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Statin use and incident dementia: A nationwide cohort study of Taiwan ☆

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ABSTRACT

Background: Statins are widely used in clinical treatment. However, an U.S. Food and Drug Administration issued health alert has raised concerns for the adverse effects of statin-associated confusion and memory loss in the elderly people. It is necessary to clarify the relationship between statin use and risk of incident dementia as well as whether class effects exist.
Methods: In this population-based retrospective cohort study, total 33,398 patients aged ≥ 60 years were selected from a subset of the Taiwan National Health Insurance Research Databases and followed up for tracking the occurrence of any type of dementia from 2000 to 2010. The Cox proportional hazards models were used.
Results: Compared to nonusers, statin users had a significantly lower risk of incident dementia (hazard ratio [HR], 0.78; 95% CI, 0.72–0.85, $p < 0.001$). The potency and the cumulative duration of statin utilized were associated with the reducing risk of dementia. After stratifying by gender, the risk of incident dementia was lower in female statin users (HR, 0.76; 95% CI, 0.68–0.85, $p < 0.001$) than in male statin users (HR, 0.86; 95% CI, 0.75–0.98, $p = 0.024$). Higher potency and longer cumulative duration of statin use were required for reducing the risk of incident dementia in male patients than in female patients.
Conclusion: Statin use was associated with a significantly lower risk of dementia in the elderly patients in Taiwan. The potency and the cumulative duration of statin utilized played critical roles.

1. Introduction

Hyperlipidemia is associated with various diseases, including hypertension and cerebrovascular, cardiovascular, and renal diseases [1]. Clinical studies have indicated that lipid-lowering agents (LLAs) improve the condition of patients with cardiovascular diseases, reduce mortality and stroke rates, and even delay the progression of atherosclerosis [1,2]. Hydroxymethylglutaryl-CoA reductase inhibitors (statins), the first-line and the globally highest-selling class of LLAs, are well tolerated and are considered to have minimal adverse effects [2]. However, a health alert issued in the early 2012 by the U.S. Food and Drug Administration (FDA) has raised serious concerns about the adverse effects of statin-associated confusion and memory loss in the elderly people [3].

Dementia is an age-related disease and characterized by a gradual decline of mental abilities that affects reasoning, memory, and other cognitive functions [4]. The World Health Organization (WHO) postulated that the proportion of the global population aged 60 will be 22% by 2050 [5]. Since the impact of age-related diseases is crucial to the financial and health care system in Taiwan, it's critical to determine whether statin use will increase the risk of dementia and exacerbate the decline in cognitive functions in the elderly people.

Relevant evidences of the association between statin use and the risk of dementia still remain controversial today. Nested case-controlled and population-based cohort studies have showed protective effects of statins in cognitive function, dementia and Alzheimer disease (AD) in elderly patients [6–9]. However, studies have also determined that statins may deteriorate cognition in patients with dementia or have no significant benefits [10–14]. More importantly, the relevant East Asia population-based study is rare. Therefore, we conducted a population-based propensity-matched cohort study by using the comprehensive

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information from the Taiwan's National Health Insurance Research Databases (NHIRD), and evaluated the association between statin use and the risk of dementia.

2. Methods

2.1. Data sources

The main data source used for this study was the Longitudinal Health Insurance Database 2000 (LHID2000) which is a randomly sampled data subset of one million individuals from the original NHIRD cover the period of 1996 to 2010. The NHIRD contains registration files, original claim data for reimbursement and comprehensive information regarding clinical visits, including prescription details and diagnostic codes [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code and A code], of all the beneficiaries of the Taiwan National Health Insurance (NHI) program which nearly 99% of Taiwanese residents have been enrolled. There were no statistically significant differences of distribution in gender, age, or health care costs between the patients of LHID2000 and original NHIRD, as reported by the National Health Research Institute of Taiwan. In this data set, each patient's original identification number was encrypted to protect privacy. The study has been approved by the Institutional Review Board of National Yang Ming University, Taiwan (B-010-014-MY3).

