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Statin use and risk of multiple myeloma: an analysis from the Cancer Research Network

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Abstract

Animal and human data suggest statins may be protective against developing multiple myeloma; however, findings may be biased by the interrelationship with lipid levels. We investigated the association between statin use and risk of multiple myeloma in a large US population, with an emphasis on accounting for this potential bias. We conducted a case-control study nested within 6 US integrated healthcare systems participating in the National Cancer Institute-funded Cancer Research Network. Adults aged ≥40 years who were diagnosed with multiple myeloma from 1998–2008 were identified through cancer registries (N=2532). For each case, 5 controls were matched on age, sex, health plan, and membership duration prior to diagnosis/index date. Statin prescriptions were ascertained from electronic pharmacy records. To address potential biases related to lipid levels and medication prescribing practices, multivariable marginal structural models were used to model statin use (≥6 cumulative months) and risk of multiple, with examination of multiple latency periods. Statin use 48–72 months prior to diagnosis/index date

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was associated with a suggestive 20–28% reduced risk of developing multiple myeloma, compared to non-users. Recent initiation of statins was not associated with myeloma risk (risk ratio range 0.90–0.99 with 0–36 months latency). Older patients had more consistent protective associations across all latency periods (risk ratio range 0.67–0.87). Our results suggest that the association between statin use and multiple myeloma risk may vary by exposure window and age. Future research is warranted to investigate the timing of statin use in relation to myeloma diagnosis.

Keywords

statin; multiple myeloma; marginal structural models; time-varying confounding

Introduction

Multiple myeloma is a rare malignancy of clonal plasma cells that originate in the bone marrow and normally secrete antibodies against foreign antigens.[1, 2] Despite substantial improvements in treatment since the early 2000s, multiple myeloma remains a lethal disease, with an overall 5-year survival rate of 48.5%.[3–5] The time between first appearance of symptoms and definitive diagnosis is often prolonged.[6] Known risk factors for multiple myeloma include obesity and other unmodifiable factors, such as being older age, male, and African-American.[7, 8] As a result, the need to identify modifiable risk factors, and particularly protective factors, remains a priority.

Epidemiological studies have suggested that statin use reduces the risk or recurrence of several cancer types,[9] including prostate cancer,[10–12] hepatocellular carcinoma,[13, 14] digestive cancers,[15, 16] and breast cancer,[17–20] although results have been inconclusive.[21] A recent meta-analysis of 20 hematological cancer studies suggests a protective association between statin use and hematological cancer risk overall, while a second meta-analysis of 14 studies observed a statistically significant 19% reduced risk of non-Hodgkin lymphoma and a non-significant 11% reduced risk of multiple myeloma.[22, 23] Few studies have examined an association with statin use and multiple myeloma specifically, and case numbers were generally small.[19, 23–25] Experimental evidence suggests that statins, which act via the mevalonate pathway, may halt growth and induce apoptosis in multiple myeloma cancer cells, although not all myeloma cell lines have been sensitive to statin-induced apoptosis.[26, 27] Existing evidence, while inconclusive, suggests that statin use may reduce the risk of multiple myeloma.[19, 23, 24, 28]

In addition, patients with multiple myeloma may have lower cholesterol levels than healthy controls,[29, 30] independent of statin use. However, to our knowledge, no epidemiological study of statins and hematological cancer has incorporated longitudinal serum cholesterol levels to account for this possible influence on statin prescribing practices. The objective of the present longitudinal study was to investigate the association between statin use and risk of multiple myeloma in a large, well-defined population with detailed pharmacy records and validated cancer registry data, by employing marginal structural modeling (MSM) to account for time-varying serum cholesterol measures as well as statin use. We also focused

on identifying the etiologically relevant exposure window for statin use by examining multiple latency periods.

