RESEARCH ARTICLE

Duration of Current Statin Use and Amyotrophic Lateral Sclerosis Risk

A Norwegian Population-Based Cohort Study

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Abstract

Background and Objectives

Although hypercholesterolemia may contribute to long-term amyotrophic lateral sclerosis (ALS) risk, it can also seem as a secondary effect during the early, prediagnostic phase of the disease. We aimed to investigate the relationship between short-term and long-term use of statins and subsequent ALS risk.

Methods

We designed a cohort study where information on cardiovascular risk factors among Norwegian participants in large population-based health surveys was linked to nationwide administrative data on subsequent statin use and ALS diagnosis. Duration of statin use was calculated based on cumulative defined daily doses and analyzed as time-varying exposure with 3 levels: 0–1 year (short-term), 1–5 years, and 5–17 years (long-term). In Cox regression models adjusted for sex, age, health survey participation, triglyceride and cholesterol levels, body mass index, smoking, diabetes, and hypertension, we calculated hazard ratios (HRs) for ALS according to time-varying statin exposure. In a negative control analysis, we examined whether exposure to renin-angiotensin system (RAS)–acting agents was associated with ALS risk.

Results

A total of 425,564 participants (54% women), aged 40–65 years in January 2005, were followed for a mean period of 16 years (SD 2.3) during which 493 ALS cases (44% women) were identified. Compared with no current statin use, the HR for ALS was 3.56 (95% CI 2.58–4.90) for those with 0–1 year, 0.85 (95% CI 0.59–1.23) for those with 1–5 years, and 0.67 (95% CI 0.45–1.00) for those with 5–17 years of current use. The associations between both short-term and long-term statin use and ALS risk were most evident in men, with HRs for ALS of 4.03 (95% CI 2.72–5.95) and 0.47 (95% CI 0.26–0.86), respectively. There was no clear association between either short-term or long-term use of RAS-acting agents and ALS risk.

Discussion

The strong association between short-term current statin use and increased ALS risk is consistent with reverse causality, where statin initiation in the prediagnostic phase may occur when lipid levels rise and individuals seek medical attention due to emerging ALS symptoms. Long-term statin use was associated with reduced risk of ALS in men.

Introduction

Dysregulation of lipid metabolism may play a role in the pathogenesis of amyotrophic lateral sclerosis (ALS). Some, but not all, large-scale cohort studies have shown that elevated circulating levels of low-density lipoprotein cholesterol (LDL-c), as well as high apoB and apoB: apoA ratios, measured long before ALS diagnosis are associated with increased ALS risk.[1-4] Findings from Mendelian randomization analyses further suggest causal relationships between

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Glossary

ALS = amyotrophic lateral sclerosis; **ATC** = Anatomical Therapeutic Chemical; **BMI** = body mass index; **DDD** = defined daily dose; **HR** = hazard ratio; **ICD-10** = International Classification of Diseases, 10th Revision; **LDL-c** = low-density lipoprotein cholesterol; **NorPD** = Norwegian Prescribed Drug Registry; **NPR** = Norwegian Patient Registry; **RAS** = renin-angiotensin system.

this lipid profile and ALS.[5,6] Statins are competitive inhibitors of hydroxymethylglutaryl-coenzyme A reductase, the rate-limiting enzyme in cholesterol biosynthesis and other isoprenoids, and are widely used for primary and secondary prevention of myocardial infarction and ischemic stroke.[7] In addition to their cholesterol-lowering effects, statins have been suggested neuroprotective by other mechanisms of action, such as control of microglial activation and neuroinflammation.[8] Thus, these drugs could affect mechanisms relevant to the development of ALS.

Several studies have explored whether statin use is associated with ALS risk, but the results have been inconsistent. Although some observational[9,10] and Mendelian randomization studies[6,11] reported a decreased risk among statins users, others found no association[12,13] or even an increased risk of ALS after statin use.[14-16] There are several possible explanations for these discrepant results. Mendelian randomization studies are prone to bias due to their use of prevalent populations to infer risk.[17] The prodromal phase in ALS could last several years, and the temporal relationship between triglycerides, total cholesterol, and ALS risk suggests that levels of these lipid biomarkers increase as a consequence of ALS.[2] The increased rates of statin initiation observed in the years before ALS diagnosis[14] could therefore reflect health-seeking behavior and early disease signs. In addition, pharmacoepidemiologic studies are prone to confounding by indication, where factors influencing drug prescription may also be associated with the disease state. For instance, an elevated body mass index (BMI) is associated with both a reduced risk of ALS[18] and an increased likelihood of being prescribed statins.[19] Therefore, it is critical to account for background risks before statin initiation, but this has typically not been fully accounted for in former studies.

