

Antidiabetics, statins and the risk of amyotrophic lateral sclerosis

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Background: Medications that are used for treatment of metabolic disorders have been suggested to be associated with the development of amyotrophic lateral sclerosis (ALS).

Methods: To examine the associations of antidiabetics and statins with the subsequent risk of ALS we conducted a population-based nested case-control study of 2475 Swedish residents diagnosed with ALS during July 2006 to December 2013 and 12 375 population controls (five for each ALS case). We extracted information on filled prescriptions of antidiabetics and statins for both cases and controls from the Swedish Prescribed Drug Register during the years before ALS diagnosis. Conditional logistic regression was used to calculate odds ratios (ORs) for the associations of these medications with ALS risk.

Results: Patients with ALS were less likely to have been prescribed with antidiabetics compared with controls [OR, 0.76; 95% confidence intervals (CI), 0.65–0.90]. Conversely, statins were not associated with ALS risk overall (OR, 1.08; 95% CI, 0.98–1.19), although a positive association was noted among women (OR, 1.28; 95% CI, 1.10–1.48). The latter association was mostly explained by ALS cases being more likely to have a first prescription of statins during the year before diagnosis compared with controls (OR, 2.54; 95% CI, 1.84–3.49).

Conclusions: The inverse association of antidiabetics with ALS is consistent with the previously reported inverse association between type 2 diabetes and ALS risk. The increase in prescription of statins during the year before ALS diagnosis deserves attention because it might reflect an acceleration of the course of ALS due to statin use.

Introduction

Alterations in glucose and lipid metabolism are known features of patients with amyotrophic lateral sclerosis (ALS) [1,2]. These alterations may occur long before ALS diagnosis. For example, type 2 diabetes, especially long-term type 2 diabetes, is associated with a lower risk of ALS and patients with ALS might have higher low-density lipoprotein cholesterol, apoB and apoB:apoA-I ratio during the 20 years before diagnosis

compared with controls [3–5]. The role of metabolic alterations in ALS is, however, complex. The associations of type 1 and type 2 diabetes with ALS are probably different and, despite the protective effect of type 2 diabetes on risk, impaired glucose tolerance is common in patients with ALS [3,4,6]. Furthermore, despite increased serum lipid levels being associated with a higher ALS risk, hyperlipidemia has been linked to a better prognosis in some, but not all, studies [1,5,7].

Drugs used to treat alterations in glucose and lipid metabolism have been suggested as risk factors or therapeutic targets for ALS. Antidiabetics might prevent ALS by protecting motor neurons against

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oxidative imbalance and glutamate-induced excitotoxicity [8,9]. However, a phase II trial of the antidiabetic pioglitazone in patients with ALS under riluzole (a glutamate-modulating agent itself) was stopped for futility [10]. As hyperglycemia may be beneficial in ALS, the antidiabetic effect may also be detrimental [11]. Harmful effects of the antidiabetic metformin on the course of ALS have been suggested in *SOD1*^{G93A} mice [12]. Deleterious effects of statins on motor neurons have been suggested, through for instance impairment of the liver X receptor signaling [13]. Similar to antidiabetics, however, the reduction of oxidative stress triggered by statins may protect these neurons [14]. Surveillance databases have linked statin treatment with ALS, whereas in two large epidemiological studies statin use was not associated with increased ALS risk [15–17].

To clarify these issues, we described the association of the prescription of antidiabetics and statins with the future risk of ALS in the Swedish population.

Methods

Study design

The Swedish Total Population Register includes information on birth, emigration and death of all Swedish residents since 1968. We linked all individuals included in this register who were born in Sweden and lived in Sweden on 1 July 2006 to the Longitudinal Integration Database for Health Insurance and Labour Market Studies to identify the area of residence as of 31 December 2005. Individuals with missing information on area of residence were excluded, leaving 6 090 927 in the final cohort. The cohort was then followed from 1 July 2006 to ALS diagnosis, emigration out of Sweden, death or 31 December 2013, whichever came first. Within this study base, we conducted a nested case-control study. This study complied with the Declaration of Helsinki and was approved by the Regional Ethical Review Board in Stockholm (Karolinska Institutet), Sweden.

