Statins, diabetes mellitus and prognosis of amyotrophic lateral sclerosis: data from 501 patients of a population-based registry in southwest Germany

J. Schumacher, R. S. Peter, G. Nagel, D. Rothenbacher, A. Rosenbohm, A. C. Ludolph and J. Dorst

ALS Registry Swabia Study Group*

*Department of Neurology, University of Ulm, Ulm; and Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm, Germany

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Background and purpose: A wide variety of metabolic changes, including an increased incidence of diabetes mellitus (DM) and dyslipidaemia, has been described in amyotrophic lateral sclerosis (ALS). The aim of this study was to investigate the associations of statin use and history of DM with onset of disease and survival in patients with ALS.

Methods: In all, 501 patients (mean age 65.2 ± 10.9 years; 58.5% male) from the ALS Registry Swabia recruited between October 2010 and April 2016 were included in this prospective cohort study. Data were collected using a standardized questionnaire.

Results: Statin use (n = 65) was not associated with overall survival (P = 0.62). Age of ALS onset in patients with DM was 4.2 years later (95% confidence interval 1.3–7.2 years) than in patients without DM (P < 0.01). The overall survival of patients with high body mass index at study entry (>27.0 kg/m², upper quartile, n = 127) was prolonged by more than 5 months compared to patients with low body mass index (<22.0 kg/m², lower quartile, n = 123; P = 0.04).

Conclusions: This study supports the view that statin use is not associated with overall survival of ALS patients, suggesting that statins are not harmful and should not be discontinued in ALS. Furthermore, the delayed onset of ALS in patients with DM may mirror the potentially protective metabolic profile associated with type 2 DM. Consistently, this study provides further evidence that high body mass index is a positive prognostic factor in ALS.

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal motor neurone disease characterized by progressive degeneration of upper and lower motor neurons in the spinal cord and brain. This results in progressive paralysis of voluntary muscles which affects mobility, breathing, communication and swallowing. On average, ALS leads to death within 2–4 years [1], often due to respiratory failure. Riluzole is the only known specific disease-modifying drug which prolongs life by approximately 3 months [2,3]. Various gene mutations (SOD1, FUS, TDP-43 etc.) have been identified as aetiological factors in ALS which can be divided into a hereditary (5%–10%) and a sporadic form (90%–95%). The mean age of onset in Caucasians is about 64 years for women and 66 years for men [4].

Since the mid-1990s, it has been known that weight loss is an independent prognostic factor in patients with ALS, causing a 7.7 times higher risk of death [5,6]. Although the mechanisms are still not fully understood, it has been revealed that these patients have an increased resting energy expenditure [7,8]
which occurs before motor symptoms [9] and remains stable during disease progression. A higher respiratory workload or fasciculations cannot sufficiently explain this phenomenon [7]. During the pioglitazone trial, it was noticed that weight gain as the most common side effect of pioglitazone did not occur in ALS patients [10] – a possible indication for a hypothalamic dysfunction [11]. Accordingly, subsequent imaging studies showed hypothalamic atrophy which is associated with weight loss and TDP-43 pathology, emphasizing that ALS is a multisystemic disease [12,13].

Disease-related hypermetabolism is accompanied by alterations of the carbohydrate and lipid metabolism. ALS patients have generally higher serum cholesterol and low density lipoprotein (LDL) levels as well as higher amounts of free fatty acids [14,15]. Furthermore, dyslipidaemia was suspected to be an independent prognostic factor, corroborated by one study which found survival to be more than 12 months longer for patients with an increased LDL/high density lipoprotein ratio [14]. Another retrospective analysis, however, could not confirm the association between serum lipid levels and survival [16].

Based on the assumption that high serum lipid levels are a possible positive prognostic factor, a potential effect of statins on survival has been discussed as well. One prospective study with 164 patients found an association between intake of statins and overall survival, patients with higher statin use scores [17]. However, one meta-analysis [18] and one retrospective study [19] did not confirm this finding.

Regarding carbohydrate metabolism, an increased incidence of impaired glucose tolerance and type 2 diabetes mellitus (DM) based on increased insulin resistance as well as decreased insulin secretion has been described in patients with ALS [15,20]. Possible explanations include an increased insulin resistance due to muscular atrophy as well as a lipotoxic destruction of pancreatic beta cells by free fatty acids [21]. On the other hand, population-based registries suspected an association between type 2 DM and a later age of ALS onset [22,23].

