

Editor's Note

LESS IS MORE

Statin-Associated Myopathy—An Elusive Clinical Problem

Gregory Curfman, MD

Muscle disorders resulting from statin therapy, the most common manifestation of statin intolerance, are vexing to both patients and physicians. Statin-associated myopathy may appear as a spectrum of manifestations that include myalgias, myopathy, myositis, myonecrosis, and rhabdomyolysis.¹

Myonecrosis and rhabdomyolysis are uncommon, occurring in fewer than 1% of statin-treated patients, but myalgias and myopathy without creatine kinase elevation are reported in up to 5% of patients in clinical trials and in 25% or more



Related article

in observational studies and clinical experience. To aid in the diagnosis of this often enigmatic condition, the American College of Cardiology provides a statin intolerance mobile app (<http://www.acc.org/statinintoleranceapp>).

Risk factors include hypothyroidism, prolonged vigorous exercise, low levels of vitamin D, other underlying muscle disorders, coadministration of statins with drugs that inhibit cytochrome P450 3A4 (CYP3A4), and the specific statin prescribed (eg, fluvastatin sodium and pravastatin sodium are associated with a lower risk of muscle toxic effects). Treatment options often begin with a drug holiday, which may lead to permanent drug discontinuation for patients with lower cardiovascular risk. For those who require ongoing low-density lipoprotein-lowering therapy, options include switching to fluvastatin, pravastatin, or ezetimibe; alternate-day therapy

with rosuvastatin calcium; and discontinuing or modifying the dosages of drugs that inhibit CYP3A4, such as cyclosporine, amiodarone hydrochloride, and macrolide antibiotics.²

In this issue of *JAMA Internal Medicine*, Caughey et al³ provide evidence of an association between statin therapy and idiopathic inflammatory myositis (IIM), a specific muscle condition. Using a case-control design and data from an Australian myositis registry, the researchers found that cases of IIM had a significantly higher rate of statin exposure than population-based controls (adjusted odds ratio, 1.79; 95% CI, 1.23-2.60).

Proper interpretation of this study depends on 2 factors. First, the diagnosis of myositis must be histologically confirmed; in the study by Caughey et al,³ all registry patients had muscle biopsy-confirmed IIM. Second, exposure to statin therapy must be accurately classified. This study assessed statin exposure by different methods for cases (drug history in the medical record) and controls (prescription dispensing records), which may have resulted in misclassification bias. Thus, the association of IIM with statin therapy reported by Caughey et al cannot be considered definitive, although these are likely the best data currently available.

Statin-associated myopathy as well as muscular aches and pains will continue to be a concern to patients and a diagnosis elusive to physicians. This debilitating adverse effect underscores the importance of prescribing statins only to patients who will clearly have a net benefit.

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Association of Statin Exposure With Histologically Confirmed Idiopathic Inflammatory Myositis in an Australian Population

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+ Editor's Note

IMPORTANCE Statin medications are widely prescribed for cardiovascular risk reduction. Myalgia and rhabdomyolysis are well-recognized adverse effects of statins, and they resolve with the cessation of statin therapy. Idiopathic inflammatory myositis (IIM) is a heterogeneous group of autoimmune myopathies that may also be associated with statin use. Recently, statin-associated autoimmune myopathy has been recognized as a distinct entity with the presence of specific autoantibodies against hydroxymethylglutaryl-coenzyme A reductase, which results in a necrotizing myositis that does not resolve with cessation of statin therapy and requires treatment with immunosuppressive agents.

OBJECTIVE To examine the association between histologically confirmed IIM and current exposure to statin medications.

DESIGN, SETTING, AND PARTICIPANTS Population-based case-control study using the South Australian Myositis Database of all histologically confirmed cases of IIM diagnosed between 1990 and 2014 in patients 40 years or older (n = 221) and population-based controls from the North West Adelaide Health Study (n = 662), matched by age and sex in a 3:1 ratio of controls to cases. Data analysis using conditional logistic regression was performed from June 1, 2016, to July 14, 2017.

