Original Investigation

Diabetes Mellitus, Obesity, and Diagnosis of Amyotrophic Lateral Sclerosis
A Population-Based Study

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IMPORTANCE Although prior studies have suggested a role of cardiometabolic health on pathogenesis of amyotrophic lateral sclerosis (ALS), the association with diabetes mellitus has not been widely examined. Amyotrophic lateral sclerosis is the most common motor neuron disorder. Several vascular risk factors have been associated with decreased risk for ALS. Although diabetes is also a risk factor for vascular disease, the few studies of diabetes and ALS have been inconsistent.

OBJECTIVE To examine the association between diabetes and obesity, each identified through *International Statistical Classification of Diseases*, Eighth or Tenth Revision codes in a hospital registry, and ALS using data from the Danish National Registers.

DESIGN, SETTING, AND PARTICIPANTS Population-based nested case-control study of 3650 Danish residents diagnosed as having ALS between January 1, 1982, and December 31, 2009, and 365 000 controls (100 for each ALS case) matched on age and sex. The analysis was conducted in September and October 2014.

MAIN OUTCOMES AND MEASURES Adjusted odds ratio for ALS associated with diabetes or obesity diagnoses at least 3 years prior to the ALS diagnosis date.

RESULTS When considering diabetes and our obesity indicator together, the estimated odds ratio for ALS was 0.61 (95% CI, 0.46-0.80) for diabetes and 0.81 (95% CI, 0.57-1.16) for obesity. We observed no effect modification on the association with diabetes by sex. We did find a significant modification by age at ALS diagnosis and age at first mention of diabetes in the hospital registers. The protective association was stronger with increasing age at ALS diagnosis ($P = .01$), and the odds ratio for first mention of diabetes was 1.66 (95% CI, 0.85-3.21) before age 40 years but 0.52 (95% CI, 0.39-0.70) for older ages. These results are consistent with different associations for type 1 vs type 2 diabetes.

CONCLUSIONS AND RELEVANCE In this Danish nationwide study to investigate the association between diabetes and ALS diagnosis, our findings are in agreement with previous reports of a protective association between vascular risk factors and ALS and suggest that type 2 diabetes, but not type 1, is protective for ALS.

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Amyotrophic lateral sclerosis (ALS) is a fatal neurode-generative disease characterized by progressive degeneration of the upper and lower motor neurons,[1] with approximately half of the patients dying within 3 years of onset.[2] The ALS incidence rate is between 1.5 and 2.5 per 100 000 persons per year[3] and increases with increasing age, although incidence appears to decrease after age 80 years.[4] Although a recent study found ALS heritability to be higher than previously reported,[5] the etiology of ALS pathogenesis is not completely understood, with environmental contributions likely contributing to the disease.[2] Because of the rarity of the disease, large-scale cohort studies are difficult and so have not commonly been used to investigate potential risk factors, but the need for more such studies has been recognized.[6]

Recent reports have found a protective association between vascular risk factors, such as obesity or higher body mass index (BMI; calculated as weight in kilograms divided by height in meters squared),[7] higher cholesterol levels[8] and hyperlipidemia,[9,10] and ALS incidence as well as ALS survival.[11-14] These findings, coupled with reports that energy metabolism and homeostasis are also involved in ALS pathogenesis,[9] suggest that the pathophysiology of ALS is multifactorial.[15] Patients with type 2 diabetes mellitus have, on average, higher BMI, elevated blood lipid levels,[16] and defective energy metabolism.[17] Moreover, diabetes is a metabolic disorder with increasing prevalence globally.[18] However, the association between diabetes and ALS has not been widely explored. Recently, a case-control study in the Netherlands reported a protective, albeit insignificant, association between diabetes and ALS onset.[8]

To assess the potential link between diabetes and risk of ALS, we examined the association between hospital admissions for diabetes and ALS diagnosis between January 1, 1982, and December 31, 2009, in the entire Danish population. We used data obtained from the Danish National Registers system, through which details of all Danish residents can be linked.[19]

Methods

Data Collection

Data were obtained from the Danish National Registers system, through which details on demographic characteristics and certain health outcomes of all approximately 6 million Danish residents can be linked based on a 10-digit unique personal identifier. The Danish National Patient Register (NPR) was established in 1977 and is a comprehensive patient register, including nationwide clinical and administrative records for all somatic inpatient data. Outpatient data have also been included in the NPR since 1995[20] and are considered in our analyses. The ALS cases in this study were diagnosed between January 1, 1982, and December 31, 2009. The analysis was conducted in September and October 2014. This study was determined to be exempt by the Harvard School of Public Health Institutional Review Board and was approved by the Danish Data Protection Agency. Participants in our analyses were not required to provide informed consent; by Danish legislation, participants are not required to provide informed consent when no biological samples are obtained.

