ICD-9-CM codes identified by AHRQ-CCS category 164 (ICD-9-CM codes: 6000, 60000, 60001, 6001, 60010, 60011, 6002, 60020, 60021, 6003, 6009, 60090, and 60091)
2. ED: included ICD-9-CM code 60784
3. Infertility: included ICD-9-CM codes 6060, 6061, 6068, and 6069
4. Testicular dysfunction: included ICD-9-CM codes 2572, 2578, and 2579
5. Psychosexual dysfunction: included ICD-9-CM codes 3027, 30270, 30271, 30272, 30274, and 79981
6. All psycho-gonadism disorders: included all ICD-9-CM codes for ED, infertility, testicular dysfunction, and psychosexual dysfunction as detailed above

Data and statistical analysis

Patient demographics and medication use were characterized at baseline. Patients' comorbidities were identified by ICD-9-CM codes and were described individually and well as in composite as Charlson Comorbidity Index (CCI) scores. CCI scores were calculated using the method of Deyo et al.²²

For our primary analysis, we determined the association between statin use and sexual dysfunction using a propensity score-matched cohort. We included 79 variables in the derivation of the propensity scores, including: age, 17 comorbid conditions as defined by Deyo et al.,²² total CCI score, obesity, alcohol dependence/abuse, illicit drug use, cigarette smoking, healthcare utilization (number of outpatient visits and inpatient admissions during baseline period, and number of encounters for immunization or prevention of infectious diseases), 16 cardiovascular disease groups as defined by AHRQ-CCS categories, 1 cerebrovascular disease group that comprises 3 AHRQ-CCS categories, 17 other groups of comorbidities as defined by AHRQ-CCS, and the utilization of 19 medication groups (Appendix). We used a logistic regression model to create the propensity score and test the balance of covariates,²³ then, performed 1:1 matching to the nearest matching number with a caliper of 0.001.²⁴ Baseline characteristics of the statin-user and non-user groups were compared using the chi-square or Fisher's exact test for categorical variables and an unpaired 2-tailed t-test for continuous variables. We then used conditional logistic regression to determine the association between statin use and individual patient outcomes (Table 2). Since baseline characteristics of statin-users and non-users were balanced in this cohort, no further adjustments were needed in determining the risk of outcomes.

We then conducted secondary analyses using two, non-propensity score-matched cohorts: (1) all patients who met inclusion criteria and (2) all patients who met inclusion criteria, but had no Charlson comorbidities (i.e., CCI score of 0).

We also conducted two sensitivity analyses, in which we used all patients who met inclusion criteria, but restricted statin-users to: a) 2-year cumulative statin use and b) 4-year cumulative statin use.

For each of these secondary or sensitivity analyses, we used logistic regression to determine the association between statin use and outcomes, while adjusting for the propensity score (Table 2). Adjustment was conducted using a multivariable logistic regression model, with the outcome as the dependent variable, statin use as the independent variable, and the propensity scores as covariates.

Bivariable comparisons with a p-value ≤ 0.05 were considered to be statistically significant. Logistic regression results were presented as odds ratios (OR) and 95% confidence intervals (CI). Statistical analyses were performed using commercial software (Stata, ver. 12, StataCorp Inc, Cary, NC.; and SPSS, ver. 19, SPSS Inc, Aronak, NY.).

Results

Patient population

Overall, 20,731 patients met study inclusion criteria, of which 7,947 (38.3%) were statin-users and 12,784 were non-users (61.7%). The most commonly prescribed statins included: simvastatin (71.4%), atorvastatin (23.9%), pravastatin (3.0%), and rosuvastatin (1.5%). The mean (standard deviation) cumulative duration of statin use was 6.08 (2.24) years.. Among statin-users, 40.4% received high-intensity statin therapy and 85.1% received moderate-intensity statin as defined in the American College of Cardiology guidelines for cholesterol management,²⁵ at some time during the follow-up period.

