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Documented Statin Exposure and Multiple Sclerosis in Southeast Alabama

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Abstract

Background

Statins inhibit cholesterol biosynthesis and may influence central nervous system repair through lipid-dependent and immunomodulatory pathways. Preclinical and clinical evidence concerning statins in multiple sclerosis (MS) has been inconsistent. This pilot study examined whether documentation of MS among decedents differed according to documented statin exposure and evaluated the feasibility of an institutional electronic medical record research workflow.

Methods

We conducted an exploratory retrospective review of 26,710 rows from an Epic-generated report structured as one row per decedent recorded as deceased from February 2021 through July 14, 2025 at a regional health system in southeast Alabama. The rows were treated as unique decedents, although duplicate identifiers were not independently audited. The records were classified according to the presence or absence of documented statin exposure. The clinical outcome was explicit MS documentation in the report. Fisher's exact test was the primary inferential analysis because the outcome was rare. Operational feasibility was described by completion of the institutional approval, secure access, report generation, and record review process.

Results

Documented statin exposure was present in 3,025 records and absent in 23,685. MS was documented in 10 records, including eight with documented statin exposure (0.264%) and two without documented exposure (0.008%). Fisher's exact test showed an unadjusted association between statin documentation and MS documentation (conditional odds ratio: 31.39, exact 95% confidence interval: 6.26 to 303.58; $p = 9.78 \times 10^{-7}$). The institutional workflow produced a project-specific report in a secure environment and supported completion of the record review. Only 10 outcome events were available, so adjusted modeling was not performed.

Conclusions

MS was more frequently documented among decedents whose records also documented statin exposure. Because every record represented a decedent and exposure ascertainment depended on the available documentation, the analysis cannot estimate the effect of statins on mortality, MS onset, or MS progression. The clinical result is hypothesis- generating. This pilot study also demonstrates that a governed pathway for student-led electronic medical record research can be implemented within a regional health system.

Categories: Therapeutics, Cardiology, Medical Education
Keywords: death certificates, electronic medical records, feasibility studies, multiple sclerosis, pharmacoepidemiology, retrospective studies, statins

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by demyelination, neuroaxonal injury, and variable neurologic disability [1]. The development of MS reflects interactions among immune, genetic, and environmental factors. MS affects women more often than men, and its prevalence varies substantially across regions and populations [2]. As people with MS age, vascular disease and other comorbidities become increasingly important to disability and survival [3,4].

Cholesterol is required for normal myelin formation and maintenance. Experimental work has shown that high cholesterol availability is essential for myelin membrane growth [5]. In the mevalonate pathway, HMG-CoA reductase converts HMG-CoA to mevalonate, which contributes to downstream sterol and isoprenoid synthesis. Cholesterol is incorporated into sphingolipids, phospholipids, and myelin proteins during myelin membrane assembly [6]. Statins competitively inhibit HMG-CoA reductase and reduce circulating low-

density lipoprotein cholesterol. They also have anti- inflammatory and immunomodulatory effects that may be relevant to MS.

The relationship between statins and MS biology is not straightforward. Experimental work has suggested that simvastatin can impair oligodendrocyte precursor differentiation and remyelination under specific conditions [7]. Small clinical studies of statins alone or combined with interferon beta have produced conflicting results [8-11]. A phase 2 trial of high-dose simvastatin reported reduced whole-brain atrophy in secondary progressive MS [11], while the subsequent phase 3 trial did not show slower disability progression [12]. Observational evidence has also not consistently supported clinical harm from conventional statin therapy [10,13].

We performed a pilot retrospective record review in a regional health system in southeast Alabama. The primary clinical objective was to compare the frequency of MS documentation among decedents with and without documented statin exposure. The secondary objective was to describe whether a governed institutional workflow could support electronic medical record research by trainees. The analysis was designed to generate hypotheses and evaluate feasibility rather than estimate a causal effect of statins on mortality.