ALS Case Ascertainment

We identified ALS cases based on their *International Classification of Diseases* (*ICD*) discharge diagnoses, ie, *ICD-8* code 348.0 (ALS) until 1993 and *ICD-10* code G12.2 (motor neuron disease) thereafter. As the diagnosis date (index date), we used the date of the first relevant code. We only included patients who were at least 20 years old when diagnosed and we restricted analyses to cases identified after 1982 to avoid inclusion of prevalent cases in the early years of the NPR. In a validation substudy, we obtained 173 medical records for ALS cases identified through the NPR. Of these, only 13 had no ALS (7.5%). The estimated positive predictive value, including the clinically suspected ALS cases, was 0.93 (95% CI, 0.88-0.96).[21]

Control Selection

Controls were selected through the Danish Civil Registration System, which was established in 1968 and includes administrative records (eg, date and place of birth, vital status, and history of civil status and addresses) on all persons living in Denmark, and records are kept even when a person dies or emigrates.[19] We selected 100 controls for each identified case, alive at the time of the matched case's ALS diagnosis (the index date) and individually matched on sex and year of birth.

Diabetes Ascertainment

Diabetes is a disease caused by either insulin deficiency or a decreased responsiveness to insulin. Type 1 diabetes (formerly called *juvenile* or *insulin-dependent diabetes*), in most cases of autoimmune etiology, is associated with complete or almost complete insulin absence. Conversely, type 2 diabetes (non–insulin-dependent diabetes) is characterized by insulin resistance and occurs later in life as a syndrome of mainly overweight adults.[22] We identified diabetes cases based on hospital discharge *ICD* codes for type 1 and type 2 diabetes in the NPR starting in 1977. Specifically, we used *ICD-8* codes 249 and 250, respectively, and *ICD-10* codes E10 and E11, respectively. Identification of diabetic patients using hospital data has been found to be highly reliable,[23] but misclassification between type 1 and 2 diabetes is likely[24] and a complete classification by type is not possible.[25] This is also borne out in our own data, in which we found 74% of those with type 1 diabetes to also have a code for type 2. We therefore did not conduct separate analyses for type 1 and type 2 diabetes as distinguished by the *ICD* codes.

Our main analysis only considered diabetes discharges that occurred at least 3 years prior to the index date to minimize the chance that any observed association with diabetes could be due to the effects of underlying but not yet diagnosed ALS. To assess the robustness of our results, we repeated our analyses using only diabetes discharges that occurred at least 5 and 7 years prior to the index date.

Obesity and Lipid Metabolism Disorders

We used hospital discharge data to identify patients diagnosed as having obesity and lipid metabolism disorders. Specifically, we considered obesity admissions using *ICD-8* code 277.99 and *ICD-10* codes E65.0 to E66.9.[26] We refer to this throughout the article as obesity, but it should be noted that this is not based on a BMI greater than 30, the typical defini-

tion of obesity, and most likely reflects a much more elevated BMI. We also obtained hyperlipidemia and hypercholesterolemia data from the NPR (*ICD-8* code 279.00 and *ICD-10* codes E78.0-E78.5). As for diabetes, our main analyses used discharges that occurred at least 3 years prior to the index date.

Covariates

We additionally considered marital status (nonmarried, married, divorced, and widowed), residence region at the index date (Copenhagen, ie, the capital, Copenhagen suburbs, other large cities, provincial towns, rural areas, Greenland, and unknown), and socioeconomic status (SES) in our analyses. We coded SES as the highest level attained by either the participant or his or her spouse based on his or her job title. Job titles were categorized in 5 groups according to the Danish Institute of Social Sciences, which reasonably captures SES variation in Denmark.[27] Group 1 includes corporate managers and participants in academia; group 2, proprietors, managers of small businesses, and teachers; group 3, technicians and nurses; group 4, skilled workers; and group 5, unskilled workers. We included a separate group for participants with unknown job titles.

The NPR does not include data on potential individual-level confounders such as smoking. We therefore used chronic obstructive pulmonary disease (COPD) codes (*ICD-8* codes 490-493 and 518 and *ICD-10* codes J40-J47) at least 1 year prior to the index date as an indicator for smoking. In developed countries, up to 70% of COPD cases are among tobacco smokers,[28] and COPD is thus recognized as an indicator for smoking.

Statistical Analysis

For both diabetes and obesity, we ran conditional logistic regressions with strata defined by the 1:100 case-control sets adjusting for SES. We also ran models including COPD, marital status, and region of residence at the index date as covariates. Finally, we considered obesity and diabetes together in a model and assessed the association with diabetes in models stratified by obesity levels.

