RESEARCH PAPER

Exploring the fitness hypothesis in ALS: a population-based case-control study of parental cause of death and lifespan

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ABSTRACT

Objective To investigate the theory of premorbid fitness in amyotrophic lateral sclerosis (ALS), we studied whether a common genetic profile for physical or cardiovascular fitness was manifest in progenitors leading to less cardiovascular death and a longer lifespan in parents of patients with ALS compared with parents of controls.

Methods Patient and disease characteristics, levels of physical activity, parental cause and age of death were obtained using a structured questionnaire from a population-based, case–control study of ALS in the Netherlands. Logistic regression was used for the analyses of parental cause of death and levels of physical activity. Cox proportional hazard models were applied to study the association between parental survival and ALS, or specific patient subgroups. All models were adjusted for age at inclusion, level of education, body mass index, diabetes, hypercholesterolaemia and hypertension.

Results 487 patients and 1092 controls were included. Parents of patients died less frequently from a cardiovascular disease compared with parents of controls (OR=0.78, p=0.009). Their survival, however, was neither significantly longer nor shorter. Neither rates of cardiovascular causes of death, nor survival of parents was related to the extent to which patients were physically active in leisure time (all p>0.05).

Conclusions Exploring the fitness hypothesis in the pathogenesis of ALS, our findings provide evidence for a shared mechanism underlying a favourable cardiovascular fitness profile and ALS susceptibility.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a devastating disease characterised by motor neuron degeneration, leading to progressive weakness and death, on average within 3 years after symptom onset. It is believed that sporadic ALS (approximately 90%–95% of all cases) is the result of the interplay between multiple exogenous and genetic factors.1 2

Environmental and lifestyle risk factors have been suggested, including physical activity. We have previously shown that leisure time physical activity is associated with an increased ALS risk.3 The lack of association with occupational physical activity and absence of a dose–response relationship in this study supports the hypothesis that not increased physical activity per se but rather a genetic profile or lifestyle promoting physical fitness increases ALS susceptibility.4 This is also indicated by a cohort study of 684459 men in Sweden, in which they found phenotypic physical fitness to be a risk factor for death from ALS at a relatively early age.5 The hypothesis that patients with ALS who are premorbidly physically fitter is further supported by a favourable cardiovascular risk.6 7

If unambiguous evidence emerges that factors associated with physical or just cardiovascular fitness are important, future focused fundamental research may provide a worthwhile path to unravelling the ALS pathophysiology. We hypothesise that a common genetic profile for these traits will also manifest in progenitors, thus leading to less cardiovascular death and a longer lifespan in parents of patients with ALS compared with parents of controls. In this large population-based, case–control study, we explored parental causes of death and survival in patients with ALS and in matched controls, or in subsets of participants with specific characteristics.

METHODS

Study design and participants

The Prospective ALS study the Netherlands (PAN) is a population-based, case–control study aiming, by means of questionnaires, to register data on environmental and lifestyle risk factors as well as record an extensive family history from all patients with ALS and related disorders in the Netherlands, and from control subjects. The Netherlands is a densely populated country where healthcare is accessible to all inhabitants and all residents are registered with a general practitioner. This promotes accurate acquisition of population-based cases and controls. Patients are continuously enrolled through multiple sources: neurologists, the Dutch Neuromuscular Patient Association and rehabilitation physicians. In addition, participants can be registered via a website (http://www.alsonderzoek.nl/). Controls are acquired through the general practitioner of the participating patient, who is asked to select subjects from his register in alphabetical order starting at the surname of the patient. Spouses or blood relatives of the patients are not eligible to prevent over-matching. Patients and controls are matched for age (±5 years), gender and residential area.8

We included matched patients and controls who completed the questionnaire between 1 May 2010 and 21 April 2014. Patients were diagnosed with
possible, probable—laboratory supported, probable or definite ALS according to the revised El Escorial criteria.9 We excluded subjects if one of their parents died of ALS. All participants gave written informed consent and the study was approved by the medical ethical committee.