Materials And Methods

Study design and setting

This exploratory retrospective study reviewed an Epic-generated deceased patient report from Southeast Health System. A death record was defined as one row in this report for a patient recorded as deceased with a date of death from February 2021 through July 14, 2025. February 2021 was selected as the start of the study period because it marked Southeast Health's transition to the Epic electronic medical record and therefore the beginning of the available electronic record period for this review. All report rows within the date range were eligible. No record was excluded from the primary analysis on the basis of age, sex, race, comorbidity, statin duration, or the temporal order of statin and MS documentation.

The report was structured as one row per decedent; thus, the 26,710 rows were treated as 26,710 unique decedents. The research team did not independently compare patient identifiers to audit duplicate rows. The unit of analysis was therefore a report row representing a decedent. The study did not include a cohort of living patients and did not compare survival time between treatment groups.

Institutional review and data governance

The Alabama College of Osteopathic Medicine Institutional Review Board determined the study to be exempt under Category 4 for secondary research using private information collected for purposes other than the present study (protocol 24-09-04-001; approved September 17, 2024). Data collection was completed on July 14, 2025, during the approval period. Access followed institutional requirements for research registration, human subjects and privacy training, principal investigator oversight, health system review, minimum necessary data access, and secure storage.

Protocol and analytical status

The approved protocol specified a retrospective chart review examining the association between statin use and MS. It proposed collecting demographic characteristics, statin treatment dates, MS diagnosis dates, and comorbidities. The protocol also proposed a statin duration threshold and temporal ordering between statin exposure and MS diagnosis. These dates and durations could not be verified consistently in the available records; thus, they were not used as eligibility requirements in the reported analysis.

The final comparison using the full deceased patient report, the documentation-based exposure and outcome definitions, the descriptive feasibility criteria, and the neuromyelitis optica sensitivity analysis were developed during the exploratory review after the structure and limitations of the extract were known. They were not prespecified in the approved protocol. The reported analyses should therefore be interpreted as post hoc and hypothesis generating.

Pilot electronic medical record access workflow

This pilot study used a documented sequence that connected academic review with health system data governance. For this report, operational feasibility was defined descriptively as completion of the required approvals and training, creation of project-specific access, delivery of the requested data extract to a secure location, and completion of record screening. Access time, cost, user satisfaction, and reproducibility at another institution were not prospectively measured (Table *1*).

Stage	Documented action
1. Research registration	Register the project and identify a principal investigator.
2. Ethics review	Submit the protocol and data request materials for institutional ethics review.
3. Researcher readiness	Complete required human subjects, responsible conduct, privacy, and security training.
4. Health system authorization	Obtain legal, privacy, security, and research authorization from the health system.
5. Secure access	Create individual time-limited credentials and a project-specific secure folder. Never share credentials.
6. Data delivery and review	Generate the approved minimum necessary report and review it in the secure environment.
7. De-identification and closeout	Remove identifiers before external use, terminate access, and archive the project under policy.

TABLE 1: Deidentified stages of the pilot electronic medical record research workflow

Screening, chart verification, and data extraction

Project-specific Epic report was screened for documented statin exposure and explicit MS documentation. The same screening rules were applied throughout the report. Next, the full available Epic chart was reviewed for the 10 records with MS documentation to verify the available medication, diagnosis, and demographic information. Abstracted variables included age at death, sex, race, statin agent, statin dose when available, MS diagnosis date or the age when available, selected cardiovascular and metabolic comorbidities, and indicators of incomplete documentation. The data were entered into a de-identified spreadsheet using study numbers. Missing values were retained as missing and were not imputed.

Exposure and outcome definitions

Documented statin exposure was defined as a named statin in the project report or available Epic chart. Search terms included atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. For chart verification, sources included active and historical medication lists, medication reconciliation, and relevant clinical notes when available. The assessment period extended from the earliest medication information visible in Epic, including historical entries carried into Epic, through the date of death. A recorded dose, minimum duration, adherence measure or defined interval between statin and MS documentation was not required. Records without evidence of a named statin were classified as having no documented statin exposure. This category indicates absence of documentation rather than confirmed nonuse.

Chart review covered all available sources for each patient, but the availability and completeness of those sources varied. Some charts were scant, particularly the two records with MS documentation and no documented statin exposure, which mainly contained an emergency department note and a death note. Their medication lists were incomplete and did not provide a reliable longitudinal medication history. Applying the same classification rule therefore did not ensure equally complete exposure ascertainment across records.