We also assessed potential effect modification by sex and age. For the effect modification, we included an interaction term between our exposure variable (diabetes or obesity) and sex or age in separate models, adjusting for SES, and examined the statistical significance of the interaction term at the α = .05 level.

Because misclassification in hospital diagnoses for type 1 and 2 diabetes is likely,[24,25] in an effort to separate potentially different effects, we attempted to separate types of diabetes based on the age at first mention of diabetes in the hospital registers. Those with diabetes onset at younger ages are more likely to have type 1 diabetes. We therefore conducted analyses considering separately diabetes with early and late first hospital discharge codes. We used a lower cutoff of age 40 years (the decade closest to but lower than the first decile of the age distribution at first diabetes-related admission) and then also considered different cutoffs at older ages in 5-year increments.

All statistical analyses were conducted using R statistical software version 3.0.3 (R Foundation for Statistical Computing).

Results

We identified 3650 ALS cases in the NPR between January 1, 1982, and December 31, 2009, that satisfied our inclusion criteria. The mean (SD) age at diagnosis was 65.4 (11.6) years and 46.5% of all cases were female. The distributions of the SES groups, marital status, region of residence, obesity, and COPD status are presented in **Table 1** by sex and diabetes status.

Using NPR records, we identified 9294 participants with diabetes at least 3 years prior to the index date (date of ALS diagnosis or the same date for the matched controls), 55 of whom were subsequently diagnosed as having ALS. The mean (SD) age at the first diabetes-related diagnosis was 59.7 (12.1) years and there was no significant difference between cases and controls (*P* = .07). Among patients with ALS who had diabetes, the first diabetes-related admission occurred a mean (SD) of 9.8 (6.1) years before the ALS diagnosis.

We observed a strong protective association between prior diabetes-related admissions and ALS (**Table 2**); the crude odds ratio (OR) was 0.59 (95% CI, 0.45-0.77). Adjusting for SES, marital status, region of residence, and prior COPD admissions did not change the effect estimates, nor did adjusting for our obesity indicator (OR = 0.61; 95% CI, 0.46-0.80). The ORs were similar when excluding diabetes in the 5 or 7 years before the index date (OR = 0.66; 95% CI, 0.50-0.88; and OR = 0.69; 95% CI, 0.50-0.96, respectively).

We identified 4536 participants with a hospital record for obesity at least 3 years prior to the index date. Effect estimates for obesity in unadjusted models or adjusting for SES, COPD status, marital status, and residence at diagnosis were similar to those for diabetes, but when diabetes was included in the model the association was weakened and was no longer significant (OR = 0.81; 95% CI, 0.57-1.16) (Table 2). Further, we observed no effect modification by diabetes (*P* = .99). We identified 4168 participants with a discharge for either hyperlipidemia or hypercholesterolemia. We observed no association between these and ALS.

We found no evidence for effect modification by sex of either the diabetes association (*P* = .84) or the obesity association (*P* = .72). We also found no effect modification by age at ALS diagnosis of the association with obesity (*P* = .42). Conversely, a significant effect modification by age at ALS diagnosis on the association between diabetes and ALS was observed (*P* = .01), with lower effect estimates observed at older ages. Specifically, the effect of diabetes on ALS was increased until age 51 years (eg, at ALS diagnosis at age 35 years, OR = 1.68; 95% CI, 0.75-3.78), although this increase did not reach statistical significance. The effect estimates became protective at older ages (statistically significant at ages ≥61 years, eg, at 65 years, OR = 0.65; 95% CI, 0.50-0.85) (**Figure 1**).

We also found a significant effect modification by age at first diabetes diagnosis, as a proxy to separate between type 1 and type 2 diabetes (**Figure 2**). The distribution of age at first diabetes-related diagnosis is presented in the eFigure in the Supplement. When the cutoff for age at diabetes diagnosis was 40 years, the difference in effect estimates for diabetes among those older and younger than the cutoff was significant

Table 1. Distribution of SES, Marital Status, Region, Obesity, and COPD Diagnosis by Sex and Diabetes Mellitus Status Among Controls

