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ORIGINAL ARTICLE

Statins were not associated with hepatocellular carcinoma after controlling for time-varying confounders in patients with diabetes

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Abstract

Background and Objectives: We examined the association between statin use and hepatocellular carcinoma (HCC) incidence in patients with diabetes using marginal structural models (MSMs) estimated by inverse probability weight (IPW), which adjusts for time-varying confounders that are also mediators, and we compared the results with conventional regression methods.

Methods: This retrospective cohort study included 245,122 patients with type 2 diabetes who were new users of lipid-lowering drugs identified using the claims data of a universal health insurance program. Statin exposure was time-updated every three months during the follow-up period. Stabilized IPW was calculated and accounted for chronic liver diseases considering as time-dependent confounders affected by past statin exposure.

Results: Over a median follow-up of 5.2 years, 1,694 patients developed HCC. In the conventional regression analysis, the hazard ratio of HCC associated with statin use was 0.88 (95% confidence interval CI: 0.79−0.97) after adjusting for baseline covariates and 0.97 (95% CI: 0.87−1.08) after additionally adjusting for time-varying covariates. The hazard ratio increased to 1.11 (95% CI: 0.94−1.31) using the MSM approach.

Conclusion: Statin use was not associated with the risk of developing HCC in patients with diabetes. Our findings highlight the importance of controlling time-varying confounders in observational studies.

Keywords: Inverse probability weight; Marginal structural model; Retrospective cohort study; Type 2 diabetes mellitus; Time-varying confounding; Mediators

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. Globally, HCC ranks sixth in cancer incidence and fourth in cancer mortality [1,2]. Meta-analyses of epidemiological studies have demonstrated that patients with diabetes have a two-to-threefold higher risk of HCC incidence than do patients without diabetes [3,4]. Potential pathophysiological mechanisms underlying the association between diabetes and HCC development include hyperglycemia, insulin resistance, hyperinsulinemia, and the activation of insulin-like growth factor signaling pathways [5,6]. Diabetes and associated metabolic dysfunction are related to liver diseases such as nonalcoholic fatty liver disease, and cirrhosis, which predispose patients to a higher risk of HCC [7,8].

Accumulating experimental evidence over the past decade suggests that statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), which are widely used lipid-lowering medications, induce growth inhibition and apoptosis of HCC cell-lines [9,10]. Several observational epidemiological studies have also reported a lower risk of HCC in statin users than in nonusers [11−13]. However, there are only two nested case-control studies in this area designed specifically to evaluate patients with diabetes [12,14]. Furthermore, treatment decisions in observational studies using real-world data

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What is new?

Key findings

- Statin use was associated with a reduced risk of HCC after adjusting for baseline covariates, but the association no longer existed after additionally controlling for chronic liver diseases, which were considered as time-varying confounders that were also intermediate variables.

What this adds to what was known?

- Our findings suggest no association between statin use and reduced risk of HCC in patients with type 2 diabetes and highlight the importance of accounting for time-varying confounding due to chronic liver diseases.

What is the implication and what should change now?

- When studying effect of time-dependent drug use using observational data, not appropriately controlling for time-varying confounders may yield a biased estimate.

are complex and dynamic [15], and time-varying confounders that are affected by previous treatments (i.e., mediators) likely exist [16,17]. For example, physicians are often reluctant to prescribe statins for patients with chronic liver disease owing to concerns regarding potential hepatotoxicity [18]. In addition, in the recent years, evidence has also suggested that statins may have beneficial effect in the pathobiology of chronic liver disease [11,19]. Therefore, liver diseases may act as time-varying confounders that are also mediators in the association between statin use and HCC risk. However, there is a paucity of studies accounting for this issue to date [20].

Marginal structural models (MSMs) with inverse probability weight (IPW) estimate the effects of time-varying treatments in the presence of time-varying confounders affected by prior treatment in observational studies [16,21,22]. In this study, we harnessed this approach to examine the association between statin use and HCC incidence in patients with diabetes newly treated with lipid-lowering drugs. We compared the results of the IPW of an MSM with conventional regression adjustment to assess the impact of accounting for such time-varying confounding.