Importantly, most of the data mentioned above were derived from hospital-based registries which are prone to selection bias. Therefore, the aim of this study was to investigate the association of statin use and DM with age of onset and prognosis in patients with ALS from a population-based ALS registry.

Methods

Study design and participants

The study is based on data from the prospective ALS Registry Swabia [4,24,25]. Approximately 8.4 million people live in the catchment area of Swabia, a defined geographic region in southwest Germany. The recruitment period was between October 2010 and April 2016. The registry pursued the goal to estimate epidemiological parameters, to investigate potential risk factors and to describe the natural history of ALS [26].

The collection of data was conducted using an interview-based questionnaire based on the standardized case report form of the European ALS consortium (EURALS) and medical documentation. Information on age, age of onset, site of onset, diagnostic delay, body mass index (BMI), functional status [ALS Functional Rating Scale Revised (ALSFRS-R)] [27] and medical history including morbidity and medication was collected. The interview was performed at the time of inclusion into the registry, which occurred 3.5 (2.1–5.7) months (median, interquartile range) after the patient had been diagnosed with ALS in the respective centre.

Furthermore, an annual systematic mortality update was done via the regional registration office to identify the exact dates of death for all patients included in the registry. Overall, 501 patients with suspected, possible, laboratory-supported, probable and definite ALS according to the revised El Escorial criteria [28] were included in the present analyses.

Assessment of exposure and outcome variables

Disease onset was defined as onset of first paresis as reported by the patient. Disease duration was defined as time between disease onset and either date of death or date of the last systematic mortality update (18 April 2016).

ALS patients were identified as suffering from DM if they met at least one of the following criteria: (i) Diagnosis of DM in the questionnaire (self-reported). (ii) Anti-diabetic medication was used at/before the time of ALS diagnosis as listed in the medication records.

In order to analyse a possible dose-dependent association of statins and overall survival, patients with statins were classified into two subgroups based on the common statin dosages of 20 and 40 mg/day.

For progression rate, two groups were defined based on a recent publication [29]: fast progressors (loss of ALSFRS-R ≥ 1.1 points/month) and slow progressors (loss of ALSFRS-R < 1.1 points/month). Loss of ALSFRS-R per month was calculated as follows: (48 – ALSFRS-R at first visit)/(time between first symptom and first visit in months). Twenty-two patients were excluded from the ALSFRS-R analysis because of insufficient data.
Statistical analysis

Sociodemographic, medical and clinical characteristics at recruitment were displayed in a descriptive way. The association of DM and disease onset was analysed using the unequal-variance t test (Welch t test) and a multiple linear regression model to adjust for BMI and site of onset. Six patients with unknown site of onset were excluded from this model.

The nonparametric Kaplan–Meier method and the log-rank test ( Mantel–Cox test) were used to estimate survival times. Adjusted hazard ratios were estimated by multiple analysis using Cox’s proportional hazards regression model. The following well-established prognostic factors were adjusted for: age of onset (<50 years, 50–65 years, 65–80 years, >80 years), site of onset (spinal, bulbar), BMI (<22.0 kg/m\(^2\), 22.0–24.2 kg/m\(^2\), >24.2–27.0 kg/m\(^2\), >27.0 kg/m\(^2\)), ALSFRS-R at inclusion (<34, 34–39, ≥39–43, ≥43) and progression rate (<1.1/month, ≥1.1/month). The cut-offs for BMI and ALSFRS-R represent respective quartiles. Significance level was set at \( P = 0.05 \). All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethics statement

The ALS Registry Swabia was approved by the ethical boards of Ulm University and the regional medical associations of Baden-Württemberg and Bavaria, Germany.

Results

Demographic data

The study included 501 ALS patients with a mean age of ALS onset of 65.2 ± 10.9 years. The characteristics of the study cohort are presented in Table 1. At study inclusion, 65 patients (13.0%) were taking statins and 59 (11.8%) had DM.