Materials and Methods

Study population and data sources

This study was conducted as part of the Cancer Research Network, a National Cancer Institute-funded, nationwide consortium of research-oriented organizations affiliated with 14 non-profit integrated healthcare delivery systems, which provide comprehensive services to a defined population. In each system, medical charts and automated data systems document the characteristics and care of all enrollees. Together, the participating Cancer Research Network sites represent over 3.5% of the US population.[31, 32] Six health plans participated in the present analysis: Henry Ford Health System/Health Alliance Plan (Detroit, MI), and Kaiser Permanente (KP) in Washington (Seattle, WA), Colorado (Denver, CO), Georgia (Atlanta, GA), Northern California (Oakland, CA), and Southern California (Pasadena, CA). Members of the health plans have electronic data on diagnoses, procedures and laboratory results from clinical encounters as well as pharmacy use. Participating sites identify cancer cases through linkage to the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) Program or to a state tumor registry (KP Colorado). Data was accessed through the Cancer Research Network's Virtual Data Warehouse, a series of standardized variable definitions and data coding extracted from clinical and administrative sources and maintained at each site.

Study eligibility included age ≥40 years, continuous health plan enrollment with prescription drug benefits for at least 2 years, and no evidence of HIV infection or history of organ transplant. Individual members contributed person-time to the base population until the earliest date of cancer diagnosis or health plan disenrollment. We conducted a case-control study nested within this defined base population. This study was approved by the Institutional Review Board at Henry Ford Health System and all participating health systems.

Case and control selection—We identified all incident diagnoses of multiple myeloma and other plasma cell tumors (histology/morphology codes 9731–9734) during 1998–2008.

Up to 5 controls were selected per case, matched by age (2 year age-strata), sex, health plan/study site, and duration of continuous health plan membership at the date of diagnosis (2 year strata). Controls were assigned their matched case's diagnosis date as the index date, in order to give cases and controls the same period of health plan membership during which statin exposure was ascertained. Controls were selected via risk-set sampling without replacement. Controls who were later diagnosed with multiple myeloma were also included as cases and assigned their own set of controls.

Data collection—The observation period for each subject began at the date of continuous plan enrollment until the diagnosis/index date. Information regarding statin use (medication type, dates of prescription, and prescribed dose) was obtained for all participants from pharmacy databases; data were also collected on use of anion exchange resins, fibrates,

nicotinic acid, ezetimibe, and prescription non-steroidal anti-inflammatory drugs (NSAIDs). Laboratory results throughout the study period were obtained for total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) blood tests.

Statistical analysis

To evaluate the association between initiation of statin use and risk of multiple myeloma, the primary analysis used MSM to account for biases in the likelihood of prescribing statins, as well as statin use.[33, 34] Specifically, MSM allowed us to address potential bias due to lipid levels, which could be both a confounder of the statin-lymphoma association, as well as a result of statin exposure. In particular, in contrast to the more common approach to analyze case-control study data, where all exposures prior to the diagnosis/index data are collapsed together, MSM allows the timing of lipid level relative to the initiation of statin use (if any) to be taken into account. It should be noted that although MSM methods were developed for cohort study designs, they have been evaluated for application to case-control designs similar to ours.[35] A portion of the adaptation of MSM to the case-control design involved upweighting the controls to more accurately represent the larger population of persons without multiple myeloma.

MSM analysis

Person-period dataset: We constructed a person-period dataset for the MSM analysis in which time was represented in 30-day intervals ("person-month") for each individual. Observation time at each site began at the earliest date at which electronic records existed for both lipid measurements and statin prescription fills (1996 for KP Washington and KP Southern California; 1997 for Henry Ford Health System/Health Alliance Plan, KP Georgia and KP Northern California; and 2000 for KP Colorado). All individuals with ≥1 total cholesterol and HDL measurement during follow-up were included. Cases without lipid measurements were dropped from the analytic cohort along with their corresponding controls. Controls without lipid measurements were also dropped; however, cases were retained as long as at least 1 control remained.

Model construction—A participant was considered to be a statin user when they had 6 months of cumulative statin usage. Participants with <6 months of cumulative statin use were treated as unexposed. Separate models were fit with cumulative duration of statin use equal to ≥6, ≥12, ≥18 and ≥24 months. A 3-month run-in period was used to identify prevalent statin users, who were excluded, since the extent of their previous statin use could not be reliably ascertained. Thus all participants included in this analysis were assumed to begin the study as non-users of statins.

