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ORIGINAL RESEARCH ARTICLE

Statin Use and Cataract Surgery: A Nationwide Retrospective Cohort Study in Elderly Ethnic Chinese Patients

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Abstract

Background Since a report of lenticular opacities in dogs treated with high dosages of statins, the debate on the relationship between statin therapy and cataracts has not reached a conclusion.

Objective The aim of this study was to evaluate the association between statin therapy and the risk of cataract surgery in an elderly ethnic Chinese population using time-dependent analysis to minimize immortal time bias.

Methods A retrospective cohort study using the Longitudinal Health Insurance Database 2005 randomly sampled from the National Health Insurance Research Database, Taiwan, was conducted. A total of 50,165 adults aged between 65 and 90 years in 1998 without records of statin therapy or diagnosis of cataracts between July 1997 and December 1997 were included in the analysis. The first record of lens extraction within the follow-up period (1998–2009) was set as the study endpoint. A propensity score was derived using a logistic regression model to model the receipt of statin therapy as a function of the baseline characteristics for every subject. We used the time-dependent Cox regression model to test the relative hazard of undergoing cataract surgery between statin users and non-users, while use of statins was treated as a time-dependent variable, controlling for baseline age and individual propensity score.

Results Of the 50,165 enrolled subjects, 17,670 individuals with an incident lens extraction were identified during a median follow-up of 10.7 years. The incidence of cataract surgery was 49.7/1,000 person-years in the statin-using period compared with 38.5/1,000 person-years in the statin-non-using period. The adjusted hazard ratio of cataract surgery was 1.20 (95 % CI 1.14–1.27; $P < 0.001$) in statin users compared with statin non-users.

Conclusion Statin therapy was associated with a modestly increased risk of cataract surgery. We suggest regular checks for lens opacity in statin users.

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1 Background

Age-related cataracts are the leading cause of blindness, accounting for 50 % of blindness all over the world [1]. The prevalence of lens opacity in elderly individuals aged 65 years and older was 68 % among African Americans and 55 % among Caucasians in a survey conducted on the Eastern Shore of the state of Maryland, USA in the 1990s

[2]. In Taiwan, the prevalence of age-related cataracts has been estimated to be 51 % among residents aged over 50 years [3] and 59 % among those aged over 65 years [4].

Statins reduce serum levels of total cholesterol and low-density lipoprotein cholesterol through inhibition of the 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, the rate-limiting enzyme in the cholesterol biosynthesis pathway [5]. Many large randomized trials have shown that reduction of low-density lipoprotein cholesterol with statin therapy is associated with reduced cardiovascular morbidities and mortality [6–8]. Nevertheless, with increasing use, some adverse effects related to statins have been recognized [9, 10].

Concern about the potential of statins to affect the lens was stimulated by a report of an animal study [11], in which dogs were administered high doses of different HMG-CoA reductase inhibitors, including simvastatin (10–90 mg/kg/day) and lovastatin (30–180 mg/kg/day). The authors found rapid development of lenticular opacities in some dogs after 9–28 weeks of statin treatment. They also demonstrated a positive dose-response relationship between the dose of statin and the incidence of lens opacities in all four HMG-CoA reductase inhibitors studied. Because cholesterol is needed for membrane formation and lens transparency, statins might result in lens opacity through inhibition of cholesterol biosynthesis in the lens [12]. However, human studies exploring the association between statin therapy and the incidence of cataracts have produced conflicting results. Some studies have found no evidence of harmful effects of statins on the lens [13–18]. Some studies have concluded that statin therapy was significantly protective for the incidence of cataracts [19–21]. In two studies, statins were found to be associated with an increased risk of cataracts [22, 23]. Moreover, one study suggested that longer-term statin use was protective against cataract surgery, while shorter-term statin use was associated with an increased risk of cataract surgery [24].