Statins

Amongst 65 ALS patients with use of statins, 54 were taking simvastatin, six atorvastatin, three pravastatin and two fluvastatin. Use of statins was not associated with overall survival \( (P = 0.62) \) (Fig. 1a). ALS patients with statins \( (n = 65) \) had a median survival time of 29.2 months [95% confidence interval (CI) 23.4–36.5], whereas patients without statins \( (n = 436) \) had a median survival time of 32.3 months (95% CI 29.2–35.4).

| Table 1 Patient characteristics |
|---------------------------------|
| **n (%)** | **Mean ± SD** |
| Age of onset (years) | 501 | 65.2 ± 10.9 |
| Male | 293 (58.5) | 64.4 ± 11.2 |
| Female | 208 (41.5) | 66.4 ± 10.4 |
| Site of onset | | |
| Bulbar | 160 (31.9) | | |
| Spinal | 335 (66.9) | | |
| Unknown | 6 (1.2) | | |
| BMI (kg/m\(^2\)) | | 24.7 ± 4.2 |
| Male | 293 (58.5) | 25.0 ± 4.0 |
| Female | 208 (41.5) | 24.1 ± 4.5 |
| Statins use at recruitment | 65 (13.0) | |
| Diabetes mellitus | 59 (11.8) | |
| Deaths during follow-up | 287 (57.3) | |
| Diagnostic delay (months) | 501 | 6.0 (3.0–10.0) |
| Follow-up duration (months) | 501 | 14.3 (7.4–22.3) |
| ALSFRS-R (points) | 479 | 39.0 (34.0–43.0) |
| ALSFRS-R decline (per month) | 479 | 0.9 (0.5–1.5) |

Baseline data were collected at the time of inclusion into the registry. ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Score Revised; BMI, body mass index; IQR, interquartile range.

Furthermore, different doses of statins were not associated with overall survival \( (P = 0.59) \) (Fig. 1b). ALS patients with a statin dose of 20 mg/day \( (n = 42) \) had a median survival of 28.8 months (95% CI 21.2–35.3). Patients with a statin dose of 40 mg/day \( (n = 23) \) had a median survival of 37.0 months (95% CI 22.1 to >65.0).

Diabetes mellitus

Amyotrophic lateral sclerosis patients with DM \( (n = 59) \) had a median survival of 23.4 months (95% CI 20.2–29.2 months). Patients without DM \( (n = 442) \) had a median survival of 32.9 months (95% CI 29.9–36.3 months). Therefore, the median survival of patients with DM was 9.5 months shorter compared to patients without DM. However, this result was not statistically significant \( (P = 0.06) \) (Fig. 2). Multiple Cox regression analysis showed no difference with regard to overall survival in patients with DM compared to patients without DM after adjustment for age of onset, site of onset, BMI, progression rate and ALSFRS-R at inclusion (Table 2). In order to analyse a potential effect of the timing between onset of diabetes and onset of ALS, the overall survival of patients above and below the median (69.1 months).
between diagnosis of diabetes and onset of ALS was compared. No effect on overall survival was found ($P = 0.21$).

Age of ALS onset in patients with and without DM was significantly different ($P < 0.01$). Age of ALS onset in patients with DM (69.1 ± 8.6 years, 95% CI 66.6–71.2) was 4.4 years later than in patients without DM (64.7 ± 11.1 years, 95% CI 63.7–65.8). Multiple linear regression including BMI and site of onset showed a statistically significant association of DM with age of onset (Table 3). After adjustment, the mean onset of ALS for patients with DM was 4.2 years later than in patients without DM.

**Other prognostic factors**

Kaplan–Meier analysis revealed a significant positive association between increased BMI and overall survival. The upper quartile of BMI was significantly associated with increased overall survival compared to the lower quartile ($P = 0.04$) (Fig. 3). Patients with BMI < 22.0 kg/m$^2$ ($n = 123$) had a median overall survival of 29.5 months (95% CI 23.9–33.5). Patients with BMI ≥ 27.0 kg/m$^2$ ($n = 127$) had a median overall survival of 34.8 months (95% CI 28.6–42.0).