Propensity score-matched analysis

Using propensity score analysis, we matched 3,302 statin-users with 3,302 non-users. The most common comorbidities in this cohort included: hypertension (53.0%), obesity (13.0%), and diabetes with or without complications (13.3%). Frequently prescribed medications included: NSAIDs, aspirin, and anti-hypertensive medications. Testosterone use was uncommon (1.0%). Patients had frequent outpatient (27.0 ± 35.0) visits, but few inpatient admissions (0.2 ± 0.7) in the baseline period. Among statin-users in this cohort, 31.1% used high-intensity statin at some point during the followup period. After matching, there were no significant differences in baseline characteristics between groups (Table 1).

The most common patient outcomes included: psychosexual dysfunction (37.0%), BPH (32.0%), and ED (23.1%). Testicular dysfunction (5.0%) and infertility (0.6%) were uncommon. The occurrence of these outcomes among statin-users and non-users was similar. The results of our propensity score-matched conditional logistic regression model demonstrated that statin use was not significantly associated with an increased or decreased risk of BPH (OR 1.08; 95% CI 0.97-1.19), ED (OR 1.01; 95% CI 0.90-1.13), infertility (OR

1.22; 95% CI 0.66-2.29), testicular dysfunction (OR 0.91; 95% CI 0.73-1.14), psychosexual dysfunction (OR 1.02; 95% CI 0.92-1.15), or all psycho-gonadism disorders (OR 1.03; 95% CI 0.94-1.14) (Table 2).

Secondary analyses

For our first secondary analysis, we included all patients meeting inclusion criteria (n=20,731) as described above. Statin-users in this cohort were older, used more medications, and had a higher proportion of obesity, smoking, comorbid conditions, and healthcare utilization. After adjustment for the propensity score, statin use was found to be associated with a slight, but significant increase in all psycho-gonadism disorders (OR 1.10; 95% CI 1.01-1.20). Statin use was not significantly associated with BPH, ED, infertility, testicular dysfunction, or psychosexual dysfunction (Table 2).

For our second analysis, we included 14,354 patients with no Charlson comorbidities, of which 3,542 (24.7%) were statin-users and 10,812 (75.3%) were non-users. After adjustment for propensity score, statin use was significantly associated with an increased risk for BPH (OR 1.21; 95% CI 1.08-1.35). Statin use was not significantly associated with ED, infertility, testicular dysfunction, psychosexual dysfunction, or all psycho-gonadism disorders (Table 2).

Sensitivity analysis—The 2-year cumulative statin use cohort included 7,042 statin-users and 12,785 non-users, and the 4-year cumulative statin use cohort included 5,531 statin-users and 12,785 non-users. The risk of outcomes in these cohorts is shown in table 2.

Discussion

This retrospective study demonstrated that statin use was not associated with an increased or decreased risk of gonadal or sexual dysfunction in men, including BPH, ED, infertility, testicular dysfunction, or psychosexual dysfunction in our primary, propensity score-matched analysis. In secondary analyses, we found a slight, but significant, increased risk for combined psychosexual dysfunction. This may be due to the larger sample size assessed in the overall cohort. It may also be due to less robust control of confounding variables in this non-propensity score-matched cohort. In addition, we found an increased risk for BPH in our cohort of patients with no Charlson comorbidities. This could suggest that statin use may be a more important risk factor for BPH among healthier men. Propensity score is a statistically generated score from different variables that identify the propensity of an individual to receive an intervention or experience an outcome in a model. Propensity score creation involves a non-parsimonious model so allow investigators to put many more covariates into the prediction models than traditional regression models. Once generated, a propensity score can be used either in matching between exposed and non-exposed groups, or as a covariate in a standard regression model. The advantage of the former is that matched groups share similar characteristics and make direct comparison more feasible; however, it comes at the expense of losing a large number of study participants who could not be matched. Whereas in the latter, all identified patients are included in analysis, which increases the study power at the expense of including patients who are very different in baseline characteristics; fair comparisons then depend on statistical adjustment in regression

analysis.²⁶ For example, our propensity score matched cohort was only 3304 pairs of patients from an original cohort of 20,731 who patients met study inclusion criteria.