2. Materials and methods

2.1. Data source and study cohort

The National Health Insurance (NHI) program is a compulsory social insurance program for which the enrollment rate exceeds 99% of the entire population of Taiwan [23]. In this retrospective cohort study, we used claims data of a cohort comprising 120,000 patients randomly selected each year from all NHI beneficiaries who were newly diagnosed with diabetes between January 1, 1999, and December 31, 2013. Diabetes was defined by at least two outpatient claims or one inpatient claim recorded with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 250.xx or 648.8 within 1 year, or any prescription for anti-diabetic drugs. The claims contained individual-level data, including birth date, sex, medical diagnosis, prescription drugs, and information on medical services for inpatient, outpatient, and emergency room visits.

Using the diabetes dataset, we assembled a cohort of patients with at least three prescription records of antidiabetic drugs (Anatomical Therapeutic Chemical [ATC] code A10) within 6 months who were new users of lipid-lowering drugs (ATC code C10) between January 1, 2001, and December 31, 2012. A new user was defined as initiating therapy with lipid-lowering drugs after the first prescription of antidiabetic medications and had at least three prescriptions within 6 months. To ensure that patients were new users, we excluded patients who were prescribed lipid-lowering drugs before their first prescription of antidiabetic medications, identified by retrospectively searching claims back to 1999. We used the date of 6 months after the first prescription for lipid-lowering drugs as the date of cohort entry. Exclusion criteria were as follows: data on sex and birth date were unavailable, younger than 40 years of age on the cohort entry date, and diagnosis of type 1 diabetes or cancer of any site (Fig. 1) (diagnosis codes in Supplemental Table 1). We excluded patients with type 1 diabetes because the pathophysiology, risk factors, and managements differ between type 1 and type 2 diabetes [24]. Patients with type 1 diabetes were identified whether they received a catastrophic illness certificate for a diagnosis of type 1 diabetes. The institutional review board of

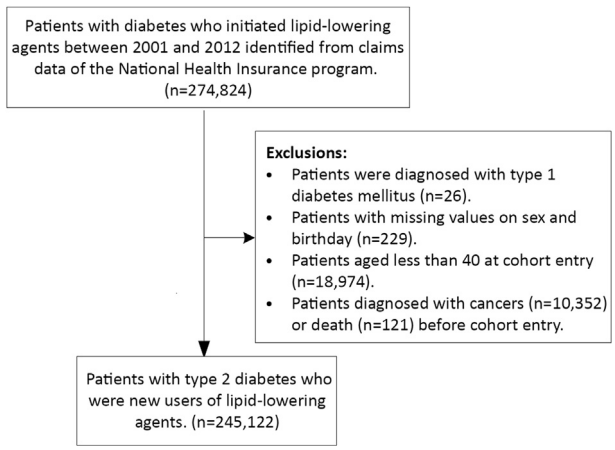

Fig. 1. Flow chart of the study.

Changhua Christian Hospital approved this study (IRB: 181,226). The need for informed consent was waived because this was an analysis of de-identified data.

2.2. Exposure measurement

The study cohort comprised patients with type 2 diabetes who were new users of lipid lowering drugs. All patients were classified into two groups, statin use or no statin use, according to their status of exposure to statins at cohort entry and per 3 months during follow-up. At the time of cohort entry (time 0), exposure to statins was defined as the receipt of at minimum a cumulative 28-day prescription for statins within 180 days before cohort entry. Exposure status was time-updated every 3 months during the follow-up period, starting on the date of cohort entry. At each 3 month time point, patients were categorized into mutually exclusive groups: patients that had received at least one prescription for statins during this period were classified as "users"; all other patients were classified as "nonusers." Patients were considered to have continued statin use if they received a repeated prescription or requested prescription refills within 14 days following the end of the previous prescription.