Identification of patients with amyotrophic lateral sclerosis

Since 1964/1965, the Swedish National Board of Health and Welfare has compiled data on individual hospital discharge diagnoses according to the Swedish Revisions of the International Classification of Diseases (ICD-7 before 1969, ICD-8 1969–1986, ICD-9 1987–1996, ICD-10 since 1997). The coverage became nationwide in 1987. This Patient Register also collects information on outpatient visits to specialist care since

2001 (>80% of the entire country). All individuals with inpatient or outpatient visits concerning a diagnosis of ALS were identified as patients with ALS. The date of the first ALS-related visit was used as the date of diagnosis. We identified 2475 ALS cases that were first diagnosed between July 2006 and December 2013 (ICD-10 code G12.2).

We also linked all patients with ALS to the Swedish Multi-Generation Register and identified all traceable first- and second-degree relatives (i.e. grandparents, parents, uncles/aunts, siblings, children, nephews/nieces and grandchildren). If any of the relatives had a diagnosis of ALS in the Patient Register (during 1964–2013), the proband patients were classified as familial ALS (i.e. with a family history of ALS), whereas the other proband patients were classified as sporadic ALS. Because the Multi-Generation Register includes primarily familial links for individuals born from 1932, familial information was not complete for patients born before 1932.

Selection of controls

All individuals in the cohort were eligible controls for a specific ALS case if they were alive, had never emigrated and had never been diagnosed with ALS by the date of diagnosis of the case (index date of the case). Using incidence density sampling, each case was individually matched to five controls of the same sex, year of birth and area of residence (Northern, Central or Southern Sweden). The date of selection was used as the index date for controls.

Identification of prescribed medications

The Swedish Prescribed Drug Register encompasses data on all prescribed medications dispensed in Swedish pharmacies since 1 July 2005 and drugs are coded according to the Anatomical Therapeutic Chemical (ATC) system. We extracted information on first recorded prescription of drugs for treating diabetes (ATC code A10) and lipid-modifying agents (ATC code C10). We studied the first recorded prescription of any antidiabetics and specifically of insulin, metformin and sulfonylureas. Because statins (ATC code C10AA) constitute the vast majority of prescribed lipid-modifying agents, we studied the first recorded prescription of any statin and of simvastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin, separately.

Statistical analysis

Conditional logistic regression models were fitted to estimate odds ratios (ORs) and 95% confidence

intervals (CI) for the associations between medications and subsequent risk of ALS. We computed the overall ORs and by age at index date, sex and family history of ALS. For results by age at index date we considered either two main subgroups (≤ 65 , >65 years) or quartiles of the age distribution (62, 69 and 77 years) as cutoffs.

For each medication studied, individuals who had been prescribed before 1 July 2006 were classified as prevalent users. Individuals with a first prescription after 1 July 2006 were classified as new users and the time interval between the first prescription and the index date was calculated. To investigate duration of medication use, we calculated ORs of ALS for prevalent users overall (because we could not identify the first prescription of the prevalent users due to lack of information before July 2005) and for new users overall as well as during <1 year, 1–2, 2–3, 3–4, 4–5 or 5–8 years before the index date. To investigate the specific contributions of antidiabetics and statins and their subtypes, independent of each other, we calculated the ORs after mutual adjustment.

Insulin, the main treatment for type 1 diabetes, might also be prescribed for type 2 diabetes. In an additional analysis, we attempted to separate insulin used for type 1 diabetes from insulin used for type 2 diabetes. We identified from the Patient Register diagnoses of insulin-dependent (ICD-10 E10) or non-insulin-dependent (ICD-10 E11) diabetes since 1997. We then reassessed the association of insulin with ALS after excluding (i) individuals who were prescribed with insulin and had at least one diagnosis of insulin-dependent diabetes (i.e. focusing on insulin for type 2 diabetes) and (ii) individuals who were prescribed with insulin and had only diagnoses of non-insulin-dependent diabetes (i.e. focusing on insulin for type 1).

Results

In total, 1402 ALS cases (57%) were male and average age at diagnosis was 68 (SD 12) and 70 (SD 12) years for men and women, respectively. Among these cases, 82 (3%) were classified as familial ALS.