Conflicting results exist in the literature regarding the effect of statin use on ED in men. Small, non-randomized, open-label studies noted that statin therapy resulted in objective improvement in ED.²⁷⁻²⁹ Other studies have demonstrated an improvement in ED when a statin is added to existing phosphodiesterase-5 inhibitor therapy, by improving vasodilation through nitric oxide production.^{30,31} Gokce et al. demonstrated that atorvastatin alone significantly improved ED, but greater effect was seen when atorvastatin and tadalafil were used concomitantly.³² Another small, randomized study noted that atorvastatin use was associated with a statistically significant, but modest, improvement in erectile function in 131 men with ED unresponsive to sildenafil.³³ Additionally, in vitro and animal research suggested that statins may have a favorable effect on ED.^{13, 34}

In contrast, other studies have either failed to demonstrate an association between statin use and ED³⁵⁻³⁷ or have found an increased risk of ED following statin use.³⁸⁻⁴⁰ In addition to several case reports,⁴¹ a review of the Spanish Pharmacovigilance system identified 38 cases of ED associated with statin use, of which 93% resolved after discontinuation of statins.⁴⁰ Furthermore, a survey of two groups of 339 age-matched men without previous cardiovascular disease found the risk of reporting ED was higher among men who used statins compared to non-users (OR 1.51; 95% CI 1.26-1.80).¹⁰

Although several studies have examined the role of statins in ED, there is a paucity of data on the effect of statins on other forms of sexual dysfunction. The statin-induced reduction in cholesterol synthesis may result in lower testosterone levels, which could predispose patients to testicular or psychosexual dysfunction. A prior study by Corona et al. aimed to evaluate the effect of statins on hormonal parameters in a large cohort (n=3,484) of patients seeking care for ED.³⁸ After adjustment for confounding factors, statin use was associated with lower total and calculated free testosterone levels, lower prolactin levels, higher follicle-stimulating hormone levels, reduced testis volume, and higher prevalence of hypogonadism-related signs and symptoms. A recent systematic review and meta-analysis of randomized controlled trials (501 men in 5 trials and 368 women in 6 trials) concluded that statins lowered testosterone by 0.44 nmol/L (95% CI 0.75-0.13).⁴² In contrast, other studies have demonstrated no significant effect of statins on testosterone levels or sexual development.⁴³⁻⁴⁶

In recent years, there has been an increase in data to support the role of inflammation in the development of BPH.⁴⁷⁻⁴⁹ Statins' anti-inflammatory properties may help to prevent BPH, but few studies have examined this association. In a cohort of 2,447 men, St. Sauver et al. demonstrated that statin use was significantly associated with a reduction in BPH development (OR 0.4; 95% CI 0.23-0.69) after adjustment for potential confounders.¹⁵ While this study demonstrates the potential use of statins for BPH prevention, a randomized controlled trial found that atorvastatin was ineffective in reducing symptoms related to BPH.⁵⁰

Our study contributes to the literature in several ways. This is the first large cohort study to examine the risk of gonado-sexual dysfunction in men in relation to statin use. The results of our study suggest that statins may not be beneficial for prevention of sexual dysfunction, nor do they increase the risk for such events. This provides further clarification for the controversy surrounding statins in gonado-sexual function. Our study is strengthened by the relatively homogenous sample of patients in regards to health care system accessibility and utilization. The military health care system maintains a comprehensive electronic system which allows for comprehensive medical record review at any military health care facility. It also provides for medication distribution data regardless of the dispensing pharmacy.