Clinical outcome was an explicit MS entry in the deceased patient report. It did not require MS to be the underlying or contributing cause of death and did not constitute an independently adjudicated MS diagnosis. A record was retained in the primary analysis when the report documented MS even if detailed chart review identified diagnostic discordance. One such record contained neuromyelitis optica rather than typical MS in the detailed chart. The sensitivity analysis removed this record entirely from the analytic cohort rather than reclassifying it as a non-MS record.

Statistical analysis

Counts and percentages were used to summarize the data. A two-by-two table compared MS documentation according to statin documentation. Fisher's exact test was selected as the primary inferential test because the expected count for one MS cell was below five. We calculated the conditional maximum likelihood estimate of the odds ratio with a two-sided exact conditional 95% confidence interval. The Pearson chi-square analysis without Yates continuity correction and the phi coefficient (ϕ) were retained as secondary descriptive summaries for continuity with the initial analysis. The phi coefficient was calculated as the square root of χ^2/N and was reported numerically without a qualitative strength label. The asymptotic chi-square p-value was not used as the basis for primary inference because of the sparse expected cell count. Fisher's exact tests were two-sided, and $p < 0.05$ was considered statistically significant. Analyses were independently verified with Python version 3.12 (Python Software Foundation; Beaverton, Oregon, USA) and SciPy version 1.17. Adjusted regression was not performed because only 10 outcome events were

observed.

Results

Feasibility outcome

The institutional workflow was completed and produced a project-specific report in a secure environment. Individual research access was time-limited under health system policy. The report supported screening of 26,710 rows and detailed abstraction of the 10 records that documented MS. This pilot study therefore met its descriptive feasibility definition. No prospective measures of processing time, cost, user experience, or portability to another institution were collected.

Clinical outcome

Among 26,710 records for deaths occurring during the study period, 3,025 (11.3%) had documented statin exposure and 23,685 (88.7%) did not. MS was documented in 10 records (0.037%). Eight of the 3,025 records with documented statin exposure included MS (0.264%), compared with two of the 23,685 records without documented exposure (0.008%) (Table 2).

Statin documentation	MS documented	MS not documented	Total
Documented exposure	8	3,017	3,025
No documented exposure	2	23,683	23,685
Total	10	26,700	26,710

TABLE 2: Multiple sclerosis documentation according to documented statin exposure

MS: multiple sclerosis

The Fisher exact test identified an unadjusted association between statin documentation and MS documentation (conditional odds ratio: 31.39, exact 95% confidence interval: 6.26 to 303.58; $p = 9.78 \times 10^{-7}$). The confidence interval was wide because the result was based on only 10 records with MS documentation.

The secondary Pearson chi-square analysis without continuity correction yielded $\chi^2(1, N = 26{,}710) = 46.98$, asymptotic $p = 7.17 \times 10^{-12}$ and $\phi = 0.042$. One expected cell count was 1.13, limiting the validity of the chi-square approximation. Fisher's exact test therefore remained the basis for primary inference. The phi coefficient describes the table association and should not be interpreted as a measure of clinical importance.

Characteristics of records with MS documentation

Nine of the 10 records with MS documentation were for women, and nine were for White decedents. The age at death was available for nine records. Among the eight records with documented statin exposure, atorvastatin was documented in five, pravastatin in two, and simvastatin in one. The two records classified as having no documented statin exposure were scant and mainly contained an emergency department note and a death note. Their medication lists were incomplete, so unrecorded previous statin exposure could not be excluded. Table 3 presents available characteristics according to exposure status. Detailed demographic, comorbidity, and documentation variables were collected only for the 10 records with MS documentation; thus, comparable data were not available for the entire 26,710 record cohort (Table 3).