2.2. Patient population and propensity-based matching

This is a population-based, retrospective cohort study. Due to the low prevalence of dementia below the age of 60, and for minimizing the effect of survival bias, the study population in this cohort was limited in age 60 to 100. We only included patients who were enrolled in the LHID2000 and did not have a statin prescription or be diagnosed with any type of dementia (ICD-9-CM code: 290.x, 294.1, and 331.0; A code: A210) in 3 years prior to the cover period of cohort (i.e., 1997–1999). We also excluded patients who had been diagnosed with any type of dementia before been prescribed statins during the cover period of cohort. The eligible patients were then divided into exposure group (statin users) or nonexposure group (statin nonusers). Statin users were defined as patients who received at least one prescription of statins in the cover period of cohort. Patients who had at least one ambulatory care visit but did not receive any statin prescriptions in this period were defined as statin nonusers. The index date was defined as the first-time statins prescribed for statin users and the first-time ambulatory care visit made for the propensity score (PS) matched statin nonusers.

The PS matching technique is well established in addressing possible confounding by indication and in balancing two test groups across all measured covariates [15]. In this study, statin users and nonusers were matched on a 1:1 ratio by PS, gender, and the year of index date. Only matched 16,699 statin users and 16,699 nonusers were finally included in cohorts for subsequent analyses. The process of sample selection was illustrated in Fig. 1.

2.3. Statin exposure

In accordance with Anatomic Therapeutic Chemical (ATC) classification system code, we selected simvastatin (C10AA01, C10BA02, C10BX01, and C10BX04), lovastatin (C10AA02 and C10BA01), pravastatin (C10AA03, C10BA03, and C10BX02), fluvastatin (C10AA04), atorvastatin (C10AA05 and C10BX03), and rosuvastatin (C10AA07) as statins of interest for prescription analysis. In order to investigate the association between the pharmacologic characteristics of statins and the risk of dementia, statins were further classified according to their lipid-lowing potency (high: rosuvastatin, atorvastatin, and simvastatin; low: lovastatin, fluvastatin, and pravastatin) and lipophilicity (lipophilic: atorvastatin, lovastatin, fluvastatin, and simvastatin; hydrophilic: pravastatin and rosuvastatin) [16]. The cumulative duration of statins exposure was defined as the sum of days in prescripting statins to patients, and was classified as ≤1 year, 1–3 years, and >3 years.

2.4. Follow-up

Incident cases of dementia were defined by the date of first diagnostic codes associated with any type of dementia (ICD-9-CM code: 290.x, 294.1, and 331.0; A code: A210) including Alzheimer's disease (ICD-9-CM code: 331.0) and vascular dementia (ICD-9-CM code: 290.4) during the study follow-up period. Patients were followed from the index date until diagnosed incident dementia, disenrolled from the NHI program, or December 31, 2010. The dementia incidence rate was calculated as the number of dementia patients divided by the observed person-time. To avoid surveillance bias, patients who were diagnosed with any type of dementia within 1 year after index date or had less than 1 year of follow-up were excluded.

2.5. Covariates

Demographic (age and gender) and socioeconomic status (SES, including insurance level, geographic location and urbanization level of residence) variables were defined as the values at index year. Age was classified into three categories: 60–69, 70–79, and over 80 years old. The insurance amount was classified into one of three categories: less than US$640 (NTD20,000), US$640–1280 (NTD20,000–39,999), and US$1281 (NTD40,000) or more. Demographic variables at index date included baseline values of age and gender. Socioeconomic status (SES) variables at index date included baseline values of insurable income/category level, geographic location, and urbanization level of residence. Preexisting comorbidities at index date were also included as control variables