2.3. Outcomes and follow-up

We identified patients newly diagnosed with HCC during the follow-up period based on the diagnostic code (ICD-9-CM code 155.0) recorded by the Registry for Catastrophic Illness Patients. In Taiwan, patients diagnosed with diseases classified as catastrophic by the Ministry of Health and Welfare can apply for a catastrophic illness certificate. Relevant documents such as diagnosis certificates and pathological reports are reviewed; if approved, patients are exempted from copayment for medical care. Follow-up commenced at the time of cohort entry and ended on the date of earliest occurrence of HCC, any cause of cancer excluding HCC, withdrawal from NHI, death, or study completion (December 31, 2013).

2.4. Baseline and time-varying covariates

We considered several baseline and time-varying covariates as potential confounders of the association between statin use and HCC. Baseline covariates comprised demographic variables, including age at cohort entry, sex, and geographic region of NHI registration (northern, central, southern, and eastern/offshore islands); calendar year of cohort entry (2001–2003, 2004–2006, 2007–2009, and 2010–2012); utilization of healthcare services, including number of outpatient clinic visits and hospital admission (yes vs. no); comorbidities, such as cirrhosis, alcoholic liver damage, nonalcoholic fatty liver disease, and hepatitis B and/or C infection; use of medications, including metformin, sulfonylurea, thiazolidinediones, other oral antidiabetic agents, insulin, and aspirin; and duration between diabetes diagnosis (i.e., date of the first prescription of antidiabetic drugs) and cohort entry. All baseline covariates were evaluated in the year preceding cohort entry. Comorbidities were defined as at least two outpatient visits or one hospital admission with the relevant diagnosis codes (Supplemental Table 1). Time-varying covariates included cirrhosis, alcoholic liver damage, nonalcoholic fatty liver disease, and hepatitis B and/or C infection, the status (yes vs. no) of which was updated to the current 3 months. Patients with chronic conditions such as chronic liver diseases may not seek medical consultations every 3 months. Therefore, to avoid misclassification of the status of the chronic liver diseases, patients were assumed to stay in the group of having a chronic liver disease after their first diagnosis of that disease. These time-varying confounders were potential mediators of the association between statin use and risk of HCC. Continuous variables such as follow-up time, age, duration from diabetes diagnosis to cohort entry, and number of outpatient visits were modeled as restricted cubic spline with three knots (fifth, 50th, and 95th percentiles) [22].

2.5. Statistical analyses

To analyze the association between statin use and risk of developing HCC, we fitted pooled logistic regression models treating each 3-month follow-up per patient as an observation. The odds ratio produced by this approach approximated the hazard ratios (HRs) from Cox proportional hazards models [25]. In addition, the pooled logistic regression model that enabled the incorporation of time-varying weights was adopted to approximate a weighted Cox model, also termed a marginal structural Cox model. The 95% confidence intervals (CIs) were calculated using a robust variance estimator. Detailed information on MSM with IPW is provided in Supplemental Methods and Supplemental Tables 3 and 4.

We developed four models to investigate whether MSM with IPW produced different HRs from the unweighted models with or without adjustments for time-varying confounders. In all models, statin use was a binary independent variable treated as a time-dependent exposure. Models one to three were unweighted models with different levels of confounder adjustment. Model one was a crude model that only included time-varying statin exposure. Model two was additionally adjusted for all baseline covariates. In Model three, we included all Model two variables and all time-varying confounders. Model four was an MSM with IPW, a weighted model controlling for the potential confounding effects of baseline covariates and time-varying covariates that were also mediators. In MSM, the contribution of each patient to the risk set at a given threemonth follow-up interval was weighted by the inverse probability of treatment (i.e., status of statin use) and censoring. Both time-varying and baseline covariates were considered in the estimation of treatment and censoring weights. We used stabilized weights, which were preferred because they were less variable than traditional weights [21]. Details of the

weight estimation and modeling process are described in online Supplementary Materials (Supplemental Methods, Supplemental Tables 1–5, and Supplemental Figure 1). To assess the robustness of the result, we also performed several sensitivity analyses using MSM with IPW (Supplemental Methods). All statistical analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

