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Association Between Statin Use and Risk of Dementia After a Concussion

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IMPORTANCE Concussions are an acute injury that may lead to chronic disability, while statin use might improve neurologic recovery.

OBJECTIVE To test whether statin use is associated with an increased or decreased risk of subsequent dementia after a concussion.

DESIGN, SETTING, AND PARTICIPANTS Large extended population-based double cohort study in Ontario, Canada, from April 1, 1993, to April 1, 2013 (enrollment), and continued until March 31, 2016 (follow-up). Dates of analysis were April 28, 2014, through March 21, 2019. Participants were older adults diagnosed as having a concussion, excluding severe cases resulting in hospitalization, individuals with a prior diagnosis of dementia or delirium, and those who died within 90 days.

EXPOSURE Statin prescription within 90 days after a concussion.

MAIN OUTCOME AND MEASURE Long-term incidence of dementia.

RESULTS This study identified 28 815 patients diagnosed as having a concussion (median age, 76 years; 61.3% female), of whom 7058 (24.5%) received a statin, and 21 757 (75.5%) did not receive a statin. A total of 4727 patients subsequently developed dementia over a mean follow-up of 3.9 years, equal to an incidence of 1 case per 6 patients. Patients who received a statin had a 13% reduced risk of dementia compared with patients who did not receive a statin (relative risk, 0.87; 95% CI, 0.81-0.93; $P < .001$). The decreased risk of dementia associated with statin use applied to diverse patient groups, remained independent of other cardiovascular medication use, intensified over time, was distinct from the risk of subsequent depression, and was not observed in patients after an ankle sprain.

CONCLUSIONS AND RELEVANCE In this study, older adults had a substantial long-term risk of dementia after a concussion, which was associated with a modest reduction among patients receiving a statin.

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Editorial
Author Audio Interview
Supplemental content

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Concussions are a common cause of brain injury occurring in more than 1 million Americans each year and disproportionately involving older adults.[1-4] The subacute consequences vary widely and include fatigue, headache, irritability, insomnia, inattention, photophobia, vertigo, and cognitive difficulties.[5-9] Most patients recover from a concussion within weeks, although some can develop lingering mood disorders or chronic neuropsychiatric disorders.[10-14] The extent of complications after a concussion is uncertain, and effective pharmacologic treatments remain elusive.[15-17] Unfortunately, many medical treatments for traumatic brain injury that showed promise in animal models have subsequently failed in human clinical trials.[18-22]

Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are a class of medications prescribed for the treatment of hyperlipidemia.[23,24] Preclinical data suggest that statin use might mitigate injury-related brain edema, oxidative stress, amyloid protein aggregation, and neuroinflammation.[25-29] The potential neuroprotective benefits from statins have also been speculated and include preserved cerebral blood flow, leading to decreased risks of Alzheimer disease, vascular dementia, and age-related cognitive decline.[30-35] Together, these findings suggest that statin use could contribute to microvascular homeostasis and immune modulation independent of systemic lipid levels. However, statins do not improve cognition for patients already diagnosed as having dementia.[36-38]

The role of statins in recovery after a concussion has rarely been investigated.[39,40] Furthermore, small sample sizes, selective enrollment, and brief follow-up have limited past studies[41-43] assessing the long-term consequences of concussion. On the one hand, the potential neuroprotective associations of statin use may prevent subsequent dysfunction by neuron preservation and neural stem cell activation.[44-47] On the other hand, the neurohazardous associations of statin use might contribute to memory difficulties from altered neurophysiology.[48-54] We conducted a large extended population-based double cohort study using linked databases to test whether statin use is associated with an increased or decreased risk of dementia in older adults after a concussion.

Key Points

Question Is statin use associated with an increased or decreased risk of subsequent dementia after a concussion?

Findings In this large extended population-based double cohort study following 28 815 patients after a concussion, the 5-year incidence of dementia was substantial and statin use was associated with a significantly reduced risk of subsequent dementia.

Meaning Concussions are associated with an increased long-term risk of dementia, which is modestly reduced for patients receiving a statin.