The aim of this study was to evaluate the association between statin therapy and risk of cataract surgery in an elderly ethnic Chinese population. A retrospective cohort study using longitudinal health care claims data from the National Health Insurance Research Database (NHIRD) of Taiwan was conducted.

2 Methods

2.1 Source of Data

Taiwan launched a single-payer National Health Insurance Programme on 1 March 1995. As of 2007, a total of 22.60 million of Taiwan's 22.96 million population (98.4 %) were enrolled in this programme. All original claims data for reimbursement, including details of inpatient/outpatient orders/prescriptions and details of prescriptions dispensed at contracted pharmacies are collected electronically. The database also contains registration files, including characteristics of hospitals/clinics, characteristics and specialties of physicians/medical personnel and a registry for beneficiaries. Therefore, the database can provide all the longitudinal health care information reimbursed by the National Health Insurance Programme, except medical expenditure via self-payment by beneficiaries. These data files are de-identified by scrambling the identification codes of both patients and medical facilities and sent to the National Health Research Institutes to form the original files of the NHIRD [25]. From registration data of the National Health Insurance Programme during the period of 1 January 2005 to 1 January 2006, 1 million beneficiaries were drawn by random sampling. All the longitudinal registration and claims data of these 1 million individuals collected by the NHIRD since 1996 constitute the Longitudinal Health Insurance Database 2005 (LHID2005). There was no significant difference in the sex distribution between patients in the LHID2005 and the original NHIRD [25].

The LHID2005 during the period of 1 January 1997 to 31 December 2009 was used in this study. We obtained drug exposure information from records of dispensations at hospitals/clinics and contracted pharmacies. The diagnoses were derived from inpatient/outpatient orders, which were provided as *International Classification of Diseases-Clinical Modification*, 9th revision (ICD-9-CM) codes by the NHIRD/LHID2005.

The information obtained from the database was entirely anonymous, and the study was approved by the local Institutional Review Board.

2.2 Cohort Definition and Follow-Up

All adults aged between 65 and 90 years in 1998 (born between 1 January 1908 and 31 December 1932) were identified and their longitudinal claims data extracted from the LHID2005. Subjects without any claims data in the LHID2005 during the 1-year period from 1 January 1997 to 31 December 1997 were excluded. Background characteristics and comorbidities of the enrolled subjects were assessed during the baseline 6-month wash-out period (1 July 1997–31 December 1997). Subjects with any diagnosis related to cataracts (ICD-9-CM code 366.X) or lens extraction (13.X) within the baseline 6-month wash-out period were excluded. We also excluded subjects who had already had any statin prescription (Anatomical Therapeutic Chemical Classification System [ATC] code C10AA and C10B) in the baseline 6-month wash-out period.

All enrolled subjects were followed from 1 January 1998 until they had an incident cataract surgery or the last record in LHID2005 prior to the end of the study at 31 December 2009. Because we could not differentiate between healthy subjects who did not have any claims records throughout the follow-up period and ill subjects who died early in the follow-up period through LHID2005, subjects without any claims records throughout the follow-up period were treated as early death and were excluded from the base-case analysis.

2.3 Study Endpoint

Because a diagnosis of cataracts appearing in the claims record might only reflect a physician's tentative clinical impression rather than a confirmatory diagnosis, we restricted the study endpoint to cataract surgery as the first appearance of procedure code concerning lens extraction (ICD-9-CM code 13.X) in the follow-up years.

2.4 Exposure Measures: Statins

Statin prescription was extracted as ATC code C10AA or C10B from the electronic claims data. Because we intended to evaluate the class effect of all statins, no discrimination was made between subjects receiving only one statin throughout the study period (single statin users) and subjects switching from one statin to other statins (sequential multiple statins users), and the total days of supply of all statins were accrued cumulatively. According to the reimbursement regulation of the National Health Insurance Programme in Taiwan, the medical prescription for chronic illness is based on durations of 3 months or 90 days. We therefore defined a statin user as a study cohort member who had more than a total of 90 days supply of statins. When a subject had fulfilled the definition of statin user, the date when the first following prescription of statins was dispensed was set as the index date and the follow-up period of statin-using started. Those who were never dispensed a statin and who received a total of 90 days or fewer supply of statins were classified as non-users.