In this study, using a large cohort where information on cholesterol levels, blood pressure, BMI, diabetes, and smoking behavior was collected before statin initiation, we aimed to investigate the association between short-term and long-term current use of statins and the subsequent ALS risk.

Methods

Setting and Study Population

The study population included Norwegian citizens who took part in population-based regional health surveys. The Age 40 program, conducted between 1985 and 1999, targeted individuals aged 40 to 45 across all counties in Norway, except for Oslo. A total of 417,098 people participated, with a mean attendance rate of 69%.[20] In addition, the combined Cohort of Norway, established from 1994 to 2003, collected standardized health data and blood samples through 10 regional health surveys, involving 173,236 individuals and an overall attendance rate of 58%.[21] Each health survey included a questionnaire that gathered information on morbidity and lifestyle, such as smoking and alcohol habits. Trained personnel conducted a physical examination, which involved objective measurements of height, weight, heart rate, and blood pressure. A nonfasting blood sample was also analyzed for circulating levels of triglycerides, total cholesterol, and glucose. From these surveys, we collected data on sex, year and month of birth, year and month of screening, height and weight, blood pressure, levels of triglycerides and total cholesterol, and self-reported information on statin use, diabetes, myocardial infarction, stroke, and smoking status.

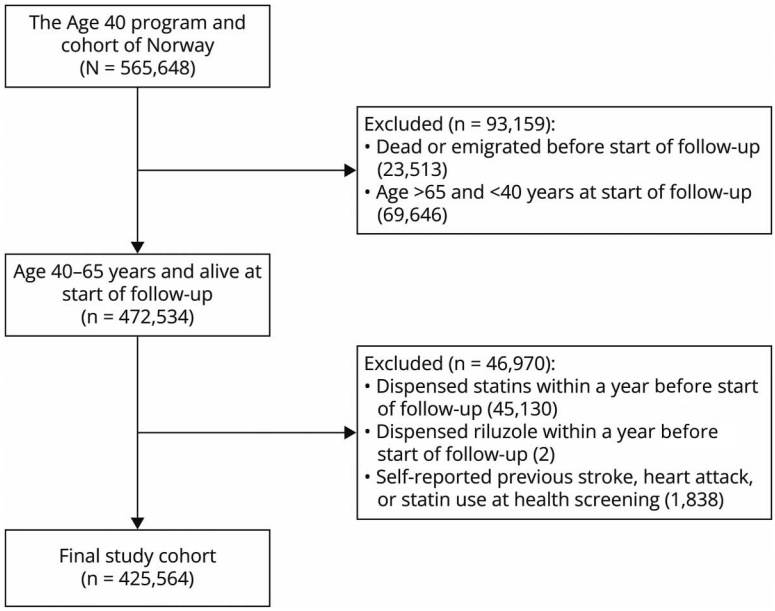
To minimize confounding by age and period, we restricted cohort participants to those aged 40–65 years at the start of follow-up. Data were linked to the Norwegian Prescribed Drug Registry (NorPD) to obtain information on prescriptions between the years 2004 and 2021. NorPD was established in 2004 and includes complete information on all prescriptions filled at all pharmacies in Norway, including Anatomical Therapeutic Chemical (ATC) codes. To correctly calculate duration of statin exposure, we aimed to include only incident users. We therefore both excluded those having dispensed statins in the year before the start of follow-up (January 1, 2005) and those reporting statin use, stroke, or heart attack at the time of the health survey. Ultimately, we excluded those having filled prescriptions for riluzole (ALS therapeutic offered to almost all patients with ALS in Norway since the late 1990s) before the start of follow-up (Figure 1).

Vital status and emigration for all cohort participants were collected from The National Population Registry. Norway provides government-funded universal health care, and a unique personal identifier assigned to every citizen enables linkage across health and administrative registries.

Case Ascertainment

We used 3 nationwide registries to ascertain ALS. We obtained data on all riluzole prescriptions (ATC code N07XX02) from NorPD for the period spanning January 1, 2004, to July 31, 2021. The Norwegian Patient Registry (NPR) serves as an administrative health register for all inpatient and outpatient admissions at Norwegian hospitals and

Figure 1 Selection of Participants



public-reimbursed private practice specialists. Individual patient data have been available since March 1, 2007, and include electronically registered admission dates and discharge diagnoses based on the International Classification of Diseases, 10th Revision (ICD-10). We specifically collected data on all entries with ICD-10 code G12.2 (ALS) from January 1, 2008, to July 31, 2021. Furthermore, the Norwegian Cause of Death Registry compiles and processes all death certificates, providing digitalized data on the direct, contributing, and underlying causes of all deaths in Norway since 1951, with ICD-10 coding starting in 1996. We gathered data for all individuals who died between December 31, 2004, and December 31, 2020, who had ICD-10 code G12.2 listed as a cause of death at any level on their death certificates.