Methods

Study Setting

This population-based multicenter double cohort study of older adults diagnosed as having a concussion throughout Ontario, Canada, was performed from April 1, 1993, to April 1, 2013 (enrollment period of 20 years), providing a minimum follow-up for survivors of 3 years and reflecting all data available. Ontario is Canada's largest province, with a population of 12 407 300 in 2004 (the study midpoint), an annual incidence of dementia was 19 cases per 1000 patients for adults 65 years and older, and societal costs of dementia estimated at $18 440 per patient-year.[55-58] During our study, universal health insurance covered outpatient medical care for all individuals, with no out-of-pocket costs to patients.[59] In addition, the Ontario Drug Benefit Program covered prescription medications for all patients 65 years and older.[60] The study protocol was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, including a waiver for direct patient consent. All data are available through the Institute for Clinical Evaluative Sciences in Ontario.

Patient Identification

We identified patients 66 years and older diagnosed as having a concussion by assessing physician billing data using the concussion diagnostic criterion (*International Classification of Diseases, Ninth Revision* [*ICD-9*] code 850) from the Ontario Health Insurance Plan.[61] This code for a concussion diagnosis has been validated with high specificity (99%) and moderate sensitivity (46%-76%).[62,63] Patients who were admitted to a hospital within 2 days of a concussion or who survived less than 90 days were excluded to reduce confounding from severe brain injury.[64] Patients with a history of dementia or delirium in the prior 5 years were also excluded to reduce confounding from past neuropsychiatric conditions.[65] No patients were excluded otherwise. Patients with more than 1 concussion during the study were counted once based on the first incident.

Statin Medication Prescriptions

The prescription of a statin was identified through the Ontario Drug Benefit Program database, which has an accuracy exceeding 99% in this setting.[66] The specific statins included were atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. We classified patients based on the specific statin received immediately after their concussion. The primary analysis compared patients who had received a statin prescription in the 90 days immediately after a concussion with patients who had not. Secondary analyses explored statin prescriptions in the 90 days before the concussion and also considered statins as time-dependent exposures in analyses to account for fluctuating prescriptions over time.[67]

Baseline Patient Characteristics

Additional baseline characteristics were defined on the day of the concussion and obtained by computerized linkage to health care records.[68] A demographic registry was used to determine the patient's age, sex, socioeconomic quintile, and home location.[69,70] A physician services databases provided data on clinic visits, emergency department contacts, and hospitalizations in the prior year.[60,71] The Ontario Drug Benefit Program database provided data on additional cardiovascular medications, neuropsychiatric medications, and miscellaneous medications.[72-74] The available databases contained no information on smoking status, daily exercise, education level, family history, genetic factors, hearing loss, social isolation, or other factors that can alter dementia risk.[75,76]

Outcome Identification

The primary study outcome was a physician diagnosis of dementia (*ICD-9* codes 290, 331, and 797) ascertained through the validated Ontario Health Insurance Plan database, as established in past research.[77] These codes had a specificity of about 99% and a sensitivity of about 20% for dementia.[78] To avoid false-positive results, we required a dementia diagnosis on 2 separate dates.[79] Therefore, this outcome definition was highly specific and provided a conservative estimate of the incidence of dementia after a concussion. To corroborate this outcome, we also identified more extensive documentation of the diagnosis that could signify a worsening course over 3 years of follow-up. The available codes did not distinguish specific conditions underlying the dementia diagnosis.

Double Cohort Control Analysis

To test the importance of a potential association between statin use and subsequent dementia, we replicated our entire selec-

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tion strategy and analysis, focusing instead on older adults diagnosed as having an ankle sprain rather than a concussion. The objective of this secondary parallel analysis was to distinguish the long-term prognosis for patients who had an acute neurologic injury (concussion cohort) from patients who had a peripheral orthopedic injury (ankle sprain). We then assessed the long-term incidence of dementia for patients who received a statin after an ankle sprain compared with patients who did not receive a statin after an ankle sprain. If a patient experienced both a concussion and an ankle sprain, the individual was included in both cohorts (the exclusion of overlap patients yielded similar results).