EXPOSURES Current statin medication use.

MAIN OUTCOMES AND MEASURES Unadjusted and adjusted (for diabetes and cardiovascular disease) odds ratios and 95% CIs for likelihood of inflammatory myositis.

RESULTS A total of 221 IIM cases met the inclusion criteria with a mean (SD) age of 62.2 (10.8) years, and 132 (59.7%) were female. Statin exposure at the time of IIM diagnosis was 68 of 221 patients (30.8%) and 142 of 662 matched controls (21.5%) ($P = .005$). There was an almost 2-fold increased likelihood of statin exposure in patients with IIM compared with controls (adjusted odds ratio, 1.79; 95% CI, 1.23-2.60; $P = .001$). Similar results were observed when patients with necrotizing myositis were excluded from the analysis (adjusted odds ratio, 1.92; 95% CI, 1.29-2.86; $P = .001$).

CONCLUSIONS AND RELEVANCE In this large population-based study, statin exposure was significantly associated with histologically confirmed IIM. Given the increased use of statins worldwide and the severity of IIM, increased awareness and recognition of this potentially rare adverse effect of statin exposure is needed.

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Statin medications inhibit the enzyme hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase to lower low-density lipoprotein cholesterol to reduce both primary and secondary cardiovascular risk.¹ More than 200 million people worldwide are estimated to use statin therapy, which is generally well tolerated by most patients.² There are potential harms associated with statins, including well-known musculoskeletal adverse effects that include myalgia (estimated prevalence, 7%-29% of all statin users) and the rare, yet severe condition of rhabdomyolysis (incidence, 0.4 per 10 000 person-years).²⁻⁴ In most instances these adverse effects resolve when statin treatment is discontinued. However, in the past 2 decades, numerous case reports have suggested that statins might also be associated with the development of inflammatory myositis.⁵ A recent systematic review identified 16 publications reporting a total of 100 patients with statin-associated autoimmune myopathy.⁶ These case reports have been further supported by a small case-control study from France⁷ of 37 patients that reported a significant association between statin exposure and chronic muscle disease, including inflammatory myositis (odds ratio [OR], 2.73; 95% CI, 1.21-6.14), by comparison with population-based matched controls.⁷

Idiopathic inflammatory myositis (IIM) is a group of rare, clinically heterogeneous, autoimmune muscular disorders with an estimated incidence of 0.1 per 100 000 persons per years to 1.0 per 100 000 persons per years.^{5,8} They are severe, debilitating conditions that can result in permanent disability and death. Idiopathic inflammatory myositis commonly appears as painless, proximal limb girdle weakness with multisystem involvement.⁵ Creatinine kinase levels are commonly elevated, and treatment includes high-dose corticosteroids and other forms of immunosuppressive therapies.^{5,9} There are a number of distinct subsets of IIM that are distinguished by clinical features, characteristic histopathologic features, and the presence of myositis-specific autoantibodies. Subsets of IIM include polymyositis, dermatomyositis, inclusion body myositis, and immune-mediated necrotizing myositis.⁹ The latter, immune-mediated necrotizing myopathy, has been reported in association with a number of factors, including viral infections, connective-tissue disorders, or exposure to a statin medication.⁹ More recently, statin-associated autoimmune myopathy has been recognized as a distinct entity, with the presence of a specific autoantibody against HMG-CoA reductase.^{10,11}

To date, no epidemiological studies have investigated exposure to statins in patients with histologically confirmed IIM. The aim of this study was to examine the association between current exposure to statins and histologically confirmed IIM. In addition, we sought to investigate the prevalence of specific types of IIM and temporal changes in the proportion of IIM cases exposed to statins.