Moreover, significant positive associations for younger age of onset ($P < 0.001$), spinal onset ($P < 0.01$), lower progression rate ($P < 0.001$) and

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**Figure 1** Statins and survival. (a) Statin use and overall survival. Kaplan–Meier survival curves for ALS patients with ($n = 65$; red) and without ($n = 436$; blue) statins. Censored patients are marked with +. $P = 0.62$ (log-rank test). (b) Statin dosages and overall survival. Kaplan–Meier survival curves for patients with statin dosages of 20 mg/day ($n = 42$; blue) and 40 mg/day ($n = 23$; red). Censored patients are marked with +. $P = 0.59$ (log-rank test). [Colour figure can be viewed at wileyonlinelibrary.com]

**Figure 2** Diabetes and overall survival. Kaplan–Meier survival curves for patients with ($n = 59$; red) and without diabetes mellitus ($n = 442$; blue). Censored patients are marked with +. $P = 0.06$ (log-rank test). [Colour figure can be viewed at wileyonlinelibrary.com]
higher ALSFRS-R at inclusion \((P < 0.001)\) with increased overall survival were found in the univariate analysis (Table 2). Adjusted analysis confirmed a statistically significant association with overall mortality for age of onset, site of onset, progression rate and ALSFRS-R at inclusion. For BMI, only the group with BMI > 24.2–27.0 kg/m\(^2\) showed a significant effect \((P = 0.01)\). Patients with BMI > 24.2–27.0 kg/m\(^2\) had a 37% decreased overall mortality compared to patients with BMI < 22.0 kg/m\(^2\) (Table 2).

**Discussion**

Recently, metabolic changes have been increasingly recognized as a prominent feature in ALS and have been suggested as prognostic factors as well as potential therapeutic targets. Some prognostic metabolic factors, such as hypermetabolism and weight loss, have been firmly established, whilst others, including the role of serum lipid levels and statins as well as carbohydrate metabolism and diabetes, are still discussed controversially. In this registry-based cohort study including \(n = 501\) patients with ALS, no association of statin use with overall survival was found.

Patients with DM were older when ALS was diagnosed than patients without DM, a finding which has to be interpreted with caution as older age is associated with DM; therefore, this finding could also be a result of confounding.

**Statins and ALS**

The prevalence of statin use in our study population was 13% and therefore lower compared to data published for non-ALS patients between 65 and 79 years in Germany which indicated a prevalence of 27% [29]. This result is in line with previous publications which found a lower prevalence of hyperlipidaemia and statin use for ALS patients [30]. The use of statins was not associated with overall survival in this study \((P = 0.62)\). Dyslipidaemia was previously suspected to be an independent positive prognostic factor for ALS in a retrospective study [14], although other studies did not confirm this finding [16]. Furthermore, a relationship between LDL, apolipoprotein B, apolipoprotein B/apolipoprotein A ratio and the risk of ALS has been discussed [31]. A retrospective analysis showed a beneficial effect for

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**Table 2** Prognostic factors and overall mortality

| Variable          | Unadjusted analysis (log-rank) | Adjusted analysis (Cox regression) |
|-------------------|--------------------------------|-----------------------------------|
|                   | Overall survival               | Overall mortality                 |
|                   | \(n\)                          | Median 95% CI \(P\) value HR 95% CI \(P\) value |
| Age of onset      |                                | <0.001 (ref.*)                    | <0.001 |
| <50 years         | 45                             | 58.6 36.6–58.6                    | 1.58 0.90–2.79 0.11 |
| 50–65 years       | 182                            | 36.5 33.9–42.4                    | 2.59 1.48–4.53 <0.001 |
| 65–80 years       | 242                            | 27.6 24.6–30.2                    | 4.78 2.41–9.50 <0.001 |
| >80 years         | 32                             | 20.2 14.8–24.4                    |                 |
| Site of onset     |                                | <0.01 (ref.*)                     | 0.13 0.06 |
| Spinal            | 335                            | 34.8 30.0–37.0                    | 1.34 1.04–1.73 0.02 |
| Bulbar            | 160                            | 27.4 24.4–31.4                    |                 |
| BMI 0.13 \(<22.0\) kg/m\(^2\) | 123                            | 29.5 23.9–33.5                    | 0.79 0.57–1.11 0.18 |
| 22.0–24.2 kg/m\(^2\) | 126                            | 31.4 27.9–40.0                    | 0.63 0.45–0.88 0.01 |
| >24.2–27.0 kg/m\(^2\) | 125                            | 32.4 25.7–50.1                    | 0.76 0.54–1.07 0.11 |
| >27.0 kg/m\(^2\)  | 127                            | 34.8 28.6–42.0                    |                 |
| Diabetes 0.06     |                                | No 442 32.9 29.8–36.3 (ref.*)     | 1.05 0.74–1.49 0.80 |
| Yes               | 59                             | 23.4 20.2–29.2                    | 3.04 2.30–4.02 <0.001 |
| Progression rate  |                                | <0.001 (ref.*)                    | 0.01 |
| <1.1/month        | 303                            | 40.5 36.3–44.8                    | 1.05 0.74–1.49 0.80 |
| ≥1.1/month        | 176                            | 21.0 20.0–23.7                    | 3.04 2.30–4.02 <0.001 |
| ALSFRS-R <0.001   |                                | <34 109 22.1 20.2–24.6 (ref.*)    | 0.61 0.44–0.84 <0.01 |
| 34–39             | 121                            | 30.4 28.8–40.5                    | 0.70 0.50–0.98 0.04 |
| >39–43            | 126                            | 33.5 28.8–40.6                    | 0.60 0.40–0.90 0.01 |
| >43               | 123                            | 44.8 35.6–46.5                    |                 |

