

Statins and New-Onset Diabetes Mellitus and Diabetic Complications: A Retrospective Cohort Study of US Healthy Adults

Ishak Mansi, M.D.^{1,2}, Christopher R. Frei, Pharm.D., M.Sc.^{3,4}, Chen-Pin Wang, Ph.D.⁵, and Eric M. Mortensen, M.D., M.Sc.^{1,2}

¹Department of Medicine, VA North Texas Health System, Dallas, TX, USA; ²Departments of Medicine and Clinical Sciences, University of Texas Southwestern, Dallas, TX, USA; ³Pharmacotherapy Division, College of Pharmacy, The University of Texas at Austin, Austin, TX, USA; ⁴Pharmacotherapy Education and Research Center, School of Medicine, University of Texas Health Science Center, San Antonio, TX, USA; ⁵University of Texas Health Science Center, San Antonio, TX, USA.

BACKGROUND: Statin use is associated with increased incidence of diabetes and possibly with increased body weight and reduced exercise capacity. Data on the long-term effects of these associations in healthy adults, however, are very limited. In addition, the relationship between these effects and diabetic complications has not been adequately studied.

OBJECTIVE: To examine the association between statin use and new-onset diabetes, diabetic complications, and overweight/obesity in a cohort of healthy adults.

RESEARCH DESIGN: This was a retrospective cohort study.

PARTICIPANTS: Subjects were Tricare beneficiaries who were evaluated between October 1, 2003 and March 1, 2012. Patients were divided into statin users and nonusers.

INTERVENTION: We excluded patients who, at baseline, had a preexisting disease indicative of cardiovascular diseases, any positive element of the Charlson comorbidity index (including diabetes mellitus), or life-limiting chronic diseases. Using 42 baseline characteristics, we generated a propensity score to match statin users and nonusers.

MAIN MEASURES: Outcomes assessed included new-onset diabetes, diabetic complications, and overweight/obesity.

KEY RESULTS: A total of 25,970 patients (3982 statin users and 21,988 nonusers) were identified as healthy adults at baseline. Of these, 3351 statin users and 3351 nonusers were propensity score-matched. Statin users had higher odds of new-onset diabetes (odds ratio [OR] 1.87; 95 % confidence interval [95 % CI] 1.67–2.01), diabetes with complications (OR 2.50; 95 % CI 1.88–3.32), and overweight/obesity (OR 1.14; 95 % CI 1.04–1.25). Secondary and sensitivity analyses demonstrated similar findings.

CONCLUSIONS: Diabetes, diabetic complications, and overweight/obesity were more commonly diagnosed among statin-users than similar nonusers in a healthy cohort of adults. This study demonstrates that short-term

clinical trials might not fully describe the risk/benefit of long-term statin use for primary prevention.

KEY WORDS: Overweight/obesity; Diabetes; Diabetic complications; Adverse events; Observational study; Statins; Primary prevention.

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INTRODUCTION

Despite their effectiveness in lowering cardiovascular morbidity and mortality, statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase [HMGR] inhibitors) have been shown to be associated with a small risk of incident diabetes mellitus.¹ A recent cross-sectional study noted higher caloric and fat intake and increased body mass index among statin users in contrast to nonusers.² Additionally, achieving a "cholesterol goal" through swallowing a tablet might result in false self assurance, and may encourage poor dietary choices and a sedentary lifestyle.³ Several randomized trials and observational studies have noted that statin users have higher hemoglobin [Hb]A_{1C} and fasting plasma glucose measurements than nonusers.^{4–8} Hence, it can be surmised that statins may increase the risk of diabetic complications.

Most studies reporting an increased risk of new-onset diabetes among statin users included high-risk populations¹; data are limited regarding incident diabetes risk in healthy populations. For example, patients in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) study had hypertension and three or more cardiovascular risk factors.⁹ The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT),¹⁰ West of Scotland Coronary Prevention Study (WESCOPS),¹¹ and ASCOT-LLA studies actually included patients who had evidence of preexisting cardiovascular disease (8, 14.2, and 18.5 %, respectively). As a result, some investigators have proposed that statin use is associated with incident diabetes only in the highest-risk population.¹²

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The objective of this study was to examine the association between statin use and new-onset diabetes, diabetes with complications, and overweight/obesity in a propensity score-matched “healthy” cohort of statin users and nonusers.

RESEARCH DESIGN AND METHODS

Study Design

This study was approved by the institutional review boards at Brooke Army Medical Center and the VA North Texas Health Care System, and was a retrospective cohort study of patients enrolled in the San Antonio Military Area as Tricare Prime/Plus. Tricare is a US health care program for almost 9.5 million beneficiaries worldwide—including active duty service members, national guard and reserve members, retirees, their families, survivors, certain former spouses, and others registered in the US Department of Defense enrollment eligibility reporting system.¹³ We extracted archival data from October 1, 2003 to March 1, 2012, which encompassed administrative, clinical, and financial data, regardless of point-of-care location or affiliation.¹⁴ Data included outpatient and inpatient electronic medical records, medical benefits claims data, laboratory data performed within the military system, and pharmacy data. Pharmacy data included details of dispensed medications regardless of pharmacy location or affiliation. The reliability and reproducibility of Tricare data have been previously described.¹³

The study was divided into two periods: 1) a baseline period (October 1, 2003 to September 30, 2005), which was used for description of baseline characteristics; and 2) a follow-up period (October 1, 2005 to March 1, 2012), which was used to capture outcome events. All patients were enrolled in the system throughout the study period; hence, there were no missing data.

Patient Population

Inclusion Criteria. The study included all patients aged 30 to 85 years who were enrolled in the San Antonio area and who met the following criteria:

1. Were enrolled in Tricare Prime/Plus throughout the study.
2. Had at least one outpatient visit during the baseline period and one outpatient visit during the follow-up period.
3. Received at least one prescription medication during the baseline period.