| | No. (%) | | | |
| | Women | | Men | |
Characteristic	Diabetes (n = 3826)	No Diabetes (n = 165 774)	Diabetes (n = 5413)	No Diabetes (n = 189 987)
SES group				
1 (High)	229 (6.0)	15 158 (9.1)	451 (8.3)	19 635 (10.3)
2	270 (7.1)	17 899 (10.8)	549 (10.1)	21 609 (11.4)
3	546 (14.3)	28 854 (17.4)	936 (17.3)	35 659 (18.8)
4	923 (24.1)	42 172 (25.4)	1563 (28.9)	54 722 (28.8)
5 (Low)	1056 (27.6)	32 293 (19.5)	1364 (25.2)	38 262 (20.1)
Unknown job title	802 (21.0)	29 398 (17.7)	550 (10.2)	20 100 (10.6)
Marital status				
Nonmarried	229 (6.0)	10 964 (6.6)	547 (10.1)	17 927 (9.4)
Married	1126 (29.4)	56 063 (33.8)	3135 (57.9)	115 704 (60.9)
Divorced	510 (13.3)	18 830 (11.4)	745 (13.8)	19 849 (10.4)
Widowed	1961 (51.3)	79 917 (48.2)	986 (18.2)	36 507 (19.2)
Region of residence at diagnosis/index date				
Copenhagen, capital	479 (12.5)	21 741 (13.1)	656 (12.1)	19 989 (10.5)
Copenhagen suburbs	713 (18.6)	35 806 (21.6)	1235 (22.8)	40 980 (21.6)
Other cities, Aarhus and Odense	474 (12.4)	18 816 (11.4)	642 (11.9)	20 518 (10.8)
Provincial towns	1536 (40.1)	63 329 (38.2)	1979 (36.6)	76 282 (40.2)
Rural areas	623 (16.3)	25 043 (15.1)	899 (16.6)	30 434 (16.0)
Greenland	0	598 (0.4)	1 (0.02)	1029 (0.5)
Unknown	1 (0.03)	441 (0.3)	1 (0.02)	755 (0.4)
Obesity hospital discharge				
No	3066 (80.1)	163 766 (98.8)	4730 (87.4)	188 933 (99.4)
Yes	760 (19.9)	2008 (1.2)	683 (12.6)	1054 (0.6)
COPD				
No	3454 (90.3)	159 289 (96.1)	4880 (90.2)	182 482 (96.0)
Yes	372 (9.7)	6485 (3.9)	533 (9.8)	7505 (4.0)

Abbreviations: COPD, chronic obstructive pulmonary disease; SES, socioeconomic status.

Table 2. Effect Estimates for Any Diabetes Mellitus or Obesity Admission at Least 3 Years Prior to Amyotrophic Lateral Sclerosis Diagnosis

| | No. | | Odds Ratio (95% CI) | | |
Group	Cases	Controls	Unadjusted	Adjusted[a]	Mutually Adjusted[b]
Diabetes status					
No diabetes	3595	355 761	1 [Reference]	1 [Reference]	1 [Reference]
Diabetes	55	9239	0.59 (0.45-0.77)	0.59 (0.45-0.77)	0.61 (0.46-0.80)
Obesity status					
No obesity	3619	360 495	1 [Reference]	1 [Reference]	1 [Reference]
Obesity	31	4505	0.69 (0.48-0.98)	0.72 (0.50-1.02)	0.81 (0.57-1.16)

[a] Adjusted for socioeconomic status, prior chronic obstructive pulmonary disease, marital status, and residence at amyotrophic lateral sclerosis diagnosis.
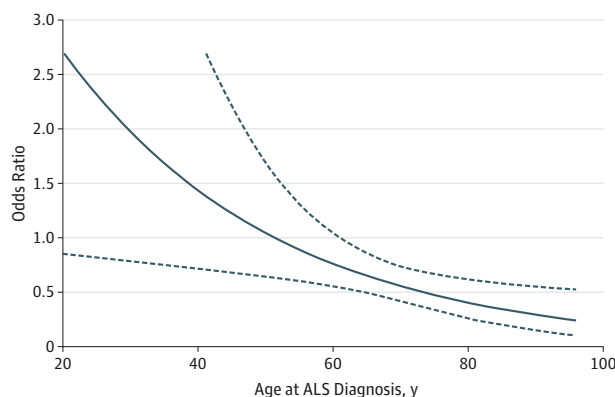
[b] Same as adjusted, with diabetes and obesity simultaneously included in the model.

(*P* = .002), with a significantly protective association among participants older than 40 years at first diabetes-related diagnosis (OR = 0.52; 95% CI, 0.39-0.70) and harmful effects for participants younger than 40 years (OR = 1.66; 95% CI, 0.85-3.21), although the increased OR did not reach statistical significance (*P* = .14). For all examined cutoffs, the associations in the category of older age at diabetes diagnosis remained robust and similar to that in the main analysis. With decreasing cutoff age, however, we observed an upward trend in the association with diabetes among those in the younger group.