Our study has potential limitations. First, we utilized a retrospective cohort study design, which might be subject to misclassification bias and confounding by unmeasured variables. Multivariable logistic regression and propensity score matching techniques were used in an attempt to account for confounders and limit any potential biases; however, these methods are not equivalent to a prospective, randomized study. Propensity score matching in itself does not guarantee non-bias; the strategies of covariate selection for inclusion in the propensity score can affect its performance and accuracy.⁵¹ The use of electronic medical records for data collection is also subject to limitations. Electronic medical data are created for the purpose of patient care, not for research, and might contain errors. There might be variation in the extent of physician reporting of certain medical conditions; variability might lead to inaccuracy of the CCI score and other variables. Furthermore, the presence of absence of hyperlipidemia could have affected study results, as hyperlipidemia was likely more common among statin-users. It is also important to note that this study was unable to capture improvements in pre-existing conditions; rather, the study design captured only new diagnoses. Other drugs that may affect prostate and sexual function such as phosphodiesterase inhibitors and alpha blockers, were not accounted for. Finally, prior studies have demonstrated that patients with sexual dysfunction often do not seek medical treatment, nor do clinicians routinely ask about sexual health;⁵² however, this limitation, despite its significance, would be expected to affect both statin-users and non-users equally. Additionally, the prevalence of BPH and ED in our cohort is similar to reported prevalence of other studies including patient surveys.^{53, 54}

Conclusions

In conclusion, in this propensity score-matched cohort of statin-users and non-users, statin use did not contribute to or reduce the risk of being diagnosed with gonadal or sexual dysfunction in men. Further studies using larger sample size may be needed to demonstrate differences in risks of psycho-gonadal dysfunction and BPH in statin-users, if such risks exist.

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Appendix

Baseline characteristics incorporated in propensity score matching (78 variables)

Baseline Characteristic	Definition / Comment
17 components of Charlson comorbidity score (acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, rheumatologic diseases, peptic ulcer disease, mild liver disease, diabetes mellitus, diabetes mellitus with complications, hemiplegia/paraplegia, renal disease, malignancy, moderate/severe liver disease, metastatic neoplasm, and HIV)	Charlson comorbidities as described by Deyo et al. ²²
Charlson comorbidity score	Using Deyo et al method. ²²
Total number of outpatient medical encounters, total number of inpatient admissions, and total number of medical encounter's for immunization and screening for infectious disease during the baseline period	
Obesity, Illicit drug abuse, cigarette smoking, alcohol dependence/abuse at baseline period	ICD-9-CM codes as defined in AHRQ-CCS
Each of the following <i>comorbid disease groups at baseline period</i> : diabetes mellitus, diabetes mellitus with complications	AHRQ-CCS categories 49 and 50, respectively
Each of the following <i>cardiovascular disease groups at baseline period</i> : heart valve disorders; cardiomyopathy, endocarditis or pericarditis; essential hypertension; hypertension with complications and secondary hypertension; acute myocardial infarction; coronary atherosclerosis and other heart disease; pulmonary heart disease; heart disease, not otherwise specified; conduction disorders; cardiac dysrhythmias; cardiac arrest and ventricular fibrillation; congestive heart failure; nonhypertensive acute cerebrovascular disease; peripheral vascular diseases, peripheral, and visceral artery aneurysms; and aortic and peripheral arterial embolism or thrombosis	AHRQ-CCS categories: 96, 97, 98, 99, 100, 101, 103, 104, 105, 106, 107, 108, 109, 114, 115, 116, respectively
Each of the following <i>cerebrovascular disease groups at baseline period were considered together as one group</i> : (occlusion or stenosis of precerebral arteries; other and ill-defined cerebrovascular disease; transient cerebral ischemia; peripheral and visceral atherosclerosis; aortic)	AHRQ-CCS categories (110, 111, 112)
Each of the following <i>pulmonary disease groups at baseline period</i> : chronic obstructive pulmonary disease and bronchiectasis; asthma; respiratory failure, insufficiency, arrest	AHRQ-CCS categories: 127, 128, 131, respectively
Each of the following <i>renal disease groups at baseline period</i> : (nephritis and nephrosis, and renal sclerosis; chronic kidney disease as one disease group); acute and unspecified renal failure	AHRQ-CCS categories: (156, 158 as one category), 157, respectively
Each of the following <i>disease groups at baseline period</i> : (rheumatoid arthritis and related disease; systemic lupus erythematosus and connective tissue disorders as one group); pathological fracture; Rehabilitation	AHRQ-CCS categories: (202; 210 as one group); 207, 254, respectively
Each of the following <i>psychological disease groups at baseline period</i> : schizophrenia and other psychotic disorders; suicide and intentional self-inflicted injury	AHRQ-CCS categories: 659, 662, respectively
Each of the following <i>gastrointestinal disease groups at baseline period</i> : gastro-duodenal ulcers; gastro-doudenitis, gastrointestinal hemorrhage	AHRQ-CCS categories: 139, 140, 153, respectively
Each of the following <i>Musculoskeletal disease groups at baseline period</i> : Arthropathies; use-related injury	AHRQ-CCS categories (203, 204, 205) and (categories 225 and 232), respectively
19 medications classes used during baseline period: beta-blockers, diuretics, dihydropyridine calcium channel blockers, non-statin cholesterol lowering medications, angiotensin-receptor blockers & angiotensin converting enzyme inhibitors, oral hypoglycemic agents, aspirin, other antiplatelet drugs, non-steroidal anti-inflammatory, serotonin-reuptake inhibitors, anti-psychotics, sedatives and hypnotics, tricyclic antidepressants, systemic steroids, testosterone, bisphosphonate, proton-pump inhibitors, warfarin, and Cytochrome P450 metabolized medications as defined in a recent FDA report ⁵⁵	