Exclusion Criteria.

- Trauma and burn patients (based on International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes), as defined by the

Agency for Health Research and Quality Clinical Classifications Software (AHRQ-CCS), category 240,¹⁵ and previous publications.¹⁶

- Patients who were newly started on statins after September 30, 2005 (end of baseline period). This exclusion allowed the creation of statin user and nonuser groups with similar periods of follow-up.
- Patients who received statins for less than 90 days.

To identify a healthy cohort who used statins for primary prevention and without severe comorbidities, we excluded patients with the following diseases:

1. Patients who had any positive elements of the Charlson comorbidity index at baseline using Deyo’s method.¹⁷
2. Patients with ICD-9-CM codes that suggested the presence of cardiovascular disease or their equivalents at baseline as defined by several AHRQ-CCS disease categories (Appendix A).
3. Patients with ICD-9-CM codes for comorbid conditions that might limit life expectancy or physical activity, as defined by the following AHRQ-CCS disease categories¹⁵: chronic obstructive pulmonary disease and bronchiectasis; respiratory failure, insufficiency, arrest in adult; nephritis, nephrosis, renal sclerosis; chronic kidney disease; rheumatoid arthritis and related disease; systemic lupus erythematosus and connective tissue disorders; pathological fracture; schizophrenia and other psychotic disorders; or suicide and intentional self-inflicted injury (Appendix A).

We identified two treatment groups:

1. **Statin users:** patients who filled a statin for at least 90 days between October 1, 2004 and September 30, 2005. This group was further classified as either:
 - a. High-intensity statin users: patients who were prescribed high-intensity statin therapy, as defined by the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA),¹⁸ at any time during the study.
 - b. Moderate/low-intensity statin users: patients who did not receive high-intensity statin therapy over the duration of the study.¹⁸
2. **Nonusers:** patients who did not receive statins at any time during the study.

Outcomes

We utilized pre-specified diagnosis groups to define our outcomes, as follows:

1. Diabetes mellitus: as identified in AHRQ-CCS category 49 (diabetes mellitus without complications), excluding V codes signifying preexisting conditions (Appendix B).¹⁵

2. Diabetes mellitus with complications: as identified in AHRQ-CCS category 50 (Appendix B).¹⁵
3. Overweight/obesity: included selected ICD-9-CM diagnosis codes from category 56 of the AHRQ-CCS (other nutritional; endocrine disorders; metabolic) related to overweight, obesity, and hyperalimentation (Appendix B).

AHRQ-CCS is a diagnosis and procedure categorization scheme that is based on ICD-9-CM codes in which meaningful categories of disease diagnoses are created to enable more useful identification of populations for relatively specific conditions.¹⁵ The method of creation and validation of AHRQ-CCS was previously published.^{19–23} AHRQ-CCS disease categories have been widely used in numerous publications to identify comorbidities and outcomes,^{24–29} predict mortality,^{30,31} and estimate utilization and costs.^{32–35} AHRQ-CCS disease categories are recognized by the Department of Defense Military Health System and are incorporated into Tricare data as an industry standard.¹³

AHRQ-CCS category 49 (diabetes without complication) and category 50 (diabetes with complications) have been used in clinical research^{36,37} and to generate reports on utilization and cost statistics in relation to diabetes and diabetic complications in various health care settings.^{38–42} Additionally, ICD-9 codes have been widely used to ascertain outcomes of “diabetes mellitus” and “diabetes mellitus with complications,” as these two outcomes are essential components in calculating the Charlson comorbidity index using Deyo’s method¹⁷ and the Elixhauser comorbidity score⁴³ from administrative data, and both of these scores are widely used.⁴⁴ The sensitivity and specificity of ICD-9 codes for diagnosing diabetes without complications were 77.7 and 98.4 %, and for diabetes with complications were 63.6 and 98.9 %, respectively.⁴⁵ In a study using the VA database, the sensitivity and specificity of ICD-9 codes in comparison to chart review to identify diabetes were 78.3 and 95.7 %, respectively.⁴⁶

The use of ICD-9 codes in general and AHRQ-CCS codes in particular in order to extract obesity diagnoses has been described in the literature^{47–50}; AHRQ-CCS codes for obesity have also been used to generate reports on utilization and cost statistics in relation to obesity.^{51–53} In general, the use of ICD-9 codes to identify obesity has been noted as having low sensitivity but high specificity^{45,54}; using chart review as the gold standard, the sensitivity, specificity, positive predictive value, and negative predictive value were 24.6 %, 99.3 %, 75.9 %, and 93.6 %.⁴⁵

Data and Statistical Analyses

In the present study, patients’ comorbidities were identified using ICD-9-CM codes (Appendix B and Appendix C), and their Charlson comorbidity index was calculated using Deyo’s method.¹⁷ Using propensity scores, we matched statin users to similar nonusers using 42 variables (Table 1).⁵⁵

Propensity Score Matching. We used a logistic regression model to create the propensity score and test the balance of covariates.⁵⁶ We performed 1:1 nearest neighbor matching with a caliper of 0.01.⁵⁷

Primary Analysis. We examined risks of outcomes in statin users and nonusers in the propensity score-matched cohort using conditional logistic regression analysis.