Discussion

We conducted a retrospective population-based study to examine the association between diabetes- and obesity-related hospital admissions and risk of ALS diagnosis. When including both in the same model, we observed a significantly protective association with diabetes, but not obesity, on risk of ALS. As we noted, however, a hospital discharge code for obesity likely reflects much more severe obesity than the typical definition of obesity as a BMI greater than 30. The association with

Figure 1. Adjusted Odds Ratios for Diabetes Mellitus by Age at Amyotrophic Lateral Sclerosis (ALS) Onset

Solid line indicates the odds ratio; dashed lines, 95% CI.

Figure 2. Adjusted Odds Ratios for the Association Between Diabetes Mellitus and Amyotrophic Lateral Sclerosis by Age at First Diabetes-Related Admission

For each of the 7 age cutoffs presented (ages 40-70 years by 5-year increments), we conducted a separate analysis for each cutoff age comparing those with an age at first diabetes-related diagnosis before the cutoff age and at or later than the cutoff age vs those without a diabetes diagnosis. Error bars indicate 95% CI.

diabetes was modified by both age at ALS diagnosis and age at diabetes diagnosis, with older age at diagnosis for either disease associated with lower risk for ALS. Both earlier age at ALS diagnosis and earlier age at first diabetes mention in the hospital registers increase the likelihood that the diabetes is type 1. These results thus may suggest that the protective association is with type 2 diabetes but not type 1, which may have the opposite association, ie, an increased risk of ALS.

The association between diabetes and ALS has not been widely examined, with inconsistent findings initially.[29] A recent case-control study in the Netherlands reported a protective association that did not reach statistical significance; misclassification due to self-reported diabetes could have contributed to the attenuated association.[8] Our results, however, are consistent with a recent study in Sweden that reported an OR of 0.66 (95% CI, 0.45-0.80) for diabetes at least 3 years prior to ALS diagnosis.[30]

Previous studies found a protective association between vascular risk factors and ALS and found that obesity was uncommon among patients with ALS.[31] Scarmeas et al[32] found that individuals who had always been slim were at a significantly higher risk for ALS. O'Reilly et al[7] reported that ALS rates were significantly lower among obese individuals (relative rate = 0.73; 95% CI, 0.55-0.96). While the reasons for this association remain unclear, the protective association between higher BMI and ALS is consistently observed,[7,32,33] and this has been suggested to be related to hypermetabolism that is also often observed with ALS.[9,15] Hyperlipidemia and elevated cholesterol levels have also been associated with lower ALS risk.[8,10,31]

The underlying pathophysiological mechanisms of ALS are likely multifactorial, with defective energy metabolism and homeostasis likely playing an important role in pathogenesis.[9,15] Overweight and obese people are at higher risk for type 2 diabetes,[34] and those with type 2 diabetes are at higher risk for elevated cholesterol levels, hyperlipidemia, and vascular disease.[35] Our findings are thus consistent with prior reports suggesting an inverse association between cardiometabolic health and ALS. In addition, higher levels of physical activity
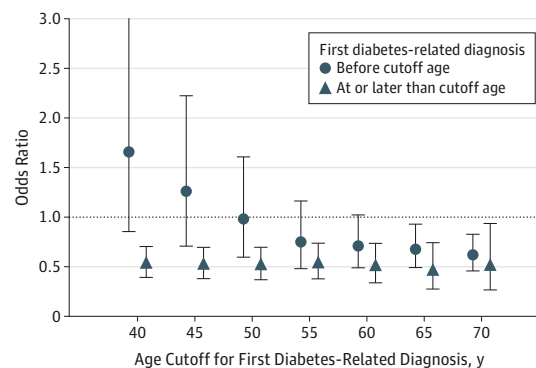
have been associated with increased risk of ALS[32] and are also generally associated with lower BMI, lower risk of diabetes, and generally better cardiometabolic health. It is possible that associations with BMI and diabetes are simply the result of their own association with physical activity. On the other hand, effects of physical activity on cardiometabolic health in general could be the reason for the association between physical activity and ALS. Studies with detailed data on all of these factors, including relevant timing, will be critical for sorting out the relationships between these variables and risk of ALS. We also cannot rule out the possibility that genetic risk factors that give rise to ALS are protective for cardiometabolic disorders and, specifically, diabetes.