Methods

Study Sample and Design

A retrospective, population-based, case-control study was conducted of people 40 years and older within South Australia. Cases were defined as patients with histologically confirmed

Key Points

Question What is the association between current exposure to statin medications and histologically confirmed idiopathic inflammatory myositis?

Findings In this population-based case-control study of 221 patients with idiopathic inflammatory myositis and 662 age- and sex-matched controls, there was a statistically significant 79% increased likelihood of statin exposure in patients with idiopathic inflammatory myositis compared with controls.

Meaning Given the increased use of statin medications worldwide and the severe adverse effects of idiopathic inflammatory myositis, increased awareness and recognition of this potentially rare adverse effect with statin exposure is needed.

IIM identified from the South Australian Myositis Database,^{12,13} a comprehensive registry of all adult patients with biopsy-confirmed myositis, between 1990 and 2014. This registry included the histopathologic and clinical features of the disease and the use of prescription medications as documented in the patient's rheumatology medical records.¹² Cases of IIM were identified from muscle biopsy results using histopathologic criteria for the diagnosis of polymyositis, dermatomyositis, inclusion body myositis, necrotizing myositis, and non-specific chronic inflammatory myositis by investigators at the Neuropathology Laboratory, Institute of Medical and Veterinary Science, Adelaide, Australia, as previously described.^{12,13} Current medication use obtained from the patient's rheumatology medical record at the time of biopsy that resulted in the diagnosis of IIM was used to determine exposure to medications, including statin exposure. This information of medication use was self-reported and obtained either directly from the patients or from the referring rheumatologist, who provided a report of medications that the patient was receiving at the time of biopsy. Included within this documentation were cases in which the patient reported not receiving any prescription medicines. Patients who did not report medication use in the medical record were excluded; patients younger than 40 years were also excluded because of the limited use of statins in this age group.¹⁴ An a priori power calculation was conducted that was based on an OR of 2.0, 20% of the study cohort exposure to statins, a risk of .05 defining statistical significance, power equal to 90%, and a 3:1 ratio of 450 controls to 150 cases, the minimum number required for the study. This study was approved by the Royal Adelaide Hospital, Adelaide, Australia, and the University of South Australia Human Research Ethics Committees, Adelaide, South Australia. Participant written informed consent was obtained by the Royal Adelaide Hospital.

Population-based controls were obtained from the North West Adelaide Health Study¹⁵ between 2004 and 2006 and randomly matched by age and sex in a 3:1 ratio of controls to cases. Ages of patients referenced in the cases at the time of the diagnosis of IIM were matched to those of the controls within a 2-year range. North West Adelaide Health Study is a representative population cohort study of 4056 randomly selected adults 18 years or older who were recruited from

Table 1. Demographic and Clinical Characteristics of Patients With Idiopathic Inflammatory Myositis and Matched Population-Based Controls

Characteristic	No. (%) [95% CI]		P Value
	Cases (n = 221)	Controls (n = 662)	
Age, mean (SD), y	62.2 (10.8)	62.1 (10.7)	NA ^a
Females	132 (59.7)	395 (59.7)	NA ^a
Statin exposure	68 (30.8) [24.7-36.9]	142 (21.5) [18.3-24.6]	.005
Comorbid conditions			
Cardiovascular disease	52 (23.5)	226 (34.1)	.003
Diabetes	9 (4.1)	11 (1.7)	.04
Gout	5 (2.3)	18 (2.7)	.71
Osteoporosis	7 (3.2)	27 (4.1)	.54
NSAID medication use	14 (6.3)	72 (10.9)	.05

Abbreviations: NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug.