To be classified as an incident ALS case, we required either a minimum of 1 entry in at least 2 different registries, or 2 entries in NPR. Date of first riluzole dispense in NorPD or first ALS-code in NPR entry was set as incidence date, whichever came first. We have previously shown that of 182 deceased patients with ALS confirmed through hospital file review, 174 (96%) were retrieved in the Norwegian Cause of Death Registry.[22] Furthermore, of 375 patients coded with ALS at hospitals, only 12 (3%) were both misclassified and coded with ALS twice or more.[23]

Exposure

We incorporated data on all dispensed prescriptions of statins classified under ATC codes beginning with C10AA from 2004 until the conclusion of the follow-up period. The quantity of the drug dispensed was reported as the number of defined daily doses (DDDs), which represents the assumed average daily maintenance dose for a medication used for its primary indication in adult populations.[24] Given the variability in the types of statins prescribed both among different individuals and within the same individual over time, we used DDDs to establish a standardized measurement unit that facilitates comparative analysis across various statin formulations.

We allowed current exposure to statins (exposed/not exposed) to vary over time. The date of filling the first prescription was set as start of exposure. Each exposed individual was assigned an end of exposure according to the cumulative amount of DDDs dispensed, without accounting for interruptions in exposure. We added 1 year to this date to accommodate for a grace period, after which they were again considered unexposed. The grace period serves the purpose of both allowing for minor irregularities in the dispensing pattern and taking into account the typical prodromal phase before ALS diagnosis in which individuals might change their medication use patterns.

Risk of ALS by duration of current treatment was further investigated in 3 stages: 1–365 DDDs, 366–1,825 DDDs, and >1,825 DDDs. Although DDDs do not precisely align with days of use, the cut off points will roughly correspond to 0–1, >1–5, and >5 years of treatment, which is the unit of duration we will use throughout in the remainder of the article. Each individual's treatment duration was time-dependent and was updated if they either continued or reinitiated the treatment.

Covariates

To minimize possible confounding from factors associated with both statin initiation and ALS risk, we included a range of covariates in addition to age (continuous) and sex. Thus, from

the health surveys, we added BMI (weight/height^2) (continuous), circulating levels of triglycerides and total cholesterol (mmol/L) (continuous), health survey (categorical), current smoker status (yes/no), diabetes (not differentiating between type 1 and type 2, yes/no), and hypertension (yes/no). We constructed the categorical hypertension-covariate by first calculating mean blood pressure from the last 2 of 3 measurements. We then defined hypertension as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg.

Statistical Analyses

The start of follow-up was set to January 1, 2005. Each person was followed until ALS onset, death, emigration, or July 31, 2021, whichever occurred first. We cross-tabulated the distribution of patient characteristics by statin ever/never user separately for men and women. In both current nonusers, users, and subgroups of different durations of use, we calculated the number of person years, ALS events, and incidence rates. Cox regression analysis with statin use modeled as a time-dependent variable was used to calculate hazard ratios (HRs) for ALS. Time (years) since start of follow-up was used as the timescale. In a basic model, we included age at the start of follow-up and sex as covariates. In our fully adjusted model, we additionally included BMI, circulating levels of triglycerides and total cholesterol, smoking status, diabetes, and hypertension at time of the health survey. In addition, we adjusted for health survey. Results were presented for both sexes combined and separately for men and women. Using no current statin use as reference, we calculated HR for ALS for both any duration of current statin use, and for 0–1, >1–5, and >5–17 years of duration. Effect modification by age and cholesterol levels was tested using a likelihood ratio test between the basic model and a model including an interaction term between statin use duration categories and age (continuous) and cholesterol level (continuous), respectively. We also fitted a Fine-Gray model specified in the same way as the Cox model, to assess the effect of competing risk.

To address the possibility that prodromal ALS and health seeking behavior in the year leading up to diagnoses could lead to statin initiation (protopathic bias), we first plotted the statin initiation proportions in patients with ALS for each year before diagnosis, by dividing the number of statin initiators on the number still "at risk" of initiating statins. Next, we implemented a lag time analysis, where the exposure status at a given time point was replaced with the exposure status from 1 year earlier.