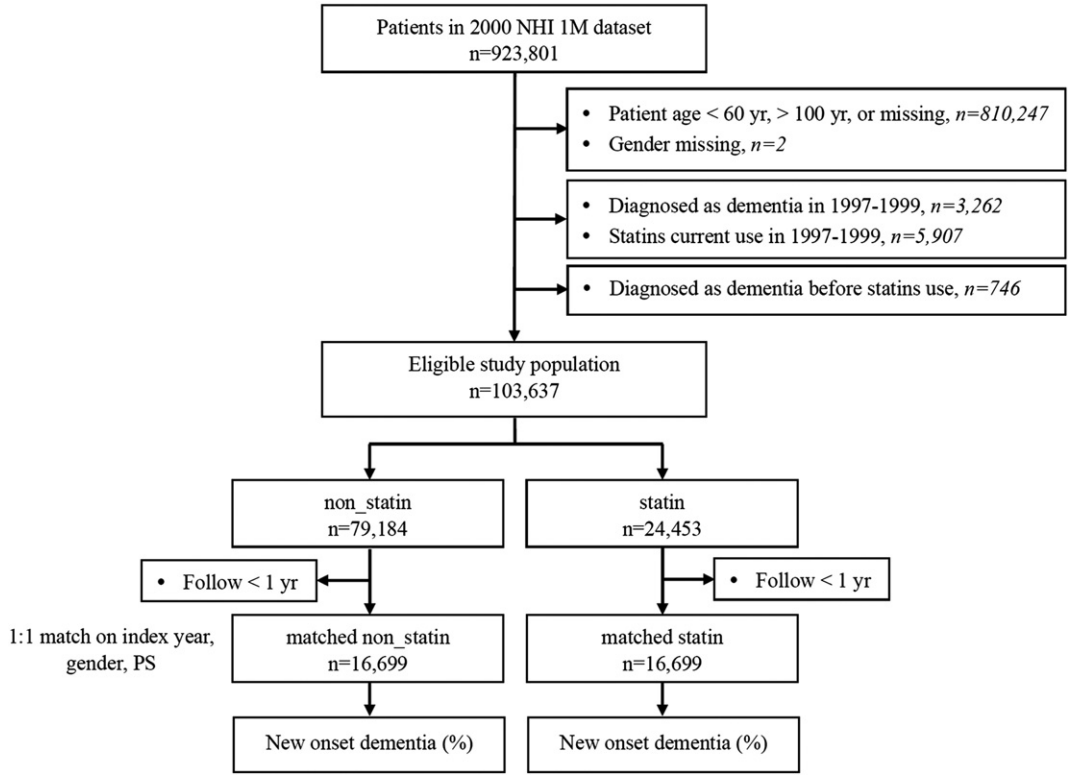

Fig. 1. Flow chart of criteria used to select participants for the study.

and defined as the diagnosis codes of claims that had been appeared more than 2 times in the ambulatory care visits during the year of the index date, including hypertension (ICD-9-CM codes 401 to 405, or A codes A260 and A269), hyperlipidemia (272), coronary artery disease (410 to 414, or A270 and A279), dysrhythmia (427 and A281), heart failure (428), peripheral arterial disease (440, 443.9, and A300), venous thromboembolism (453.2, 453.4, 453.8, 453.9, and 415.1), ischemic stroke (433, 434, 436, and 437.1, or A292 and A293), intracerebral hemorrhage (430 to 432.9, or A290 and A291), diabetes mellitus (250 or A181), chronic obstructive pulmonary disease (491, 492, and 496), chronic liver disease (571, 572, and A347), chronic renal disease (580 to 587) and malignancy (140 to 239, A08, A090 to A095, A099 to A101, A109 to A115, A120 to A126, A129, A130, A139 to A141, A149 to A156, A159, A16, and A17).

2.6. Statistical analysis

The statistical analyses involved descriptive and inferential analyses. The dissimilarities in patient characteristics between the statin users (exposure group) and statin nonusers (nonexposure group) were assessed using chi-square tests for categorical variables and *t* tests for continuous variables. Cox proportional hazards models were applied to estimate the crude and adjusted hazard ratios (HRs and aHRs) and 95% confidence intervals (CIs). Sensitivity analyses were also conducted for excluding vascular dementia from the observed outcome or constructing various comorbidity (i.e., hypertension, diabetes, hyperlipidemia, and stroke) measures at the baseline. SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA) and SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA) were used for data linkage and processing. A 2-tailed $p < 0.05$ was considered statistically significant.

3. Results

Our cohort study included 16,699 statin users and 16,699 nonusers, among whom 17,988 (53.9%) were female. The mean follow-up was 5.05 years with SD 2.68 years. The comparisons of the demographic and clinical variables between statin users and nonusers were listed in Table 1. After matching of propensity scores, the statin users and nonusers in both sexes showed nonsignificant differences in most covariates except a slight variation in the categories of age and preexisting comorbidities.