Data collection
Using a structured questionnaire, data on demographic information, parental year of birth, parental cause and age of death, body mass index (BMI), (year of) diagnosis of diabetes, hypercholesterolaemia and hypertension were collected for this study from all participants. The questionnaire was designed to collect data on a variety of risk factors; participants were unaware of the hypotheses being tested to reduce recall bias. All questionnaires were checked thoroughly by two persons for missing data or inconsistencies, and participants were approached by telephone to complete or correct the data. After patients had given informed consent, medical records were obtained for clinical information. The survival status of patients was derived from the municipal population register or by contacting the general practitioner on a 3-monthly basis, or both. Data were coded to ensure blinding.

Highest level of education was categorised into four groups: (1) No education or elementary school, (2) lower secondary school or technical school, (3) higher secondary school and (4) higher professional education or university.

Parental cause of death was classified into the following categories based on expert opinion: cardiovascular diseases, neurodegenerative diseases, psychiatric disorders, cancer, infectious diseases, autoimmune diseases, surgery, trauma, severe trauma, old age, other and unknown. A distinction between trauma and severe trauma was made to distinguish those who perished in events such as a traffic accident or war (severe trauma) and those who died after minor trauma at an already vulnerable age.10

Data on lifetime physical activity was gathered by asking for the description of the activity participated in, duration per week and the year of initiation and stop year. All reported sports and hobbies were objectively quantified using the internationally accepted compendium of physical activities, assigning metabolic equivalent of task (MET) scores to the leisure time activities. A more extensive description of this classification has been reported previously.7

For the analyses of subsets of participants, patients were categorised as ‘sporadic ALS’, ‘familial ALS’ and ‘with C9orf72 repeat expansion’. ‘Familial ALS’ was defined as those with a first, second or third degree family member with ALS, or with a repeat expansion in the C9orf72 gene. In patients we determined the C9orf72 repeat expansion by performing a repeat-primed PCR as described in previous studies.11 12

Statistical analysis
Multivariate logistic regression was used to compare causes of death between parents of patients and parents of controls, and in particular to analyse whether parents of patients were less likely to die of cardiovascular diseases. We chose to adjust all models for age at time of inclusion, educational level, BMI, diabetes, hypercholesterolaemia and hypertension. In the subset analyses of patients with ‘familial ALS’ and ‘C9orf72 repeat expansion’, we restricted the model adjustment to age at time of inclusion and educational level, because of the smaller sample sizes. Age of subjects was included because we assume that older subjects will have parents who were born earlier in the 20th century. As life expectancy changed during the previous century, this might influence both the cause of death and the average lifespan. Moreover, it has been previously hypothesised that the age at onset might be influenced by (prenatal) environmental factors, such as dietary habits or exposure to smoking in utero, which could result in both an increased ALS risk and a reduced parental life expectancy.11 Educational level was included because we feel it serves as a good proxy for socioeconomic status of subjects and their direct environment, assuming this covers confounding factors such as the subjects’ alcohol use, smoking habits and BMI. Educational level is associated with morbidity, mortality and life expectancy in parents. A diagnosis of diabetes, hypercholesterolaemia and/or hypertension was adjusted to the period before symptom onset for patients and study inclusion for controls. The same model was used to determine the association between leisure time physical activity and cardiovascular death. A multivariate Cox proportional hazard model was used to study the association between parental survival and ALS. This model was also used to determine the association of parental age with patient and disease characteristics, and with levels of physical activity. To relate patient survival to parental age, only deceased patients were included in the model. With regard to disease characteristics and physical activity, survival and MET scores were categorised into quartiles. All survival analyses were stratified for fathers and mothers to include subjects for whom information on only one parent was available. In the stratified analysis, subjects whose parent died following severe trauma were excluded. Censoring age was calculated based on the parental year of birth, using 1 July of the corresponding year. As censoring date we used the date of study inclusion. Again, we adjusted for age at time of inclusion, educational level, BMI, diabetes, hypercholesterolaemia and hypertension in the analyses of patients with ‘sporadic ALS’ and age at time of inclusion and educational level in the survival analyses of the patients with ‘familial ALS’ and ‘C9orf72 repeat expansion’. The level of significance was set at p<0.05.