Secondary and Sensitivity Analyses. Table 2 summarizes the study cohorts and statistical methods. We examined risks of outcomes in the following cohorts using multivariable logistic regression with adjustment for propensity score:

1. Healthy cohort: this cohort included all 25,970 patients in the study population, not just those who were propensity score-matched. Four comparisons were made to assess the risks of outcomes:
 - a. Statin users (3982 patients) versus nonusers (21,988 patients).
 - b. High-intensity statin users (1155 patients) versus nonusers (21,988 patients).
 - c. Two-year statin users (3308 patients) versus nonusers (21,988 patients).
 - d. Four-year statin users (2933 patients) versus nonusers (21,988 patients).
2. Overweight/obesity incident cohort: This cohort included only those patients in the “healthy cohort” who did not have a diagnosis of overweight/obesity at baseline. One comparison was made to assess the risk of outcomes:
 - a. Statin users (3415 patients) versus nonusers (20,176 patients).
3. Statin-user cohort: This cohort included only those 3982 statin users from the “healthy cohort.” One comparison was made to assess the risks of outcomes:
 - a. High-intensity statin users (1155 patients) versus moderate/low-intensity statin users (2827 patients).

Baseline characteristics for comparator groups were assessed using chi-square for categorical variables and the Student’s *t* test for continuous variables. Comparisons were considered to be statistically significant at *p* values ≤ 0.05 . Statistical analyses were performed using Stata software (Version 12; StataCorp LP, College Station, TX, USA) and SPSS software (Version 19; IBM Corp., Armonk, NY, USA).

RESULTS

Based on our initial inclusion and exclusion criteria, 43,438 patients were identified (13,626 statin users and 29,812 nonusers). To develop the healthy cohort, we excluded 13,311 subjects with any positive elements in their Charlson

Table 1 Baseline Characteristics of Propensity Score-Matched Statin Users and Nonusers

	Statin nonusers no. (%) (n=3351)	statin users no. (%) (n=3351)	P value
Age in years, mean±SD	53±11	53±11	0.72
Female sex	1285 (38.3)	1314 (39.2)	0.48
Smoking	241 (7.2)	237 (7.1)	0.89
Alcohol-related disorders	29 (0.9)	31 (0.9)	0.80
Substance-related disorders	12 (0.4)	8 (0.2)	0.38
Comorbidities in baseline period			
Charlson comorbidity score ^a , mean (SD)	0 (0.0)	0 (0.0)	
Overweight/obese	493 (14.7)	455 (13.6)	0.19
Hypertension ^b	1704 (50.9)	1678 (50.1)	0.54
Acute kidney injury	5 (0.1)	5 (0.1)	1.0
Asthma ^b	102 (3.0)	96 (2.9)	0.71
Gastrointestinal hemorrhage	118 (3.5)	108 (3.2)	0.27
Gastritis/duodenitis	61 (1.8)	68 (2.0)	0.59
Nonspecific chest pain ^c	301 (9.0)	326 (9.7)	0.31
Heart disease not otherwise specified ^c	18 (0.5)	15 (0.4)	0.73
Osteoarthritis, arthropathy, and back disorder	1534 (45.8)	1548 (46.2)	0.75
Sprains, strains, and trauma-related joint disorders	596 (17.8)	603 (18)	0.85
Fracture of bone	103 (3.1)	110 (3.3)	0.68
Osteoporosis	132 (3.9)	112 (3.3)	0.22
Rehabilitation care, fitting of prostheses, and adjustment of devices	506 (15.1)	544 (16.2)	0.21
Health care utilization at baseline			
Number of inpatient admissions during baseline period, mean±SD	0.08±0.3	0.08±0.3	0.82
Number of outpatient medical encounters during baseline period, mean±SD	21.1±22.7	21.1±19.1	0.97
Number of encounters for immunization during baseline period, mean±SD	0.40±1.1	0.42±1.14	0.37
Receive immunization and screening for infectious disease	643 (19.2)	670 (20)	0.41
Medications at baseline			
Beta-blocker	428 (12.8)	459 (13.7)	0.28
Diuretic	728 (21.7)	742 (22.1)	0.71
ACE/ARB	886 (26.4)	899 (26.8)	0.72
Calcium channel blocker	384 (11.5)	395 (11.8)	0.70
Proton pump inhibitor	861 (25.7)	863 (25.8)	0.98
Aspirin	777 (23.2)	826 (24.6)	0.16
NSAID	1911 (57.0)	1926 (57.5)	0.73
Bisphosphonate	215 (6.4)	201 (6.0)	0.50
Sedatives	519 (15.5)	525 (15.7)	0.84
SSRI	441 (13.2)	456 (13.6)	0.62
Antipsychotic	30 (0.9)	26 (0.8)	0.69
Tricyclic anti-depressants	7 (0.2)	5 (0.1)	0.77
Systemic corticosteroid	63 (1.9)	72 (2.1)	0.49
Hormone replacement therapy	436 (13.0)	420 (12.5)	0.58
Testosterone	15 (0.4)	14 (0.4)	1.0
Cytochrome p450	182 (5.4)	193 (5.8)	0.60
Non-statin lipid lowering drugs	194 (5.8)	217 (6.5)	0.26
Oral hypoglycemic	16 (0.5)	16 (0.5)	1.0
Antiplatelet agents (other than aspirin)	10 (0.3)	13 (0.4)	0.68
Warfarin	16 (0.5)	14 (0.4)	0.86

ACE/ARB angiotensin receptor blockers and angiotensin-converting-enzyme inhibitors, Cytochrome p450 medications that inhibit the cytochrome p450 system as identified in a recent FDA warning,⁵⁵ HIV human immunodeficiency virus, NSAID non-steroidal anti-inflammatory drugs, SD standard deviation, SSRI selective serotonin reuptake inhibitors

^aDiagnosis is based on ICD-9-CM codes as identified in the Deyo method for applying the Charlson comorbidity score¹⁷

^bWe included patients with hypertension but excluded those with hypertension with complications, secondary hypertension, or end-organ damage. Similarly, we included patients with asthma but excluded those with chronic obstructive pulmonary disease, bronchiectasis, respiratory failure, or insufficiency as detailed in the "Research Design and Methods" section

^cAlthough these patients had no other diagnosis codes indicative of cardiovascular disease, they were more likely to be seen by cardiologists and to be started on statin therapy; therefore, we included these baseline characteristics in the propensity score matching

comorbidity index, 3876 subjects with diagnoses suggestive of cardiovascular disease, and 281 patients with other comorbidities that might limit life expectancy or physical activity at baseline (Fig 1). Hence, our final healthy cohort included 25,970 patients (3982 statin users and 21,988 nonusers). Overall, 77 % of prescriptions of statins were for simvastatin, 19 % for atorvastatin, 3 % for pravastatin, and 1 % for rosuvastatin. Table 3 describes selected characteristics of the population that met the study criteria. Statin users were older, had higher proportions of men and smokers, had a higher prevalence of comorbidities, and utilized other classes of

medications more frequently except for non-steroidal anti-inflammatory drugs and testosterone therapy.