Propensity scores/inverse probability of treatment weights (IPTW)—Variables used to calculate the probability (or propensity) of statin initiation were sex, calendar year, log values of HDL and total cholesterol, and indicator variables for index year, age (10-year categories), study site, and histories of coronary heart disease, stroke, hypertension, diabetes, prescription NSAID use, and any autoimmune disease. Baseline variables (e.g., sex and medical history) were based on information reported at the earliest available date. Time-varying variables (up until the diagnosis or index date) for HDL, LDL, and total cholesterol

were created for each month of follow-up, and the last observation was carried forward and assumed to be constant. Due to missing data, LDL was excluded from final models. To calculate the stabilized weight ratios for use in MSM, logistic regression models were constructed among the controls only to model statin use in approximation of a discrete time survival model.[36] The resulting model parameters were then used to estimate the probability ratio among the cases.

Using discrete time survival modeling, the person-period dataset was used to assess the association of statins with multiple myeloma risk.[36] MSM addresses confounding using the propensity for statin use to compute inverse probability of treatment weights (IPTW). We computed the CIs about the risk ratios using robust standard errors. For primary results, the stabilized IPTW were truncated at the first and 99th percentiles.[37] In sensitivity analyses, we examined the impact of truncating weights at the third and 97th or fifth and 95th percentiles, but the results did not change substantially. Therefore, we retained minimal truncation to maximize the estimates' stability. Models were adjusted for matching factors, as well as history of coronary heart disease, stroke, hypertension, diabetes, and time-varying serum HDL and total cholesterol levels. Since serum cholesterol levels have been observed to decrease closer in time to clinical diagnosis of multiple myeloma (Alford SH, Havstad S, Chao C, Habel LA, Janakiraman N, Wang Y, et al., unpublished data), the MSM models incorporated time-varying serum cholesterol measurements to adjust for potential time-varying confounding by cholesterol levels. It should be noted that although some covariables were included in both the computation of IPTW and the modeling stages, statin exposure is only present as a term in the final model.

To examine possible modification of the association between statin use and multiple myeloma, additional analyses stratified the models separately by gender and age group (<70 vs ≥70 years). All tests of statistical significance were two-sided.

Sensitivity analyses—Since multiple myeloma may be biologically present prior to a definitive diagnosis,[6, 38] we performed sensitivity analyses with the diagnosis/index date shifted earlier in time by 12, 24, 36, 48, 60 or 72 months ("latency" analysis) to minimize the impact of subclinical disease that is present but undiagnosed. In these analyses, we ignored data collected after this revised diagnosis/index date.

MSM and IPTW approaches constrained how readily multilevel statin exposure could be characterized in the MSM models. To provide a comparison to other common analytic approaches, 2 secondary analyses were performed for comparison. We first employed a survival model similar to MSM, with time-varying statin exposure and covariates, but without IPTW. The second analysis used multivariable conditional logistic regression (CLR) models with all pre-diagnosis/index date data collapsed as fixed covariates (Supplementary Methods); by design, these models did not incorporate time-varying confounders. These sensitivity analyses helped to interpret the more complex potential confounding relationship between lipid levels, statin use and multiple myeloma. In the CLR models, statin use was categorized as never use or current use (80% of prescriptions filled: <6 months, 6–12 months, 12–24 months, or >24 months prior to the diagnosis/index date).

Results

In our study population, we identified 3134 incident cases of multiple myeloma across 6 participating study sites, and 12,725 matched controls meeting eligibility criteria; after excluding participants missing lipid measurements (374 cases and 2124 controls) and with prior statin exposure (187 cases and 796 controls), or no matched control (41 cases), the final analysis included 2532 cases (82%) and 9805 controls (77%). The subjects without lipid measurements were slightly younger (mean age 66 vs. 68) and less likely to have documented comorbidities (for example, only 8% of subjects with hypertension lacked lipid values, versus 25% of those without hypertension). Participants were enrolled in their health care plans for an average of 71 months, and 54% of the population was male (Table 1). Twenty-five percent of cases and 28% of controls used statins for a cumulative ≥6 months ($p = 0.01$). Cases had lower average serum cholesterol levels (total, HDL and LDL) compared to controls ($p < 0.001$). On average, cases reported 12.3 months of statin use over the study period, compared to 13.7 months of statin use for controls ($p=0.01$). Thirty-four percent of eligible subjects (4174/12,337) had at least 1 statin prescription. Of the 4174 statin users, 368 (8.8%) started statin use so late in their observation period that they could not have met the criterion set for statin exposure prior to the index/diagnosis date. Another 334 (8.0%) statin users quit use within 6 months of initiation, and 375 (9.0%) quit later, but 3097 (74.2%) continued to use statins (defined as having a prescription or statin medication on hand) on the index/diagnosis date.