Statistical Analysis

Our primary analysis evaluated the incidence of dementia after a concussion, comparing patients who received a statin with patients who did not. Graphical displays were created using cumulative incidence curves. Statistical testing was based on proportional hazards analysis taking into account censoring for interval deaths and the study follow-up end date of March 31, 2016. Statistical testing examined associations before adjusting for measured baseline patient characteristics (basic analysis) and after adjusting for measured baseline patient characteristics (adjusted analysis) to check the robustness of relative risk estimates. All *P* values were 2 tailed, and .05 was the threshold for statistical significance.

Secondary Analyses

Additional analyses explored the potential role of statins in preventing dementia after a concussion. Lipophilic statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin) were compared with hydrophilic statins (pravastatin and rosuvastatin).[80] Higher dosages of statins (maximum accepted treatment dosage for a specific statin) were compared with lower dosages of statins (all smaller dosages for a specific statin).[81] We also evaluated the incidence of dementia among patients receiving the most commonly used statins separately. Patients who received a statin before and after the concussion (continuous use) were also distinguished from patients who received their statin only after the concussion (initiation) and patients who stopped their statin after the concussion (discontinuation).

We conducted 3 further statistical analyses to explore the robustness of the primary analysis. The first analysis applied 1:1 propensity score matching of patients receiving statins with control patients to account for possible imbalances in baseline characteristics and unmeasured indications for statins. The second analysis introduced time-dependent covariates to account for subsequent changes in statin prescriptions over time and fluctuating adherence to statins. The third analysis considered the possible competing risks of other causes of death that might obscure a subsequent diagnosis of dementia.[82] Each of the 3 statistical analyses was conducted before and after adjusting for measured baseline patient characteristics to check the robustness of relative risk estimates.

In addition, we used tracer analysis to check for confounding by replacing the dementia outcome with an alternative clinical end point. Specifically, we reasoned that subsequent depression, instead of dementia, is a different adverse neuropsychiatric outcome that is frequent, serious, important, and similar in some shared clinical features to a dementia diagnosis in older patients.[83] However, the risk of depression is not substantially reduced by statins (due to distinct pathophysiology) but can be associated with shared determinants (eg, alcohol use and physical inactivity).[84-86] Therefore, we repeated the analyses and examined the risk of depression rather than the risk of dementia after a concussion.

Results

Descriptive Overview

A total of 28 815 patients (median age, 76 years; 61.3% female) were diagnosed as having a concussion during the study. Overall, 7058 patients (24.5%) received a statin during the 90 days after a concussion, and 21 757 patients (75.5%) did not receive a statin. The distribution of baseline demographic characteristics was similar for both groups (**Table 1**). The typical patient receiving a statin was a 76-year-old woman who was also taking additional medications. On average, patients receiving statins had more cardiovascular medications and more prior physician visits than control patients. The frequency of neuropsychiatric medication use also tended to be higher (not lower) for patients receiving statins. About one-quarter (23.6%) of patients had a hospital admission in the prior year, with no imbalance between the 2 groups.

Risk of Subsequent Dementia

A total of 4727 patients developed dementia over a mean follow-up of 3.9 years after a concussion (**Figure 1**A). The absolute incidence was 1 case per 6 patients, and most (83.4%) had extensive documentation of dementia during follow-up. Patients receiving statins accounted for 1050 dementia cases over 28 129 patient-years (mean, 4.0 years), equal to an incidence of 37 cases per 1000 patients annually (twice the population norm).[87] Control patients accounted for 3677 dementia cases over 85 339 patient-years (mean, 3.9 years), equal to an incidence of 43 cases per 1000 patients annually (more than twice the population norm). Together, statin use was associated with a 13% (95% CI, 7%-19%; $P < .001$) reduced risk of dementia compared with patients who did not receive a statin (relative risk, 0.87; 95% CI, 0.81-0.93; $P < .001$), equal to a number needed to treat of about 50 patients.