Log-rank test for median overall survival. Multivariable Cox regression model adjusted for age of onset, site of onset, BMI, progression rate and ALSFRS-R. ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Score Revised; BMI, body mass index; CI, confidence interval; HR, hazard ratio. Significant bold values indicates \(P\)-values \((P < 0.05)\). *Reference category.
triglycerides and cholesterol on survival, which was not independent but related to associated prognostic factors such as BMI [32]. Accordingly, Paganoni et al. suggested that BMI was an independent prognostic factor, but not dyslipidaemia [33].

The question of whether or not dyslipidaemia is a positive prognostic factor has significant clinical importance since lipid-lowering drugs such as statins could have a negative effect accordingly. One prospective study originally showed a faster disease progression in ALS patients with statins [34]. A retrospective analysis from Israel did not find statins to be a negative prognostic factor [35]. Nefussy et al. suspected a gender-based effect of statins [34] whereas a meta-analysis did not show an association with ALS incidence or disease progression [18].

More recent studies showed conflicting results regarding the relationship between the risk of ALS and statins. Smaller case series initially showed a slightly higher risk for patients with statins [36,37], but a population-based case-control study from Denmark (556 ALS cases and 5560 controls) could not confirm this finding [38].

Importantly, the vast majority of data refer to hospital-based registries, therefore carrying the risk of selection bias. Warnings regarding the use of statins in ALS were mainly derived indirectly from studies on dyslipidaemia and not from studies investigating the effect of statins on survival directly. In this population-based study, no effect of statins on survival was found, suggesting that they do not induce a negative disease-modifying effect.

### Diabetes mellitus and ALS

In this study, DM was not independently associated with overall survival, supporting recent studies [39]. However, the onset of ALS in patients with DM was 4 years later ($P < 0.01$) compared to patients without DM. This finding is consistent with previous studies that have shown an association between DM and a later age of onset in ALS [39].

### Table 3: Diabetes mellitus and age of ALS onset

| Age of onset (SD), years | Mean age of ALS onset in specific strata | Multiple linear regression | 95% CI |
|-------------------------|-----------------------------------------|---------------------------|--------|
| Diabetes mellitus       |                                         |                           |        |
| No (ref.) ($n = 437$)   | 64.7 (11.1)                             | $4.2^*$                    | 1.3–7.2|
| Yes (n = 58)            | 69.1 (8.6)                              |                           |        |
| Site of onset           |                                         |                           |        |
| Spinal ($n = 335$)      | 64.0 (11.2)                             | $3.6^*$                    | 1.5–5.6|
| Bulbar (n = 160)       | 67.8 (10.1)                             |                           |        |
| BMI (kg/m²)             |                                         |                           |        |
| $<24.7$ (ref.) ($n = 276$) | 65.6 (11.3)                         | $-1.0$                     | $-2.9$ to $1.0$ |
| $\geq 24.7$ ($n = 219$) | 64.7 (10.5)                             |                           |        |

Multiple linear regression model including age of onset, diabetes, site of onset and BMI. Dependent variable: age of onset (years). Independent variables: diabetes, site of onset, BMI (kg/m²). ALS, amyotrophic lateral sclerosis; BMI, body mass index; CI, confidence interval. $^a$Regression coefficient. $^b$Reference category. $^*P < 0.01$.