We did not observe a consistently significant association between statin use and risk of multiple myeloma in multivariable MSM analysis incorporating up to 48 months of latency time. However, a suggestive protective association was evident with a latency period of 60–72 months, suggesting a possible impact on early subclinical disease only (Table 2). Risk ratios ranged from 0.99 (95% CI: 0.83, 1.18; 12 months latency time, N cases = 2155) to 0.72 (95% CI: 0.53, 0.97; 60 months latency time, N cases = 1142).

The association between statin use and multiple myeloma risk varied somewhat by age at diagnosis/index date in the MSM analysis (Table 3). When models were stratified by age (<70 vs ≥70 years), the protective association between statin use and multiple myeloma risk was more consistent among older patients, regardless of any latency period considered (risk ratio range 0.67–0.87 for ≥70 years old vs risk ratio range 0.69–1.19 for <70 years old group; p interaction range 0.003–0.95). With shorter latency periods, the association between statin use and multiple myeloma risk was positive, yet not statistically significant, among younger participants only.

In analyses stratified by gender, we observed a similar general pattern of decreasing risk with increasing latency time, which was slightly more pronounced among males (Table 3; p interaction range 0.22–0.98). Associations for males were likely slightly more protective due to larger case numbers and increased precision. Taken together, all models showed protective, yet imprecise, associations with statin use with additional latency time; however, case numbers were reduced in each time period, and confidence intervals were wide.

Sensitivity analyses incorporating survival models without IPTW showed associations between statin use and multiple myeloma risk similar in magnitude and significance to the MSM with IPTW (Supplementary Tables 1 and 2). Sensitivity analyses using CLR showed protective associations between statin use and multiple myeloma risk with longer duration of current statin use (≥12 months of use) appearing more protective (Supplementary Tables 3A–3E). Point estimates from the CLR analysis indicated a more protective association between long-term statin use and multiple myeloma risk than the results of the MSM analysis.

Discussion

Statins are among the most commonly prescribed medications in the United States,[39] with 50% of men and 36% of women aged 65–74 years in 2005–2008 reporting statin use during the past month.[40] Recently, epidemiological studies have investigated possible associations between statin use and cancer risk; however, results have varied by cancer type and have largely been inconsistent.[41] To our knowledge, ours is the largest study to date of multiple myeloma risk associated with statin use, and one of the few to consider exposure years before diagnosis. In this case-control study nested within a population of integrated health plan patients with longitudinal assessment of statin use, we observed a suggestive protective association between statin use and risk of multiple myeloma for individuals exposed to statins at least 60 months prior to diagnosis/index date. The stronger protective associations observed with longer latency periods suggest the protective role of statins may be against early stages of the carcinogenic process. Initiation of statin use in the years just prior to diagnosis did not appear associated with decreased risk of developing multiple myeloma, perhaps because the disease was already biologically present. These associations did not vary significantly by gender and appeared more consistently protective among older patients.