No documented statin exposure (n=2)	No documented statin exposure (n=2)	No documented statin exposure (n=2)
Women	7 (87.5%)	2 (100%)
White race	8 (100%)	1 (50%)
Black race	0	1 (50%)
Age at death available	7 (87.5%)	2 (100%)
Median age at death, years	67	81.5
Age range, years	44 to 80	81 to 82
MS diagnosis date or age available	7 (87.5%)	2 (100%)
Hypertension	5 (62.5%)	2 (100%)
Diabetes mellitus	3 (37.5%)	0
Dyslipidemia	3 (37.5%)	0
Atrial fibrillation	2 (25.0%)	0
Myocardial infarction or coronary artery disease	2 (25.0%)	0
Stroke	2 (25.0%)	0
Any selected cardiovascular or metabolic comorbidity*	6 (75.0%)	2 (100%)
Record explicitly described as incomplete or sparse	1 (12.5%)	2 (100%)

TABLE 3: Characteristics of decedents with multiple sclerosis documentation according to documented statin exposure

*Defined as documentation of hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, myocardial infarction, coronary artery disease, or stroke. Percentages are descriptive, and no between-group statistical tests were performed. Comorbidity counts represent documented diagnoses; absence of documentation does not establish absence of a condition. The incomplete or sparse category reflects descriptive chart review rather than a standardized completeness score.

One record retained in the primary outcome group had neuromyelitis optica documented in the detailed chart rather than typical MS. The sensitivity analysis removed this record entirely, leaving 26,709 records (Table *4*).

Statin documentation	MS documented	MS not documented	Total
Documented exposure	7	3,017	3,024
No documented exposure	2	23,683	23,685
Total	9	26,700	26,709

TABLE 4: Sensitivity analysis after exclusion of the record with neuromyelitis optica

After exclusion, Fisher's exact test gave a conditional odds ratio of 27.47 (exact 95% confidence interval: 5.23 to 271.11; p-value: 6.93×10^{-6}). The direction of the unadjusted association was unchanged.

Discussion

Principal findings and interpretation

In this pilot review, MS was documented more often in death records that also contained documented statin exposure. The magnitude of the unadjusted odds ratio was large, but the exact confidence interval was very wide, and the estimate was based on only 10 outcome records. The sensitivity analysis excluding the record

with diagnostic discordance produced a similar direction of association.

The central limitation of interpretation is the study denominator. Every record represented a person who had died. The analysis therefore compares documentation patterns among decedents and does not compare mortality between people with MS who did and did not receive statins. It cannot establish whether statins increased the risk of death, shortened survival, contributed to MS onset, or altered disease progression. The appropriate conclusion is that statin documentation and MS documentation were associated within this death record dataset.

Relationship to previous evidence

A biologic rationale for studying statins in MS exists because cholesterol is required for myelin membrane formation and the mevalonate pathway also supplies isoprenoids involved in cell signaling. Accumulation of selected 8,9-unsaturated sterol intermediates promoted oligodendrocyte formation and remyelination in experimental systems [14]. In a cuprizone model, simvastatin administered during selected repair phases reduced oligodendrocyte precursor responses and remyelination [7]. Those experimental conditions do not establish that routine statin treatment impairs myelin repair in humans.

Human evidence has been mixed. An early open-label phase 2 study of oral simvastatin in relapsing-remitting MS reported reduced gadolinium-enhancing lesion activity [15]. A small trial reported increased clinical or magnetic resonance imaging activity when high-dose atorvastatin was combined with interferon beta [8]. A larger randomized study found no benefit from adding atorvastatin to interferon beta, but it did not identify a consistent worsening of predefined MS outcomes [9]. A population-based cohort study found no difference in long-term disability progression with conventional statin treatment [10]. The MS-STAT phase 2 trial reported a lower rate of whole brain atrophy with high-dose simvastatin [11], while MS-STAT2 found no reduction in confirmed disability progression [12].

Observational mortality data also argue against interpreting our result as evidence of harm. Independent population studies have associated comorbidity with increased mortality among people with MS [3,4]. In a large English cohort, lipid-lowering treatment, which was predominantly statin therapy, was associated with lower all-cause mortality among people with MS after multivariable adjustment [13]. That study and our pilot study differ substantially in design, outcome definition, exposure ascertainment, and capacity for adjustment. Together, the literature indicates that effects may differ by statin, dose, MS phenotype, concomitant disease-modifying therapy, and outcome measured.