### Figure 3: BMI and overall survival

Kaplan–Meier survival curves for patients with BMI $< 22.0$ kg/m² ($n = 123$; blue), BMI 22.0–24.2 kg/m² ($n = 126$; red), BMI $> 24.2$–27.0 kg/m² ($n = 125$; green) and BMI $> 27.0$ kg/m² ($n = 127$; brown). Censored patients are marked with +. BMI $< 22.0$ kg/m² vs. BMI $> 27.0$ kg/m²: $P = 0.04$ (log-rank test). [Colour figure can be viewed at wileyonlinelibrary.com]
DM. A multiple linear regression model confirmed this finding after adjustment for site of onset and BMI. Since there was no control group, it cannot be decided whether the delayed onset of ALS was due to the fact that patients with DM are generally older or due to a real protective effect of DM as suggested by a previous retrospective, population-based study [23].

A recent study by Mariosa et al. [40] found that type 1 DM was associated with an increased risk and type 2 DM with a decreased risk of ALS, suggesting that the specific metabolic profiles associated with type 1 and type 2 DM may be associated with these findings. Supporting this hypothesis, an increased risk of ALS has been described in patients with low BMI which is often associated with type 1 DM [41]. Other studies suggested that the risk of ALS may be increased for individuals with a slim body type and athletic lifestyle [42]. Consistently, type 2 DM is associated with high BMI, which is known to have a protective role in ALS [43,44]. D’Ovidio et al. recently found a 70% decreased risk of ALS for patients with type 2 DM in a population-based study [44]. Accordingly, high adiponectin serum levels, which are associated with high body weight and type 2 DM, have been found to be also associated with a decreased risk of ALS [45]; in the same study, the opposite effect was described for high leptin serum levels, which are associated with low body weight [45]. Additionally, high serum levels of retinol-binding protein 4 (RBP4), a protein contributing to insulin resistance and DM, are inversely related to risk for and prognosis of ALS [46].

Other prognostic factors in ALS

The overall survival of patients with high BMI was prolonged by more than 5 months compared to patients with low BMI \( (P = 0.04) \). This confirms the protective role of a high BMI [8,26,31] and is in line with our findings regarding DM. Furthermore, previously established negative prognostic factors including older age of onset, bulbar onset and lower ALSFRS-R at time of diagnosis were confirmed [47]. Importantly, fast progressors with an ALSFRS-R decline \( \geq 1.1 \) points/month had a significantly shorter survival \( (P < 0.001) \), which has to be considered in clinical trials with regard to stratification as highlighted by recent studies [48,49].

Strengths and limitations

The main strength of this study is the large sample size including long-term follow-up data. As opposed to previous studies investigating metabolic risk factors, data are based on a population-based registry rather than a hospital-based cohort; the latter is more likely to be prone to selection bias. The registry also includes a large defined geographical area with a very high inclusion coverage and completeness of ALS patients and comprises high-quality, repeated follow-up data [24].

The following limitations have to be mentioned. The diagnosis of DM and statin use were derived from patients’ records, self-reports or the existence of anti-diabetic drugs rather than direct evidence. No data about specific dietary measures which may have influenced the results were collected. Information on vital capacity, which is known as an independent prognostic factor, was not collected. Finally, measurement of progression rate was based on potentially imprecise anamnestic information and does not take into account the nonlinear character of the ALSFRS-R.

Conclusion

In this study, statins did not affect overall survival, suggesting that they do not induce a negative disease-modifying effect in ALS. Therefore, it can be assumed that they are not harmful and may be continued in ALS. Furthermore, ALS patients with DM had an age of onset 4.2 years later, suggesting a potential protective role of the metabolic profile associated with type 2 DM as suggested by previous studies. Consistently, higher BMI was associated with prolonged overall survival. However, further studies including an appropriate control group are needed to confirm these observations.

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Disclosure of conflicts of interest

All authors state that they have no conflicts of interest.

Data sharing

Individual participant data that underlie the results reported in this article, after de-identification (text, tables and figures), as well as the study protocol will

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be available. Data will be available beginning 3 months and ending 5 years following article publication. Data will be shared with researchers who provide a methodologically sound proposal. Data will be shared for analyses to achieve the aims in the approved proposal. Proposals should be directed to johannes.dorst@uni-ulm.de; to gain access, data requestors will need to sign a data access agreement. Data are available for 5 years at https://www.uniklinikum-ulm.de/neuroologie.html.