Adjusting for Patient Characteristics

The decreased risk of dementia associated with statin use after a concussion was similar in the first half and second half of the cohort and persisted after adjusting for patient characteristics (**Table 2**). As expected, older age was associated with an increased risk of dementia, as was greater health care use (total prescriptions, physician visits, and prior hospitalizations). Patient sex was not associated with a consistent difference in dementia risk. Lower socioeconomic status and urban home location were associated with an increased risk of dementia. Adjustment for all measured baseline characteristics suggested that statin use was associated with a 16% (95%

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Table 1. Characteristics of Patients With Concussion[a]

Variable	Patients Receiving Statin (n = 7058)	Control Patients (n = 21 757)
Age, y		
66-69	1585 (22.5)	4768 (21.9)
70-74	1832 (26.0)	5253 (24.1)
75-79	1640 (23.2)	4625 (21.3)
≥80	2001 (28.4)	7111 (32.7)
Sex		
Male	2978 (42.2)	8178 (37.6)
Female	4080 (57.8)	13 579 (62.4)
Socioeconomic quintile[b]		
Higher	2676 (37.9)	8287 (38.1)
Middle	1366 (19.4)	4293 (19.7)
Lower[c]	3016 (42.7)	9177 (42.2)
Home location		
Urban	6064 (85.9)	18 475 (84.9)
Rural[c]	994 (14.1)	3282 (15.1)
Cardiovascular medications		
Nonstatin lipid-lowering drug	474 (6.7)	752 (3.5)
ACE inhibitor	3144 (44.5)	5328 (24.5)
ARB agent	1302 (18.4)	1488 (6.8)
β-Blocker	2667 (37.8)	3930 (18.1)
Calcium channel blocker	2625 (37.2)	4959 (22.8)
Diabetes medication	1827 (25.9)	2109 (9.7)
Neuropsychiatric medications		
Benzodiazepine	1981 (28.1)	6126 (28.2)
Antipsychotic	193 (2.7)	655 (3.0)
Cholinesterase inhibitor	43 (0.6)	97 (0.4)
Antidepressant	1984 (28.1)	4538 (20.9)
Miscellaneous medications		
Thyroid supplement	1252 (17.7)	3162 (14.5)
Gastric acid suppressor	3029 (42.9)	6865 (31.6)
Inhaled bronchodilator	1076 (15.2)	2579 (11.9)
Glaucoma eyedrops	654 (9.3)	1910 (8.8)
Total prescriptions[d]		
≥5	6163 (87.3)	15 606 (71.7)
≤4	895 (12.7)	6151 (28.3)
Physician visits[e]		
≥13	5177 (73.3)	14 180 (65.2)
≤12	1881 (26.7)	7577 (34.8)
Hospital admissions[e]		
≥1	1675 (23.7)	5117 (23.5)
None	5383 (76.3)	16 640 (76.5)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

[a] Data are number (%) of each column.

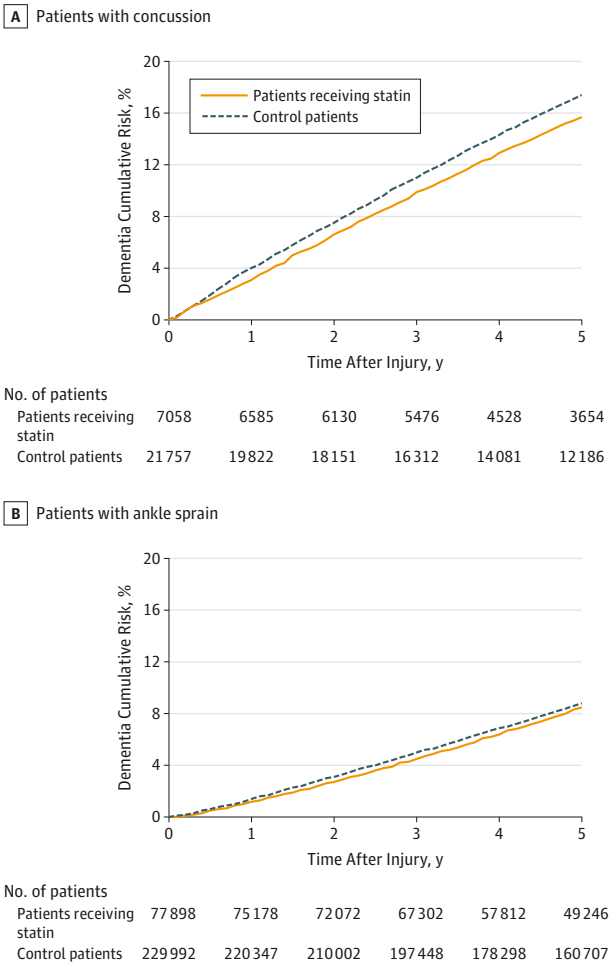
[b] Based on home location and Statistics Canada[55] algorithm.