Sensitivity Analyses

We performed 3 sensitivity analyses. First, we extended the period between when the drug was last dispensed and the time when individuals were again considered unexposed (grace period) to 2 years. Second, we restricted the case definition to those identified with a minimum of 1 riluzole prescription. Riluzole is typically offered to most patients with ALS in Norway; however, a cross-validation study of different registries in Norway indicated that only about 75% of all patients with ALS can be ascertained from riluzole prescription only.[23] Still, NorPD was operative throughout the entire follow-up period, and riluzole availability and reimbursement practice have not changed during follow-up. Therefore, any temporal ascertainment bias from our main case definition should be detected in this sensitivity analysis. Third, we modeled the duration of statin exposure as days from the first filled statin prescription to the last, disregarding cumulative DDDs. When using cumulative DDDs as the basis of exposure time, different medication dosages are taken into account. However, calculated cumulative DDDs may not always reflect the actual time under exposure.

Negative Control Analysis

Statin users may differ from nonusers in health-seeking behavior and unmeasured cardiovascular factors, which could also relate to the likelihood of being diagnosed with ALS. In addition, a temporal increase in both statin prescription practice[25] and ALS mortality[22] could confound our results. To address these possibilities, we performed an additional analysis using renin-angiotensin system (RAS)–acting agents as the exposure. RAS-acting agents include angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, and direct renin inhibitors, and they are another type of cardiovascular preventive drug with no presumed effects on ALS risk. Users of RAS-acting agents likely have similar health-seeking behavior to statin users, and these medications have, like statins, been increasingly prescribed throughout the follow-up period. The use of RAS-acting agents was defined as drug dispensation with ATC codes C09A, C09B, C09C, or C09D. We modeled this analysis in the same manner as for statin users.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the regional ethics committee (REC South East reference number 2016/1731). All participants signed informed consent at the time of screening.

Data Availability

The authors do not have permission to share pseudonymized data, according to Norwegian law.

Results

Of a total of 425,564 (54% women) participants, 493 (44% women) were identified with ALS during a mean follow-up of 16.0 (SD 2.4) years (9.8 [SD 4.6] years among ALS cases). The mean age at the start of follow-up on January 1, 2005, was 52.8 (SD 4.5) years among statin ever users and 51.7 (SD 4.6) years among statin never users. Mean age at health screening, from when cohort characteristics were collected, was 41.3 (SD 4.1) years among statin ever users and 40.9 (SD 3.8) years among statin never users. More men (42%) than women (36%) had used statins at some point during follow-up. Although the age at first statin exposure was the same between sexes, men generally had longer statin exposure durations (mean 9.2 [SD 9.5] vs 7.1 [SD 7.6] years) (Table 1). The

levels of triglycerides and total cholesterol before statin exposure were generally higher in men than women.

No overall association was found between current statin use and ALS risk in both women and men (Table 2). When categorizing current statin use by duration, a clear pattern emerged. Short-term current statin use (less than 1 year) was associated with an increased ALS risk (HR 3.56, 95% CI 2.58–4.90) in both sexes, with a stronger effect size observed in men (Table 2). By contrast, long-term current statin use (more than 5 years) was associated with a reduced ALS risk, although this was statistically significant only in men (HR for both sexes combined was 0.67, 95% CI 0.45–1.00; HR for men was 0.47, 95% CI 0.26–0.86). Overall, the strength of the associations was greater for both short-term (positive) and long-term (negative) use in men.

There was no evidence of effect modification by neither age at start of follow-up ($p = 0.23$) nor cholesterol levels at health screening ($p = 0.22$).

Results from the Fine-Gray model were similar to those from the Cox model (eTable 1).

In patients with ALS, there was a marked increase in statin initiation rates in the last year before diagnosis (Figure 2). In the lag-time analysis, short-term statin use (less than 1 year) was no longer associated with an increased ALS risk (eTable 2).

Sensitivity Analyses

In all 3 sensitivity analyses, the results remained consistent with our main analysis. In the analyses where the grace period was extended, short-term current statin use was associated with an HR of ALS of 3.62 (95% CI 2.62–4.99), while long-term current statin use was associated with an HR of ALS of 0.68 (95% CI 0.46–1.00) (eTable 3). In the analysis where we limited our case definition to riluzole use, the HR for ALS among short-term statin users was 3.48 (95% CI 2.44–4.97), and among long-term statin users, it was 0.61 (95% CI 0.39–0.96) (eTable 4). In the last sensitivity analysis, we calculated the duration of statin use based on the dates of the first and last filled prescriptions, rather than on cumulative DDDs after the initial drug exposure. Short-term current statin use was associated with an HR of ALS of 3.73 (95% CI 2.70–5.15), while long-term statin use was associated with an HR of ALS of 0.89 (95% CI 0.65–1.23) (eTable 5).