^a Matching criteria.

the northern and western regions of Adelaide, South Australia. This region represents approximately half of the metropolitan area and is representative of one-third of the total population of South Australia. Detailed study methods have been previously described.¹⁵ Survey data from a self-reported questionnaire were used to collect participant demographics and health-related information, with data used for this study taken from stage 2 of the North West Adelaide Health Study between 2004 and 2006. Data of medication use were obtained from national dispensing data from Australia's Pharmaceutical Benefits Scheme¹⁶ linked to the North West Adelaide Health Study cohort. All medicines were coded using the Anatomical Therapeutic Chemical codes, and statin exposure was identified by use of C10AA or C10B (combination products).¹⁷

The comorbid conditions were identified using the validated pharmaceutical-based comorbidity index Rx-Risk-V (Australian adaptation).¹⁸ The following Anatomical Therapeutic Chemical codes were used to identify cardiovascular disease (codes C01-C03, C07, C08, and C09), diabetes (A10A and A10B), gout (M04), osteoporosis (M05B), and nonsteroidal anti-inflammatory drug use (M01A). A number of drug to drug pharmacokinetic interactions may interfere with statin metabolism and alter systemic bioavailability to potentially increase the risk of statin-associated myopathy.¹⁹ Concomitant medications that can interfere with statin metabolism and uptake via effects on cytochrome P450 (eg, CYP3A4 and CYP2D6), organic anion transporter proteins (eg, OATP1B1), and P-glycoprotein were examined.²⁰

To provide a quantification of statin use at the population level during the study period, monthly use of statins in Australia was examined from January 1, 2000, to December 31, 2014. Data were obtained from Medicare Australia Statistics²¹ for all statin prescriptions (codes C10AA and C10B). The total number of statin medications dispensed per month was calculated per population of 100 000 Australians by using population statistics obtained from the Australian Bureau of Statistics.²² This rate of dispensing statin medications was averaged across five 3-year cohorts: 2000 to 2002, 2003 to 2005, 2006 to 2008, 2009 to 2011, and 2012 to 2014.

Statistical Analysis

Descriptive analysis of characteristics of cases and controls were examined using unpaired and 2-tailed *t* tests and χ^2 tests for trend. The unadjusted and adjusted ORs and 95% CIs were calculated using the conditional logistic regression analysis for the risk of statin exposure associated with IIM. Covariates used in the multivariate model included diabetes and cardiovascular disease because these comorbid conditions are likely to be associated with statin use. Analyses were also conducted excluding cases of necrotizing myositis, as statins are reported to be associated with necrotizing myositis together with the presence of autoantibodies against HMG-CoA reductase.^{10,11} Given the changing use of statins worldwide during the study period,²³ a sensitivity analysis was also conducted that was limited to cases diagnosed within a 2-year period of the control patients. All analyses were conducted from June 1, 2016, to July 14, 2017, using SPSS, version 22 (SPSS Inc). A 2-sided *P* < .05 was set a priori to indicate statistical significance.

Results

A total of 221 cases were identified from the South Australian Myositis database^{12,13} that met the inclusion criteria. Demographic and clinical characteristics of the IIM cases and population-based controls matched for age and sex are given in **Table 1**. The mean (SD) age of the 221 cases was 62.2 (10.8) years and 132 (59.7%) were female, whereas the mean (SD) age of the 662 controls was 62.1 (10.7) years and 395 (59.7%) were female. Statin exposure at the time of diagnosis of IIM was 68 of 221 cases (30.8%; 95% CI, 24.7-36.9) and 142 of 662 matched controls (21.5%; 95% CI, 18.3-24.6) (*P* = .005). There were statistically significant differences between the cases and controls with respect to the comorbidities of diabetes (9 of 221 cases [4.1%] vs 11 of 662 controls [1.7%]; *P* = .04) and cardiovascular disease (52 cases [23.5%] vs 226 controls [34.1%]; *P* = .003).