Propensity Score-Matched Analysis

Using propensity scores, we matched 3351 statin users to 3351 nonusers. After matching, there were no significant differences in baseline characteristics between groups (Table 1). In the propensity score-matched cohort (primary analysis), the mean (SD) cumulative duration of statin use among statin users was as follows: mean (SD)=2001 (895) days, median

Table 2 Cohort Groups and Study Methods

Cohort name	Cohort description	Covariates included in analysis	Number of statin nonusers	Number of statin users
<i>Primary analysis</i>				
Propensity score-matched cohort	Pairs of statin users and nonusers were matched based on propensity score	None, since cohort groups were matched with no imbalance	3351	3351
<i>Secondary and sensitivity analyses</i>				
Healthy cohort	Healthy individuals who met the inclusion and exclusion criteria	Propensity score	21,988	3982
High-intensity statin-user cohort	A subset of the “healthy cohort,” restricting statin users to those who used high-intensity statins at any point of their follow-up	Propensity score	21,988	1155
Two-year statin-user cohort	A subset of the “healthy cohort,” after excluding statin users who used statins for less than 2 years	Propensity score	21,988	3308
Four-year statin-user cohort	A subset of the “healthy cohort,” after excluding statin users who used statins for less than 4 years	Propensity score	21,988	2933
Overweight/obesity incident cohort	A subset of the “healthy cohort,” after excluding patients who were diagnosed in the baseline period with overweight/obesity	Propensity score	20,176	3415
High-intensity statin users among statin users only	All statin users only in the “healthy cohort,” comparing outcomes between high-intensity statin users and moderate/low-intensity statin users	Propensity score	None included	3982

(interquartile range)=2170 (1350–2775) days. At some point during the study period, 28 % of statin users received a high-intensity statin and 87 % received a moderate-intensity statin.¹⁸

Primary Analysis

In the propensity score-matched cohort, statin users had higher ORs for diabetes (OR 1.87; 95 % confidence interval [95 % CI] 1.67–2.01), diabetes with complications (OR 2.50; 95 % CI 1.88–3.32), and overweight/obesity (OR 1.14; 95 % CI 1.04–1.25) (Table 4). Table 5 describes the breakdown of diabetes complications.

During the follow-up period, the mean (SD) number of inpatient admissions for nonusers and statin users were 0.46 (1.19) and 0.45 (1.07), respectively ($p=0.7$); and the mean (SD) of number of outpatient medical encounters for nonusers and statin users were 60.80 (61.6) and 65.8 (58.9), respectively ($p=0.001$). Since statin users had more visits with providers than nonusers, we repeated the analysis introducing the number of inpatient admission and outpatient medical encounters during the follow-up period as covariates in the regression model to account for any possible ascertainment bias. Our results continued to be significant; statin users had higher ORs for diabetes (OR 1.85; 95 % CI 1.65–2.07), diabetes with complications (OR 2.53; 95 % CI 1.90–3.38), and overweight/obesity (OR 1.12; 95 % CI 1.02–1.23).

Secondary and Sensitivity Analyses

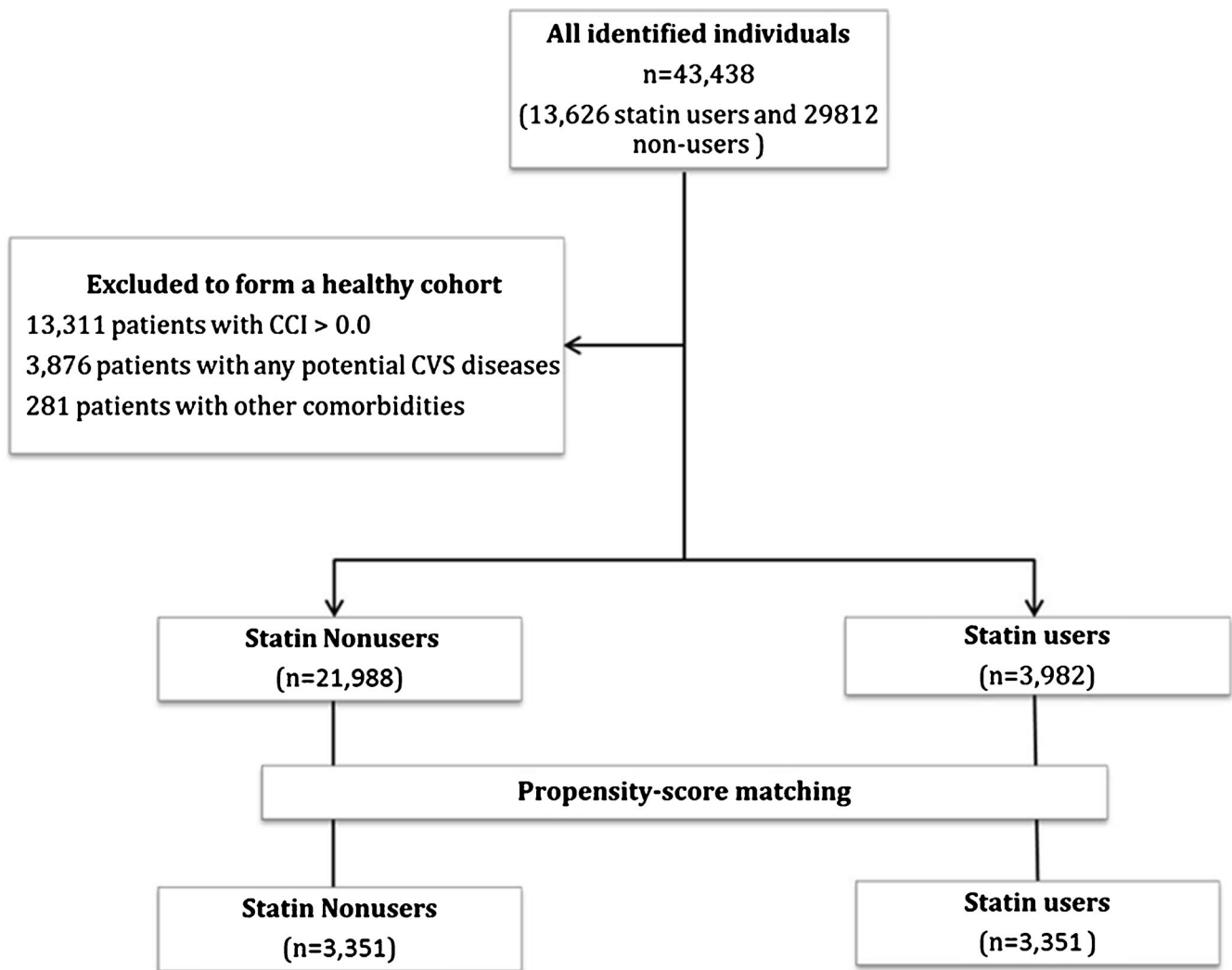
The adjusted ORs for high-intensity statin users were higher than moderate/low-intensity statin users (Table 6). The adjusted ORs for the secondary and sensitivity analyses were higher