Negative Control Analysis

Baseline characteristics of the participants in the study investigating use of RAS-acting agents in relation to ALS risk were similar to those observed in the statins study (eTable 6). During the follow-up period, more men (39%) than women (31%) had used RAS-acting agents. In addition, men had a longer average duration of drug exposure compared with women (mean 10.3 [SD 9.6] vs mean 8.8 [SD 8.2] years). Before exposure to RAS-acting agents, a higher percentage of men (27%) were hypertensive compared with women (12%) (eTable 6).

Table 1 Cohort Characteristics by Statin Ever User Status and Sex

	Men		Women	
	Statin ever user	Statin never user	Statin ever user	Statin never user
Participants, n (%)	81,861 (42)	114,858 (58)	82,275 (36)	146,570 (64)
Age at start of follow-up, y, mean (SD)[a]	52.7 (4.5)	51.8 (4.6)	52.9 (4.5)	51.6 (4.6)
Age at first exposure, y, mean (SD)	61.0 (6.3)	—	61.1 (6.1)	—
Years under exposure, mean (SD)	9.2 (9.5)	—	7.1 (7.6)	—
Characteristics according to health screening before start of follow-up				
Age at health screening, y, mean (SD)	41.2 (4.1)	40.9 (3.9)	41.3 (4.1)	40.9 (3.8)
Time from health screening to start of follow-up, y, mean (SD)	11.6 (4.7)	10.9 (4.5)	11.6 (4.6)	10.8 (4.4)
BMI, kg/m^2, mean (SD)	26.0 (3.3)	25.4 (3.1)	24.8 (4.1)	24.1 (3.8)
Triglycerides, mmol/L, mean (SD)	2.2 (1.4)	1.9 (1.1)	1.5 (0.9)	1.2 (0.7)
Total cholesterol, mmol/L, mean (SD)	5.9 (1.2)	5.4 (1.1)	5.7 (1.1)	5.1 (1.0)
Current smoker, n (%)	33,970 (42)	38,540 (34)	35,892 (44)	51,958 (36)
Hypertension, n (%)	28,389 (35)	29,937 (26)	14,841 (18)	16,903 (12)
Diabetes, n (%)	931 (1)	285 (0)	844 (1)	373 (0)

Abbreviations: ALS = amyotrophic lateral sclerosis; BMI = body mass index.
[a] January 1, 2005.

Table 2 Risk (HR) of ALS According to Statin Use and Duration of Current Use

	Cases	Person-years, y	Incidence per 100,000 person-years	Minimally adjusted[a] HR (95% CI)	Fully adjusted[b] HR (95% CI)
Both sexes					
No current statin use	391	7,971,173	6.7 (6.1–7.4)	Reference	
Duration of current statin use, y					
0–17	102	6,370,999	10.3 (8.5–12.5)	1.18 (0.94.1.47)	1.15 (0.91–1.44)
0–1	43	2,597,362	27.8 (20.6–37.5)	3.70 (2.70–5.08)	3.56 (2.58–4.90)
>1–5	31	2,428,761	7.0 (4.9–10.0)	0.86 (0.60–1.25)	0.85 (0.59–1.23)
>5–17	28	1,344,876	7.1 (4.9–10.3)	0.69 (0.47–1.03)	0.67 (0.45–1.00)
Men					
No current statin use	218	3,615,075	8.4 (7.3–9.6)	Reference	
Duration of current statin use, y					
0–17	58	3,190,883	11.3 (8.7–12.6)	1.11 (0.82–1.49)	1.08 (0.80–1.46)
0–1	29	1,290,272	37.6 (26.2–54.2)	4.13 (2.80–6.09)	4.03 (2.72–5.95)
>1–5	17	1,203,673	7.5 (4.7–12.2)	0.77 (0.47–1.26)	0.74 (0.45–1.22)
>5–17	12	696,938	5.7 (3.2–10.0)	0.49 (0.27–0.89)	0.47 (0.26–0.86)
Women					
No current statin use	173	4,356,098	5.4 (4.7–6.3)	Reference	
Duration of current statin use, y					
0–17	44	3,180,116	9.2 (6.9–12.4)	1.31 (0.93–1.83)	1.29 (0.91–1.83)
0–1	14	1,307,090	18.0 (10.7–30.4)	3.04 (1.76–5.25)	2.85 (1.61–5.02)
>1–5	14	1,225,088	6.5 (3.8–10.9)	1.03 (0.59–1.77)	1.03 (0.60–1.80)
>5–17	16	647,938	8.7 (5.3–12.2)	1.02 (0.61–1.72)	1.03 (0.60–1.75)

