ORIGINAL ARTICLE

Statin treatment is associated with a decreased risk of active tuberculosis: an analysis of a nationally representative cohort

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ABSTRACT

Background Epidemiological data suggest that statins improve the clinical outcome of respiratory infections. We sought to examine whether statin therapy decreases the risk of active TB.

Methods We conducted a nested case-control study on data obtained from a national health insurance claims database between 1999 and 2011. The use of statins was classified as current, recent, past or chronic use. Three conditional logistic regression models were used to estimate the incidence rate ratios (IRRs). The first assessed the effect of statin use without further adjustment; the second adjusted (individually) for 75 potential confounders; and the third adjusted for the Disease Risk Score (DRS).

Results A total of 8098 new TB cases and 809 800 control patients were examined. All four types of statin users showed a decreased risk of active TB. Chronic use (>90 days in a calendar year) of statins was associated with the lowest unadjusted risk of TB (RR 0.74; 95% CI 0.63 to 0.87). The protective effect of active TB remained after adjusting for individual confounders (RR 0.66; 95% CI 0.56 to 0.78) and after DRS adjustment (RR 0.62; 95% CI 0.53 to 0.72). The effect estimates obtained for chronic and current use of statins were very similar. We also found that the active TB protection increased with increasing length of statin prescription.

Conclusions We found that statin therapy was associated with a decreased risk of active TB, and the length of statin therapy affected the TB protection. Given the observational nature of this study, the protective effect against active TB must be confirmed in future randomised trials.

INTRODUCTION

Statins (3-hydroxy-3-methylglutaryl-coenzyme-A inhibitors) are a widely used class of medication for the primary and secondary prevention of cardiovascular diseases.1 Statins reduce the serum levels of low-density lipoprotein cholesterol by inhibiting cholesterol synthesis in the liver.2 In addition to modifying lipid metabolism, statins exhibit pleiotropic effects on the immune and coagulation systems.3-7 Basic research has shown that statins could reduce the production of proinflammatory cytokines, lower platelet aggregability, prevent coagulation, and reduce injury caused by oxidative stress.8-9 Because local and systemic inflammation play critical roles in human infectious disease, several meta-analyses have found that the use of statins could improve clinical outcome in patients with severe infections such as sepsis and pneumonia.10-13

METHODS

Study population

Taiwan’s National Health Insurance is a government-run single-payer compulsory system that enrolls approximately 24 million residents with 99.6% coverage. All NHI participants receive the same access to healthcare services regardless of income. Using the claims database established by...
the National Health Insurance Research Database (NHIRD) of Taiwan, we conducted a population-based nested case–control study. The NHIRD consists of 1 million subjects who were randomly sampled from the 24 million individuals enrolled in Taiwan’s National Health Insurance. Complete outpatient and inpatient electronic claim records, individual diagnoses, surgical procedures and prescribed medications are available in the NHIRD database. Several studies have shown that the NHIRD is appropriate for pharmacoepidemiologic investigations.20–22 Our study was approved by the institutional review board of the National Taiwan University Hospital.

Study cohort
The study cohort consisted of all patients from the NHIRD who were followed longitudinally between January 1999 and December 2011. All patients aged 18 years or older on 1 January 1999 were eligible for inclusion in this study. We designated 1999 as a pre-enrolment period for the assessment of drug exposure status for cases and controls occurring in 2000. Thus, cohort members were followed from 1 January 2000 until the onset of these four occurrences, whichever of the following occurred first: active TB diagnosis, termination of health insurance coverage, death or the end of the study.

Selection of cases and controls
We identified newly diagnosed active TB cases using the following criteria: at least one outpatient visit or one hospital admission with ICD-9-CM codes for TB (010–018, including all subcategories), plus the prescription of more than two anti-TB medications for more than 28 days. Patients with a subsequent diagnosis of non-TB mycobacterial infection or lung cancer were excluded. This TB case definition has been used in previous studies and was validated in a linked survey database.21 23 The index date referred to the first date of TB diagnosis. The 1-year period preceding the index date was used for the assessment of statin exposure status. For each case, 100 controls were randomly selected using the incidence density sampling method and were matched by index date, 5-year age group and sex.