2.5 Potential Confounders

In addition to baseline age (in 1998) and sex, we controlled the analysis for the potential confounders diabetes mellitus under treatment (ATC code A10), hypertension under treatment (C02A, C02B, C02C, C02D, C02KA, C02KB, C02KC, C02KD, C02L, C02N, C03, C07, C08, C09), Romano's implementation [26] of the Charlson Index [27] and individual comorbidities in the panel of the Charlson Index such as myocardial infarction, cerebrovascular disease, chronic pulmonary disease, renal disease, liver disease and malignancy. Besides this, oral estrogen replacement therapy (ATC code G03C, G03F), corticosteroids (oral: H02AB, H02B, M01BA, or inhaled: R03BA), non-steroidal anti-inflammatory drugs (M01A), aspirin (B01AC06, N02BA01), proton pump inhibitors (A02BC) or H2 receptor antagonists (A02BA), number of distinct prescription drugs dispensed, number of hospitalizations and number of physician visits were also included in the list of potential confounders. All the potential confounders were assessed during the baseline 6-month washout period and many of them were strongly associated with the study outcome (with or without cataract surgery) (Supplementary Appendix Table 1).

2.6 Statistical Analysis

Categorical data are presented in contingency tables, and continuous variables are presented as median values and inter-quartile range. The χ^2 test and Wilcoxon rank-sum test were used to test differences in demographic data between statin users and non-users.

Individuals who ended up in the statin users group had to be event free for a preceding time period (i.e. immortal time, or wait time) until the treatment definition was fulfilled, otherwise they would be classified as non-users if they had suffered from any event prior to the time when the treatment definition was fulfilled. If this immortal time was attributed to the statin users group, it could bias the results in favour of the statin treatment by conferring a spurious advantage to the treated group; this issue has been clarified as immortal time bias [28, 29]. The correct analysis is to classify this immortal person-time as non-user and the subsequent person-time as user, even though both periods of person-time came from the same subject. Therefore, in our study, a time-dependent analysis was applied where the person-days of follow-up in the statin users before the treatment definition was met were classified as statin-non-using period, and the person-days of follow-up after the treatment definition was met were classified as statin-using period. Accordingly, incidence rates for cataract surgery in the statin-non-using period and the statin-using period were calculated respectively by dividing the number of cases by the number of person-years of distinct exposure experience.

A propensity score was derived using a logistic regression model to model the receipt of statin therapy as a function of the baseline characteristics for every subject enrolled in this study [30]. All the potential confounders (Supplementary Appendix Table 1) were included in the list of regressors (C statistic: 0.657). We used the time-dependent Cox regression model to test the relative hazard of undergoing cataract surgery between statin users and non-users, while use of statins was treated as a time-dependent variable, controlling for baseline age and

individual propensity score. We also calculated the number needed to harm (NNH) based on the annualized incidence rate according to the method proposed by Mayne et al. [31].

Various sensitivity analyses were conducted. In the first model, subjects who were excluded from the base-case analysis because of absence of claims record throughout the 12-year follow-up period were treated as healthy subjects and coded as non-users. In the second model, age was set as another time-dependent variable. Specifically, for statin non-users and the statin-non-using period of statin users, baseline age was included in the regression model. However, for the statin-using period of statin users, baseline age was replaced by age on the index date to further account for the aging effect between the statin users and non-users. In the third model, the follow-up in statin users was censored at the last prescription of statins to comply with as-treated analysis in order to reduce the influence of exposure misclassification due to the prolonged follow-up period. In the fourth model, the follow-up duration was shortened from 12 to 6 years to comply with the study design of the 4S (Scandinavian Simvastatin Survival Study) [16]. Another two specific analyses were conducted to estimate the magnitude of immortal time bias [28, 29]. In the fifth model, we deleted the immortal time in statin users and analysed by time-fixed Cox regression model. Both plots of the natural logarithm of the negative of the natural logarithm of the survival curves for statin users and non-users and goodness-of-fit test were consistent with the proportional hazards assumption ($P = 0.39$) in the fifth model. The final sensitivity analysis attributed the immortal time to statin users and also analysed by time-fixed Cox regression model. However, both the graphic method and the goodness-of-fit test revealed that the proportional hazards assumption was violated ($P < 0.0001$) in this model.