Figure 1 shows the specific subtypes of IIM identified in the cohort and the prevalence of statin exposure in each of the groups. Polymyositis was the most common subtype of IIM with 89 cases (40.3%); of these, 27 (30.3%) were exposed to a

statin. Almost 66 cases (29.9%) had inclusion body myositis; of these, 20 (30.3%) were exposed to a statin. While only 24 cases (10.9%) were identified as necrotizing myositis, 12 (50.0%) of these were exposed to a statin. The only signifi-

cant difference observed between the type of IIM and the prevalence of statin exposure was between dermatomyositis (4 of 23 cases [17.4%]) and necrotizing myositis (12 of 24 cases [50.0%]) ($P = .02$).

Examination of the association of statin exposure with IIM, both unadjusted and adjusted, for the comorbidities of diabetes and cardiovascular disease is given in Table 2. There was an almost 2-fold (79%) increased likelihood of statin exposure in patients with IIM by comparison with controls (adjusted OR, 1.79; 95% CI, 1.23-2.60; $P = .001$). Similar results were observed when patients with necrotizing myositis were excluded from the analysis (adjusted OR, 1.92; 95% CI, 1.29-2.86; $P = .001$).

Seven patients with IIM were receiving concomitant medications known to affect statin pharmacokinetics through inhibition of the metabolism or transport of selected statins, resulting in increased drug exposure and an increased risk of myopathy. Four patients treated with atorvastatin calcium or simvastatin were coprescribed a CYP3A4 inhibitor, and 3 patients were exposed to OATP1B1 inhibitors.

There was an increase in the total number of cases of IIM and the proportion of patients with IIM exposed to statins between 2000 and 2014 (Figure 2). From 2000 to 2002, 1 of 18 patients (5.6%) with IIM was exposed to a statin, increasing to

Figure 1. Prevalence of Specific Types of Disease Among 221 Patients With Idiopathic Inflammatory Myositis in Southern Australia

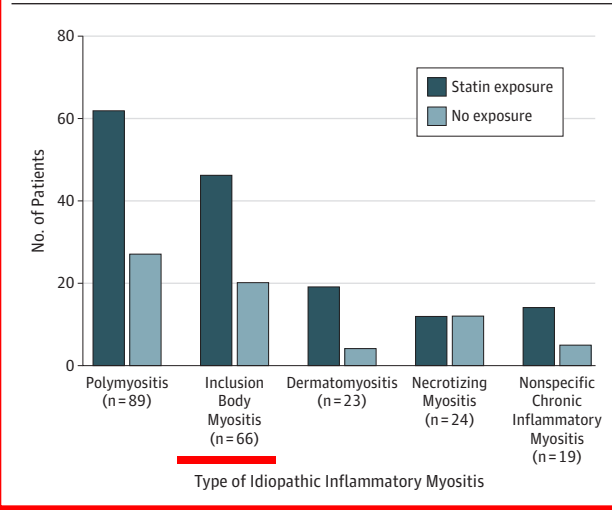


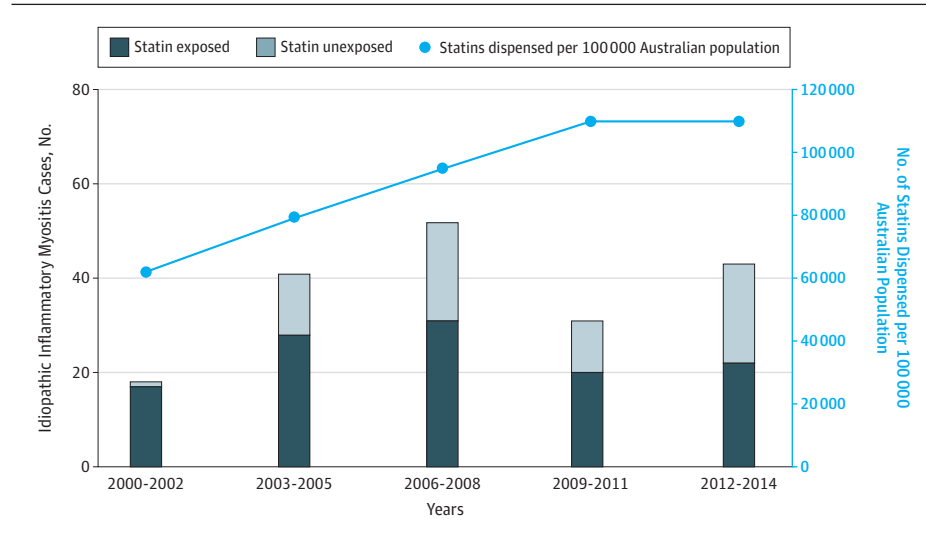
Table 2. Unadjusted and Adjusted OR (95% CI) for IIM With Statin Exposure Overall and Stratified by Time