RESULTS
Between 1 May 2010 and 21 April 2014 we included 754 patients with ALS in the PAN, of which 568 patients with ALS returned the questionnaire (response rate 75.3%). Baseline characteristics were comparable between the two groups (online supplementary table S1). After excluding 14 patients whose parent died of ALS, a total of 1579 subjects (487 patients with apparent sporadic ALS and 1092 controls) were found eligible for inclusion. Data were available on both parents of 475 patients. In 12 patients, data were only completed for one parent (1 father and 11 mothers). Data were available on both parents of 1054 controls. In 38 controls, data were only completed for one parent (2 fathers and 36 mothers). Table 1 represents the baseline characteristics for both groups.

Cardiovascular disease was significantly less frequently the cause of death in parents of sporadic patients with ALS compared with parents of controls (31.2% vs 35.8%; OR (95% CI) = 0.78 (0.64 to 0.94), p=0.009) (table 2). The survival of parents who died from a cardiovascular disease was similar in patients and controls. The rates of a cardiovascular cause of death, as well as the age at death from a cardiovascular disease, were comparable between parents of patients who were least (lower 25th percentile), and parents of patients who were most (upper 25th percentile) physically active in leisure time (26.3% and 24.6%; 74.0 and 72.5 years; online supplementary table S2).
We also found that parents of sporadic patients with ALS (4.0%) more often die from diseases categorised as ‘other’ when compared with parents of controls (2.3%) (OR (95% CI) = 2.09 (1.27 to 3.40), p=0.003), without a difference in survival. This category includes a variety of diseases of the kidneys, liver or lungs.

Parents of patients with familial ALS were more likely to die from neurodegenerative diseases (all dementia) than parents of controls (67.6% dementia, 27% Parkinson’s disease, 2.7% multiple sclerosis and 2.7% Huntington’s disease) (OR (95% CI) = 2.77 (1.33 to 5.76), p=0.01), without a difference in the parental age at death. A similar trend was also seen in parents of patients with a C9orf72 repeat expansion (online supplementary table S3).

An overview of the number of deceased and censored parents and the age at death or, when alive, age at moment of filling in the questionnaire (censoring age) is provided in table 3. Due to a longer life expectancy in women, more mothers (20.6% of the patients, 25.0% of the controls) than fathers (8.8% of the patients, 9.7% of the controls) were alive at the time the questionnaire was filled in. The median age at death was similar in the patients, 25.0% of the controls) than fathers (8.8% of the patients, 74.0 years) and controls (75.0 years), as well as in fathers of patients (74.0 years) and controls (75.0 years).

Figure 1 displays the Kaplan-Meier survival curves, showing a similar survival for parents of sporadic patients with ALS and controls. HR, adjusted for age at time of inclusion and education, were 1.04 (95% CI 0.92 to 1.17, p=0.55) for fathers, and 1.03 (95% CI 0.90 to 1.17, p=0.66) for mothers. The same holds for parents of 55 patients with familial ALS (61.8% with a C9orf72 repeat expansion), and parents of 35 patients with a C9orf72 repeat expansion (14.3% having at least one family member with ALS): their survival was similar to the survival of parents of controls. HRs for parents of patients with familial ALS compared with controls were 1.08 (95% CI 0.79 to 1.46, p=0.64) for fathers, and 1.25 (95% CI 0.91 to 1.73, p=0.17) for mothers; for parents of patients with C9orf72 repeat expansion compared with controls were 1.07 (95% CI 0.72 to 1.58, p=0.73) for fathers, and 1.46 (95% CI 0.98 to 2.16, p=0.06) for mothers.

No association was found between site of onset and parental survival (HR_ElEscorial definite = 0.89, p=0.29; HR_ElEscorial probable = 1.11, p=0.39), nor was there an association between disease duration until death of parents and survival of parents (HR_disease duration = 1.02, p=0.93; HR_disease duration = 1.21, p=0.35). No difference was found in parental survival between patients who were least active and those who were most active in leisure time (HR_activity = 1.33, p=0.07; HR_activity = 0.97, p=0.84) (online supplementary table S4).