VACS= VA Cohort of aging study; AHRQ-CCS = Agency for Healthcare Research and Quality-Clinical Classification Software

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Table 1
Selected baseline characteristics of propensity score-matched cohort of statin-users and non-users

	Non-users (n = 3,302)	Statin-users (n = 3,302)	P-value
Age (years), mean $\pm$ SD	53.7 $\pm$ 11.9	53.6 $\pm$ 12.2	0.60
Charlson comorbidity score, mean $\pm$ SD	0.54 $\pm$ 1.17	0.54 $\pm$ 1.11	0.91
Comorbidities, n (%)			
Alcohol abuse/dependence	52 (1.6)	46 (1.4)	0.54
Illicit drug use	6 (0.2)	7 (0.2)	0.78
Smoking	268 (8.1)	264 (8.0)	0.86
Obesity	425 (12.9)	436 (13.2)	0.69
Diabetes mellitus	322 (9.8)	351 (10.6)	0.24
Diabetes mellitus with complications	94 (2.8)	110 (3.3)	0.26
Valvular heart disease	152 (4.6)	149 (4.5)	0.86
Hypertension	1,765 (53.5)	1,737 (52.6)	0.49
Coronary artery disease	136 (4.1)	158 (4.8)	0.19
Congestive heart failure	40 (1.2)	38 (1.2)	0.82
Peripheral vascular disease	57 (1.7)	64 (1.9)	0.52
Cerebrovascular disease	54 (1.6)	61 (1.8)	0.51
Chronic obstructive pulmonary disease	318 (9.6)	313 (9.5)	0.83
Psychosis	12 (0.4)	12 (0.4)	1.00
Encounters during baseline period, mean $\pm$ SD			
Outpatient visits	27.0 $\pm$ 35.0	26.7 $\pm$ 26.1	0.72
Inpatient admissions	0.2 $\pm$ 0.7	0.2 $\pm$ 0.7	0.53
Immunization encounters	0.5 $\pm$ 1.9	0.5 $\pm$ 1.3	0.83
Medications, n (%)			
Beta-blocker	460 (13.9)	470 (14.2)	0.72
Diuretic	756 (22.9)	749 (22.7)	0.84
Calcium channel Blocker	437 (13.2)	438 (13.3)	0.97
Non-statin lipid lowering drugs	223 (6.8)	230 (7.0)	0.73
Aspirin	942 (28.5)	953 (28.9)	0.76
NSAID	1,884 (57.1)	1,918 (58.1)	0.40
SSRI	332 (10.1)	311 (9.4)	0.38
Antipsychotic	34 (1.0)	32 (1.0)	0.81
Systemic corticosteroid	117 (3.5)	113 (3.4)	0.79
Testosterone	36 (1.1)	32 (1.0)	0.63

ACEI/ARB=angiotensin converting enzyme inhibitor/angiotensin receptor blocker; NSAID: non-steroidal anti-inflammatory drugs; SD=standard deviation; SSRI=selective serotonin reuptake inhibitors