Antidiabetics

A lower proportion of cases were prescribed with antidiabetics before the index date compared with controls, leading to an overall inverse association between antidiabetics and ALS risk (Table 1). This result varied only marginally by sex, age and family history with ORs quite similar across age groups (ranging from OR, 0.70 for age >77 years to OR, 0.88 for age <62 years). The inverse association was primarily attributable to prevalent use (OR, 0.66; 95%

CI, 0.54–0.81) because new users had a risk similar to that of non-users (OR, 1.00; 95% CI, 0.77–1.30, Fig. 1). Indeed, prescription of antidiabetics at least 5 years prior to the index date was inversely associated with ALS (OR, 0.71; 95% CI, 0.53–0.96).

A strong overall inverse association was noted for insulin, metformin and sulfonylureas, with the strongest association for sulfonylureas (Table 2). Adjustment for statins, as well as mutual adjustment, changed these results only marginally. Also, these associations did not differ clearly by sex or age (Table S1).

Among 74 cases and 514 controls that were prescribed with insulin, 41 cases and 266 controls had at least one diagnosis of insulin-dependent diabetes. After excluding these 307 individuals, the association of insulin (i.e. used for type 2 diabetes mainly) with ALS became slightly stronger (OR, 0.66; 95% CI, 0.45–0.95). After excluding 26 cases and 176 controls that were prescribed with insulin and had only diagnoses of non-insulin-dependent diabetes, the association of insulin (i.e. used for type 1 diabetes mainly) was almost unchanged (OR, 0.70; 95% CI, 0.52–0.96).

Statins

Statins were prescribed to most individuals with a prescription for lipid-modifying agents (4111/4191, 98%). Statins were not associated with the subsequent risk of ALS overall, whereas we found an increased risk in younger statin users (<62 years: OR, 1.38; 95% CI, 1.07–1.77) that decreased with age (62–69 years: OR, 1.10; 95% CI, 0.91–1.34; 69–77 years: OR, 0.99; 95% CI, 0.82–1.18; >77 years: OR, 1.00; 95% CI, 0.83–

Table 1 Association between prescription of antidiabetics and risk of amyotrophic lateral sclerosis (ALS)

Variable	No. of cases using antidiabetics	No. of controls using antidiabetics	OR ^a (95% CI)	P value ^b
Overall	177 (7.15)	1,133 (9.16)	0.76 (0.65–0.90)	
Sex				
Male	109 (7.77)	726 (10.36)	0.73 (0.59–0.90)	0.49
Female	68 (6.34)	407 (7.59)	0.82 (0.63–1.07)	
Age at the index date (years)				
≤ 65	43 (4.88)	250 (5.68)	0.85 (0.61–1.19)	0.46
>65	134 (8.41)	883 (11.07)	0.74 (0.61–0.90)	
Family history of ALS				
Yes	6 (7.32)	36 (8.78)	0.82 (0.33–2.02)	0.88
No	171 (7.15)	1,097 (9.17)	0.76 (0.64–0.90)	

CI, confidence intervals; OR, odds ratio. Data are given as *n* (%).
^aORs from the conditional logistic regression model are by design adjusted for the matching factors (age, sex and area of residence).
^bP value from the Wald test for the multiplicative interaction between antidiabetics and the reported variable.

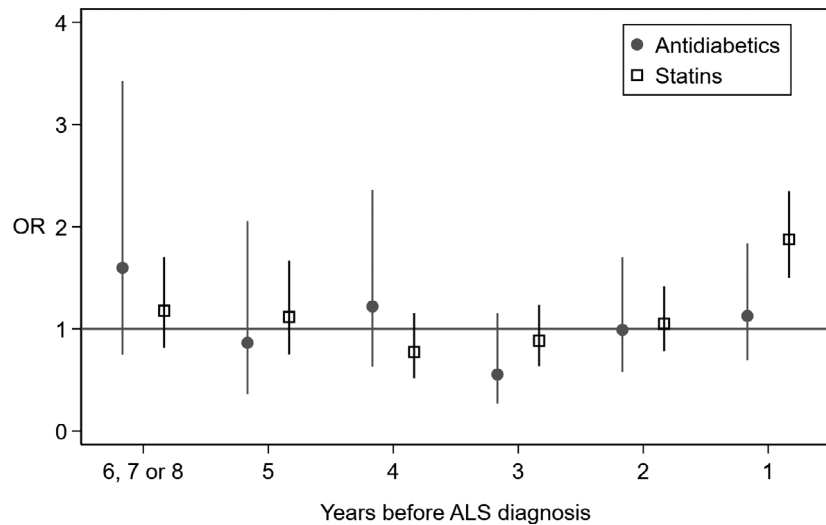


Figure 1 Associations of new use of antidiabetics and statins with amyotrophic lateral sclerosis (ALS) risk. Odds ratios (ORs) of ALS for new use of antidiabetics or statins during the 8 years before ALS diagnosis.