A recent meta-analysis of 20 studies saw a statistically significant 19% reduction in hematological cancer incidence associated with statin use,[23] but data for multiple myeloma were imprecise (risk ratio: 0.86, 95% CI: 0.19, 4.0) and no adjustment for cholesterol levels was conducted in the original studies. A Japanese case-control study observed a higher frequency of statin use in patients with lymphoid malignancy (lymphoma and myeloma) compared to control patient groups,[25] while a small US case-control study found a reduced risk of multiple myeloma for women using statins for at least 6 months 1 year prior to diagnosis/index date (odds ratio: 0.4, 95% CI: 0.2–0.8).[28] A larger European case-control study also saw a protective association between statin use and multiple myeloma risk (odds ratio: 0.47, 95% CI: 0.22, 0.99), although there were few statin users.[24] Statin use was also associated with decreased overall and disease-specific mortality in a cohort of US veterans with multiple myeloma.[42]

Existing experimental evidence supports a protective relationship between statins, which inhibit the enzyme HMG-CoA reductase, and multiple myeloma. Malignant myeloma cell lines exposed to statins have increased rates of cell death and inhibition of proliferation,[26, 27, 43] and the mevalonate pathway, on which statins act, may trigger apoptosis.[26, 44] In addition, patients with relapsed or refractory multiple myeloma treated with a combination of thalidomide, dexamethasone and lovastatin experienced longer overall

and disease-specific survival compared to patients not receiving lovastatin in a randomized trial.[45] Taken together, the epidemiological and experimental evidence supports a protective role for statins against the development of multiple myeloma.

In our study, myeloma diagnoses were validated through tumor registries, including the NCI SEER Program and state registries. Although diagnoses made out of state could have been missed, since myeloma is a rare cancer, we believe the number of missed diagnoses is small. Comorbid conditions, including autoimmune diseases, were identified objectively by International Classification of Diseases, Ninth Revision, codes from electronic medical encounter data, and serum cholesterol measurements were taken directly from laboratory data. However, covariates were restricted to those available from automated data sources, and some information may have been missed, although we expect the amount of missing data to be small and non-differential between cases and controls or by exposure status. To minimize the amount of missing data, each study site began contributing observation time only when both statin prescription fills and serum cholesterol measurements were available in their Virtual Data Warehouse electronic databases. Due to differences in data collected at each study site, we did not have sufficient data on body mass index from all sites to include in our multivariable models, and we cannot exclude the possibility of unmeasured confounding by this factor. However, statins are more commonly prescribed among overweight and obese patients,[46] and therefore, the inverse association observed in this study between statin prescription and multiple myeloma incidence should be a conservative estimate of the association that would be observed if body mass index could have been adjusted for in the analysis.

We ascertained statin use through pharmacy records, which minimizes the possibility of recall bias seen in case-control studies. However, pharmacy records allow us to assess the number of statin prescriptions that were filled by a study participant, not actual use. It is possible that participants had additional prescription drug coverage that did not show up in our electronic database, or that some prescriptions may have been missed, although we expect this to account for a very small number of total prescriptions, since all participants had drug coverage as part of their health plan. As such, exposure misclassification may be possible, but unlikely to vary by case status. Since the majority of health plan members remain with their health plan for many years,[47] we were able to assess longitudinal use of statins and investigate the association with multiple myeloma risk over time. This study also incorporated longitudinal and time-updated measures of potential confounders, including serum cholesterol levels that, to our knowledge, had not been accounted for in previous research.

Since the probability of being prescribed a statin is dependent on other factors, such as diabetes, coronary heart disease, and cholesterol level, we utilized MSM for our primary analysis. IPTW allowed us to estimate the probability of statin initiation between baseline and diagnosis/index date, and also to adjust for baseline and time-varying covariates. Following the initiator/new-user approach to MSM, we attempted to reduce the bias resulting from prevalent use of statins, as prevalent users may be considered “survivors” at lower risk for more severe outcomes. Despite the possibility of unmeasured confounding affecting a small percentage of study participants, we do not believe this disqualifies our

analysis from the assumption of exchangeability. If this assumption does not hold, our results may be subject to bias.

Observed differences between the primary analysis (MSM) and sensitivity analyses (particularly CLR) suggest that the impact of time-varying confounding by serum cholesterol or comorbid conditions may play a role in interpreting the association between statin use and risk of multiple myeloma. However, results of the MSM analysis were nearly identical to those of survival models without IPTW, demonstrating an overall consistency of associations between modeling techniques, and a more robust estimate of the association between statin use and risk of multiple myeloma.