**DISCUSSION**

In this extensive population-based, case–control study, we found that parents of patients died significantly less often from a cardiovascular disease than parents of controls. A relation between cardiovascular fitness and being more physically active could not be shown in our study, as neither parental cardiovascular death nor survival was related to the extent to which patients are physically active. As the heritability of cardiovascular diseases is relatively high,16 our results strengthen the concept that a favourable cardiovascular fitness profile is associated with developing ALS. These findings are in line with previous studies showing a lower rate of hospital admissions for coronary heart disease, less frequent use of medication for hypertension or congestive heart failure, and a lower frequency of a history of a myocardial infarction or cardiac arrhythmia among patients with ALS compared with the general population or to controls and a lower rate of stroke and myocardial infarction in relatives of patients with ALS compared with relatives of controls. Moreover, the prevalence of cardiovascular risk factors, such as diabetes

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**Table 1** Baseline characteristics of patients with sporadic amyotrophic lateral sclerosis and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=487)</th>
<th>Controls (n=1092)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>307 (63.0)</td>
<td>643 (58.9)</td>
</tr>
<tr>
<td>Age at onset, years, median (range)</td>
<td>64.6 (23.5–86.6)</td>
<td>64.4 (17.6–86.2)</td>
</tr>
<tr>
<td>Age at diagnosis, years, median (range)</td>
<td>65.6 (23.8–86.9)</td>
<td>64.4 (17.6–86.2)</td>
</tr>
<tr>
<td>Age at time of inclusion, years, median (range)</td>
<td>66.0 (23.8–87.2)</td>
<td>64.4 (17.6–86.2)</td>
</tr>
<tr>
<td>Level of education, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No education or elementary school</td>
<td>37 (7.6)</td>
<td>69 (6.3)</td>
</tr>
<tr>
<td>Lower secondary school or technical school</td>
<td>286 (58.7)</td>
<td>590 (54.0)</td>
</tr>
<tr>
<td>Higher secondary school</td>
<td>32 (6.6)</td>
<td>116 (10.6)</td>
</tr>
<tr>
<td>Higher professional education or university</td>
<td>132 (27.1)</td>
<td>317 (29.0)</td>
</tr>
<tr>
<td>El Escorial criteria, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>82 (16.8)</td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td>191 (39.2)</td>
<td></td>
</tr>
<tr>
<td>Probable-laboratory supported</td>
<td>139 (28.5)</td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>63 (12.9)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Site of onset, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulbar</td>
<td>168 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Spinal</td>
<td>310 (63.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (1.8)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>24.9 (3.7)</td>
<td>26.1 (3.8)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>28 (6.4)</td>
<td>82 (8.3)</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>134 (31.8)</td>
<td>330 (33.9)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>161 (38.1)</td>
<td>338 (35.0)</td>
</tr>
</tbody>
</table>

BMI, body mass index.

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Table 2  Cause of death in parents of 487 patients with sporadic amyotrophic lateral sclerosis and 1092 controls