Medication exposure
Users with exposure to medications of interest were defined as having a drug prescription record ≥7 days. Statins were defined as drugs containing any of the following compounds: simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin and pitavastatin. Exposure was defined using four different time frames. Current user status referred to patients with a statin prescription that was filled within 30 days of the index date. Recent user status referred to patients with a statin prescription filled between 31 and 90 days prior to the index date. Past user status referred to patients with a statin prescription filled between 91 days and 1 year prior to the index date. Chronic use status referred to patients with a cumulative prescription length of more than 90 days in the year in which the TB diagnosis was made.

Statistical analysis
The baseline characteristics of the enrollees were described and compared among TB cases and controls (table 1). Categorical variables (type of statin user, sex, index year, area of stay, insurance premiums, baseline cardiovascular comorbidities, conditions included in the Charlson index, additional comorbidities, risk factors and medication use) were presented as a frequency and percentage and were compared between cases and controls using the χ² test. Continuous variables were presented as the mean±SD or as the median and IQR, depending on the normality of the variable distribution. Outpatient department (OPD) visits and hospitalisation were described using medians and IQRs due to non-normality and were compared between cases and controls using the Mann–Whitney U test. Age was described using means and SDs and was compared between cases and controls using the t test.

Under a time-matched case-control sampling scheme, the OR estimates the rate ratio. The incidence rate ratios (RRs) of active TB (plus 95% CIs) were estimated by three conditional logistic regressions using the Proc logistic plus Strata command. The first assessed the effect of statin use without further adjustment; the second adjusted (individually) for 75 potential confounders (see online supplementary appendix 1); and the third adjusted for the Disease Risk Score (DRS). For all the conditional logistic regressions, a stratum was created for each case and his/her specific controls, comprising a total of 8098 strata. Each stratum was defined by three variables: index date, 5-year age group and gender. Thus, three matching variables (year of TB diagnosis, age and gender) were not entered in any of the regression models.

A study-specific DRS was created using the all adults in the source population using the approach initially proposed by Miettinen.24–27 The DRS was defined as the probability of developing active TB among all adult participants not exposed to statins, conditional on each individual’s baseline covariates. Operationally, we calculated the DRS by a logistic regression model wherein active TB was used as the dependent variable and all empirical clinical predictors were treated as independent variables. In online supplementary appendix 1, we report the c-statistics of the DRS model, component variables, the respective weights of the component variables, and the same set of covariates used in the individual confounder and the DRS model. Briefly, the covariates are: cardiovascular comorbidities, risk factors for TB, the burden of comorbidity conditions, indicators for frailty, and the use of specific medications. Risk factors for TB include COPD; silicosis; cancer; diabetes mellitus; chronic renal failure; solid organ transplantation; malnutrition-related disorders such as cachexia, anorexia, and abnormal loss of weight; alcoholism-related diseases; and post-gastric surgery. The groups of medications included were systemic corticosteroids, non-steroidal anti-inflammatory drugs, aspirin, and systemic immunosuppressive agents and biological drugs.

To further assess the robustness of our results, we performed subgroup analyses. Predefined subgroups included area of stay, insurance premium, the presence of cardiovascular diseases, the presence of diabetes and the presence of obesity. In addition, we performed duration response analyses by testing the linear association between drug use duration and the risk of active TB. All analyses were carried out using SAS V9.3 for Windows (SAS Institute Inc, Cary, North Carolina, USA), and the data are reported in accordance with STROBE guidelines.

RESULTS
Participant enrolment and baseline characteristics
Table 1 summarises the baseline clinical characteristics of 8098 active TB cases and 809 800 controls. The mean duration of follow-up for the cases and controls was 9.8 years. The distributions of living region and insurance premiums were significantly different between the TB cases and the control group. In general, the patients with TB exhibited a higher burden of comorbidity, a higher prevalence for TB risk factors, more OPD visits, and a greater use of cardiovascular medicine than the control group.
Table 1  The baseline characteristics of 8098 active TB cases and 809 800 controls