Table 2 shows the adjusted HRs for dementia according to the types and pharmacologic characteristics of statins been utilized. Statin users exhibited a significantly lower HR for dementia (HR, 0.78; 95% CI, 0.72–0.85, $p < 0.001$) when compared with statin nonusers. Female statin users (HR, 0.76; 95% CI, 0.68–0.85, $p < 0.001$) had a lower risk of dementia than male statin users (HR, 0.86; 95% CI, 0.75–0.98, $p = 0.02$). In the subgroup analysis performed according to age (60–69, 70–79, and ≥80 years), the HRs were similar in each stratified group. In particular, the HRs for dementia were correlated with the potency of statins which were estimated by half maximal inhibitory concentration (IC_{50}). High potency statins (i.e., rosuvastatin, atorvastatin, and simvastatin) had relatively lower HRs for dementia when comparing with low potency statins (i.e., fluvastatin, lovastatin, and pravastatin). Regarding the lipophilicity of statins, HRs for dementia were both significantly decreased in lipophilic (HR, 0.83; 95% CI, 0.76–0.91, $p < 0.001$)

Table 2
HRs and 95% CIs for the association between statin use and dementia.

Variables	No.	HR[a]	(95%CI)	*p* value
Statin use				
No	16,699	1		
Yes	16,699	0.78	(0.72–0.85)	<0.001***
Gender				
Male	7705	0.86[b]	(0.75–0.98)	0.02*
Female	8994	0.76[b]	(0.68–0.85)	<0.001***
Age (years)				
60_69	5352	0.81	(0.67–0.97)	0.026*
70_79	8885	0.80	(0.71–0.89)	<0.001***
≧80	2462	0.81	(0.68–0.98)	0.029*
Type of statin (IC_{50}[c])				
Rosuvastatin (5.4 nM)	1845	0.49	(0.37–0.65)	<0.001***
Atorvastatin (8.2 nM)	5438	0.74	(0.65–0.84)	<0.001***
Simvastatin (11.2 nM)	3303	0.82	(0.70–0.96)	0.01*
Lovastatin (24 nM)	3218	0.95	(0.82–1.10)	0.51
Fluvastatin (27.6 nM)	1581	0.90	(0.74–1.10)	0.32
Pravastatin (44.1 nM)	1314	0.92	(0.75–1.14)	0.46
Potency of statin				
High	10,586	0.73	(0.65–0.81)	<0.001***
Low	6113	0.93	(0.83–1.04)	0.22
Lipophilicity of statin				
Hydrophilic	3159	0.70	(0.59–0.83)	<0.001***
Lipophilic	13,540	0.83	(0.76–0.91)	<0.001***
Duration of statin use				
≤1 yr	8932	1.07	(0.97–1.19)	0.17
1–3 yr	4904	0.76	(0.66–0.87)	<0.001***
>3 yr	2863	0.35	(0.28–0.43)	<0.001***

Abbreviations: HR = hazard ratio. *p<0.05; **p<0.01; ***p<0.001.
[a] Adjusted for gender, PS, age, SES and comorbidities.
[b] Adjusted for PS, age, SES and comorbidities.
[c] Dose (milligrams) needed for 50% inhibition of hydroxymethylglutaryl-coenzyme A reductase.

Table 1
Baseline characteristics of participants.

	Male (n = 15,410)					Female (n = 17,988)				
	Non-statin No. (%)		Statin No. (%)		*p* value	Non-statin No. (%)		Statin No. (%)		*p* value
Propensity score	0.16	±0.2	0.16	±0.2	0.99	0.14	±0.18	0.14	±0.18	0.94
Age at entry (years)										
60_69	2248	(29.2)	2415	(31.1)	0.01	2794	(31.1)	2937	(32.7)	<0.001
70_79	4224	(54.8)	4115	(53.4)		4617	(51.3)	4770	(53.0)	
≧80	1233	(16.0)	1175	(15.3)		1583	(17.6)	1287	(14.3)	
Comorbidity										
Hypertension	5023	(65.2)	4599	(59.7)	<0.001	5978	(66.5)	5616	(62.4)	<0.001
Hyperlipidemia	2509	(32.6)	2597	(33.7)	0.13	2526	(28.1)	2621	(29.1)	0.12
CAD	2148	(27.9)	2176	(28.2)	0.62	2144	(23.8)	1851	(20.6)	<0.001
Dysrhythmia	639	(8.3)	582	(7.6)	0.09	677	(7.5)	641	(7.1)	0.30
Heart failure	418	(5.4)	411	(5.3)	0.80	516	(5.7)	434	(4.8)	0.01
Ischemic stroke	899	(11.7)	850	(11.0)	0.21	723	(8.0)	658	(7.3)	0.07
ICH	74	(1.0)	69	(0.9)	0.67	57	(0.6)	41	(0.5)	0.11
PAD	155	(2.0)	167	(2.2)	0.50	158	(1.8)	163	(1.8)	0.78
VTE	508	(6.6)	449	(5.8)	0.05	388	(4.3)	348	(3.9)	0.13
Diabetes mellitus	18	(0.2)	13	(0.2)	0.37	26	(0.3)	13	(0.1)	0.04
COPD	495	(6.4)	492	(6.4)	0.92	442	(4.9)	459	(5.1)	0.56
Chronic liver disease	2508	(32.6)	2449	(31.8)	0.31	2833	(31.5)	2947	(32.8)	0.07
Chronic renal disease	894	(11.6)	854	(11.1)	0.31	501	(5.6)	455	(5.1)	0.13
Malignancy	442	(5.7)	461	(6.0)	0.52	525	(5.8)	420	(4.7)	<0.001