for statin users across all groups for all outcomes (Table 7). The ORs were highest among high-intensity statin-user cohort.

DISCUSSION

This study demonstrated that statin use was associated with an increased likelihood of new diagnoses of diabetes mellitus, diabetic complications, and overweight/obesity. Whereas the increased risk of diabetes with statins is well known, the increased risk of diabetic complications has not been previously described.

The overall proportion of patients who developed diabetes during the follow-up period was approximately 14 %, which is similar to recent national trends.⁵⁸ The increased risk of diabetes among statin users is well described in several studies.^{1,59} In a meta-analysis of 13 statin clinical trials (mean follow-up duration from 1.9 to 6 years), the OR of incident diabetes was 1.09 (95 % CI 1.02–1.17).¹ However, these trials used different methods for diagnosing diabetes, and some trials were missing diabetes incidence data. Moreover, all statin primary prevention trials used intention-to-treat analysis, despite high rates of dropout or quitting the study medication (12–33 %), which can result in underestimation of side effects.⁶⁰ Both lipophilic and hydrophilic statins were associated with a similar risk of diabetes,¹ although other studies have noted that the risk varied with different types of statins.⁶¹ In a secondary analysis of the Women’s Health Initiative data, statin use was associated with an increased risk of diabetes (adjusted hazard ratio [HR] 1.48; 95 % CI 1.38–1.59).⁶² Other



CCI = Charlson Comorbidity Index; CVS = Cardiovascular

Fig. 1 Study cohort

observational studies have noted higher adjusted risk of incident diabetes among statin users versus nonusers, ranging from 2.8 to 4.7.^{63,64}

Importantly, our study demonstrated that high-intensity statin therapy was associated with the highest risk of diabetes, diabetic complications, and overweight/obesity (adjusted OR 2.55, 3.68, and 1.58, respectively), thereby demonstrating a dose–response relationship. A recent observational study⁵⁹ and a meta-analysis of five clinical trials (32,752 patients) noted that higher-potency statins were also associated with a higher risk of diabetes compared to lower-potency statins.⁶⁵

In this study, our intent was to examine the risk of outcomes in a healthy population, excluding patients who had ischemic heart diseases or their equivalents, patients with any Charlson comorbidity (which include renal failure, mild liver disease, HIV, and any malignancy other than skin cancers), and patients with any chronic disease that might limit life expectancy

or physical activity (including rheumatologic diseases, psychosis, and prior suicide attempts). In contrast, a meta-analysis of statin use and the risk of incident diabetes included patients with several comorbidities, including prior cardiovascular diseases, peripheral vascular diseases, heart failure, and elevated C-reactive protein (CRP).¹ Therefore, our study adds a new perspective to the association between statins and risk of incident diabetes.

The association between the use of statins and diabetic complications has not been reported thus far, and deserves further study. In a recent nested matched study of a Danish population, 15,679 statin users were matched to 47,037 nonusers on the basis of sex, age at diabetes diagnosis, year of diabetes diagnosis, and history of cardiovascular disease⁶⁶; the median follow-up was 2.7 years (range 0–13). The study noted that statin users had lower cumulative incidence of diabetic retinopathy (HR 0.60; 95 % CI 0.54–0.66) and

Table 3 Selected Baseline Characteristics of the Healthy Cohort of Statin Users and Nonusers