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Case group N=8098</th>
<th>Control group N=809 800</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male; n (%)</td>
<td>5573 (68.8)</td>
<td>557 300 (68.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Age, years; mean±SD</td>
<td>60.3±19.3</td>
<td>60.2±19.2</td>
<td>0.741</td>
</tr>
<tr>
<td>Site; n (%)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Area: urban region</td>
<td>3529 (43.6)</td>
<td>375 847 (46.4)</td>
<td></td>
</tr>
<tr>
<td>Area: metro area</td>
<td>2047 (25.3)</td>
<td>204 415 (25.2)</td>
<td></td>
</tr>
<tr>
<td>Area: suburban area</td>
<td>1621 (20.0)</td>
<td>155 078 (19.2)</td>
<td></td>
</tr>
<tr>
<td>Area: countryside area</td>
<td>901 (11.1)</td>
<td>67 010 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Insurance premiums; n (%)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dependent</td>
<td>712 (8.8)</td>
<td>75 058 (9.3)</td>
<td></td>
</tr>
<tr>
<td>$1–$19 999</td>
<td>2918 (36.0)</td>
<td>239 135 (29.5)</td>
<td></td>
</tr>
<tr>
<td>$20 000–$39 999</td>
<td>3400 (42.0)</td>
<td>329 046 (40.6)</td>
<td></td>
</tr>
<tr>
<td>≥$40 000</td>
<td>1068 (13.2)</td>
<td>159 110 (19.6)</td>
<td></td>
</tr>
<tr>
<td>Conditions included in the Charlson index; n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>496 (6.1)</td>
<td>44 277 (5.5)</td>
<td>0.040</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>957 (11.8)</td>
<td>68 749 (8.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial infarction/acute coronary syndromes</td>
<td>245 (3.0)</td>
<td>18 847 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1582 (19.5)</td>
<td>128 220 (15.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dementia</td>
<td>441 (5.5)</td>
<td>27 636 (3.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>3601 (44.5)</td>
<td>254 492 (31.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Rheumatologic disease</td>
<td>262 (3.2)</td>
<td>19 101 (2.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>2977 (36.8)</td>
<td>246 737 (30.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>2358 (29.1)</td>
<td>190 530 (23.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes without chronic complications</td>
<td>1868 (23.1)</td>
<td>136 266 (16.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes with chronic complications</td>
<td>707 (8.7)</td>
<td>42 452 (5.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemiplegia or paraplegia</td>
<td>386 (4.8)</td>
<td>27 248 (3.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Renal disease</td>
<td>834 (10.3)</td>
<td>53 708 (6.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any malignancy, including leukaemia and lymphoma</td>
<td>878 (10.8)</td>
<td>59 997 (7.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Moderate or severe liver disease</td>
<td>90 (1.1)</td>
<td>3554 (0.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Metastatic solid tumour</td>
<td>121 (1.5)</td>
<td>6932 (0.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AIDS/HIV</td>
<td>17 (0.2)</td>
<td>397 (0.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Additional comorbidities; n (%)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alcohol/drug use</td>
<td>399 (4.9)</td>
<td>16 622 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorder</td>
<td>2299 (28.4)</td>
<td>201 356 (24.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>592 (7.3)</td>
<td>36 877 (4.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Obesity</td>
<td>26 (0.3)</td>
<td>5276 (0.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cancers except metastatic solid tumours</td>
<td>2205 (27.2)</td>
<td>189 124 (23.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>COPD</td>
<td>2780 (34.3)</td>
<td>182 130 (22.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Silicosis</td>
<td>15 (0.2)</td>
<td>860 (0.1)</td>
<td>0.010</td>
</tr>
<tr>
<td>Gastrointestinal or oesophageal haemorrhage</td>
<td>653 (8.1)</td>
<td>37 338 (4.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Risk factors; n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid organ transplantation, such as kidney or heart</td>
<td>7 (0.09)</td>
<td>134 (0.01)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>98 (1.2)</td>
<td>3062 (0.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Post-gastric surgery</td>
<td>5 (0.06)</td>
<td>130 (0.01)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OPD and hospitalisation (within 1 year before the index date); median and inter-quartile range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The number of OPD visits</td>
<td>20 (8–37)</td>
<td>15 (5–29)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>The number of emergency department visits</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>The number of hospitalisations</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medication use; n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>3076 (37.9)</td>
<td>247 727 (30.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1271 (15.7)</td>
<td>112 824 (13.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systemic immunosuppressive agents and biologics</td>
<td>49 (0.6)</td>
<td>1413 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td>1520 (18.8)</td>
<td>92 717 (11.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Disease-modifying anti-rheumatic drugs</td>
<td>162 (2.0)</td>
<td>7475 (0.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>858 (10.6)</td>
<td>77 402 (9.6)</td>
<td>0.020</td>
</tr>
<tr>
<td>β blockers</td>
<td>926 (11.4)</td>
<td>93 141 (11.5)</td>
<td>0.440</td>
</tr>
<tr>
<td>Angiotensin II antagonists</td>
<td>608 (7.5)</td>
<td>62 186 (7.7)</td>
<td>0.249</td>
</tr>
<tr>
<td>Nitrates</td>
<td>486 (6.0)</td>
<td>41 115 (5.1)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Table 1  Continued