Abbreviations: ALS = amyotrophic lateral sclerosis; HR = hazard ratio.
[a] Adjusted for age at start of follow-up (January 1, 2005) and sex (unless stratified analysis).
[b] Additionally adjusted for the following variables collected from prior health screenings: circulating levels of triglycerides and total cholesterol (continuous), body mass index (continuous), smoker (yes/no), diabetes (yes/no), hypertension (yes/no), and health screening (categorical).

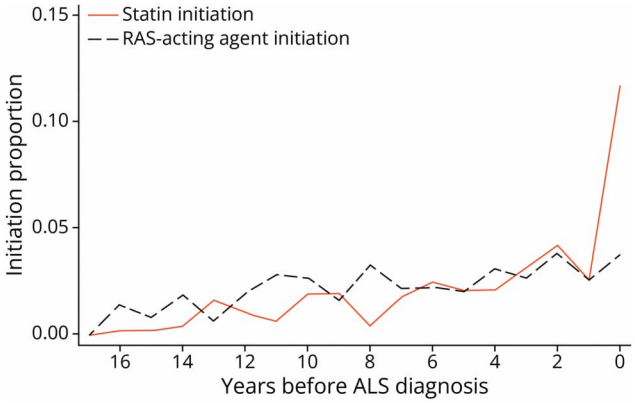
We found no association between current use of RAS-acting agents and risk of ALS, irrespective of the duration of exposure (Table 3 and Figure 3). Different from statins, no clear increase in RAS-acting agent initiation was seen in the last year leading up to diagnosis in patients with ALS (Figure 2).

Discussion

In this population-based study, we found a time-varying relationship between current statin use and ALS risk. Starting statin use less than 1-year before ALS diagnosis was strongly associated with an increased risk of ALS, while long-term statin use was associated with a modest decrease in ALS risk among men. The validity of our findings was supported by a negative control analysis using RAS-acting agents as drug exposure, which showed no association with ALS risk for either short-term or long-term use.

The observed increase in prescription of statins during the year before ALS incidence, as seen in this study, aligns with findings from 2 other Scandinavian studies. These studies proposed that this association could reflect an early neurotoxic effect from statins, potentially accelerating the progression of ALS.[14,15] However, the mechanisms by which statins could contribute to ALS pathogenesis remain unclear. In a study using SOD1 G93A transgenic mice, a classical ALS model, simvastatin accelerated neuron death and disease phenotype onset, potentially due to impaired autophagic function.[26] Another SOD1 G93A mouse study found, however, delayed symptom onset in mice treated with lovastatin.[27] Furthermore, a recent population-based Norwegian study

Figure 2 Statin and RAS-Acting Agent Initiation Trends in the Years Leading up to ALS Diagnosis



ALS = amyotrophic lateral sclerosis; RAS = renin-angiotensin system.

found no association between statin use and ALS survival.[28] Although we cannot exclude a causal relationship, the association between short-term statin use and increased ALS risk is best explained by reverse causation. Given that most patients have developed symptoms and seek health care attention in the year leading up to diagnosis,[29] and that both LDL-c and total cholesterol increase during this prediagnostic period,[30] the likelihood of being prescribed a statin during this period is high.

We also found a decreased ALS risk in men associated with long-term statin use. Although this finding was less pronounced than the short-term association, it was consistent across a range of sensitivity analyses. A protective effect from long-term statin use aligns with some, but not all, observational studies, none of which were able to properly adjust for important confounding factors such as hypercholesterolemia and BMI. Two retrospective case-control studies from the United States[9,10] excluded filled statin prescriptions 1 year before diagnosis in their analyses. Both reported that statins were associated with lower ALS risk, with risk estimates of 0.87[9] and 0.46[10] among statin users. However, 2 studies from Denmark[15] and Sweden[14] did not find this relationship. These studies calculated duration of use based on time since first statin prescription, disregarding information on drug adherence. There are sensible reasons for this choice. The prodromal phase of ALS may last several years, and the time window for when exposures may act protectively is difficult to ascertain. The strategy also avoids the possible bias introduced by identifying long-term adherers, who may represent a group selected on some unmeasured health factors. Furthermore, early disease signs may change patients' drug use patterns in the time leading up to diagnosis. Still, including both adherers and nonadherers could dilute a true protective effect among long-term users. We used information on defined daily doses from each prescription and calculated duration of current use based on cumulative DDDs after the first filled prescription. We further allowed for a 1-year grace period between when the drug was last dispensed to the time after which a statin user again was considered a nonuser. This corresponds to the typical time from symptom onset to diagnosis and should therefore account for statin discontinuation secondary to prodromal symptoms. The association between long-term statin use and decreased ALS risk remained similar in a sensitivity analysis using 2 years as the grace period.