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Patients</th>
<th>Controls</th>
<th>OR*</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons deceased</td>
<td>820 (85.2)</td>
<td>1772 (82.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>256 (31.2)</td>
<td>635 (35.8)</td>
<td>0.78</td>
<td>0.64 to 0.94</td>
<td>0.009‡</td>
</tr>
<tr>
<td>Neurodegenerative</td>
<td>35 (4.3)</td>
<td>73 (4.1)</td>
<td>0.88</td>
<td>0.56 to 1.35</td>
<td>0.56</td>
</tr>
<tr>
<td>Cancer</td>
<td>206 (25.1)</td>
<td>443 (25.0)</td>
<td>1.01</td>
<td>0.82 to 1.24</td>
<td>0.96</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>4 (0.5)</td>
<td>6 (0.3)</td>
<td>1.94</td>
<td>0.49 to 6.97</td>
<td>0.31</td>
</tr>
<tr>
<td>Infectious</td>
<td>33 (4.0)</td>
<td>84 (4.7)</td>
<td>0.91</td>
<td>0.59 to 1.39</td>
<td>0.68</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>4 (0.5)</td>
<td>5 (0.3)</td>
<td>2.35</td>
<td>0.57 to 9.08</td>
<td>0.21</td>
</tr>
<tr>
<td>Surgery</td>
<td>4 (0.5)</td>
<td>10 (0.6)</td>
<td>1.00</td>
<td>0.27 to 3.09</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Old age</td>
<td>170 (20.7)</td>
<td>340 (19.2)</td>
<td>1.07</td>
<td>0.86 to 1.34</td>
<td>0.52</td>
</tr>
<tr>
<td>Unknown</td>
<td>52 (6.3)</td>
<td>94 (5.3)</td>
<td>1.24</td>
<td>0.86 to 1.79</td>
<td>0.25</td>
</tr>
<tr>
<td>Trauma</td>
<td>6 (0.7)</td>
<td>18 (1.0)</td>
<td>0.82</td>
<td>0.29 to 2.02</td>
<td>0.68</td>
</tr>
<tr>
<td>Severe trauma</td>
<td>17 (2.1)</td>
<td>23 (1.3)</td>
<td>2.30</td>
<td>1.17 to 4.46</td>
<td>0.01‡</td>
</tr>
<tr>
<td>Other†</td>
<td>33 (4.0)</td>
<td>41 (2.3)</td>
<td>2.09</td>
<td>1.27 to 3.40</td>
<td>0.003‡</td>
</tr>
<tr>
<td>Persons censored§</td>
<td>142 (14.8)</td>
<td>374 (17.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ORs are adjusted for age at time of inclusion, education, body mass index, diabetes, hypercholesterolaemia and hypertension.

10 Other includes mainly diseases of the kidneys, liver or lungs.

‡p<0.05, bootstrap resampling (1000 random samples) to correct for possible non-normality: mean difference in parental age between patients and controls for category of death 'cardiovascular': 0.62 years (95% CI −1.05 to 2.38); for category of death 'severe trauma': −8.14 years (95% CI −1.98 to 17.05); for category of death 'other': 4.24 years (95% CI −3.26 to 11.57).

§Censoring age was calculated based on the parental year of birth, calculating from 1 July of the corresponding year. As censoring date, we used the date of study inclusion.
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Table 3  Overview parental age at death

<table>
<thead>
<tr>
<th></th>
<th>Fathers</th>
<th>Mothers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>Persons deceased, n (%)</td>
<td>434 (91.2)</td>
<td>954 (90.3)</td>
</tr>
<tr>
<td>Persons censored*, n (%)</td>
<td>42 (8.8)</td>
<td>102 (9.7)</td>
</tr>
<tr>
<td>Age at death, years, median (range)</td>
<td>74.0 (26.0–101.0)</td>
<td>75.0 (24.0–101.0)</td>
</tr>
<tr>
<td>Age at censoring, years, median (range)</td>
<td>81.2 (56.8–107.2)</td>
<td>80.1 (43.7–105.3)</td>
</tr>
</tbody>
</table>

* Censoring age was calculated based on the parental year of birth, calculating from 1 July of the corresponding year. As censoring date, we used the date of study inclusion.

is in keeping with most previous papers reporting no association between cancer and ALS.24-27