3. Results

From an initial sample of 274,824 new users of lipid-lowering agents diagnosed with diabetes between 2001 and 2012, a total of 245,122 patients met the inclusion criteria (Fig. 1). Of these patients, 188,874 were statin initiators and 56,248 were noninitiators, with a median (interquartile range) follow-up for 5.0 (4.8) years and 5.7 (5.5) years, respectively. Table 1 presents the baseline characteristics of the two groups. Women accounted for a greater proportion of statin initiators than non-initiators (50.3% vs. 39.1%, respectively). The mean (standard deviation) age of statin initiators and noninitiators at cohort entry was 60.1 (10.6) years and 58.1 (11.0) years, respectively. Statin initiators tended to have better medication adherence compared to nonusers (the proportion of days covered for statins during the follow-up period, 53.2% vs. 22.1%). Before cohort entry, statin initiators had a lower prevalence of cirrhosis, alcoholic liver damage, and nonalcoholic fatty liver disease. Compared to noninitiators, statin initiators were less likely to be treated with sulfonylurea but were more likely to be prescribed thiazolidinediones, insulin, other oral antidiabetic agents, and aspirin.

During the follow-up period, 1,694 incident HCC cases were identified. The crude incidence rates of HCC for no statin use and statin use were 14.6 per 10,000 person-years and 11.3 per 10,000 person-years, respectively. Table 2 presents the HRs for the association between statin use and the risk of developing HCC. Statin use was associated with a reduced risk of developing HCC (HR: 0.74, 95% CI: 0.67–0.82) in Model 1, in which only time-varying statin exposure was included. The association was weaker but remained statistically significant after controlling for baseline covariates (HR: 0.88, 95% CI: 0.79–0.97; Model 2). However, in the model adjusted for both baseline and time-varying covariates, the HRs increased to a statistically nonsignificant level (HR: 0.97, 95% CI: 0.87–1.08; Model 3). The HRs increased further to 1.11 (95% CI: 0.94–1.31, Model 4) in the MSM with IPW. In the sensitivity analysis performed to assess the robustness of MSM with IPW (Table 3), the results of all models were similar to those of primary MSM (i.e., Model 4; Table 2).

4. Discussion

In this study, we used different models with or without adjustment for time-varying confounders to evaluate the association between statin use, which was treated as a time-varying exposure, and the risk of developing HCC in a large cohort of patients with diabetes who were new users of lipid-lowering drugs. We observed that statin use was associated with a 12% reduction in the risk of HCC after controlling for baseline covariates; however, additional adjustment for time-varying confounders eliminated this association.

Our findings are inconsistent with the results of the majority of observational studies, which demonstrated that statin use was associated with a reduced risk of HCC among various populations, including the general population [26,27], patients with diabetes [12], and individuals with chronic liver disease [13,28,29]. In the nested case-control studies consisting of patients with diabetes, statin users had a 26% and 64% reduced risk of HCC compared with nonusers [12,14]. The discrepancy in the current findings and previous reports may reflect methodological differences. First, indication bias may occur because patients with advanced liver disease are less likely to manifest hyperlipidemia and receive statin therapy [30]. Second, the majority of previous studies did not address time-varying confounders, which are likely to be present in longitudinal studies [12,13,26–29]. To address these issues, all patients must have been prescribed lipid-lowering medications (i.e., patients with hyperlipidemia) to be eligible for inclusion in our analysis. Furthermore, we used both standard regression methods and an MSM with IPW to adjust for potential time-varying confounders (i.e., chronic liver diseases) during the follow-up period. Both analyses revealed that the association between statin use and the risk of HCC was no longer present after adjusting for time-varying covariates, highlighting the importance of accounting for these confounders.

