Body mass index and survival from amyotrophic lateral sclerosis

A meta-analysis

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Abstract

Background

Several studies have examined the relationship between body mass index (BMI) and survival from amyotrophic lateral sclerosis (ALS). Many indicate that low BMI at diagnosis or during follow-up may be associated with accelerated progression and shortened survival. This study systematically evaluated the relationship between BMI and survival in patients with ALS.

Methods

The PubMed database was searched to identify all available studies reporting time-to-event data. Eight studies with 6,098 patients fulfilled the eligibility criteria. BMI was considered a continuous and ordered variable. Interstudy heterogeneity was assessed by the Cochran Q test and quantified by the I^2 metric. Fixed- or random-effects odds ratios summarized pooled effects after taking interstudy variability into account. Significance was set at $p < 0.05$.

Results

The ALS survival hazard ratio (HR) decreased approximately by 3% (95% confidence interval [CI]: 2%–5%) for each additional BMI unit when BMI was considered a continuous variable. When BMI was considered a categorical variable, the HRs for “normal” BMI vs “overweight” BMI and “obese” BMI were estimated to be as high as 0.91 (95% CI: 0.79–1.04) and 0.78 (95% CI: 0.60–1.01), respectively. The HR for the comparison of the “normal” BMI vs “underweight” BMI was estimated to be as high as 1.94 (95% CI: 1.42–2.65).

Conclusions

BMI is significantly and inversely associated with ALS survival.

Amyotrophic lateral sclerosis (ALS) represents a heterogeneous group of neurodegenerative disorders.¹ It is the third most common neurodegenerative disease and the most frequent form of motor neuron disease, with its onset in adulthood.¹ ALS is characterized by the progressive loss of motor neurons and a rapidly progressive paralysis.^{2,3} It is a serious health problem because respiratory failure usually leads to death within 2–3 years after symptom onset.^{4,5} Although the cause of ALS is unknown, genetic and environmental factors are likely to confer susceptibility to the risk of developing ALS.^{6,7}

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Body mass index (BMI) is a measure of tissue mass expressed in units of kg/m². Body weight is associated with a number of neurologic disorders, with excess body weight leading to an increased risk of MS, a neuroinflammatory disease of unknown etiology,^{8–10} and ischemic stroke.^{11–13} BMI may also be implicated in degenerative processes because decreases in BMI have been observed before the onset of Alzheimer disease, with weight remaining stable or increasing after diagnosis.¹⁴ Furthermore, patients with Parkinson disease (PD) have a significantly lower BMI than healthy controls,¹⁵ and Hoehn and Yahr stage 3 PD patients present lower BMIs than those with stage 2 disease.¹⁵

A number of exogenous factors are associated with the risk of developing ALS, including low BMI.^{16,17} Moreover, large prospective cohort studies have demonstrated that overweight and obese individuals are at significantly lower risk of developing ALS compared with those with normal pre-morbid BMIs.^{18,19} A recent systematic review suggested that a lower BMI is among the risk factors associated with ALS.²⁰

Several studies (including the systematic review mentioned earlier) have examined the relationship between BMI and survival in patients with ALS, and they indicate that a low BMI at diagnosis or during follow-up may lead to faster progression and shorter survival.^{20–25} We conducted a meta-analysis of studies examining BMI and survival in patients with ALS.

Methods

Literature search

The PubMed database from its inception until November 3, 2017, was systematically searched for studies using the terms “amyotrophic lateral sclerosis,” “body mass index,” “survival,” and “hazards.” The complete search algorithm is available in appendix e-1 (links.lww.com/CPJ/A48). Animal experiments, unpublished data, and congress presentations/abstracts were excluded. Titles and abstracts were reviewed to determine relevance. Studies lacking time-to-event data were excluded. Only articles written in English were included. The final literature search was performed on November 3, 2017. Finally, the

bibliographies of the resulting full texts were searched for other relevant citations.

Data extraction

The mean age, male-to-female ratio of the study sample, and the resulting hazard ratios (HRs) were extracted. Because the literature considers BMI as both a continuous and ordered variable, the HRs for each type of BMI description were considered separately (tables 1 and 2). Finally, we registered if the BMI was recorded before the diagnosis or at the initial visit, during the course of the disease, or at the late stages of progression.