Further support for a protective effect of statins comes from 3 recent Mendelian randomization studies, which found that genetic variants related to statin use are associated with reduced ALS risk.[6,11,31] Odds ratios for ALS among those with genetic variants associated with statin use was estimated to 0.83–0.84.[6,11] Furthermore, in wobbler mice, an animal model for ALS, atorvastatin administration suppressed denervation atrophy and attenuated approximately 30% loss of motor neurons.[32]

Given that LDL-c, and possibly total cholesterol, are suggested risk factors for ALS,[6] the observed protective effect of long-term statin use seen in our study could be attributed to its cholesterol-lowering action. However, statins also have pleiotropic effects and may provide neuroprotection in other ways, such as reducing the expression of inflammatory mediators and scavenging reactive oxygen species.[33]

In this study, the association between long-term statin use and reduced ALS risk was more pronounced in men than in women, reflecting findings from one of the US studies.[9] Statins seem to have the same lipid-lowering effect across sexes.[34] In general, men had higher baseline cholesterol levels, but we found no indication of effect modification by cholesterol levels. Statins were in general prescribed more frequently in men than women. Men were also more extensively exposed to statins, either by longer duration of use or by higher dosages. The observed sex difference may stem from statistical power issues, or sex-specific pleiotropic effects of statins, like reduction of testosterone.[35]

Our study has several strengths. First, it has a population-based and prospective design, which allowed for objective measurement of relevant confounders before statin exposure. ALS was identified through validated registries,[22,23] and drug exposure data were obtained from an administrative prescription registry, thus minimizing misclassification of drug use. Furthermore, the lack of association in our negative control analysis using RAS-acting agents instead of statins reduces the likelihood that our findings can be explained by time-related biases[36] or residual confounding from concomitant medications or comorbidities. Our study has also some limitations. Both the assessments of cardiovascular risk factors from health surveys conducted years before the start of follow-up and the identification of cases using administrative data may be subject to misclassification. Tracking of cardiovascular risk factors in a Norwegian population has demonstrated that

Table 3 ALS Risk (HR) According to Duration of Current Use of RAS-Acting Agents

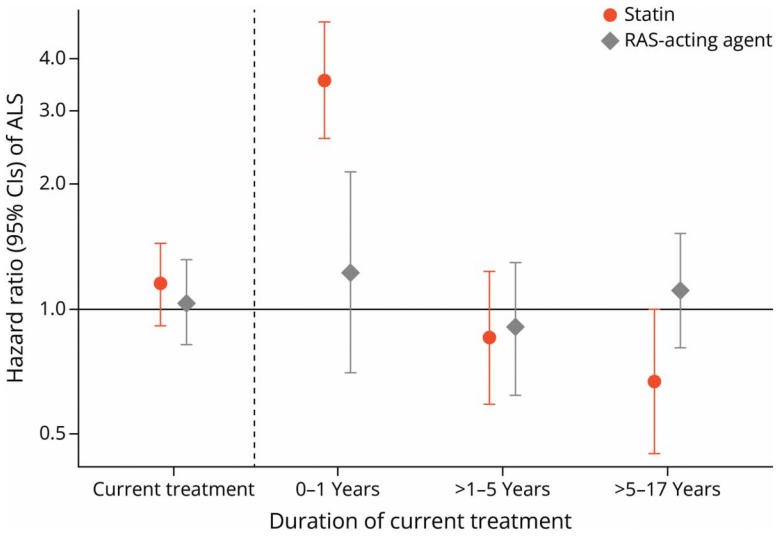
	Cases	Person-time, y	Incidence per 100,000 person-years	Minimally adjusted[a] HR (95% CI)	Fully adjusted[b] HR (95% CI)
Both sexes					
No current RAS-acting agent use	391	7,309,024	6.9 (6.2–7.6)	Reference	
Duration of current RAS-acting agent use, y					
0–17	96	5,940,655	9.4 (7.7–11.5)	1.01 (0.81–1.27)	1.03 (0.82–1.31)
0–1	13	2,336,189	9.3 (5.4–16.0)	1.20 (0.69–2.09)	1.22 (0.70–2.13)
>1–5	32	2,195,158	7.5 (5.3–10.6)	0.88 (0.61–1.27)	0.90 (0.62–1.29)
>5–17	51	1,409,308	11.3 (8.6–14.9)	1.07 (0.79–1.45)	1.11 (0.81–1.51)
Men					
No current RAS-acting agent use	221	3,408,960	8.7 (7.6–9.9)	Reference	
Duration of current RAS-acting agent use, y					
0–17	53	3,138,739	9.6 (7.3–12.6)	0.90 (0.66–1.22)	0.90 (0.66–1.24)
0–1	10	1,220,042	13.6 (7.3–25.3)	1.48 (0.78–2.78)	1.47 (0.78–2.78)
>1–5	17	1,153,040	7.4 (4.6–11.9)	0.73 (0.45–1.21)	0.74 (0.45–1.22)
>5–17	26	765,657	10.5 (7.2–15.5)	0.89 (0.58–1.36)	0.90 (0.58–1.38)
Women					
No current RAS-acting agent use	170	3,900,064	5.5 (4.7–6.3)	Reference	
Duration of current RAS-acting agent use, y					
0–17	43	2,801,916	9.2 (6.8–12.4)	1.19 (0.84–1.67)	1.26 (0.88–1.79)
0–1	3	1,116,147	4.5 (1.5–14.0)	0.72 (0.23–2.25)	0.75 (0.24–2.36)
>1–5	15	1,042,118	7.6 (4.6–12.5)	1.10 (0.65–1.87)	1.16 (0.68–1.98)
>5–17	25	643,650	12.4 (8.4–18.3)	1.37 (0.89–2.11)	1.47 (0.94–2.30)