Our observation which showed the presence of potential time-varying confounding due to chronic liver diseases likely reflect the different patterns of statin prescriptions for patients with and without chronic liver diseases. The concern of hepatotoxicity in the early years may have led to reluctance to prescribe statins in the settings of chronic liver disease. In the recent years, it is increasing recognized that statins are generally safe and not contradicted in patients with liver diseases except those with decompensated cirrhosis or acute liver failure, for whom the dose adjustments may be required [18,19]. Despite these data, recent studies revealed that statins continued to be under-prescribed for patients with nonalcoholic fatty liver disease who had indications for statin therapy such as concomitant dyslipidemia [31,32]. Therefore, chronic liver diseases may be time-dependent confounders in the association between statin use and HCC risk, as evidenced in our analysis, because a diagnosis of these liver diseases may affect the physicians' decisions on initiating or discontinuing statin therapy at baseline or during follow-up.

It is well known that nonalcoholic fatty liver disease and hepatitis can progress to cirrhosis and HCC development.

Table 1. Baseline characteristics of study participants

Characteristic	All participants (*n* = 245,122)		Noninitiators[a] (*n* = 56,248)		Statin initiators[a] (*n* = 188,874)	
	n	%	*n*	%	*n*	%
Women	117,022	47.7	21,993	39.1	95,029	50.3
Age, years						
40–54	91,845	37.5	25,140	44.7	66,705	35.3
55–64	78,240	31.9	16,140	28.7	62,100	32.9
≥65	75,037	30.6	14,968	26.6	60,069	31.8
Mean and SD	59.7	10.8	58.1	11.0	60.1	10.6
Duration from diabetes to cohort entry[b], month						
<24 mo	104,474	42.6	24,378	43.3	80,096	42.4
24–47 mo	60,641	24.7	15,048	26.8	45,593	24.1
48–71 mo	36,848	15.0	8,320	14.8	28,528	15.1
≥72 mo	43,159	17.6	8,502	15.1	34,657	18.4
Mean and SD	40.2	33.5	38.2	31.3	40.8	34.0
Calendar year of cohort entry[b]						
2001–2003	27,773	11.3	9,184	16.3	18,589	9.8
2004–2006	60,017	24.5	14,220	25.3	45,797	24.3
2007–2009	73,499	30.0	16,314	29.0	57,185	30.3
2010–2012	83,833	34.2	16,530	29.4	67,303	35.6
Geographic region of registration to the health insurance program						
Northern	99,518	40.6	21,272	37.8	78,246	41.4
Central	57,554	23.5	15,157	27.0	42,397	22.5
Southern	74,013	30.2	16,691	29.7	57,322	30.4
Eastern/offshore islands	14,037	5.7	3,128	5.6	10,909	5.8
Number of clinic visits in the year before cohort entry[b]	29.0	18.6	28.3	18.9	29.2	18.5
<12	21,226	8.7	5,638	10.0	15,588	8.3
12–23	96,233	39.3	22,829	40.6	73,404	38.9
24–35	64,853	26.5	14,111	25.1	50,742	26.9
≥35	62,810	25.6	13,670	24.3	49,140	26.0
Hospital admission in the year before cohort entry[b]	53,117	21.7	11,396	20.3	41,721	22.1
Proportion of days covered for lipid-lowering drugs[c]						
≥50%	186,561	76.1	41,097	73.1	145,464	77.0
≥80%	91,628	37.4	19,394	34.5	72,234	38.2
Comorbidities before cohort entry[b]						
Cirrhosis	4,129	1.7	1,302	2.3	2,827	1.5
Alcoholic liver damage	3,388	1.4	1,355	2.4	2,033	1.1
Nonalcoholic fatty liver disease	10,226	4.2	2,682	4.8	7,544	4.0
Hepatitis B and/or C infection	11,932	4.9	2,803	5.0	9,129	4.8
Prescriptions in the year before cohort entry[b]						
Metformin	172,672	70.4	39,300	69.9	133,372	70.6
Sulfonylurea	171,126	69.8	41,178	73.2	129,948	68.8
Thiazolidinediones	27,526	11.2	4,764	8.5	22,762	12.1
Other oral antidiabetic agents	51,828	21.1	10,052	17.9	41,776	22.1
Insulin	10,986	4.5	2,148	3.8	8,838	4.7
Aspirin	61,755	25.2	11,960	21.3	49,795	26.4