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**Appendix 1**

The help of all members of the ALS registry Swabia study group is appreciated: Dr med. Andres F., Kreiskliniken Reutlingen, Department of Neurology; Prof. Dr Arnold G., Klinikum Sindelfingen-Boeblingen, Department of Neurology; Dr Baier H., ZFP Suedwurttemberg, Department of Epileptology; Prof. Dr Baetner H., Katharinenhospital Stuttgart, Department of Neurology; Dr Beattie J., Ostalb-Klinikum Aalen, Department of Neurology; Dr Behne F., ZFP Suedwurttemberg, Department of Epileptology; Prof. Dr Bengel D., Oberschwabenklinik Ravensburg, Department of Neurology; Dr med. Boerlein A., Katharinenhospital Stuttgart, Department of Neurology; Dr med. Bracknies V., Department of Neurology, Dietenbronn; Dr Burkhard A., Klinikum Günzburg, Department of Neurology; PD Dr med. Buttmann M., Caritas Krankenhaus, Bad Mergentheim, Department of Neurology; Dr med. Dempewolf S., Department of Neurology, Ludwigsburg; Prof. Dr Dettmers C., Schmieder Kliniken Konstanz; Prof. Dr med. Freund W., Praxis Biberach; Prof. Dr Gasser T., Universitatsklinik Tübingen, Department of Neurology; Dr Gold H.-J., Klinikum am Gesundbrunnen Heilbronn, Department of Neurology; Prof. Dr Hamann G., Klinikum Guenzburg, Department of Neurology; PD Dr Hecht M., Bezirkskrankenhaus Kaufbeuren, Department of Neurology; Dr med. Heimbach B., University of Freiburg, Department of Neurology; PD Dr B. Herting, Diakonie-Klinikum Schwaebeisch Hall, Department of Neurology; Prof. Dr med. Huber R., Klinikum Friedrichshafen, Department of Neurology; Prof. Dr med. Huelscr P. J., Fachklinik Wangen, Department of Neurology; Dr Huber-Hartmann K., Kliniken Landkreis Heidenheim, Department of Neurology; Dr Jüttler E., Ostalb-Klinikum Aalen,