We conducted the analyses with SAS software (version 9.1 for Windows; SAS Institute Inc, Cary, NC, USA). All P values given are two sided. The level of significance was set to 0.05.

3 Results

3.1 Descriptive Analysis

We identified 50,320 adults aged 65–90 years in 1998 from the 1 million beneficiaries in the LHID2005. We excluded 155 subjects without any claims records throughout the 12-year follow-up period in the base-case analysis.

Of the 50,165 enrolled subjects, 13,055 had records of statin prescription within the follow-up period, and nearly half the subjects were sequential multiple statin users who had received more than one statin at different time periods (Table 1). About one third of the 9,746 subjects with cumulative statin prescriptions of more than 90 days had undergone lens extraction prior to the index date of statin prescription and were classified as statin non-users. Finally, 6,830 subjects were defined as statin users and 43,335 were defined as statin non-users. The median cumulative duration of statin prescription in statin users was 572 days (inter-quartile range 261–1,191 days).

Table 1 Distribution of statin use

	Number (%)
Total cohort	50,165 (100.0)
Never use	37,110 (74.0)
1–90 days statin use	3,309 (6.6)
>90 days statin use	9,746 (19.4)
Ever statin users	13,055 (100.0)
Single statin users	6,925 (53.0)
Sequential multiple statins users	6,130 (47.0)
Statin type ever prescribed[a]	
Atorvastatin	6,259 (47.9)
Simvastatin	4,675 (35.8)
Lovastatin	4,407 (33.8)
Fluvastatin	2,782 (21.3)
Pravastatin	2,551 (19.5)
Rosuvastatin	2,259 (17.3)

[a] The sum is more than 100 % due to sequential multiple statin prescriptions in 47 % of ever-used subjects

The background characteristics of the study subjects are shown in Table 2. Compared with statin non-users, statin users were younger and more likely to be women. They were more likely to have diabetes, hypertension, myocardial infarction, cerebrovascular disease, and higher Charlson Comorbidity Index scores based on out-patient clinic diagnosis. Statin users were more likely to have been exposed to estrogen-replacement therapy, non-steroidal anti-inflammatory drugs and aspirin. They also visited a physician more frequently and had more drugs dispensed than statin non-users.

3.2 Main Results

A total of 17,670 subjects with an incident cataract and lens extraction were identified during a median follow-up of 10.7 years. Specifically, 1,533 cases of lens extraction were identified within 30,844 person-years of the statin-using period, which corresponded to an incidence of cataract surgery of $49.7/10^3$ person-years in the statin-using period. On the other hand, 16,137 cases of lens extraction were identified within 419,323 person-years of the statin-non-using period, and the incidence of cataract surgery was $38.5/10^3$ person-years in the statin-non-using period. An increased risk of cataract surgery in statin users was

Table 2 Baseline characteristics of study subjects during the washout period (1 July 1997–31 December 1997)