<table>
<thead>
<tr>
<th>Status of statin use</th>
<th>Statin usage rates for all the TB cases</th>
<th>Statin usage rates for all the controls</th>
<th>Effect estimates matched by age group, gender and year, RR (95% CI)</th>
<th>Confounder-adjusted effect estimates**, RR (95% CI)</th>
<th>DRS, adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use</td>
<td>134/8098=0.016</td>
<td>17 836/809 800=0.022</td>
<td>0.76 (0.64 to 0.90)**</td>
<td>0.67 (0.56 to 0.80)**</td>
<td>0.64 (0.54 to 0.76)**</td>
</tr>
<tr>
<td>Recent use</td>
<td>52/8098=0.006</td>
<td>5812/809 800=0.007</td>
<td>0.87 (0.69 to 1.09)</td>
<td>0.87 (0.66 to 1.15)</td>
<td>0.78 (0.59 to 1.03)</td>
</tr>
<tr>
<td>Past use</td>
<td>148/8098=0.018</td>
<td>16 996/809 800=0.021</td>
<td>0.86 (0.72 to 1.03)</td>
<td>0.76 (0.64 to 0.93)**</td>
<td>0.72 (0.61 to 0.85)**</td>
</tr>
<tr>
<td>Chronic user</td>
<td>160/8098=0.020</td>
<td>22 153/809 800=0.027</td>
<td>0.74 (0.63 to 0.87)**</td>
<td>0.66 (0.56 to 0.78)**</td>
<td>0.62 (0.53 to 0.72)**</td>
</tr>
</tbody>
</table>

The reference group in the calculation of RR is participants who did not use statins.
**p<0.01; ***p<0.001.
DRS, Disease Risk Score; RR, incidence rate ratio.

Association between use of statins and the risk of TB
Table 2 shows the association between statin use and active TB. The statin usage rate is highest for chronic users and lowest for recent users; it is comparable among recent and past users. All four types of statin users (current, recent, past or chronic use) showed a decreased risk of active TB. The chronic use of statins was associated with the lowest unadjusted risk of TB (RR 0.74; 95% CI 0.63 to 0.87), and the decrease in TB risk remained after adjusting for individual confounders (RR 0.66; 95% CI 0.56 to 0.78) and after DRS adjustment (RR 0.62; 95% CI 0.53 to 0.72). We observed that all the different effect estimates obtained for the chronic and current use of statins are very similar.

Effect of chronic statin use on active TB risk in different patient populations
To investigate whether there is a differential risk among different populations, we performed analyses of pre-defined subgroups (table 3). The DRS-adjusted effect estimates were obtained by comparing pre-defined chronic statin users with non-users. We found that all different subgroups exhibited a decreased risk of active TB, and the countryside subgroup had the highest risk of active TB (RR 0.85; 95% CI 0.57 to 1.29). However, the interaction term did not reach statistical significance (p value <0.05) for any of the subgroups.

Duration-response analysis
To gain insight into whether increasing the length of statin therapy might affect the risk of TB, we carried out a duration response analysis. We used 7–30 days of statin usage as a reference (table 4), and found that the crude TB incidence rate and the DRS-adjusted incidence rate ratio decrease with increasing duration of statin usage. The incremental change in the risk of incidence active TB was also calculated by treating cumulative days of statin use as a continuous variable. We found that for every additional day of statin use, there was a 0.002% decrease in the risk of active TB (p<0.010).

DISCUSSION
In this population-based study, we found that the use of statins was significantly associated with a decreased risk of active TB in a nationally representative cohort. There was a consistent and protective effect against TB of statins among current, recent, past and chronic users. The effect estimates obtained for the chronic and current use of statins were very similar. We also found that the risk of active TB decreases with increasing length of statin prescription. None of the subgroups investigated appeared to modify the effect of statins on active TB.

To the best of our knowledge, this is the second study to investigate an association between the use of statins and the risk of active TB. However, there are significant differences in the study design and results between our study and Kang et al’s study conducted in South Korea. In that study, it was found that the use of statins in patients with diabetes did not affect the risk of active TB (adjusted HR 0.98; 95% CI 0.89 to 1.07). We believe that this finding cannot be applied to the general population because diabetes is associated with a threefold higher risk of TB, as determined by a meta-analysis. In line with their findings, our subgroup analyses also show that patients with diabetes have a higher risk of TB compared with patients without diabetes. Second, we observed that the protective effects of statins are mainly observed in current or chronic users but not in past users. Unfortunately, the different types of statin users were combined in Kang et al’s work. Thus, the protective effect of statins might have been overlooked.