[a] Patients who initiated lipid-lowering drugs with statin and received at minimum a cumulative 28-day prescription for statins within 180 days prior to cohort entry were defined as statin initiators; other patients were defined as non-initiators.

[b] The date of 6 months after the first prescription for lipid-lowering drugs was defined as the date of cohort entry.

[c] Proportion of days covered for lipid-lowering drugs was assessed during the enrollment period.

Table 2. Hazard ratios for the association between statin use and risk of developing hepatocellular carcinoma

Model	Follow-up person years	Number of cases	Hazard ratio	95% CI
Model 1: Unadjusted model				
No use	722,826	1,054	1.00	
Statin use	567,378	640	0.74	0.67, 0.82
Model 2: Baseline (time-fixed) covariates[a]				
No use	722,826	1,054	1.00	
Statin use	567,378	640	0.88	0.79, 0.97
Model 3: Baseline and time-varying covariates[b]				
No use	722,826	1,054	1.00	
Statin use	567,378	640	0.97	0.87, 1.08
Model 4: MSM of IPW[a,c]				
No use	722,826	1,054	1.00	
Statin use	567,378	640	1.11	0.94, 1.31

Abbreviations: IPW, inverse probability of weight; MSM, marginal structural model.

[a] The model was adjusted for the following covariates measured at baseline: age at cohort entry, sex, month since start of follow-up, geographic region of NHI registration, calendar year of cohort entry, duration of diabetes, utilization of healthcare services (number of outpatient clinic visits and hospital admission), comorbidities (cirrhosis, alcoholic liver damage, nonalcoholic fatty liver disease, hepatitis B and/or C infection), and medication use (metformin, sulfonylurea, thiazolidinediones, other oral antidiabetic agents, insulin, and aspirin).

[b] The model was adjusted for all baseline covariates in Model two and the following time-varying covariates: cirrhosis, alcoholic liver damage, nonalcoholic fatty liver disease, and hepatitis B and/or C infection in the current 3 months.

[c] The weighted MSM is described in the Supplemental Methods and Supplemental Tables 3 and 4.

In addition, accumulating preclinical and observational studies have indicated favorable effects of statins on the pathobiology of chronic liver disease and the improvement of outcomes in cirrhosis, although the beneficial effect has not yet been confirmed by randomized clinical trials [19]. Therefore, when evaluating time-varying treatment effects in the context of statins and HCC risk, chronic liver diseases are potential time-dependent confounders that might also be influenced by previous statin use. The use of standard regression methods to adjust for such confounders may partially eliminate the effects of statins acting via these variables on HCC risk as well as introduce collider-stratification bias [33]. Therefore, we used MSM with IPW, an approach that enables adequate control of time-dependent confounders affected by previous treatments [16]. Our findings from MSM with IPW suggested that after controlling for the potentially exposure-affected time-varying confounding by chronic liver diseases, there was no association between statin use and HCC risk.