	Whole cohort $n = 50,165$	Statin non-users $n = 43,335$	Statin users $n = 6,830$	p[a]
Demographics				
Age	70.4 (67.6, 74.4)	70.7 (67.7, 74.8)	69.3 (67.0, 72.5)	<0.001
Sex (women)	47.6 %	46.4 %	55.2 %	<0.001
Comorbidities				
Diabetes mellitus	8.5 %	7.2 %	17.1 %	<0.001
Hypertension	37.8 %	35.7 %	50.8 %	<0.001
Myocardial infarction	0.2 %	0.2 %	0.4 %	<0.001
Cerebrovascular disease	1.6 %	1.6 %	2.0 %	0.008
Chronic pulmonary disease	2.1 %	2.1 %	2.0 %	0.52
Renal disease	0.3 %	0.2 %	0.3 %	0.58
Liver disease	0.4 %	0.4 %	0.4 %	0.63
Malignancy	0.7 %	0.7 %	0.7 %	0.74
Charlson index[b] ≥ 1	4.5 %	4.3 %	5.9 %	<0.001
Charlson index[c] ≥ 1	3.3 %	3.2 %	3.4 %	0.37
Medications				
HRT	1.7 %	1.6 %	2.6 %	<0.001
Steroids (oral)	17.9 %	17.9 %	17.5%	0.48
Steroids (inhaled)	0.7 %	0.7 %	0.6 %	0.32
NSAIDs	46.1 %	45.6 %	49.3 %	<0.001
Aspirin	16.8 %	16.2 %	20.4 %	<0.001
PPI or H_2 receptor antagonist	10.2 %	10.3 %	9.7 %	0.15
Resource utilization				
Number of physician visit	7 (2, 14)	7 (2, 14)	9 (4, 15)	<0.001
Number of drugs dispensed	10 (3, 21)	10 (2, 21)	12 (5, 23)	<0.001
Number of hospitalization ≥ 1	7.4 %	7.4 %	7.5 %	0.86

Values are expressed as median (inter-quartile range) or %

HRT hormone-replacement therapy, *NSAID* non-steroidal anti-inflammatory drug, *PPI* proton pump inhibitor

[a] Comparison between statin non-users and statin users

[b] Charlson index based on out-patient clinic diagnosis

[c] Charlson index based on discharge diagnosis of hospitalization records

revealed by time-dependent Cox regression model with the adjusted hazard ratio (HR) of 1.20 (95 % CI 1.14–1.27; $P < 0.001$) in statin users compared with statin non-users (Table 3). The number of patients who would need to be treated with statins for 1 year to trigger an extra lens extraction for cataract (NNH_1) was 89 (95 % CI 73–115).

3.3 Sensitivity Analyses

Various sensitivity analyses (as described in Sect. 2) related to statin use remained unchanged in the analysis that included subjects without claims records throughout 12 years (model 1), as well as in the analysis that treated age as another time-dependent variable (model 2) (Table 3). In the as-treated analysis (model 3), the adjusted HR of cataract surgery in statin users compared with statin non-users inflated to 1.69 (95 % CI 1.60–1.79; $P < 0.001$). On the contrary, shortening the follow-up duration from 12 to 6 years (model 4) eliminated the association between statin use and cataract surgery (adjusted HR 1.05, 95 % CI 0.95–1.18; $P = 0.34$). In the two sensitivity analyses specifically designed to estimate the magnitude of immortal time bias, deleting immortal time in statin users (model 5) obliterated the relationship between statin use and cataract surgery (adjusted HR 1.01, 95 % CI 0.96–1.07; $P = 0.69$), and attributing immortal time to statin users (model 6) fabricated a protective effect of statins against cataract surgery (adjusted HR 0.44, 95 % CI 0.42–0.46; $P < 0.001$).

4 Discussion

These data demonstrate a modest but statistically significant association between the use of statins and incidence of cataract surgery, an indication of serious cataract disease, in an elderly ethnic Chinese population aged between 65 and 90 years after a median follow-up of 10.7 years.