Table 2
Outcome risk among statin-users in comparison to non-users

	Non-users n (%)	Statin-users n (%)	OR (95% CI)
Propensity score-matched cohort			
Benign prostatic hypertrophy	1,030 (31.2)	1,082 (32.8)	1.08 (0.97 – 1.19)
Erectile dysfunction	762 (23.1)	765 (23.2)	1.01 (0.90 – 1.13)
Infertility	18 (0.5)	22 (0.7)	1.22 (0.66 – 2.29)
Testicular dysfunction	171 (5.2)	157 (4.8)	0.91 (0.73 – 1.14)
Psychosexual dysfunction	801 (24.3)	815 (24.7)	1.02 (0.92 – 1.15)
All psycho-gonadism disorders	1,210 (36.6)	1,235 (37.4)	1.03 (0.94 – 1.14)
Overall cohort (adjusting for propensity score)			
Benign prostatic hypertrophy	2,112 (16.5)	3,263 (41.1)	1.08 (0.99 – 1.19)
Erectile dysfunction	1,719 (13.4)	2,049 (25.8)	1.08 (0.97 – 1.20)
Infertility	180 (1.4)	28 (0.4)	1.25 (0.80 – 1.96)
Testicular dysfunction	463 (3.6)	478 (6.0)	1.05 (0.87 – 1.27)
Psychosexual dysfunction	2,314 (18.1)	2,001 (25.2)	1.06 (0.96 – 1.17)
All psycho-gonadism disorders	3,334 (26.1)	3,178 (40.0)	1.10 (1.01 – 1.20)
No Charlson comorbidities cohort (adjusting for propensity score)			
Benign prostatic hypertrophy	1,527 (14.1)	1,224 (34.6)	1.21 (1.08 – 1.35)
Erectile dysfunction	1,291 (11.9)	797 (22.5)	1.08 (0.95 – 1.22)
Infertility	164 (1.5)	20 (0.6)	1.34 (0.81 – 2.21)
Testicular dysfunction	355 (3.3)	179 (5.1)	1.07 (0.85 – 1.36)
Psychosexual dysfunction	1,865 (17.2)	881 (24.9)	1.05 (0.93 – 1.18)
All psycho-gonadism disorders	2,635 (24.4)	1,319 (37.2)	1.11 (0.99 – 1.22)
Overall cohort limiting statin-users to those who used statins for 2 years (adjusting for propensity score)			
Benign prostatic hypertrophy	2,112 (16.5)	3,007 (42.7)	1.10 (0.99 – 1.22)
Erectile dysfunction	1,719 (13.4)	1,845 (26.2)	1.06 (0.95 – 1.18)
Infertility	180 (1.4)	21 (0.3)	1.33 (0.80 – 2.21)
Testicular dysfunction	463 (3.6)	424 (6.0)	1.03 (0.84 – 1.23)
Psychosexual dysfunction	2,314 (18.1)	1,771 (25.1)	1.02 (0.92 – 1.13)
All psycho-gonadism disorders	3,334 (26.1)	2,836 (40.3)	1.08 (0.99 – 1.19)
Overall cohort limiting statin-users to those who used statins for 4 years (adjusting for propensity score)			
Benign prostatic hypertrophy	2,112 (16.5)	2,490 (45.0)	1.11 (1.00 – 1.24)
Erectile dysfunction	1,719 (13.4)	1,441 (26.1)	0.94 (0.83 – 1.06)
Infertility	180 (1.4)	15 (0.3)	1.52 (0.84 – 2.75)
Testicular dysfunction	463 (3.6)	321 (5.8)	0.92 (0.74 – 1.15)

	Non-users n (%)	Statin-users n (%)	OR (95% CI)
Psychosexual dysfunction	2,314 (18.1)	1,354 (24.5)	0.91 (0.81 – 1.02)
All psycho-gonadism disorders	3,334 (26.1)	2,199 (39.8)	0.97 (0.88 – 1.07)

CI=confidence interval; OR=odds ratio

Note: bold italics indicates statistical significance