Abbreviations: CAD, coronary artery disease; ICH, intracerebral hemorrhage; PAD, peripheral arterial disease; VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease.

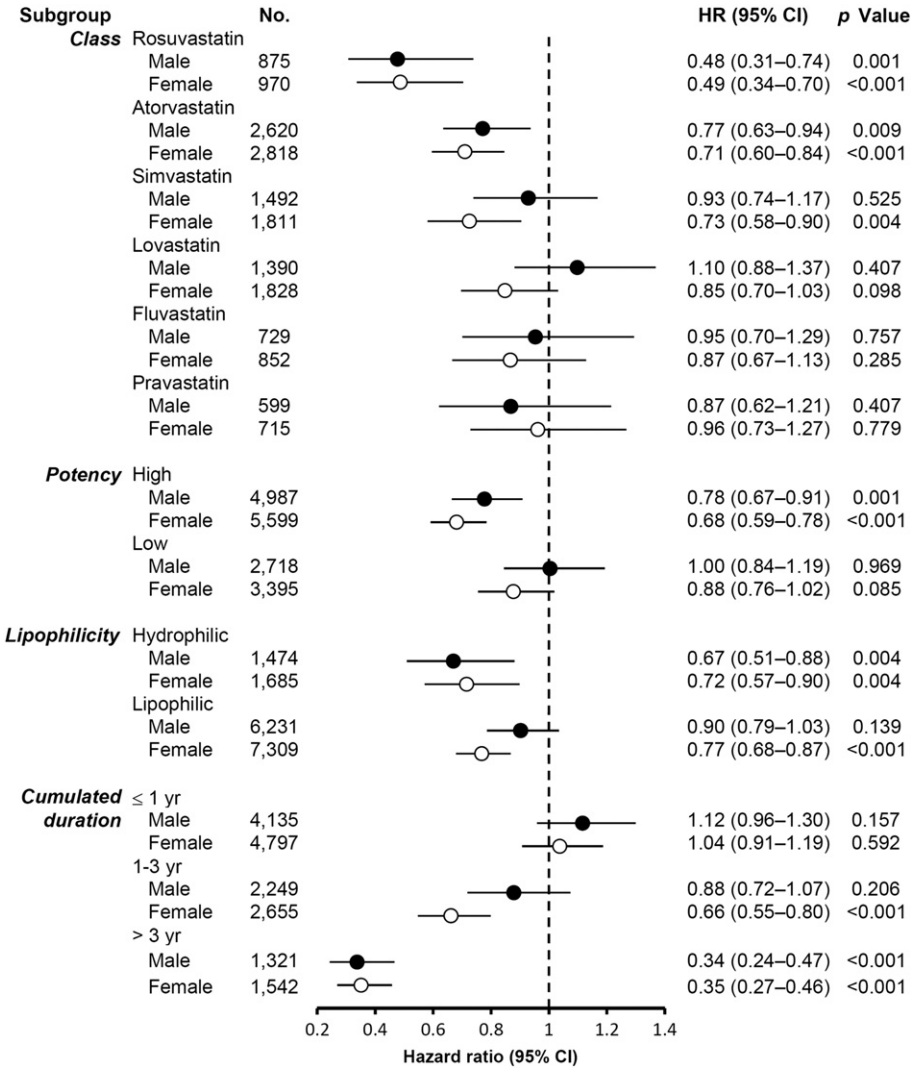

Fig. 2. Hazard ratios for incident dementia stratified by gender.

and hydrophilic (HR, 0.70; 95% CI, 0.59–0.83, $p < 0.001$) statins. We further analyzed the correlation between cumulative duration of statin utilization and the risk of incident dementia in both sexes. HRs for incident dementia significantly decreased in patients who cumulatively used statins for more than 1 year (HR, 0.76; 95% CI, 0.66–0.87, $p < 0.001$ for 1–3 yr and HR, 0.35; 95% CI, 0.28–0.43, $p < 0.001$ for >3 yr).