In general, aging, smoking, diabetes, and UV light exposure are well established risk factors for the development of cataracts [32]. Besides these, some conflicting evidence suggests that myopia, weight, fat consumption, oral corticosteroids and exogenous estrogens are also potential risk factors [32]. In studies among Taiwanese subjects, old age, female sex, smoking and diabetes were

Table 3 Relative risk of cataract surgery in statin users compared with statin non-users

	HR (95 % CI)	*P*
Base-case analyses		
Univariate analysis	1.30 (1.23, 1.37)	<0.001
Adjusted for PS	1.21 (1.15, 1.28)	<0.001
Adjusted for baseline age and PS	1.20 (1.14, 1.27)	<0.001
Sensitivity analyses		
Model 1, included subjects without claims records throughout 12 years[a]	1.21 (1.14, 1.28)	<0.001
Model 2, age was set as another time-dependent variable; also adjusted for PS	1.12 (1.07, 1.17)	<0.001
Model 3, as-treated analysis; followed till the last date of statin prescription[a]	1.69 (1.60, 1.79)	<0.001
Model 4, reduced follow-up duration from 12 to 6 years[a]	1.05 (0.95, 1.18)	0.34
Model 5, deleted immortal time in statin users; used time-fixed analysis[a]	1.01 (0.96, 1.07)	0.69
Model 6, immortal time was attributed to statin users; used time-fixed analysis[a]	0.44 (0.42, 0.46)	<0.001

CI confidence interval, *HR* hazard ratio, *PS* propensity score

[a] Also adjusted for baseline age and propensity score

associated with an increased risk of cataracts, but a history of hormone-replacement therapy among women was associated with a decreased risk of nuclear cataracts [3, 4].

4.1 Comparison with Other Studies

Since a report of lenticular opacities in dogs treated with high-dose statins in 1990 [11], the debate on the relationship between statin therapy and cataracts has not reached a conclusion. In the early 1990s, several randomized controlled trials in humans found no evidence of harmful effect of statins on lens [13–16]. Two case-control studies using the UK General Practice Research Database also concluded that statins had a neutral effect on the risk of cataracts [17, 18]. Surprisingly, in prospective cohort studies designed specifically for incident eye diseases, statins were found to reduce the risk of cataract development up to 45–48 % in both the Beaver Dam Eye Study [19] and the Blue Mountains Eye Study [20]. Chodick and coworkers, who analysed more than 180,000 subjects in the Healthcare Services database in Israel, also found that persistent statin use was significantly protective for the incidence of cataracts in men and women less than 75 years of age [21]. On the contrary, Hippisley-Cox and Coupland [22] concluded that statin use was associated with an increased risk of cataracts in both men and women after exploring the QResearch database in England and Wales, with a sample size of more than 2 million. Moreover, Machan et al. claimed that statin use was associated with nuclear sclerosis and posterior subcapsular cataract through the Waterloo Eye Study database [23]. Furthermore, Fong and Poon [24] analysed the database from the Kaiser Permanente Southern California and found that longer-term statin use was protective against cataract surgery, while shorter-term statin use was associated with an increased risk of cataract surgery.

Previous randomized controlled trials [13–16] were limited by small sample sizes and/or relatively short durations of follow-up, and the low event numbers in the reports made the conclusions toward the null. For example, the MSDRL study [14] enrolled only 192 subjects, and the Oxford Cholesterol Study [15] enrolled only 569 subjects. Although the EXCEL study [13] had a large sample size of more than 8,000 subjects, the follow-up duration was only 48 weeks. Therefore, these trials were underpowered to detect a cataract-related safety signal. Although the subsequent non-randomized observational studies possessed the advantage of large sample sizes and/or long follow-up durations [17–24], differences in data sources and study designs could introduce various kinds of confounding effects and different directions of bias. Therefore, it is not surprising to find conflicting results from observational studies.