If the protective association with diabetes results from some causal association with an aspect of diabetes rather than as a result of correlation with something else, then several possibilities could be surmised. Diabetes medications could be protective. A limited literature on a few compounds to date does not suggest such an effect,[36,37] but not all diabetic medications have been examined. Excitotoxicity or uric acid could also play a role. Glutamate excitotoxicity, a consequence of extracellular glutamate accumulation,[38] has been implicated in ALS pathogenesis.[39,40] The hyperglycemia that is characteristic of individuals with untreated type 2 diabetes[35] (only 14%-17% of individuals with type 2 diabetes are treated with insulin[41]), through enhancing glutamate uptake,[42] could protect against excitotoxic effects. Diabetes has also been associated with high concentrations of uric acid,[43] which has been associated with reduced incidence of other neurodegenerative diseases[44,45] and prolonged survival in ALS.[46]

We found that the association between diabetes and ALS varied by age at ALS diagnosis, trending toward a harmful association with earlier age at ALS diagnosis. This could reflect different associations between type 1 vs type 2 diabetes and ALS because earlier age at ALS onset would also imply earlier age at diabetes onset prior to ALS, which would therefore be

more likely to be type 1 diabetes. However, ALS at earlier ages is likely more commonly genetic in origin; for example, the presence of C9orf72 is more common among younger patients with ALS.[47-49] Therefore, the variation by age at ALS diagnosis could also suggest a different relation between diabetes and ALS when the ALS has a stronger genetic influence. We also found variation in the association with diabetes by the age at diabetes diagnosis. This more strongly suggests a possible difference in the relation of type 1 and type 2 diabetes with ALS because it did not restrict the age at ALS diagnosis. The trend toward an increased risk of ALS following type 1 diabetes is consistent with previous findings,[30,50] but more conclusive evidence will require data with more certain determination of diabetes type than what is available in the NPR.

An opposite association between type 1 diabetes and ALS could be expected based on uric acid or blood glucose levels. In contrast to those with type 2 diabetes, those with type 1 diabetes have lower uric acid levels[51] and are more prone to hypoglycemic excursions because they are all medicated and at risk for insulin treatment–induced hypoglycemia.[52,53] Furthermore, most individuals with type 1 diabetes have type 1A diabetes, ie, of autoimmune etiology,[35,53] and are at higher risk for presenting with additional autoimmune disorders.[54] Autoimmune mechanisms have also been implicated in ALS.[50,55]

Neither outcome nor exposure misclassification can be excluded from our analysis. However, both ALS[21] and diabetes-related[23] hospital discharges have been found to be highly reliable. Furthermore, using hospital diagnoses, we are likely only capturing the most severe cases of diabetes, obesity, and disorders of lipid metabolism. Diabetic individuals have reduced survival compared with nondiabetic individuals, so the possibility that survival differences could affect our results must be considered. However, if this was biasing our findings, we would expect to see stronger bias with diabetes that occurred earlier relative to ALS. Analyses restricting to diabetes at least 5 or 7 years prior to ALS showed results similar to or slightly higher than diabetes at least 3 years prior to ALS.

An additional limitation of our study is the lack of individual-level information on lifestyle factors such as smoking. In Denmark, smoking has been shown to be very highly correlated with occupational status[56]; thus, adjusting for occupation-based SES would partially also adjust for smoking status. More importantly, however, while the association between smoking and ALS is not completely consistent,[57] it appears associated with an increased risk of ALS. Because smoking is a risk factor for diabetes, this would not account for a protective association.

Conclusions

We conducted a nationwide, population-based study and observed an overall protective association between diabetes and ALS diagnosis, with the suggestion that type 2 diabetes is protective and type 1 diabetes is a risk factor. Although the mechanisms underlying this association remain unclear, our findings focus further attention on the role of energy metabolism in ALS pathogenesis.

REFERENCES

1. Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. *N Engl J Med*. 2001;344(22):1688-1700.

2. Mitchell JD, Borasio GD. Amyotrophic lateral sclerosis. *Lancet*. 2007;369(9578):2031-2041.

3. Logroscino G, Traynor BJ, Hardiman O, et al; EURALS. Descriptive epidemiology of amyotrophic lateral sclerosis: new evidence and unsolved issues. *J Neurol Neurosurg Psychiatry*. 2008;79(1):6-11.

4. Seals RM, Hansen J, Gredal O, Weisskopf MG. Age-period-cohort analysis of trends in amyotrophic lateral sclerosis in Denmark, 1970-2009. *Am J Epidemiol*. 2013;178(8):1265-1271.

5. Keller MF, Ferrucci L, Singleton AB, et al. Genome-wide analysis of the heritability of amyotrophic lateral sclerosis. *JAMA Neurol*. 2014;71 (9):1123-1134.

6. Factor-Litvak P, Al-Chalabi A, Ascherio A, et al. Current pathways for epidemiological research in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*. 2013;14(suppl 1):33-43.

7. O'Reilly EJ, Wang H, Weisskopf MG, et al. Premorbid body mass index and risk of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*. 2013;14(3):205-211.

8. Seelen M, van Doormaal PTC, Visser AE, et al. Prior medical conditions and the risk of amyotrophic lateral sclerosis. *J Neurol*. 2014;261 (10):1949-1956.

9. Dupuis L, Pradat P-F, Ludolph AC, Loeffler J-P. Energy metabolism in amyotrophic lateral sclerosis. *Lancet Neurol*. 2011;10(1):75-82.