Fig. 2 demonstrated the HRs for dementia of subgroups that were stratified by gender. In high potency statins, rosuvastatin and atorvastatin consistently showed decreased HR in both sexes, but simvastatin only showed in female (HR, 0.93; 95% CI, 0.74–1.17, $p = 0.53$ for male vs HR, 0.73; 95% CI, 0.58–0.90, $p = 0.004$ for female). All low potency statins did not have significant effect on decreasing HR in both sexes. Regarding the lipophilicity of statins, both hydrophilic and lipophilic statins showed significantly decreased HR in female, but only hydrophilic statins had such effect to male (HR, 0.67; 95% CI, 0.51–0.88, $p = 0.004$ for hydrophilic vs HR, 0.90; 95% CI, 0.79–1.03, $p = 0.14$ for lipophilic). HRs for dementia significantly decreased in female patients who cumulatively used statins for more than 1 year (HR, 0.66; 95% CI,

Table 3
Sensitivity test for the relation between statins use and dementia.

Variables	No.	HR (95%CI)		p value	aHR (95%CI)[a]		p value
Incident dementia							
VD excluded	33,138	0.77	(0.70–0.84)	<0.001***	0.79	(0.72–0.87)	<0.001***
AD only	31,430	0.82	(0.57–1.17)	0.28	0.83	(0.58–1.19)	0.31
VD only	31,560	0.92	(0.72–1.18)	0.50	0.93	(0.72–1.19)	0.56
Comorbidity at baseline							
No HTN	12,182	0.95	(0.82–1.10)	0.46	0.94	(0.81–1.09)	0.38
No stroke	30,115	0.81	(0.73–0.89)	<0.001***	0.82	(0.75–0.90)	<0.001***
No DM	33,328	0.78	(0.72–0.86)	<0.001***	0.81	(0.74–0.88)	<0.001***
No hyperlipidemia and stroke	20,555	0.87	(0.78–0.97)	0.02*	0.87	(0.77–0.97)	0.01*

Abbreviations: HR = hazard ratio; VD = vascular dementia; AD = Alzheimer disease; HTN = hypertension; DM = diabetes mellitus.
*p<0.05; **p<0.01; ***p<0.001.
[a] Adjusted for gender, PS, age, SES, comorbidities.

0.55–0.80, $p < 0.001$ for 1–3 yr and HR, 0.35; 95% CI, 0.27–0.46, $p < 0.001$ for >3 yr), but such effect revealed in male patients who cumulatively used statins for more than 3 years (HR, 0.31; 95% CI, 0.23–0.43, $p < 0.001$).

To strengthen our findings, we further stratified the analysis of HRs by subtypes of dementia and comobidities for detecting the possible effect modification (Table 3). The results of these analyses did not suggest that the effect of statins on dementia risk differed materially by these factors.

4. Discussion

To the best of our knowledge, this study was the first population-based propensity-matched cohort study of Asian population exploring the role of gender in the relationship between statins and the risk of incident dementia. Our study yielded several important findings. First, with more rigorous conditions and methods, our study determined that statin use was associated with a reduced risk of incident dementia. Second, the potency and the cumulative duration of statin use played decisive roles in the protective effect of incident dementia. Third, gender was an effect modifying factor in the relationship between utilization pattern of statins and the risk of incident dementia.

In previous randomized controlled trial (RCT) studies, several limitations have been noted, including namely confounding by indication, short observation period and limited generalizability of the results from healthy study participants [17]. Results from healthy subjects in RCT may not be representative of common statin users in clinical settings, because statin users tend to have multiple comorbidities, including diabetes, hypertension and cardiovascular, cerebrovascular and arterial diseases which are risk factors of AD and vascular dementia [18]. In this large, population-based study with a follow-up period of up to 11 years, we avoided several problems that occurred in previous cohort studies that were caused by using a short follow-up period. We used the PS method to address the confounding by indication bias commonly observed in previous observational studies. In particular, this study is the first study to evaluate the differences between sexes regarding the therapeutic effects of statin treatment in an Asian population. The findings of this study are valuable in investigating whether a specific group of patients is at a lower risk of dementia after receiving statin therapy. Because of the cardiac benefits of using statins and the projected continued growth of prescription rates of intensive statin regimens, quantifying potential long-term risks and benefits is critical in enabling physicians and patients to make informed choices.