Abbreviations: ALS = amyotrophic lateral sclerosis; HR = hazard ratio; RAS = renin-angiotensin system.
[a] Adjusted for age at start of follow-up (January 1, 2005) and sex (unless stratified analysis).
[b] Additionally adjusted for the following variables collected from prior health screenings: circulating levels of triglycerides and total cholesterol (continuous), body mass index (continuous), smoker (yes/no), diabetes (yes/no), hypertension (yes/no), and health screening (categorical).

the stability of BMI and total cholesterol levels is high over time and consistent across sexes.[37] Although it is unlikely that case misclassification would vary with drug exposure status, we addressed this in a sensitivity analysis where ALS status was based solely on prescribed riluzole. In this analysis, where the risk of misclassification is substantially reduced, the association between long-term statin use and low ALS risk was even stronger. Using defined daily doses in calculating duration of statin use can be imprecise[38] and likely underestimates[39] actual drug duration. In a sensitivity analysis using the time between the first and last statin prescription, the association between long-term statin use and low ALS risk was attenuated. Although cumulative DDDs reflect both duration and intensity of drug exposure, first-to-last prescription time only measures duration which also often are overestimated because of inclusion of nonadherers, thus reducing the risk differences. Nonetheless, we cannot exclude that the protective effect of long-term use is overestimated in our main analysis. Health survey participants may not always be representative of the general population. Nevertheless, the health surveys included in this study have been shown to be representative concerning important factors such as smoking habits, alcohol consumption, and educational attainment.[2,40] Ultimately, due to a lack of information, we were unable to stratify our analyses on ALS phenotype and genotype, or by lipophilic vs hydrophilic statins, which could be relevant.[9]

In conclusion, we found a time-varying relationship between statin use and ALS risk, with a potential protective effect associated with long-term use in men. There is a desperate need for new treatments and preventive measures in ALS. Future research should focus on elucidating the mechanisms

Figure 3 HR of ALS According to Current Use of Statins or RAS-Acting Agents and Duration of Treatment



HR calculated from Cox proportional hazard models with no current use as reference, adjusted for age, sex, triglycerides, total cholesterol, body mass index, smoking status, diabetes, hypertension, and health screening. ALS = amyotrophic lateral sclerosis; HR = hazard ratio; RAS = renin-angiotensin system.

underlying this association and clarify the role of statins in ALS prevention.

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Author Contributions

O. Nakken: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. A.M. Vaage: drafting/revision of the manuscript for content, including medical writing for content. H. Stigum: drafting/revision of the manuscript for content, including medical writing for content. K. Bjornevik: drafting/revision of the manuscript for content, including medical writing for content. T. Holmoy: drafting/revision of the manuscript for content, including medical writing for content. H.E. Meyer: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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