Table 2 Association between prescription of different types of antidiabetics and risk of amyotrophic lateral sclerosis

Antidiabetic	No. of cases using antidiabetics	No. of controls using antidiabetics	OR ^a (95% CI)	OR ^b (95% CI)	OR ^c (95% CI)
Insulin (ATC code A10A)	74 (2.99)	514 (4.15)	0.71 (0.56–0.91)	0.68 (0.53–0.88)	0.80 (0.61–1.05)
Metformin (ATC codes A10BA, A10BD)	125 (5.05)	826 (6.67)	0.74 (0.61–0.90)	0.71 (0.58–0.86)	0.84 (0.67–1.05)
Sulfonylureas (ATC code A10BB)	42 (1.70)	365 (2.95)	0.57 (0.41–0.78)	0.55 (0.40–0.76)	0.65 (0.46–0.92)

ATC, Anatomical Therapeutic Chemical; CI, confidence intervals; OR, odds ratio. Data are given as *n* (%). ^aORs from the conditional logistic regression model are by design adjusted for the matching factors (age, sex and area of residence). ^bOR adjusted for use of statins and by design adjusted for the matching factors (age, sex and area of residence). ^cOR adjusted for use of statins, mutually adjusted for use of insulin, metformin and sulfonylureas, and by design adjusted for the matching factors (age, sex and area of residence).

1.21) and a 28% higher risk among women using statins (Table 3). The latter positive association was noted among both younger (≤ 65 years; OR, 1.34; 95% CI, 0.96–1.86) and older (> 65 years; OR, 1.24; 95% CI, 1.05–1.47) women.

No increased risk was found for the 2508 participants (17%) who were prevalent users (OR, 1.00; 95% CI, 0.89–1.13). New use ($n = 1603$) was, however, associated with higher risk (OR, 1.20; 95% CI, 1.05–1.38). The positive association was largely limited to the year before index date and was stronger for women but present also for men and both younger and older ages (Figs 1 and 2).

Similar null overall association was noted for simvastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin (Table 4). Adjustment for antidiabetics and mutual adjustment did not change the results clearly. Apart from a positive association for simvastatin among women, no clear association was noted in the analysis by sex or age (Table S2).

Discussion

In this population-based nested case-control study, we observed an association of prescription of

antidiabetics with a lower risk of ALS, but an overall null association of prescription of statins with risk of ALS.

We and others have previously reported that type 2 diabetes was associated with a lower risk of ALS

Table 3 Association between prescription of statins and risk of amyotrophic lateral sclerosis (ALS)

Variable	No. of cases using statins	No. of controls using statins	OR ^a (95% CI)	<i>P</i> value ^b
Overall	714 (28.85)	3,397 (27.45)	1.08 (0.98–1.19)	
Sex				
Male	397 (28.32)	2,053 (29.29)	0.95 (0.83–1.08)	<0.01
Female	317 (29.54)	1,344 (25.05)	1.28 (1.10–1.48)	
Age at the index date (years)				
≤ 65	158 (17.93)	662 (15.04)	1.21 (0.99–1.47)	0.10
> 65	556 (34.88)	2,735 (34.30)	1.02 (0.91–1.15)	
Family history of ALS				
Yes	20 (24.39)	93 (22.68)	1.11 (0.62–1.98)	0.92
No	694 (29.00)	3,304 (27.61)	1.08 (0.97–1.19)	

CI, confidence intervals; OR, odds ratio. Data are given as *n* (%). ^aORs from the conditional logistic regression model are by design adjusted for the matching factors (age, sex and area of residence). ^b*P* value from the Wald test for the multiplicative interaction between statins and the reported variable.