[c] Includes missing values.

[d] Excluding statin prescriptions.

[e] Assessed during prior year.

Figure 1. Risk of Subsequent Dementia



Cumulative incidence plots of absolute risk of dementia after injury. The x-axis shows time after injury, spanning 5 years. The y-axis shows cumulative incidence of dementia. Numerical counts indicate the number of patients alive without dementia at the corresponding time. Results show increasing incidence of dementia with time, particularly after a concussion, with reduction in risk associated with statin use. The patients with ankle sprain show minimal healthy-user bias.

CI, 10%-22%; $P < .001$) reduction in the risk of subsequent dementia, equal to an E-value[88] of 1.67.

Additional Medications

Analysis of additional medication use suggested that the decreased risk of subsequent dementia was specific to statins. In particular, other lipid-lowering medications were not associated with a significant difference in the risk of dementia (Table 2). Other cardiovascular medications were not associated with a consistent decrease in the risk of dementia, with the possible exception of angiotensin II receptor blockers. Similarly, benzodiazepines, thyroid supplements, gastric acid suppressors, inhaled bronchodilators, and glaucoma eyedrops were not associated with a significantly decreased risk of subsequent dementia. As expected, major neuropsychiatric medications were associated with an increased risk of dementia, perhaps as a proxy for cognitive frailty in older patients.

Table 2. Factors Associated With Dementia After a Concussion

Variable	RR (95% CI)	
	Basic Analysis[a]	Adjusted Analysis[b]
Statin treatment	0.87 (0.81-0.93)	0.84 (0.78-0.90)
Age, y[c]		
70-74	2.00 (1.77-2.27)	1.99 (1.75-2.25)
75-79	3.25 (2.88-3.66)	3.22 (2.86-3.64)
≥80	6.88 (6.16-7.69)	6.76 (6.04-7.56)
Male	0.89 (0.84-0.95)	1.07 (1.00-1.14)
Socioeconomic quintile[d]		
Higher	0.95 (0.88-1.03)	0.99 (0.91-1.07)
Lower	1.15 (1.07-1.25)	1.12 (1.04-1.21)
Urban home location[e]	1.21 (1.11-1.31)	1.18 (1.08-1.29)
Cardiovascular medications		
Nonstatin lipid-lowering drug	0.94 (0.81-1.09)	1.00 (0.86-1.16)
ACE inhibitor	1.18 (1.11-1.26)	0.99 (0.93-1.06)
ARB agent	0.96 (0.87-1.06)	0.88 (0.79-0.98)
β-Blocker	1.18 (1.10-1.26)	1.01 (0.94-1.09)
Calcium channel blocker	1.15 (1.08-1.23)	0.95 (0.89-1.02)
Diabetes medication	1.13 (1.04-1.22)	1.21 (1.11-1.32)
Neuropsychiatric medications		
Benzodiazepine	1.32 (1.24-1.40)	1.05 (0.98-1.12)
Antipsychotic	2.68 (2.36-3.04)	2.01 (1.75-2.33)
Cholinesterase inhibitor	6.28 (4.96-7.94)	3.51 (2.63-4.68)
Antidepressant	1.65 (1.55-1.75)	1.53 (1.43-1.64)
Miscellaneous medications		
Thyroid supplement	1.16 (1.08-1.26)	1.00 (0.93-1.08)
Gastric acid suppressor	1.17 (1.10-1.24)	0.97 (0.91-1.04)
Inhaled bronchodilator	1.07 (0.98-1.16)	0.96 (0.88-1.05)
Glaucoma eyedrops	1.31 (1.19-1.43)	0.97 (0.89-1.07)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; RR, relative risk.