Our duration response and trend analysis suggested that increasing the length of statin use could increase the TB protective effect. We therefore investigated whether the recency of statin use had an effect in chronic users. We found that the current user group contained 30% more chronic users than the combination of recent and past users (see online supplementary appendix 2). We speculate that this might explain why current users exhibit a better protective effect than recent or past users.

Our study design does not permit mechanistic insights of the protective effects on active TB infection. However, our results are in agreement with reports that statins improve the clinical outcome of sepsis or community-acquired pneumonia.

Thus, based on basic research and the known protective effect of statins in other infectious diseases, we can speculate as to the non-exclusive biological mechanisms by which statins might prevent the active onset of TB.
The first hypothesis is that statin prevents reinfection in a subgroup of patients exposed to \( M. \) \textit{tuberculosis}. In vitro studies have demonstrated that cholesterol plays a critical role in the pathogenesis of \( M. \) \textit{tuberculosis} infections in several ways, including the entry of \( M. \) \textit{tuberculosis} into host macrophages, phagosome formation, the arrest of phagosomal maturation in \( M. \) \textit{tuberculosis}-containing phagosomes, and the energy utilisation of intracellular \( M. \) \textit{tuberculosis}. Statins can also reduce cholesterol levels within phagosomal membranes and counteract the \( M. \) \textit{tuberculosis}-induced inhibition of phagosomal maturation to promote host-induced autophagy in human macrophages and experimental mouse models. Thus, statins might exert a protective effect against TB infection.

The second hypothesis is that the use of statins can modulate the hosts’ inflammatory response, thereby resulting in reduced reactivation of latent TB. The use of statins has been found to modulate levels of T cells and cytokines during sepsis infection. T cells and cytokines are also critical for controlling immune function.

This study has strengths and weaknesses. The large number of TB cases is a main strength of this study. TB remains endemic in Taiwan, where its incidence is approximately 65–70 cases per 100 000 people per year. In contrast, the incidence of TB is approximately 5–10/100 000 in most western countries. Thus, the large number of active TB cases lends better statistical power to our analysis of different exposure categories, subgroups and covariate adjustments.

Nevertheless, several inherent limitations must be considered. First, as with all claims databases, the data describing lifestyle factors such as body mass index and smoking are not available. Thus, residual confounding variables cannot be totally excluded. However, we attempted to adjust for these missing confounding factors by including obesity and smoking-related disorders such as a diagnosis of morbid obesity, hyperlipidaemia, hypertension, ischaemic heart disease and COPD. Second, we defined active TB by ICD-9 codes and a compatible anti-TB prescription history. Although this TB definition has been found to be highly accurate using linked survey data, we cannot exclude the possibility of outcome misclassification for active TB as well as all claims databases, microbiological data are lacking. Third, a screening or surveillance bias is a possible concern in our study because users of statins were reported to have more frequent contact with physicians. To reduce this bias, we adjusted for the intensity of healthcare facility utilisation, such as the annual number of outpatient or emergency department visits as well as the annual frequency of hospitalisation. Finally, our study population precludes testing any possible interaction between intravesical BCG therapy and statin use. A previous study showed that statins might affect the treatment response of BCG therapy for patients with bladder cancer via immunomodulatory interactions between statins and BCG. It would have been interesting to compare the risk of active TB among BCG-vaccinated and non-BCG-vaccinated statin users, however there is a compulsory neonatal BCG vaccination in Taiwan, thus we could not test this.

In conclusion, if we assume that the protective effects observed in the present study were caused by chronic statin use, the number needed to treat to prevent one active TB case was 2563–3479 (see online supplementary appendix 3). We also found that the TB protective effect is consistent among different types of statin users and different patient subgroups. However, given the observational nature of this study, further randomised trials are necessary to confirm our findings.

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Contributors C-CL obtained funding, analysed the data, and wrote the first and final draft. MGL conducted statistical analysis. S-CC conducted statistical analysis, S-CC analysed the data, and provided critical feedback. C-CL designed the study, obtained funding, analysed the data and authorised the final manuscript.
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