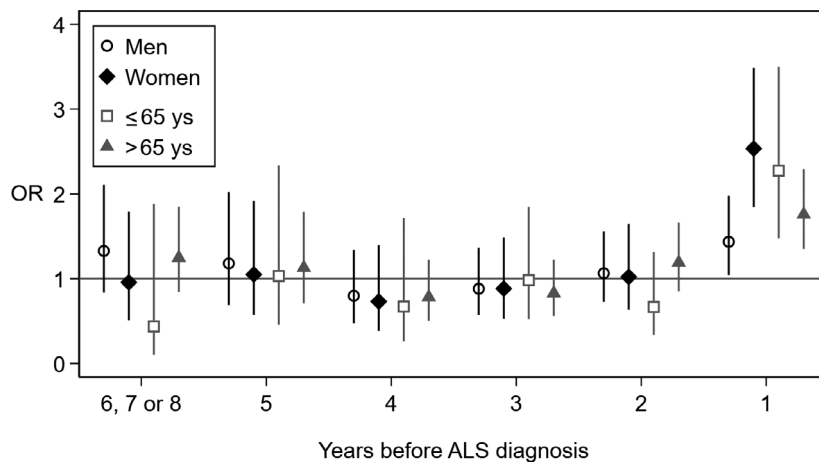


Figure 2 Subgroup-specific associations of new use of statins with amyotrophic lateral sclerosis (ALS) risk. Odds ratios (ORs) of ALS for new use of statins during the 8 years before ALS diagnosis by sex and age at ALS diagnosis.

[3,4,18]. Individuals with longer duration of diabetes appeared to have even lower risk compared with individuals with shorter duration [3]. One explanation for this finding is the longer-term use of antidiabetics among patients with longer history of diabetes. In the present study, the strong inverse association with prevalent use of antidiabetics is consistent with this hypothesis. The fact that new use for up to 8 years before the index date was not associated with risk suggests that the potential protective effect of antidiabetics or the underlying diabetes needs a long induction period. The similar results noted for different antidiabetics, insulin primarily used for type 1 diabetes and insulin primarily used for type 2 diabetes provide evidence for a generic effect of antidiabetics or the underlying altered metabolism.

The null association between statins and ALS risk in the present study corroborates the finding of a register-based study from Denmark but not a US case-control study using the Medicare database that reported an inverse association between statins and ALS risk [16,17]. Compared with the Danish study, the present study has a larger sample size that enabled us to identify an increase in the prescription of statins during the year before ALS diagnosis. Interestingly,

this observation was unique to statins and no increase in the prescription of antidiabetics was noted during the year before diagnosis. Possible reasons for the different results between the present study, Danish study and US study need to be explored and may include the different prevalence of obesity, a suggested protective factor of ALS, between Nordic countries and the USA [16,17,19].

The finding of elevated use of statins during the year before ALS diagnosis might be attributable to different reasons. Because the average diagnostic delay is about 1 year for ALS in Sweden [20], metabolic changes might have been detected during the approximately 1-year clinical evaluation, thus increasing the chance of patients being prescribed with statins. However, this positive association might also support the hypothesis that statins accelerate the disease course of ALS and symptom onset. Indeed, animal studies have suggested that statins might accelerate disease progression, primarily in female *SOD1^{G93A}* mice, and clinical trials have suggested that statins might negatively affect ALS progression among female but not male patients [21,22]. The lower statin-metabolizing enzymes and/or muscle mass might have exposed women to higher drug levels in the circulation

Table 4 Association between prescription of different types of statins and risk of amyotrophic lateral sclerosis

Statin	No. of cases using statins	No. of controls using statins	OR ^a (95% CI)	OR ^b (95% CI)	OR ^c (95% CI)
Simvastatin (ATC code C10AA01)	649 (26.22)	3,055 (24.69)	1.09 (0.98–1.21)	1.14 (1.03–1.27)	1.15 (1.03–1.27)
Pravastatin (ATC code C10AA03)	25 (1.01)	150 (1.21)	0.83 (0.54–1.27)	0.85 (0.56–1.31)	0.82 (0.54–1.26)
Fluvastatin (ATC code C10AA04)	5 (0.20)	29 (0.23)	0.86 (0.33–2.23)	0.88 (0.34–2.27)	0.85 (0.33–2.20)
Atorvastatin (ATC code C10AA05)	124 (5.01)	614 (4.96)	1.01 (0.83–1.23)	1.05 (0.86–1.28)	1.01 (0.82–1.24)
Rosuvastatin (ATC code C10AA07)	29 (1.17)	137 (1.11)	1.06 (0.71–1.59)	1.10 (0.73–1.65)	1.06 (0.70–1.61)