[a] No adjustment for baseline differences.

[b] Adjusted for age, sex, socioeconomic quintile, cardiovascular medications, neuropsychiatric medications, miscellaneous medications, total prescriptions, physician visits, and hospital admissions.

[c] Referent is group aged 66 to 69 years.

[d] Referent is middle socioeconomic quintile.

[e] Referent is rural location.

Specific Statin Analyses

Secondary analyses explored further nuances of statin use and the risk of subsequent dementia. Rosuvastatin use was associated with the largest risk reduction, and simvastatin use was associated with the smallest risk reduction (**Table 3**). Hydrophilic statins were marginally more beneficial than lipophilic statins. No greater benefit was found with higher dosages compared with lower dosages. Propensity score matching suggested that the risk reduction was not easily explained by baseline imbalances in measured patient characteristics. Patients who received a statin before and after the concussion explained most of the risk reduction. Those who initiated a statin after the concussion showed a significant risk reduction, and those who discontinued a statin after the concussion showed no significant risk reduction.

Dementia Risk After Ankle Sprain

The parallel analysis identified a total of 307 890 patients diagnosed as having an ankle sprain, of whom 77 898 (25.3%) received a statin and 229 992 (74.7%) did not receive a statin. A total of 25 956 patients developed dementia over a mean follow-up of 4.3 years (Figure 1B). Patients receiving statins accounted for 6239 dementia cases over 336 251 patient-years (mean, 4.3 years), equal to an incidence of 19 cases per 1000 patients annually. Control patients accounted for 19 717 dementia cases over 1 001 606 patient-years (mean, 4.4 years), equal to an incidence of 20 cases per 1000 patients annually. Both groups were at the population norm, and statin use was associated with a 5% (95% CI, 3%-8%; $P < .001$) reduction in the risk of dementia, equal to a number needed to treat of about 220 patients.

Depression Risk After a Concussion

The tracer analysis identified 1778 patients who were subsequently diagnosed as having depression after a concussion. The absolute incidence of depression was about 1 case per 16 patients (**Figure 2**). Patients receiving statins accounted for 440 cases of depression over 29 007 patient-years of follow-up, equal to an incidence of 15 cases per 1000 patients annually. Control patients accounted for 1338 cases of depression over 88 540 patient-years of follow-up, equal to an incidence of 15 cases per 1000 patients annually. Together, statin use was associated with an insignificant 4% (95% CI, −7% to 16%; $P = .43$) increased risk of depression before adjustment for measured baseline characteristics and an insignificant 4% (95% CI, −8% to 14%; $P = .49$) decreased risk of depression after adjustment for measured baseline characteristics.

Discussion

We studied 28 815 older adults diagnosed as having a concussion to test whether statin use might influence a patient's recovery after the concussion. In patients receiving statins, we found that the subsequent incidence of dementia was twice the population norm, and it was further accentuated in control patients who were not taking a statin. The relative reduction in dementia risk associated with statin use after a concussion was greatest for those taking rosuvastatin, was consistent for those receiving lower dosages, was accentuated after adjustments for measured patient characteristics, and was distinct from the risks for patients after an ankle sprain. No other cardiovascular or noncardiovascular medications were associated with a decreased risk of dementia after a concussion (with the possible exception of angiotensin II receptor blockers).