Statin Exposure	Unadjusted		Adjusted ^a	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Statin exposure overall				
IIM (n = 221)	1.68 (1.18-2.40)	.002	1.79 (1.23-2.60)	.001
IIM excluding necrotizing myositis (n = 197)	1.78 (1.22-2.59)	.002	1.92 (1.29-2.86)	.001
Statin exposure stratified by ±2 y from controls				
IIM (n = 88)	1.92 (1.08-3.43)	.03	1.86 (1.02-3.38)	.04
IIM excluding necrotizing myositis (n = 79)	1.72 (0.89-3.29)	.10	1.89 (0.92-2.74)	.09

Abbreviations: IIM, idiopathic inflammatory myositis; OR, odds ratio.

^a Adjusted for diabetes and cardiovascular disease.

Figure 2. Idiopathic Inflammatory Myositis Cases, Proportion of Cases With Statin Exposure, and Rate of Dispensing Statin Medication in the Australian Population Between 2000 and 2014



21 of 43 (48.8%) from 2012 to 2014. An increase in the overall use of statins in the Australian population was observed during this period, with the number of statin medications dispensed increasing from 62 378 per 100 000 population from 2000 through 2002 to 109 922 per 100 000 from 2012 through 2014 (Figure 2).

The sensitivity analyses limiting the number of cases to within 2 years of the controls to account for background changes in population statin use during the study period are given in Table 2. The adjusted OR for IIM and statin exposure was 1.86 (95% CI, 1.02-3.38; $P = .04$). After excluding cases of necrotizing myositis from the analysis, the point estimate was similar, but the results were not statistically significant (adjusted OR, 1.89; 95% CI, 0.92-2.74; $P = .09$).

Discussion

This study's results indicate that patients with histologically confirmed IIM had a significantly increased likelihood of statin exposure compared with population-based matched controls. During the study period, there was an increase in the total number of patients diagnosed with IIM and an increase in the proportion of cases of patients exposed to a statin. While the incidence of IIM is rare (0.1 per 100 000 persons per year to 1.0 per 100 000 persons per year⁸) and statin-associated autoimmune myopathy even rarer (estimated 2 per 1 000 000 persons per year),²⁴ increasing use of statins at the population level, the severity of this condition, and the need for immunosuppressive treatment highlights the importance of early recognition of this disease. Recent guidelines have recommended statin use for between 15% and 44% of the population for primary prevention of cardiovascular disease, suggesting that exposure is likely to increase in the future.²⁵

Necrotizing myopathy is characterized by muscle fiber necrosis with minimal inflammation; a proportion of these cases have been shown to be due to an autoimmune cause and are associated with statin treatment.^{6,9} Exclusion of these specific cases from the analysis did not change our study findings. An increased risk of IIM with statin exposure remained (adjusted OR, 1.92; 95% CI, 1.29-2.86; $P = .001$) in the subsample when cases of necrotizing myositis were excluded, highlighting the potential association of all types of IIM with statin exposure. A recent study using patients from the South Australian Myositis Database¹³ showed the presence of HMG-CoA reductase antibodies in all subtypes of IIM, and these were strongly associated with statin exposure and HLA-DR11. While the overall prevalence of these antibodies is low (9%)¹³ and their presence is not restricted to patients with previous statin use,²⁴ these results support an association of statin exposure with all types of IIM. We were unable to examine the association of individual types of IIM with statin exposure because of small numbers. Further research focusing on the specific types of IIM is required to elucidate the potential association with disease development and previous statin exposure and the potential role of HMG-CoA reductase antibodies.