Three possible mechanisms describing the relation of a cardiovascular and physical fitness profile to ALS risk are summarised in figure 2. The persistent finding of a favourable cardiovascular profile in patients with ALS could be the result of a genetic predisposition for increased physical fitness leading to more physical activity, which may increase the risk of ALS and decrease the risk of cardiovascular disease (figure 2A). As outlined above, this hypothesis could not be supported by our data. Alternatively, patients may have a genetic predisposition for being cardiovascularly fit as well as an increased risk of ALS; a better cardiovascular profile reduces the rate of cardiovascular diseases and may increase physical activity, and in parallel, individuals may develop ALS (figure 2B). A direct causal link between a beneficial cardiovascular profile and developing ALS is difficult to imagine. So, in addition to the hypothesis described in figure 2B, we propose another hypothesis that incorporates an independent role for cardiovascular fitness and ALS risk (figure 2C): a genetic predisposition, possibly in combination with exogenous risk factors (such as physical activity), could induce (or reduce) activation of a specific (disease) pathway, for example metabolism, leading to an increased risk of ALS and a beneficial cardiovascular risk profile. A role for hypermetabolism in developing ALS has been reported previously in a number of human and animal studies, in sporadic and in familial disease.28-33 It may be worth noting that the prevalence rates of a cardiovascular profile, hyperlipidaemia and overweight,19 is significantly lower in patients with ALS compared with controls.6,20-23 The lower cardiovascular death rate did not result in a longer survival in parents of patients. More obvious, the second most common cause of death, cancer, shortened the parental lifespan. The rates between patients and controls, however, were not different. This...
cause of death are comparable between parents of patients with sporadic ALS, parents of patients with familial ALS and parents of patients with a C9orf72 repeat expansion (online supplementary table S3), suggesting similar pathways. A combined analysis of genetic studies on physical fitness and ALS might help to further elucidate this fitness hypothesis.

We had the advantage of studying a population-based cohort with information on several confounders, such as educational level, cardiovascular risk factors, lifetime physical activities and C9orf72 genotype. Moreover, in 96.8% of the subjects, information on both parents was available. The fact that there were subjects with one living and one deceased parent at the time of study participation prevented us from combining both parents into a single survival analysis; this would have increased statistical power. However, not even a trend towards longer life expectancy is noticeable when looking at the median ages of fathers and mothers in all stratified analyses. Using questionnaire data, we were dependent on the information provided by the participants; we were unable to check the parental cause of death by death certificates in case this was missing. However, both patients and controls were contacted when data was incomplete or incorrect and the percentages of parents with an ‘unknown’ cause of death were similar in patients and controls. Since we did not have data on the leisure time activities for parents, we were limited to the use of physical activity levels of the participants, as opposed to their parents. Socioeconomic status could have been an important modifier of the association between parental causes of death or survival and ALS. Using highest educational level as indicator for socioeconomic status, we entered an interaction term between cardiovascular cause of death and educational level, or disease status and educational level in the survival analysis. In these models, no significant interaction was found. Thus, in both high and low educated patients, parents were less likely to die of a cardiovascular disease.

In this study, we specifically looked at cause of death in parents, and did not have information on parental comorbidities. Thus, we did not aim to replicate our previous finding of a mildly increased risk of dementia among parents and siblings of patients, which was found in one of our earlier population-based cohorts. Although this study did find a decreased risk of cardiovascular disease among parents and siblings of patients, supporting our data.18

In summary, exploring the fitness hypothesis in the pathogenesis of ALS, our findings provide evidence for a shared mechanism underlying a favourable cardiovascular fitness profile and ALS susceptibility.

Acknowledgements We thank Hermieneke Vergunst (University Medical Centre Utrecht) for technical assistance. We also thank the other staff members of the Dutch ALS Centre for the considerable effort they put into the organisation of the PAN study. We thank all neurologists, consultants in rehabilitation medicine and other healthcare providers for enrolling patients with ALS. Finally, we are grateful to all patients with ALS and controls for giving their valuable time to participate in this study.

Funding This work was supported by the Netherlands ALS Foundation. LHvdB received a grant from the Netherlands Organisation for Health Research and Development (Vici scheme).
Neurodegeneration

Competing interests AEV: Drafting the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; acquisition of data; statistical analysis. MS, AFCH, JArdG, ALvdK, JR, JHV: Revising the manuscript for content, including medical writing for content; study concept or design; acquisition of data. LvdB: Revising the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data; study supervision or coordination; obtaining funding.

Provenance and peer review Not commissioned; externally peer reviewed.

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*J Neurol Neurosurg Psychiatry* 2017 88: 550-556 originally published online March 14, 2017
doi: 10.1136/jnnp-2016-315071

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