Members of the 6 geographically and demographically diverse Cancer Research Network sites included in this study are likely representative of the insured US population during the study period. As individuals without health insurance may be less likely to receive statin therapy, we believe the results of this study are generalizable to the insured adult US population.

In conclusion, our study supports a protective association between statin use and multiple myeloma risk after adjusting for serum cholesterol levels. This association is most evident in individuals with 48 months or more between initiation of statin use and diagnosis/index date, as well as in older patients regardless of latency period. Since few previous studies have investigated longer-term statin exposure in relation to multiple myeloma risk, these interesting findings merit replication in other populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest: The co-authors of this manuscript have no conflicts of interest to report.

Abbreviations used

CLR	conditional logistic regression
HDL	high-density lipoprotein
IPTW	inverse probability of treatment weighting
KP	Kaiser Permanente
SEER	Surveillance, Epidemiology, and End Results Program

LDL	low-density lipoprotein
MSM	marginal structural models
NSAID	non-steroidal anti-inflammatory drugs

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Novelty and Impact

The association between statin use and risk of multiple myeloma was examined in a large, well-defined population with detailed pharmacy records and validated cancer registry data. Using multivariable marginal structural models to address potential biases related to serum lipid levels and statin prescribing practices, we observed a protective association between statin use and myeloma risk that varied substantially by exposure window.

Table 1

Characteristics of multiple myeloma cases and matched controls derived from 6 US health plans, 1998–2008

Variable	Cases (N=2,532)	Controls (N=9,805)	p-value[1]
Age in years, Mean ± SD	68.0 ± 11.0	67.3 ± 10.9	0.004
Age in years, N (%)			0.07
40–49	119 (5%)	484 (5%)	
50–59	438 (18%)	1752 (19%)	
60–69	728 (30%)	3037 (32%)	
70–79	774 (32%)	2764 (29%)	
80–89	348 (14%)	1240 (13%)	
≥90	35 (1%)	117 (1%)	
Index/diagnosis year			<0.001
1998–2001	574 (24%)	1895 (20%)	
2002–2005	1034 (42%)	4025 (43%)	
2006–2008	834 (34%)	3474 (37%)	
Study Site			0.29
Henry Ford Health System/Health Alliance Plan	66 (3%)	221 (2%)	
Kaiser Permanente (KP) Washington	131 (5%)	449 (5%)	
KP Colorado	116 (5%)	392 (4%)	
KP Georgia	41 (2%)	142 (2%)	
KP Northern California	960 (39%)	3650 (39%)	
KP Southern California	1128 (46%)	4540 (48%)	
Gender			0.27
Female	1104 (45%)	4365 (46%)	
Male	1338 (55%)	5029 (54%)	
Cumulative statin use			0.01
≥6 months	636 (25%)	2773 (28%)	
<6 months	162 (6%)	603 (6%)	
None	1734 (68%)	6429 (66%)	
Coronary heart disease[2]			0.33
Yes	134 (5%)	565 (6%)	
No	2308 (95%)	8829 (94%)	
Hypertension			<0.001
Yes	907 (37%)	3005 (32%)	
No	1535 (63%)	6389 (68%)	
Diabetes			0.93
Yes	294 (12%)	1137 (12%)	
No	2148 (88%)	8257 (88%)	
Prescription NSAID use			0.34
Yes	880 (36%)	3287 (35%)	
No	1562 (64%)	6107 (65%)	
Any diagnosed autoimmune disease[3]			0.92

Variable	Cases (N=2,532)	Controls (N=9,805)	p-value[1]
Yes	20 (1%)	79 (1%)	
No	2422 (99%)	9315 (99%)	
Months of observation time,[4] Mean ± SD	68.9 ± 38.0	72.0 ± 38.5	<.001
Total cholesterol, Mean ± SD	179.7 ± 48.9	202.1 ± 41.2	<0.001
HDL, Mean ± SD	46.2 ± 16.5	52.4 ± 16.0	<0.001
LDL,[5] Mean ± SD	104.7 ± 39.0	119.3 ± 34.7	<0.001