Statins first entered the market in Australia in 1990, and a marked increase in their use has been observed in the Australian population.²⁶ In 2015, atorvastatin and rosuvastatin calcium were the 2 most prescribed medicines in Australia, with rosuvastatin alone costing the Australian government \$203 million.²⁷ An increase in the proportion of patients with IIM who were exposed to statins was also observed in the present study, from 5.6% from 2000 through 2002 to 48.8% from 2012 to 2014. An increase in the annual incidence rate of IIM was reported from approximately 1.0 per 100 000 population to 1.6 per 100 000 population between 1990 and 2009.¹² It was postulated that the observed increase may be attributed to a number of factors, such as an increase in the number of biopsies performed, improvement of diagnosis, and awareness of the disease.¹² However, the observed increase in the incidence of IIM could also be genuine, and the large increase in statin use may be partly contributing to the increased incidence of IIM.

Limitations

Details of the type of statin, dosage, or duration of statin exposure were not available in our data. Examination of these medication-related factors will be important to further elucidate the association between statin exposure and IIM. However, we hypothesize that this is an idiosyncratic reaction restricted to a very small proportion of the population and would not expect a dose-response or exposure association. Potential pharmacokinetic drug interactions were identified in only a few of the cases, suggesting that these play a minor role. The differences in the medication data sources between the cases and controls may have influenced the results. Cases were obtained from self-reported medication use as recorded in the patient medical records, and the controls were obtained from nationwide prescription data, with the latter providing a complete medication history, potentially biasing the results toward the null hypothesis. However, a recent Australian study had reported that the positive predictive value for self-reported statin use was 97% (95% CI, 93.7%-98.7%) when compared with pharmacy dispensing data, which was used in the present study.²⁸ This may also have explained the lower prevalence of cardiovascular disease in the cases compared with the controls. However, adjustment for diabetes and cardiovascular disease in our analysis had little influence on the point estimate, suggesting no indication of confounding. Statin use has changed since the drug's introduction to clinical practice and the use of increasing doses and more potent statins.^{26,29} The timing of statin exposure and onset of IIM can vary considerably, with a median duration of 38 months of previous exposure to statin therapy before the onset of symptoms and the disease persisting even after cessation of the statin therapy.^{10,11} Furthermore, patients may have ceased statin therapy when muscle-related symptoms developed and may not have been taking the statin when they were diagnosed with IIM, potentially biasing the results toward the null hypothesis. Cases were identified during a 14-year period and increases in the use of statins during this period were observed. Matched controls were obtained from

2004 to 2006 only; therefore, their statin exposure was not representative of statin exposure for the entire period that cases were collected. A significant association was still observed between statin exposure and IIM in the sensitivity analysis limiting cases to within 2 years of matched controls. To our knowledge, our study is the first to use a large cohort of patients with histologically confirmed IIM based on well-validated criteria.

Conclusions

Statin exposure was significantly associated with histologically confirmed IIM. We cannot conclude a causative role from our observed association, but the findings highlight the need for further study. The potential risk of IIM should be considered in the assessment of risks and benefits of statin medications.

ARTICLE INFORMATION

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Author Contributions: Dr Caughey had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Caughey, Gabb, Ronson, Ward, Hill, Limaye.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Caughey, Gabb, Ronson, Limaye.

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Supervision: Caughey, Gabb, Ward, Limaye.

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Additional Information: The South Australian Myositis Database and North West Adelaide Health Study are ethics-approved databases collected with patients' consent. The manuscript was reviewed for scientific content and consistency of data interpretation by the chief investigators of the North West Adelaide Health Study.

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