10. Dupuis L, Corcia P, Fergani A, et al. Dyslipidemia is a protective factor in amyotrophic lateral sclerosis. *Neurology*. 2008;70(13):1004-1009.

11. Desport JC, Preux PM, Truong TC, Vallat JM, Sautereau D, Couratier P. Nutritional status is a prognostic factor for survival in ALS patients. *Neurology*. 1999;53(5):1059-1063.

12. Marin B, Desport JC, Kajeu P, et al. Alteration of nutritional status at diagnosis is a prognostic factor for survival of amyotrophic lateral sclerosis patients. *J Neurol Neurosurg Psychiatry*. 2011;82(6): 628-634.

13. Paganoni S, Deng J, Jaffa M, Cudkowicz ME, Wills A-M. Body mass index, not dyslipidemia, is an independent predictor of survival in amyotrophic lateral sclerosis. *Muscle Nerve*. 2011;44(1):20-24.

14. Wills A-M, Hubbard J, Macklin EA, et al; MDA Clinical Research Network. Hypercaloric enteral nutrition in patients with amyotrophic lateral

sclerosis: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet*. 2014;383 (9934):2065-2072.

15. Turner MR, Hardiman O, Benatar M, et al. Controversies and priorities in amyotrophic lateral sclerosis. *Lancet Neurol*. 2013;12(3):310-322.

16. Krauss RM. Lipids and lipoproteins in patients with type 2 diabetes. *Diabetes Care*. 2004;27(6): 1496-1504.

17. Scheuermann-Freestone M, Madsen PL, Manners D, et al. Abnormal cardiac and skeletal muscle energy metabolism in patients with type 2 diabetes. *Circulation*. 2003;107(24):3040-3046.

18. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004;27(5):1047-1053.

19. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*. 2011;39(7)(suppl): 22-25.

20. Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register: a valuable source of data for modern health sciences. *Dan Med Bull*. 1999;46(3): 263-268.

21. Kioumourtzoglou M-A, Seals RM, Himmerslev L, Gredal O, Hansen J, Weisskopf MG. Comparison of diagnoses of amyotrophic lateral sclerosis by use of death certificates and hospital discharge data in the Danish population. *Amyotroph Lateral Scler Frontotemporal Degener*. In press.

22. Widmaier EP, Raff H, Strang KT. *Vanders Human Physiology: The Mechanisms of Human Body Function*. 11th ed. New York, NY: McGraw-Hill; 2006.

23. Morris AD, Boyle DIR, MacAlpine R, et al; DARTS/MEMO Collaboration. The Diabetes Audit and Research in Tayside Scotland (DARTS) study: electronic record linkage to create a diabetes register. *BMJ*. 1997;315(7107):524-528.

24. Svensson J, Marinelli K, Eising S; Danish Childhood Diabetes Register; National Discharge Register. Comparison of registration of data from the Danish Childhood Diabetes Register and the National Discharge Register [in Danish]. *Ugeskr Laeger*. 2007;169(2):122-125.

25. Carstensen B, Kristensen JK, Ottosen P, Borch-Johnsen K; Steering Group of the National Diabetes Register. The Danish National Diabetes Register: trends in incidence, prevalence and mortality. *Diabetologia*. 2008;51(12):2187-2196.

26. Thomsen AF, Kvist TK, Andersen PK, Kessing LV. Increased relative risk of subsequent affective disorders in patients with a hospital diagnosis of obesity. *Int J Obes (Lond)*. 2006;30(9):1415-1421.

27. Hansen EJ. *Socialgrupper i Danmark*. Copenhagen, Denmark: Institute of Danish Social Science; 1984.

28. Chilvers ER, Lomas DA. Diagnosing COPD in non-smokers: splitting not lumping. *Thorax*. 2010; 65(6):465-466.

29. Lekoubou A, Matsha TE, Sobngwi E, Kengne AP. Effects of diabetes mellitus on amyotrophic

lateral sclerosis: a systematic review. *BMC Res Notes*. 2014;7(1):171.

30. Mariosa D, Kamel F, Bellocco R, Ye W, Fang F. Association between diabetes and amyotrophic lateral sclerosis in Sweden [published online January 19, 2015]. *Eur J Neurol*. doi:10.1111/ene.12632.

31. Sutedja NA, van der Schouw YT, Fischer K, et al. Beneficial vascular risk profile is associated with amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*. 2011;82(6):638-642.

32. Scarmeas N, Shih T, Stern Y, Ottman R, Rowland LP. Premorbid weight, body mass, and varsity athletics in ALS. *Neurology*. 2002;59(5):773-775.