	Statin nonusers no. (%) (n=21,988)	statin users no. (%) (n=3 982)	P value
Age (years), mean±SD	42.6±9.8	54.4±11.7	<0.001
Female sex,	9915 (45.1)	1520 (38.2)	<0.001
Comorbidities in baseline period			
Smoking	1062 (4.8)	304 (7.6)	<0.001
Overweight/obese	1812 (8.2)	567 (14.2)	<0.001
Hypertension	3116 (14.2)	2252 (56.6)	<0.001
Asthma	625 (2.8)	115 (2.9)	0.88
Osteoarthritis, arthropathy, or back disorder	8097 (36.8)	1919 (48.2)	<0.001
Osteoporosis	258 (1.2)	149 (3.7)	<0.001
Health care utilization at baseline			
Number of inpatient admissions during baseline period: mean±SD	0.10±0.37	0.09±0.34	0.006
Number of outpatient medical encounters during baseline period: mean±SD	17.1±18.1	22.1±19.9	<0.001
Number of encounters for immunization during baseline period: mean±SD	0.57±1.4	0.41±1.1	<0.001
Medications at baseline			
Beta-blocker	822 (3.7)	650 (16.3)	<0.001
Diuretic	1495 (6.8)	1008 (25.3)	<0.001
ACE/ARB	1431 (6.5)	1260 (31.6)	<0.001
Calcium channel blocker	652 (3.0)	566 (14.2)	<0.001
Proton pump inhibitor	2,915 (13.3)	1140 (28.6)	<0.001
Aspirin	1083 (4.9)	1268 (31.8)	<0.001
NSAID	13,272 (60.4)	2288 (57.5)	0.001
Bisphosphonate	475 (2.2)	272 (6.8)	<0.001
SSRI	2336 (10.6)	578 (14.5)	<0.001
Hormone replacement therapy	1,532 (7.0)	478 (12.0)	<0.001
Testosterone	41 (0.2)	19 (0.1)	0.002
Oral hypoglycemic	61 (0.3)	22 (0.6)	0.009
Warfarin	39 (0.2)	21 (0.5)	<0.001
Mean LDL-C in mg/dL during baseline period: mean±SD ^a	112±26	122±33	<0.0001
Mean HDL-C in mg/dL during baseline period: mean±SD ^a	58±17	54±15	<0.0001

ACE/ARB angiotensin receptor blockers and angiotensin-converting-enzyme inhibitors, AHRQ-CSS Agency for Health Research and Quality Clinical Classifications Software,¹⁵ NSAID non-steroidal anti-inflammatory drugs, SD standard deviation, SSRI selective serotonin reuptake inhibitors

^aLipid measurements represent the mean value for each patient throughout the baseline period; these laboratory measurements were only available in 1946 statin users and 3455 nonusers. Lipid measurements were not included in propensity score matching

diabetic neuropathy (HR 0.66; 95 % CI 0.57–0.75), but not diabetic nephropathy (HR 0.97; 95 % CI 0.85–1.10). In contrast, our study had a much longer follow-up period (6.5 years), included only healthy adults without prior cardiovascular diseases, and matched patients on 42 variables including 20 different classes of medications.

Two small trials reported that statins were associated with an improvement in diabetic retinopathy in diabetic patients.^{67,68} For example, in one of the studies, which was a randomized controlled trial (50 patients with diabetic retinopathy), simvastatin was associated with improved ophthalmologic fundus examination.⁶⁸ On the other hand, several observational and experimental studies have noted that statin use was associated with high blood glucose levels.^{4–8}

The overall proportion of overweight/obesity in our cohort was high (exceeding 40 %), but is commensurate with recent estimates of overweight/obesity.⁶⁹ Evidence from in vitro

studies indicates that statins can increase body and liver fat accumulation.⁷⁰ A recent prospective study noted that, compared to nonusers, statin users expended less metabolic equivalents, engaged in less moderate physical activity and for shorter durations, and exhibited more sedentary behavior for more minutes per day.⁷¹ In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, an increase in body weight was observed among patients in the rosuvastatin group as compared with the placebo group (0.44 kg vs 0.15 kg, respectively).⁷² A cross-sectional study (27,886 adults) from the National Health and Nutrition Examination Survey (NHANES) noted that caloric intake, fat intake, and body mass index were higher in statin users compared to nonusers.² Lastly, a Mendelian randomization study noted that common variants in the HMGR gene were associated with an LDL-lowering effect and an increase in body mass index, insulin resistance, and type 2 diabetes,⁷³ which further supports the

Table 4 Comparison of Outcomes in Statin Users and Nonusers in the Propensity Score-Matched Cohort

Outcome	Statin nonusers no. (%) (n=3,351)	Statin users no. (%) (n=3,351)	Odds ratio	95 % CI	p value
Diabetes mellitus	649 (19.4)	1037 (30.9)	1.87	1.67 2.01	<0.0001
Diabetes mellitus with complications	69 (2.1)	167 (5.0)	2.50	1.88 3.32	<0.0001
Overweight/obese	1456 (43.4)	1564 (46.7)	1.14	1.04 1.25	0.008

Table 5 Comparison of Components of Diabetes Complications in Statin Users and Nonusers in the Propensity Score-Matched Cohort

Components of diabetes complications	Statin nonusers no. (%) (n=3351)	Statin users no. (%) (n=3351)	p value
Uncontrolled diabetes and diabetes with hyperosmolar or ketotic coma	43 (1.3)	111 (3.3)	<0.0001
Diabetes with renal manifestations	11 (0.3)	26 (0.8)	0.01
Diabetes with ophthalmic manifestations	3 (0.1)	17 (0.5)	0.001
Diabetes with neurological manifestations	17 (0.5)	43 (1.3)	0.001
Diabetes with peripheral circulation manifestations	5 (0.1)	18 (0.5)	0.005
Diabetes with hypoglycemia	5 (0.1)	9 (0.3)	0.42
Diabetes with unspecified complication	3 (0.1)	10 (0.3)	0.09

link between statins and a higher risk of diabetes and obesity, and demonstrates that this is an “on-target” effect.⁷⁴ Our study offers additional evidence for the association between statins and overweight/obesity, utilizing retrospective cohort observational data.