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Department of Neurology; Dr med. Kaspar A., Oberschwabenklinik Ravensburg, Department of Neurology; Prof. Dr med. Kern, Klinikum Kempten, Department of Neurology; Prof. Dr med. Kimmig H., Kliniken Schwenningen, Department of Neurology; Prof. Dr med. Kloetzsch C., Schmieder Kliniken Allensbach; Prof. Dr Klopstock T., LMU München, Department of Neurology; Dr Kohler A., Klinikum am Gesundbrunnen Heilbronn, Department of Neurology; PD Dr med. Lichy C., Klinikum Memmingen, Department of Neurology; Prof. Dr Lindner A., Marienhospital Stuttgart, Department of Neurology; Prof. Dr med. Lingor P., TU München, Department of Neurology; Prof. Dr Luélé D., Ulm University, Department of Neurology; Oberstarzt Dr Metrikat J., Bundeswehrkranankenhaus Ulm, Department of Neurology; Dr Meudt O., Klinikum Memmingen, Department of Neurology; Prof. Dr Meyer A., Weissenau, Department of Neurology; Dr med. Naegle A., Christophshof Göppingen, Department of Neurology; Prof. Dr Naumann M., Klinikum Augsburg, Department of Neurology and Neuropsychology; Dr med. Neher K.-D., Vinzenz von Paul Hospital Rottweil, Department of Neurology; PD Dr Neuhaus O., Kliniken Landkreis Sigmaringen, Department of Neurology; Prof. Dr med. Neus C., Praxis EMSA Singen; Prof. Dr Niehaus L., Department of Neurology, Winnenden; Dr med. Raape J., ZFP Suedwurttemberg, Neurologie Weissenau; Dr med. Ratzka P., Klinikum Augsburg, Department of Neurology and Neuropsychology; Prof. Dr med. Reinhard M., Kliniken Esslingen, Department of Neurology; Dr Rothmeier J., ZFP Suedwurttemberg, Neurologie Weissenau; PD Dr med. Sabolek M., Department of Neurology, Biberach; Prof. Schabet M., Department of Neurology, Ludwigsburg; Dr med. Scheff-Vogelsang M., Diakonie-Klinikum Schwaebsisch Hall, Department of Neurology; Dr med. Schell C., Kreiskliniken Reutlingen, Department of Neurology; Dr med. Schütz K., Kliniken Schwenningen, Department of Neurology; Dr med. Schweigert B., Caritas Krankenhaus, Bad Mergentheim, Department of Neurology; Prof. Dr Sommer N., Christophshof Göppingen, Department of Neurology; Dr med. Stroick M., Klinikum Memmingen, Department of Neurology; Prof. Dr Synofzik M., Universitätsklinikum Tübingen, Department of Neurology; Dr med. Trottenberg T., Department of Neurology, Winnenden; Prof. Dr Tumani H., Department of Neurology, Dietersbronn; Prof. Dr Volkmann J., University of Würzburg, Department of Neurology; Dr med. Weiler M., University of Heidelberg, Department of Neurology; Prof. Dr med. Wick W., University of Heidelberg, Department of Neurology; Prof. Dr med. Opherk C., Klinikum am Gesundbrunnen Heilbronn, Department of Neurology; Dr med. Lewis D., Marienhospital Stuttgart, Department of Neurology; Prof. Dr med. Hemmer B., TU München, Department of Neurology; Prof. Dr med. Weiller C., University of Freiburg, Department of Neurology; Priv.-Doz. Dr Zeller D., University of Würzburg, Department of Neurology; Dr med. Baumgartner J., BKH Augsburg, Department of Psychiatry; Dr med. Born Ch., Klinikum am Weissenhof, ZIP Weinsberg, Department of Psychiatry East; Prof. Dr med. Birgul M., Klinikum Stuttgart, Department of Psychiatry; Prof. Dr med. Conenmann B., Uniklinik Ulm, Department of Psychiatry III; Univ.-Prof. Dr Eiterstorfer E., Furtenbachkranankenhaus Stuttgart, Department of Psychiatry; Dr med. Friederich H., ZIP Zwiefalten, Department of Geriatric Psychiatry; Prof. Dr Gahr M., Uniklinik Ulm, Department of Psychiatry III; Dr med. Gogolikiewicz A., ZIP Zwiefalten, Department of Psychiatry; Dr med. Greber R., Vinzenz v. Paul Hospital Rottweil, Department of Geriatric Psychiatry; Gebhardt J., ZIP Wiesloch, Department of Geriatric Psychiatry; PD Dr med. Grunze H., Klinikum am Weissenhof, ZIP Weinsberg, Department of Psychiatry East; Dr med. Henkel K., Christophshof Göppingen, Department of Geriatric Psychiatry; Prof. Dr Dr Hewer W., Christophshof Göppingen, Department of Geriatric Psychiatry; Jonuz A., Klinikum Schloss Winnenden, Department of Geriatric Psychiatry; Prof. Dr med. Joos A., Kliniken Schmieder Gailingen, Department of Psychotherapeutic Neurology; Dr med. Köhler M., ZIP Zwiefalten, Department of Geriatric Psychiatry; Dr med. Koszian R., Vinzenz v. Paul Hospital Rottweil, Department of Geriatric Psychiatry; Prof. Dr med. Laske Ch., Uniklinik Tübingen, Department of Geriatric Psychiatry; Dr med Michaelides A., Furtenbachkranankenhaus Stuttgart, Department of Psychiatry; PD Dr med. Munk M., Uniklinik Tübingen, Department of Geriatric Psychiatry; Niestroj A., ZIP Wiesloch, Department of Geriatric Psychiatry; Prof. Dr Ruchhau J., Christophshof Göppingen, Department of Psychiatry; Prof. Dr Schmauss M., BKH Augsburg, Department of Psychiatry; Dr med. Schöneberger-Stroick K., BKH Memmingen, Department of Psychiatry; Dr Schörner K., Kliniken Schmieder Gailingen, Department of Psychotherapeutic Neurology; Sheka C., Klinikum Schloss Winnenden, Department of Geriatric Psychiatry; Dr med. Spanhorst S., Klinikum Stuttgart, Department of Mental Health and Geriatrics; Steber R., BKH Memmingen, Department of Psychiatry; PD Dr med. Thomas Ch., Klinikum Stuttgart, Department of Mental Health and Geriatrics; Prof. Dr med Vasic N., Christophshof Göppingen, Department of Psychiatry.