Sources of bias and uncertainty

The observed association is vulnerable to confounding by indication and ascertainment bias. Statins are commonly prescribed to older adults with hyperlipidemia, diabetes, hypertension, and cardiovascular disease. Patients with these conditions may have more health care encounters, more complete medication reconciliation, and more detailed problem lists than patients with limited contact. Among the 10 records with MS documentation, both records without documented statin exposure were described as sparse compared with one of the eight exposed records. The two records without documented exposure mainly contained an emergency department note and a death note with incomplete medication histories. They could not establish whether a statin had been prescribed previously or used outside the health system. The same exposure rule was applied, but unequal source completeness could have produced differential exposure misclassification. The direction and magnitude of the resulting bias cannot be determined from these data. Neither the exact test nor the secondary chi-square analysis and phi coefficient correct for documentation bias or uncontrolled confounding.

Restricting the denominator to decedents also creates substantial selection bias. Inclusion depended on being recorded as deceased during the study period. If statin exposure, MS, cardiovascular disease, other comorbidities, or health care contact influenced the probability of inclusion or the completeness of documentation, conditioning on death could distort the observed association. The study cannot determine whether the exposure groups were comparable in the population from which these decedents arose.

Documentation in an Epic deceased patient report is an imperfect surrogate for confirmed disease. MS may be omitted when it is not carried into the available diagnosis or death-related documentation. Previous population research has estimated that MS appears on only 70% to 80% of death certificates among people known to have MS [16]. Although the Epic report in this study was not a vital statistics death certificate dataset, that evidence illustrates the potential for omission in death-related records. Conversely, the record with neuromyelitis optica illustrates possible diagnostic misclassification. The outcome is, therefore, best understood as documentation of MS in the report rather than a validated cohort diagnosis.

Other limitations include the single-center setting, small number of outcome events, absence of a living comparison cohort, and lack of full cohort demographic or comorbidity data. The report was structured as one row per decedent, but duplicate identifiers were not independently audited. The operational definitions and sensitivity analysis were developed post-hoc. No adjusted model could be supported. Exposure duration, dose consistency, adherence, lipid measurements, statin intensity, statin lipophilicity, MS subtype, disease

duration, disability status, and use of disease-modifying therapies or glucocorticoids were not consistently available. These limitations prevent dose-response analysis and leave substantial residual confounding.

Feasibility contribution and future research

This pilot study's most durable contribution may be operational. It connected academic research registration and ethics review with health system authorization, privacy training, project-specific access, secure report delivery, and controlled closeout. The workflow supported completion of the requested review while maintaining institutional control of protected information. A de-identified version could serve as a starting framework for future trainee investigators if the health system approves its distribution.

The workflow was implemented for one project at one health system and was not formally evaluated against another process. Future studies could prospectively record time to approval, number of revisions, staff effort, cost, access failures, and user experience. Repetition by other research teams would be needed before describing the process as reproducible or generalizable.

A definitive clinical study would begin with a cohort of people with confirmed MS rather than a cohort defined by death. It would define an index date, distinguish incident from prevalent statin use, and follow exposed and unexposed patients over time. Analyses should account for age, sex, race, cardiovascular risk, comorbidity burden, health care utilization, MS phenotype, disability, disease-modifying therapy, and competing causes of death. Dose, duration, and statin-specific properties should also be examined.

Conclusions

In this regional pilot study, MS documentation was more frequent among the decedent records with documented statin exposure than among records without documented exposure. This association is hypothesis-generating and should not be interpreted as evidence that statins cause MS or increase mortality because the study included only decedents, relied on record documentation, and could not adjust for major confounders. The pilot study also showed that a governed electronic medical record workflow could support trainee-led retrospective research within Southeast Health. Future work should validate the access pathway prospectively and evaluate statin exposure in a confirmed MS cohort with longitudinal follow-up and adequate adjustment.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Mason A. Johnson, William D. Lawrence, Tiffany Dang, Robert W. Parker

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Alabama College of Osteopathic Medicine (ACOM) IRB issued approval 24-09-04-001. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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