Our findings will need to be confirmed by other studies, as they may have significant implications. Our results indicate that extrapolating information from carefully selected patients in short-term randomized controlled studies to decades of statin use for primary prevention might not be appropriate. Additionally, statin effects on overall comorbidity, not only cardiovascular morbidity, need to become part of the risk/benefit assessment.

The purpose of our study was not to examine whether the increased risk of diabetes and its complications among statin users is outweighed by the reduced risk of atherosclerotic cardiovascular disease. Comparing risks of cardiovascular disease between statin users and nonusers in observational data may be subject to confounding by indication—that is, statin users were prescribed statins because they may have had a family history of premature cardiovascular disease, high CRP, or increasing lipid profiles over time. Some investigators have suggested doubling the observed risks to account for this bias.⁷⁵ Moreover, to appropriately account for the risk of cardiovascular disease in statin users and nonusers, both groups should be matched on lipid profile and blood pressure measurements and on Framingham or other cardiovascular risk score. This information was missing for most of our patients, and therefore our results cannot be used to examine the value of statins in primary prevention among healthy adults. Rather, they only indicate that short-term clinical studies may not fully describe the effects of statins in long-term real life utilization for primary prevention, and hence additional research utilizing prospective observational and pragmatic studies is needed. Our study also indicates that in order to examine the effects of statins in primary prevention, a measure for overall comorbidity must be developed and utilized in

reporting the benefits, rather than depending entirely on total cardiovascular mortality and morbidity.

Our study has several limitations, including its retrospective observational design, which may suffer from unrecognized confounding factors despite our best effort to identify confounders. Additionally, our study used ICD-9-CM codes of AHRQ-CCS, which may lack sensitivity toward some variables such as smoking and overweight/obesity. We also lacked data on body mass index, HbA_{1c}, serum creatinine, and urinalysis, all of which are important in supporting our outcomes. Although the use of ICD-9 codes in extracting diagnoses of diabetes with and without complications has good sensitivity and excellent specificity, we are not aware that using AHRQ-CCS codes was specifically validated in Tricare data. The use of ICD-9 codes to identify obesity as an outcome has low sensitivity but high specificity, which is another limitation to our study. However, the proportions of patients identified as overweight or obese in our outcome were similar to national trends; this may be due to the comprehensive longitudinal database, complete follow-up, easy and equal access to care within the military health care system, and the mandated routine visits for military personnel. It should be also noted that body mass index may not be reliable in identifying overweight/obesity in athletic and military populations.^{76,77} Determining baseline characteristics based on ICD-9 codes was another limitation, given the variable sensitivity and specificity of each disease group. However, we are not aware of any reason for differential ascertainment bias between statin users and nonusers (i.e., underestimation or overestimation is likely to affect both treatments equally). First, both statin users and nonusers had extensive continuous follow-up for almost 7 years and a mean number of > 60 visits (despite being a healthy population). Second, the Tricare Prime/Plus health care system has unique features that offer easy and ample access to health care, and specific aspects of health care are mandated; therefore, there was ample chance to capture diseases. Third, controlling for the number of medical encounters

Table 6 Comparison of Outcomes in High-Intensity Statin Users Versus Moderate/Low-Intensity Statin Users

Outcomes	High-intensity statin users no. (%) (n=1155)	Moderate/low-intensity statin users no. (%) (n=2827)	Adjusted odds ratio ^a	95 % CI			p value
Diabetes mellitus	454 (39.3)	839 (29.7)	1.50	1.30	1.73	0.0001	
Diabetes mellitus with complications	95 (8.2)	119 (4.2)	1.97	1.49	2.61	0.0001	
Overweight/obese	632 (54.7)	1219 (43.1)	1.61	1.40	1.84	0.0001	

^aAdjusted for propensity score

Table 7 Secondary and Sensitivity Analyses of Outcomes in Statin Users and Nonusers

Outcome	Statin nonusers	Statin users	Adjusted odds ratio ^a	95 % CI		p value
Healthy cohort (21,988 nonusers and 3982 statin users)						
Diabetes mellitus	2421 (11.0)	1293 (32.5)	2.11	1.92	2.32	<0.001
Diabetes mellitus with complications	213 (1.0)	214 (5.4)	2.78	2.18	3.53	<0.001
Overweight/obese	8608 (39.2)	1851 (46.5)	1.22	1.13	1.33	<0.001
High-intensity statin-users cohort (21,988 nonusers and 1155 statin users)						
Diabetes mellitus	2421 (11.0)	454 (39.3)	2.55	2.21	2.94	<0.001
Diabetes mellitus with complications	213 (1.0)	95 (8.2)	3.68	2.70	5.00	<0.001
Overweight/obese	8608 (39.2)	632 (54.7)	1.58	1.34	1.80	<0.001
Two-year statin-user cohort (21,988 nonusers and 3308 statin users)						
Diabetes mellitus	2421 (11.0)	1120 (33.9)	2.16	1.95	2.40	<0.001
Diabetes mellitus with complications	213 (1.0)	184 (5.6)	2.60	2.01	3.35	<0.001
Overweight/obese	8608 (39.2)	1552 (46.9)	1.24	1.14	1.35	<0.001
Four-year statin-user cohort (21,988 nonusers and 2933 statin users)						
Diabetes mellitus	2421 (11.0)	1028 (35.0)	2.24	2.01	2.49	<0.001
Diabetes mellitus with complications	213 (1.0)	169 (5.8)	2.71	2.08	3.52	<0.001
Overweight/obese	8608 (39.2)	1373 (46.8)	1.22	1.11	1.33	<0.001
Overweight/obesity incident cohort (20,176 nonusers and 3415 statin users)						
Diabetes mellitus	2045 (10.1)	1060 (31.0)	2.14	1.92	2.37	<0.001
Diabetes mellitus with complications	169 (0.8)	159 (4.7)	2.87	2.17	3.79	<0.001
Overweight/obese	7078 (35.1)	1371 (40.1)	1.26	1.16	1.38	<0.001