Reports have indicated that the potency of statins was correlated with the protective activity against cardio- and cerebro-vascular diseases [19–21]. In present study, we further demonstrated that the potency of statins played important roles in reducing the risk of incident dementia disregarding the lipophilicity of statins. It is clear that high lipophilicity prevents statins widespread tissue distribution, which may influence the pharmacological and clinical effects of statins [19,22]. However, previous findings concluded that the greatest risk reduction in dementia and AD onset were associated with the lipophilic statins [9,23]. One reason might have accounted for this discrepancy is the development of new potent hydrophilic statins (e.g. rosuvastatin) for clinical treatment as well as the coverage of studies. Therefore, our results suggested that the potency of statins may be the main pharmacologic characteristic to determine protective effects of statins for incident dementia. Furthermore, statins have beneficial effects to neurodegeneration and cognitive functions [8,24], the mechanisms underlying these effects may be attributed to not only lipid-lowering-dependent actions, but also lipid-lowering-independent actions. These so called "pleiotropic effects" of statins are involved in several aspects of mechanisms including endothelial and platelet function, cell proliferation, immunological and inflammatory response, lipid oxidation, etc., which possibly provide significant contributions to neuroprotection [24–26].

There was an association between the risk of incident dementia and the cumulated duration of statin use observed in present study. Patients who had a cumulated duration of statin use >1 year got a significant reduction in the risk of incident dementia (Table 2). When gender was taken as a covariable in this analysis, male patients did not show significant reduction in the risk of incident dementia until cumulated duration of statin use reached >3 years (Fig. 2). Our results indicated that the protective effects were more apparent in female than in male. Pathophysiological difference between female and male was a possible reason, since several drug researches had remarked the gender differences in drug efficacy [27–29]. Although the specific effects remain to be elucidated, we suggest that the phenomenon observed in elderly female patients with statin treatment may involve hormone-modulated pharmacologic or metabolistic mechanisms. Current hormonal treatment in postmenopausal women has been postulated in associating with the decrease of LDL–cholesterol levels [30–32], however, the relationship between hormonal treatment and memory decline or dementia is still largely unknown [33–36]. Furthermore, several studies indicated an age-varying association between statin use and incident dementia [37,38]. According to our data, the protective effect of statin use was not altered by age (Table 2).

Several limitations in this study must be noted. First, detail laboratory information, such as serum lipid levels and cognitive function data, were not provided in the claims data. According to relevant literature on enhancing the validity of a diagnosis of dementia, we identified patients with dementia only if they had been diagnosed with dementia at least 3 times during the study period. A similar rule was also applied in defining other comorbid medical conditions. In addition, the Taiwan Bureau of National Health Insurance annually validates this administrative data set by randomly sampling the medical claims and review charts from authorized hospitals. Because the prevalence of disease in this study is consistent with that of previous observations, we considered the data to be qualified for analyzing the issue. Second, confounding by indication is another major limitation of this observational study. Although we attempted to overcome the problem of selection bias by using a PS matching strategy, it can only be addressed using observable variables. The unobservable variables may still confound our results. Third, the lack of information on other critical confounding variables, such as smoking, alcohol consumption, physical activity, and SES, may introduce a possible confounding bias to our results. Although we attempted to include comorbidities and insurable wages as proxies for health status and SES in the models, they may not be perfect proxies. Future studies may be able to contribute in this regard. Finally, we did not thoroughly explore the potential mechanisms behind the association of statin use with risk of dementia. However, the detailed analyses of statin types and classes in this study provide suggestions for future pharmacological or pathological research in revealing the mechanisms.

5. Conclusion

We concluded that statin treatment is associated with a reduction in the risk of incident dementia in the elderly people. The beneficial effects of statin use were more apparent in women than in men. Clinical practice should consider the apparent differences between sexes regarding the class effects of statins.

Acknowledgments

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