ATC, Anatomical Therapeutic Chemical; CI, confidence intervals; OR, odds ratio. Data are given as *n* (%). ^aORs from the conditional logistic regression model are by design adjusted for the matching factors (age, sex and area of residence). ^bOR adjusted for use of antidiabetics and by design adjusted for the matching factors (age, sex and area of residence). ^cOR adjusted for use of antidiabetics, mutually adjusted for use of other statins and by design adjusted for the matching factors (age, sex and area of residence).

compared with men, leading to the noted gender difference, but the mechanisms by which statins accelerate ALS progression remain unclear [23–25]. Furthermore, the strongest association was found for simvastatin as in the analysis of the FDA Adverse Event Reporting System data [15]. However, because the sample size was relatively small for the analysis of statin subtypes, a chance finding cannot be ruled out completely. Whether different statins have different effect on ALS needs to be further studied.

This is the first study investigating medication use before ALS diagnosis with respect to both antidiabetic and lipid-lowering agents. Strengths of the study are the population-based setting, large sample size and prospectively and independently collected information on drug prescriptions and clinical diagnoses, which greatly alleviated concerns of systematic and random errors.

Limitations of our study should also be noted. Firstly, given the observational nature of the study, we were unable to disentangle whether the noted associations are due to the medications themselves or to the underlying diseases. However, the attempt to study the effect of insulin in relation to type 1 and type 2 diabetes seems to indicate that the effect of insulin on ALS is present in both types of diabetes. Second, the assumption that filling a prescription after 1 July 2005 corresponds to medication use might have led to misclassification of exposure. We do not expect that such misclassification is differential between patients with ALS and controls, and would therefore probably have biased our results towards the null. We attempted to circumvent the problem that the assessment of filled prescriptions was left-truncated on 1 July 2005 and individuals who had taken the medications only before this date were misclassified as never users by starting the study period in July 2006 so that we had at least 1 year to ascertain medication use for all participants. Most prescriptions in Sweden last for 3 months and therefore if no drugs were dispensed during the entire year, it is unlikely that the participant used such drugs before. Another limitation is that all of the information on ALS came from the ICD code for motor neuron disease. A small proportion of the patients identified might have had motor neuron diseases other than ALS but this register-based definition for ALS has high positive predictive value (91%), based on a validation study conducted during 2013–2014 in Stockholm, Sweden, and our results are unlikely to be driven by other rarer diseases [5]. Additionally, we had no information on clinical characteristics of ALS to study different subtypes of ALS that may differ with regard to metabolic alterations as well as antidiabetic and lipid-lowering drugs.

For instance, recent interventional studies have highlighted that patients with ALS respond to drugs depending on their disease progression rate [26]. If we had information on progression rate, a decrease of the association of statins with ALS by this characteristic would have supported the hypothesis that a proportion of the patients had actually started statin use after the biological onset of the disease. The only subgroup that we could investigate was familial ALS as a proxy for cases with a genetic cause; the proportion of familial cases was, however, probably underestimated due to the less optimal register coverage for individuals born before 1932.

In conclusion, a clear inverse association of antidiabetics with ALS was noted. Whether the biological mechanisms underlying this inverse association are related to prolonged use of antidiabetics or metabolic disruptions involved in the disease needs to be further investigated. Although no overall association was identified between statins and ALS risk, an increased use of statins during the year before ALS diagnosis was found, especially among women. Future studies should disentangle whether such a finding reflects an acceleration of the disease course due to statins.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Adjusted odds ratios and 95% confidence intervals for the association of prescription of insulin,

metformin or sulfonylureas with the subsequent risk of amyotrophic lateral sclerosis.

Table S2. Adjusted odds ratios and 95% confidence intervals for the association of prescription of simvastatin, pravastatin, atorvastatin or rosuvastatin with the subsequent risk of amyotrophic lateral sclerosis.

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