HDL: high density lipoprotein; KP: Kaiser Permanente; LDL: low density lipoprotein; NSAID: non-steroidal anti-inflammatory drug; SD: standard deviation

[1] p-values from t-tests (continuous variables) or chi-square tests (categorical variables)

[2] Coronary heart disease, hypertension, and diabetes defined by diagnosis codes from the International Classification of Diseases, Ninth Revision

[3] Defined by diagnosis codes from the International Classification of Diseases, Ninth Revision, for rheumatoid arthritis, systemic lupus erythematous, and Sjögren's syndrome

[4] Observation time calculated from time of study entry to diagnosis/index date

[5] Due to missing data, there are 12,516 people in the total population (2423 cases and 10,093 controls) with LDL data

Table 2

Association between ≥6 months of statin use and risk of multiple myeloma, excluding the first 3 months of observation time and incorporating varying latency periods

Latency period, months	N cases	Risk Ratio (95% CI)[1]
0	2292	0.96 (0.81, 1.14)
12	2155	0.99 (0.83, 1.18)
24	1935	0.91 (0.75, 1.10)
36[2]	1631	0.90 (0.73, 1.12)
48[2]	1365	0.80 (0.62, 1.03)
60[3]	1142	0.72 (0.53, 0.97)
72[4]	914	0.79 (0.55, 1.14)

[1] Risk Ratios from marginal structural models adjusted for age, index year, study site, gender, and time-updated coronary heart disease, hypertension, diabetes, non-steroidal anti-inflammatory drug use, diagnosed autoimmune disease, log (serum total cholesterol) and log (serum high-density lipoprotein) levels

[2] Index years 1998–2000 combined in models

[3] Index years 1998–2001 combined in models

[4] Index years 1998–2003 combined in models

Table 3

Association between statin use and risk of multiple myeloma by age group and gender, excluding the first 3 months of observation time and incorporating varying latency periods

Latency period, months	N cases	Risk Ratio (95% CI)[1]	P interaction
	Age <70 years		
0	1215	1.19 (0.94, 1.51)	
12	1132	1.18 (0.92, 1.51)	
24	1006	1.07 (0.81, 1.41)	
36[2]	827	1.04 (0.76, 1.42)	
48[2]	663	0.95 (0.66, 1.38)	
60[3]	555	0.69 (0.43, 1.12)	
72[4]	437	0.73 (0.41, 1.30)	
	Age ≥70 years		
0	1077	0.73 (0.57, 0.94)	0.006
12	1023	0.81 (0.63, 1.04)	0.04
24	929	0.76 (0.58, 0.99)	0.08
36[2]	804	0.78 (0.58, 1.05)	0.19
48[2]	702	0.67 (0.48, 0.94)	0.18
60[3]	587	0.71 (0.48, 1.05)	0.95
72[4]	477	0.87 (0.53, 1.40)	0.66
	Males		
0	1253	0.97 (0.77, 1.24)	
12	1186	1.02 (0.80, 1.29)	
24	1066	0.97 (0.75, 1.25)	
36[2]	894	0.85 (0.63, 1.14)	
48[2]	746	0.69 (0.50, 0.97)	
60[3]	614	0.62 (0.42, 0.93)	
72[4]	493	0.70 (0.43, 1.14)	
	Females		
0	1039	0.97 (0.76, 1.24)	0.98
12	969	0.97 (0.75, 1.26)	0.81
24	869	0.85 (0.64, 1.13)	0.52
36[2]	737	0.97 (0.71, 1.32)	0.55
48[2]	619	0.95 (0.66, 1.38)	0.22
60[3]	528	0.80 (0.51, 1.26)	0.42
72[4]	421	0.84 (0.49, 1.44)	0.62

[1] Risk Ratios from marginal structural models adjusted for age, index year, study site, gender, and time-updated coronary heart disease, hypertension, diabetes, non-steroidal anti-inflammatory drug use, diagnosed autoimmune disease, log(serum total cholesterol) and log (serum high-density lipoprotein) levels

[2] Index years 1998–2000 combined in models

[3] Index years 1998–2001 combined in models

[4] Index years 1998–2003 combined in models