Our study adds to prior research on statin use after traumatic brain injury due to a larger sample size, longer follow-up, more detailed statistical analysis, and a priority on concussions (eAppendix in the Supplement). Four prior randomized trials yielded conflicting results, with 2 studies[89,90] reporting a positive protective effect of statins on neurocognitive outcomes and the other 2 studies[91,92] reporting no significant effect. Eleven prior nonrandomized studies also

Table 3. Concussion and Subsequent Dementia Risk

Variable	Total Patients, No.	Subsequent Dementia, No.	RR (95% CI)[a]
Total patients receiving statin	7058	1050	0.87 (0.81-0.93)
Specific statin[b]			
Rosuvastatin	1418	182	0.78 (0.67-0.91)
Atorvastatin	3457	540	0.92 (0.84-1.00)
Simvastatin	1156	188	0.93 (0.81-1.08)
Miscellaneous	1027	140	0.75 (0.63-0.89)
Type of statin[c]			
Hydrophilic	2024	261	0.76 (0.67-0.86)
Lipophilic	5034	789	0.91 (0.84-0.98)
Dosage of statin			
Higher	1155	159	0.84 (0.72-0.99)
Lower	5903	891	0.87 (0.81-0.94)
Premorbid statin[d]			
Continuation[e]	5848	868	0.86 (0.80-0.93)
Initiation[e]	1210	182	0.85 (0.74-0.99)
Discontinuation[e]	1111	172	0.91 (0.78-1.06)
Indication for statin[f]			
Basic[g]	14 086	2162	0.82 (0.76-0.90)
Adjusted[g]	14 086	2162	0.80 (0.73-0.88)
Adherence to statin[h]			
Basic[i]	28 815	4727	0.87 (0.81-0.93)
Adjusted[i]	28 815	4727	0.81 (0.75-0.87)
Competing risks[j]			
Basic	7058	1050	0.89 (0.83-0.95)
Adjusted	7058	1050	0.90 (0.84-0.97)

Abbreviation: RR, relative risk.

[a] Referent is control patients unless otherwise noted.

[b] Miscellaneous group includes cerivastatin sodium, fluvastatin sodium, lovastatin, and pravastatin sodium.

[c] Rosuvastatin and pravastatin are hydrophilic, whereas all other statins are lipophilic.

[d] Referent is patients who received no statin before or after a concussion.

[e] Continuation is statin before and after a concussion, discontinuation is no statin after a concussion, and initiation is no statin before a concussion.

[f] Propensity score–matched design adjusts for baseline imbalances.

[g] Analysis contains patients receiving statin and 1:1 matched corresponding control patients.

[h] Time-dependent model adjusts for fluctuating patient adherence over time.

[i] Analysis contains entire cohort, including corresponding control patients who received no statin.

[j] Adjusts for competing risks through approach by Fine and Gray.[82]

yielded conflicting results, with 5 studies[93-97] reporting a positive protective association on clinical outcomes and the other 6 studies[98-103] reporting a negligible association. No prior studies indicated a detrimental influence of statin use after traumatic brain injury, but almost all previous studies focused on patients with moderate to severe injuries rather than concussions.

Limitations

Several limitations of our research merit attention. Our study was not a randomized trial, and the observed associations might reflect confounding due to earlier indications for statin use.[104] Important missing covariates included smoking status, daily exercise, drug adherence, and other factors that influence the risk of developing dementia.[105-108] These unknown differences in patients (healthy-user bias) might account for a reduction in the subsequent risk of dementia.[109,110] Our study also lacks sufficient power to disentangle whether statins make a contribution before, during, or after a concussion. In addition, the diagnostic codes for concussion and dementia were not fully sensitive and may significantly underestimate the true incidence of dementia in patients after a concussion.[111]

The generalizability of our findings is also limited by a focus on older adults, the requirement for patients to survive at least 90 days after a concussion, and the exclusion of those already diagnosed as having dementia.[112] We did not consider patients with severe brain injury that resulted in hospitalization; instead, we examined only concussion cases as the more common type of traumatic brain injury. We also lacked data on patients with injuries who did not seek medical care. Our study was based in Canada, did not account for geographic variances in health care delivery, and potentially underestimated risks due to random delays in diagnosing dementia. We also lacked nuanced data on functional status, and we found only a modest degree of healthy-user bias in our patients.[113,114]

Our study has further limitations for clinical care. Concussion and dementia are both varied disorders, so aggregate statistics do not necessarily apply to unique patients. The median follow-up duration was less than 5 years, whereas the course of dementia can span decades of subclinical changes. Our patients had years of unrecorded history and an unknown total number of concussions over a lifetime. The relative risks associated with concussions and with statin use were both modest because each addresses only one of many contributors to dementia. Our observational design also means that the unmeasured burden of cardiovascular and neuropsychiatric diseases may have been imbalanced against the patients receiving statins and may have led to analyses that underestimate the neuroprotection from statins.