Even though the increased risk of cataract surgery in statin users was only modest in our study, cataract surgery is an indication of serious cataract disease, which reflects a level of disease that is well beyond early-stage cataract. Our results were statistically significant and robust in various sensitivity analyses. Besides this, none of the previous observational studies were designed specifically to deal with the issue of immortal time bias. As revealed by a previous report [28], ignoring the immortal time bias can result in a spuriously beneficial effect of drug therapy on the study endpoints. In our study, we clearly demonstrated that incorrectly deleting immortal time in statin users eliminated the increased risk of cataract surgery in statin users. Erroneously attributing immortal time to statin users further reversed the adverse effect of statin therapy on cataract surgery to a protective effect. In the context of conflicting results of prior studies, our study lent support to the adverse effect of statins on the development of cataracts.

4.2 Biological Plausibility

The biological plausibility of these results lies in the fact that cholesterol functions to modulate the membrane-bound protein and is needed for membrane formation and

transparency of the lens [12]. The human lens derives its cholesterol from de novo synthesis, and the rate of lens cholesterol synthesis is dependent upon the concentration and function of HMG-CoA reductase. It appears possible that therapeutic doses of statins could inhibit lens cholesterol biosynthesis through inhibition of HMG-CoA reductase and result in lens opacity. Accelerated lenticular opacities have been seen in dogs administered high doses of statins [11] and in humans with hereditary cholesterol deficiency [12]. Because the rate of growth of the human lens is slow, Cenedella [12] has suggested that the long-term effect of statins on lens opacity should perhaps be viewed in units of 10–20 years. The 4S enrolled 4,444 patients with angina pectoris or previous myocardial infarction and found no evidence of any effect of simvastatin on lens opacity formation after a median follow-up period of 5.4 years [16]. As we reduced the follow-up duration from 12 to 6 years in the sensitivity analysis, the relationship between statin therapy and incident cataract surgery also faded.

4.3 Strengths and Limitations of the Study

An important strength of our study was the use of nationwide insurance claims data, which offered the advantages of a large sample size, systematic data collection and being representative of the general population. The large sample size and long duration of follow-up powered our study (Supplementary Appendix) to detect a modest association with good precision. Furthermore, a time-dependent analysis avoided immortal time bias, which had rarely been well resolved in previous observational studies.

This study also had important limitations that should be acknowledged. Firstly, although we excluded subjects with statin therapy or cataract diagnosis/lens extraction within the baseline 6-month wash-out period, the certainty that our study cohort consisted of truly incident statin users and incident cataract surgery remained in doubt because statin therapy and lens extractions in earlier eras could not be identified by the study design. Therefore, patients who had ever undergone cataract surgery or had ever received statin therapy before July 1997 were included in the study. Secondly, although we attempted to correct for major confounders, we could not rule out the effect of residual confounding. For example, some important variables, such as smoking and weight, were not provided by the insurance claims database. Furthermore, potential confounders that did not exist in the baseline wash-out period might arise during the protracted follow-up time. Finally, six different statins have been marketed in Taiwan and only half of statin users were exposed to a single statin throughout the study period. If we tried to evaluate the effect of individual statins, the sample size in each subgroup would decrease dramatically and loss of statistical power was anticipated. Therefore, the relative risk of each individual statin was not evaluated in this study.

5 Conclusion

Statin therapy was associated with a modestly increased risk of cataract surgery in this elderly ethnic Chinese population after follow-up of more than 10 years. Further investigations are needed to provide conclusive results regarding the adverse effect of statins on human lens opacity. Based on our findings, we suggest regular check-ups for lens opacity in statin users.

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Authors' contributions Conception and design: C-L Lai, W-Y Shau, C-H Chang, M-F Chen, M-S Lai. Acquisition of data: C-L Lai. Analysis and interpretation of the data: C-L Lai. Drafting of the article: C-L Lai. Critical revision of the article for important intellectual content: W-Y Shau, C-H Chang, M-S Lai. Statistical analysis: C-L Lai. Obtaining of funding: M-F Chen, M-S Lai. Administrative, technical, or material support: W-Y Shau, C-H Chang. Supervision: M-F Chen, M-S Lai. Final approval of the article: C-L Lai, W-Y Shau, C-H Chang, M-F Chen, M-S Lai.

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