^aAdjusted for propensity score

during the follow-up period did not significantly change our results. Fourth, as demonstrated in Table 1, nonusers actually had higher proportions of obesity at baseline. Lastly, the prevalence of overweight/obesity and diabetes were similar to recently published national trends,^{58,69} suggesting that the magnitude of underestimation was not sizable. Another limitation is that ICD-9-CM codes do not provide information on severity of illness. Therefore, it may be assumed that physicians were more biased to prescribe statins in patients with more severe overweight/obesity at baseline, and consequently, statin users were more likely to develop diabetes and diabetic complications. However, such bias, if it existed, is unlikely to be responsible for an approximately twofold increase in the odds of diabetes incidence and a threefold increase in the odds of diabetic complications. The use of pharmacy data to account for medication use assumes, but cannot ascertain, that patients are actually taking their medications. However, approximately 73 % of our statin users filled their statin prescriptions for 4 years, which may be considered a surrogate marker for actual use of medications. The pattern of statin use in our study, where 77 % of statin users used simvastatin, may be different from current statin utilization trends. Data from the private sector indicate that the use of atorvastatin in certain markets may be as high as 48 %, and that rosuvastatin use has risen to 65 % in some markets.^{78,79} Since using OR rather than relative risk (RR) may exaggerate the perception of risk, we calculated the RR of the outcomes using a previously published formula⁸⁰ as follows: RR of diabetes=1.60, diabetes with complications=1.90, and overweight/obesity=1.07.

In conclusion, statin use was associated with increased likelihood of patients being diagnosed with diabetes and of diabetic complications and overweight/obesity. Further investigations, including randomized controlled studies for prolonged periods and larger-scale prospective studies, are needed in order to obtain a more complete risk/benefit assessment of statin therapy for primary prevention.

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Corresponding Author: Ishak Mansi, M.D.; Department of Medicine VA North Texas Health System, 4500 S. Lancaster Rd #111E, Dallas, TX, USA (e-mail: Ishak.mansi@va.gov).

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APPENDIX

Table 8 AHRQ-CCS Disease Categories Excluded to Create a Healthy Cohort

Disease group name	AHRQ-CCS category number
AHRQ-CCS categories that suggested the presence of cardiovascular diseases or their equivalents at baseline	
Diabetes mellitus with and without complications	49 and 50
Heart valve disorders	96
Pericarditis, endocarditis, myocarditis, or cardiomyopathy	97
Hypertension with complications and secondary hypertension	99
Acute myocardial infarction	100
Coronary atherosclerosis and other heart disease	101
Pulmonary heart disease	103
Conduction disorders	105
Cardiac dysrhythmias	106
Cardiac arrest and ventricular fibrillation	107
Congestive heart failure; non-hypertensive	108
Acute cerebrovascular disease	109
Occlusion or stenosis of precerebral arteries	110
Other and ill-defined cerebrovascular disease	111
Transient cerebral ischemia	112
Peripheral and visceral atherosclerosis	114
Aortic; peripheral; and visceral artery aneurysms	115
Aortic and peripheral arterial embolism or thrombosis	116
AHRQ-CCS categories suggesting the presence of comorbid conditions that might limit life expectancy or physical activity	
Chronic obstructive pulmonary disease and bronchiectasis	127
Respiratory failure; insufficiency; arrest in adult	131
Nephritis; nephrosis; renal sclerosis	156
Chronic kidney disease	158
Rheumatoid arthritis and related disease	202
Pathological fracture	207
Systemic lupus erythematosus and connective tissue disorders	210
Schizophrenia and other psychotic disorders	659
Suicide and intentional self-inflicted injury	662

AHRQ-CCS Agency for Health Research and Quality Clinical Classifications Software¹⁷

Table 9 Outcome Groups and Their Definitions

Group name	ICD-9-CM codes
Diabetes mellitus without complication (AHRQ-CCS category 49)	24900, 25000, 25001, 7902, 79021, 79022, 79029, 7915, and 7916; excluding codes V4585, V5391, V6546
Diabetes mellitus with complications (AHRQ-CCS category 50)	24901, 24910, 24911, 24920, 24921, 24930, 24931, 24940, 24941, 24950, 24951, 24960, 24961, 24970, 24971, 24980, 24981, 24990, 24991, 25002, 25003, 25010, 25011, 25012, 25013, 25020, 25021, 25022, 25023, 25030, 25031, 25032, 25033, 25040, 25041, 25042, 25043, 25050, 25051, 25052, 25053, 25060, 25061, 25062, 25063, 25070, 25071, 25072, 25073, 25080, 25081, 25082, 25083, 25090, 25091, 25092, and 25093.
Obesity (selected ICD-9-CM codes from AHRQ-CCS category 56 [other nutritional; endocrine; and metabolic disorders])	2780, 27800, 27801, 27802, 27803, 2781, 2788, and 7831.

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Table 10 Definitions of Baseline Characteristics^a

Disease group	AHRQ-CCS category
Alcohol-related disorders	Category 660
Substance-related disorders	Category 661
Hypertension	Category 98
Acute kidney injury	Category 157
Asthma	Category 128
Gastrointestinal hemorrhage	Category 153
Gastritis/duodenitis	Category 140
Nonspecific chest pain	Category 102
Heart disease not otherwise specified	Category 104
Osteoarthritis, arthropathy, and back disorder	Categories 203, 204, 205
Sprains, strains, and trauma-related joint disorders	Categories 225, 232
Fracture of bone	Categories 226, 229, 230, 231
Osteoporosis	Category 206
Rehabilitation care; fitting of prostheses and adjustment of devices	Category 254

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^aDiagnosis is based on ICD-9-CM codes as identified in respective disease category of AHRQ-CCS