The findings of our study suggest a potential long-term protective association between statin use and the risk of dementia after a concussion that justifies future research. The study also provides estimates of event rates, time profiles, effect sizes,

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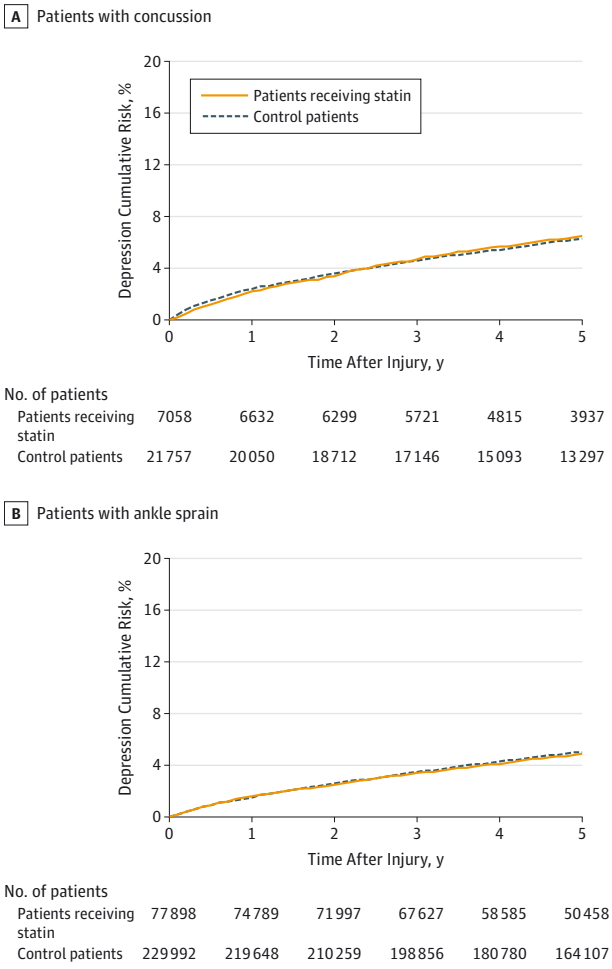
Figure 2. Risk of Subsequent Depression



Cumulative incidence plots of absolute risk of depression after injury. The x-axis shows time after injury, spanning 5 years. The y-axis shows cumulative incidence of depression. Numerical counts indicate the number of patients alive without depression at the corresponding time. Results show increasing incidence of depression with time, modest accentuation after a concussion, and no reduction in risk associated with statin use. Both patient groups show minimal healthy user bias.

and baseline frequencies needed for planning future trials. Of course, a randomized trial might face difficulties in patient enrollment because adults may not be willing to be randomized to receive a placebo rather than a statin.[92] The 20-year patient enrollment interval of our study could also be prohibitive for a prospective trial. In addition, we know of no practical method to randomize patients to receive a statin immediately before a concussion. Therefore, analytic observational research may provide the best available data for the immediate future.

Conclusions

Concussion is often popularized as a problem in athletic youth and tends to be underdiagnosed in older individuals.[115-117] The results of our study suggest that concussions are a common injury in older adults and indicate that dementia may be a frequent outcome years afterward. Therefore, more efforts to prevent concussions should be encouraged at all ages.[118] Screening for past concussions might also offer new clinical insights for patients diagnosed as having dementia.[119] A potential neuroprotective benefit may also encourage greater medication adherence for patients who are already prescribed a statin.[120,121] In addition, a concussion should not be interpreted as a reason to stop statins, and a future randomized trial is justified.[122] The long-term neurologic consequences of a concussion are substantial and merit attention.[123]

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