33. Gallo V, Wark PA, Jenab M, et al. Prediagnostic body fat and risk of death from amyotrophic lateral sclerosis: the EPIC cohort. *Neurology*. 2013;80(9): 829-838.

34. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA*. 2003;289(1):76-79.

35. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications, part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15(7):539-553.

36. Kaneb HM, Sharp PS, Rahmani-Kondori N, Wells DJ. Metformin treatment has no beneficial effect in a dose-response survival study in the SOD1(G93A) mouse model of ALS and is harmful in female mice. *PLoS One*. 2011;6(9):e24189.

37. Dupuis L, Dengler R, Heneka MT, et al; GERP ALS Study Group. A randomized, double blind, placebo-controlled trial of pioglitazone in combination with riluzole in amyotrophic lateral sclerosis. *PLoS One*. 2012;7(6):e37885.

38. Suh SW, Gum ET, Hamby AM, Chan PH, Swanson RA. Hypoglycemic neuronal death is triggered by glucose reperfusion and activation of neuronal NADPH oxidase. *J Clin Invest*. 2007;117(4): 910-918.

39. Kiernan MC, Vucic S, Cheah BC, et al. Amyotrophic lateral sclerosis. *Lancet*. 2011;377 (9769):942-955.

40. Turner MR, Kiernan MC. Does interneuronal dysfunction contribute to neurodegeneration in amyotrophic lateral sclerosis? *Amyotroph Lateral Scler*. 2012;13(3):245-250.

41. Centers for Disease Control and Prevention. *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*. Atlanta, GA: US Department of Health & Human Services; 2014.

42. Hyder F, Patel AB, Gjedde A, Rothman DL, Behar KL, Shulman RG. Neuronal-glial glucose oxidation and glutamatergic-GABAergic function. *J Cereb Blood Flow Metab*. 2006;26(7):865-877.

43. Kodama S, Saito K, Yachi Y, et al. Association between serum uric acid and development of type 2 diabetes. *Diabetes Care*. 2009;32(9):1737-1742.

44. Hooper DC, Spitsin S, Kean RB, et al. Uric acid, a natural scavenger of peroxynitrite, in experimental allergic encephalomyelitis and

multiple sclerosis. *Proc Natl Acad Sci U S A*. 1998;95 (2):675-680.

45. Chen H, Mosley TH, Alonso A, Huang X. Plasma urate and Parkinson's disease in the Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol*. 2009;169(9):1064-1069.

46. Abraham A, Drory VE. Influence of serum uric acid levels on prognosis and survival in amyotrophic lateral sclerosis: a meta-analysis. *J Neurol*. 2014;261 (6):1133-1138.

47. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. *Neuron*. 2011; 72(2):245-256.

48. Majounie E, Renton AE, Mok K, et al; Chromosome 9-ALS/FTD Consortium; French Research Network on FTLD/FTLD/ALS; ITALSGEN Consortium. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. *Lancet Neurol*. 2012;11(4):323-330.

49. Sabatelli M, Conforti FL, Zollino M, et al; ITALSGEN Consortium. C9ORF72 hexanucleotide repeat expansions in the Italian sporadic ALS population. *Neurobiol Aging*. 2012;33(8):1848.e15-1848.e20.

50. Turner MR, Goldacre R, Ramagopalan S, Talbot K, Goldacre MJ. Autoimmune disease preceding amyotrophic lateral sclerosis: an epidemiologic study. *Neurology*. 2013;81(14):1222-1225.

51. Bjornstad P, Snell-Bergeon JK, McFann K, et al. Serum uric acid and insulin sensitivity in adolescents and adults with and without type 1 diabetes. *J Diabetes Complications*. 2014;28(3): 298-304.

52. Leese GP, Wang J, Broomhall J, et al; DARTS/MEMO Collaboration. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. *Diabetes Care*. 2003;26(4):1176-1180.

53. Daneman D. Type 1 diabetes. *Lancet*. 2006;367 (9513):847-858.

54. Triolo TM, Armstrong TK, McFann K, et al. Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. *Diabetes Care*. 2011;34(5):1211-1213.

55. Appel SH, Smith RG, Engelhardt JI, Stefani E. Evidence for autoimmunity in amyotrophic lateral sclerosis. *J Neurol Sci*. 1994;124(suppl):14-19.

56. Osler M. Smoking habits in Denmark from 1953 to 1991: a comparative analysis of results from three nationwide health surveys among adult Danes in 1953-1954, 1986-1987 and 1990-1991. *Int J Epidemiol*. 1992;21(5):862-871.

57. Alonso A, Logroscino G, Hernán MA. Smoking and the risk of amyotrophic lateral sclerosis: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2010;81(11):1249-1252.