This study has several limitations. First, data on biomarkers of liver function, such as aspartate aminotransferase and alkaline phosphatase, were unavailable. Residual confounding effects may have occurred due to the use of diagnosis codes to define chronic liver diseases, which were often underdiagnosed. Second, misclassification of hyperlipidemia may have occurred because we lacked information on blood lipid levels. However, we used prescription data, which has been demonstrated to be useful for improving identification of hyperlipidemia using the claims data of Taiwan [34]. We further requested at least three prescriptions during the enrollment period to increase the likelihood of including individuals with hyperlipidemia who may have better adherence to lipid-lowering therapy. Third, information on several potential confounders, such as alcohol use, tobacco use, and obesity were unavailable in the claims data. These factors, if distributed differently between statin users and nonusers, may have confounded the observed association between statin use and HCC risk. Fourth, misclassification of statin use may have occurred due to noncompliance. To address this issue, a minimum cumulative 28-day prescription within 180 days before cohort entry was required to be eligible for inclusion as a statin initiator in our analyses, and statin use during the follow-up period was considered a time-varying exposure. Noncompliance may therefore be less of a concern by adopting these approaches. Furthermore, the main results did not change in the sensitivity analyses restricted to patients with a proportion of days covered of $\geq$50% and $\geq$80%. Finally, selection bias might occur because only subjects remaining under follow-up at the date of cohort entry were eligible for inclusion. However, only 810 (0.43%) statin initiators and 237 (0.42%) non-initiators were excluded because of having had cancer, withdrawal from NHI, or death before cohort entry. The selection bias, if present, probably did not have a substantial impact on our findings.

In summary, in this nationwide cohort study of patients with diabetes treated with lipid-lowering drugs, we did not identify a significant association between statin use and the risk of developing HCC. We used MSMs with IPW to quantify the relationship between statin use and the risk of HCC to adjust for time-varying confounders that may have acted as intermediate variables. Our findings highlight the

Table 3. Sensitivity analyses for the association between statin use and risk of developing hepatocellular carcinoma estimated using MSM with inverse probability weight

Sensitivity analysis	Follow-up person-years	Number of cases	Hazard ratio[a]	95% CI
MSM with IPTW				
No use	722,826	1,054	1.00	
Statin use	567,378	640	1.08	0.93, 1.24
SW of IPCW accounting for statin switch [b]				
No use	625,561	960	1.00	
Statin use	50,620	577	1.09	0.92, 1.30
Exposure did not lag				
No use	790,222	1,290	1.00	
Statin use	622,380	578	0.95	0.76, 1.17
Exposure lagged for 1 y				
No use	658,229	976	1.00	
Statin use	510,233	561	1.01	0.87, 1.18
Proportion of days covered ≥50%[c]				
No use	537,796	771	1.00	
Statin use	452,537	493	1.09	0.92, 1.30
Proportion of days covered ≥80%[c]				
No use	252,334	382	1.00	
Statin use	241,612	257	0.93	0.78, 1.10
Extreme SW was replaced by the 0.01th and 99.99th percentiles				
No use	722,826	1,054	1.00	
Statin use	567,378	640	1.03	0.92, 1.16
Trimmed SW between the 0.01th and 99.99th percentiles				
No use	722,683	1,051	1.00	
Statin use	567,250	635	0.98	0.88, 1.09

Abbreviations: IPCW, inverse probability of censoring weight; IPTW, inverse probability of treatment weight; MSM, marginal structural model; SW, stabilized weight.

[a] The model was adjusted for the following covariates measured at baseline: age at cohort entry, sex, month since start of follow-up, geographic region of NHI registration, calendar year of cohort entry, duration of diabetes, utilization of healthcare services (number of outpatient clinic visits and hospital admission), comorbidities (cirrhosis, alcoholic liver damage, nonalcoholic fatty liver disease, hepatitis B and/or C infection), and medication use (metformin, sulfonylurea, thiazolidinediones, other oral antidiabetic agents, insulin, and aspirin).

[b] In the IPCW estimation, statin initiators were censored at the time of switching to alternative medication during the follow-up period.

[c] Proportion of days covered for lipid-lowering drugs assessed during the enrollment period.

importance of accounting for these confounders in observational studies.

CRediT authorship contribution statement

Yi-Chun Yeh: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Visualization, Project administration. **Yen-Yu Chen:** Resources, Data curation, Writing – review & editing. **Pei-Chun Chen:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

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Supplementary data

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