Quality appraisal

Two reviewers (E.D. and V.S.) appraised the articles according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.²⁶ Reporting clarity was considered as “high” if the study authors reported at least 80% of the STROBE checklist items (18 of 22 items) and as “low” otherwise. In cases of disagreement, the 2 authors reached a consensus after consulting a third coauthor (A.G.B.). PRISMA statement for reporting reviews and meta-analyses was applied.²⁷

Statistical analysis

Interstudy heterogeneity was measured and quantified by the I² metric (“low,” “moderate,” “high,” and “very high” corresponding to values of up to 25%, 50%, 75%, and 100%, respectively). Baujat plots were used to visualize contributions to overall heterogeneity. Fixed- or random-effects odds ratios summarized pooled effects after taking inter-study variability into account. Forest plots were used to visualize effect sizes and their 95% confidence intervals (CIs) for each study and the pooled effects. Subgroup analysis was performed to explain interstudy heterogeneity. The outcomes were stratified in terms of the timing of BMI measurement. The leave-one-out method was used to pinpoint the most influential study. Funnel plots were used to visually assess publication bias, verified by the Egger linear regression test. Significance was set at $p < 0.05$ for all analyses. All statistical analyses were performed using R statistical environment (“meta” package).^{28,29}

Table 1 Characteristics of studies with body mass index as an ordered variable

Reference	Year	Country	Study design	Timing of measurement	No. of cases	No. of controls	Mean age (SD)	Male-to-female ratio	Compliance with STROBE (at least 80% of items)
31	2013	European multicenter	Prospective cohort (“the EPIC cohort”)	A	222	—	NA	0.55	Yes
38	2013	US	Retrospective cohort	A	728	—	61.5 (NA)	1.23	Yes
36	2016	US	Retrospective case-control	A	467	975	60 (53–67)	13.33	Yes

Abbreviations: NA = not available; STROBE = STrengthening the Reporting of OBservational studies in Epidemiology.

The current meta-analysis concentrated on data from a large number of participants (n = 6,098) to investigate the effect of BMI on the survival of patients with ALS.

Results

Literature results

A flowchart of the selection of eligible studies is presented in figure 1. The search of the PubMed database yielded 71 articles using the terms “amyotrophic lateral sclerosis,” “body mass index,” and “survival” and 12 using the terms “amyotrophic lateral sclerosis,” “body mass index,” and “hazards.” After the removal of duplicates, 72 studies (published between October 1995 and October 2017) were available for further review. Two independent reviewers screened records, full-text articles, titles, and abstracts. Sixty-four studies were removed (as not relevant, animal experiments, lacking time-to-event data, or no English language). Eight potentially eligible studies (5 with BMI as a continuous variable, 2 with BMI as an ordered variable, and 1 with BMI both as a continuous and ordered variable), published between 2008 and 2017, were retained and finally included in the quantitative meta-analysis.

Characteristics of eligible studies

Eight studies involving 6,098 patients fulfilled the eligibility criteria and formed the basis of the current meta-analysis. Desport et al.³⁰ originally studied the effect of BMI on the survival of patients with ALS. Because of the rarity of ALS, most

studies were retrospective analyses of data gathered in clinical trials or registries.^{31–33} The majority of evidence derived from developed countries with increased health care awareness such as Europe and the United States.^{30,33–38} Most patients were in the sixth decade of life, and there was an obvious variability in the male-to-female ratio among the gathered studies, while the majority of the studies were compliant with the STROBE statement (tables 1 and 2).

BMI as a continuous variable

Six articles examined the effect of BMI as a continuous variable on ALS survival (table 2). There was no significant overall interstudy heterogeneity ($I^2 = 41\%$, $p = 0.13$), with most variability attributed to the studies of Eaglehouse et al.³⁴ and Henriques et al.³⁵ (figure 2A). The HR decreased by 3% (95% CI: 2%–5%) for each additional BMI unit when the BMI was measured before or at the time of diagnosis (figure 2B). On the other hand, there was significant statistical heterogeneity ($I^2 = 78\%$, $p = 0.03$) in studies measuring the BMI during the disease progression. No study was based on BMI measurements at late disease stages. All studies equally influenced the overall result (figure 2C). The relevant literature was not free of publication bias ($p < 0.05$) (figure 2D).

BMI as an ordered variable

Three articles examined the effect of BMI as a categorical variable on ALS survival (table 1). The “normal” BMI was the reference level in all studies, while the overall heterogeneity was moderate ($I^2 = 73\%$, $p < 0.01$), with the study by Traxinger et al.³⁸ contributing largely to the overall heterogeneity (figure 3A). The heterogeneity was eliminated after stratifying the results according to the individual comparisons. Thus, the HR for the comparison of the “normal” subgroup with the “overweight” subgroup was estimated to be as high as 0.91 (95% CI: 0.79–1.04). Similarly, the HR for the comparison of the “normal” subgroup with the “obese” subgroup was estimated to be as high as 0.78 (95% CI:

Table 2 Characteristics of studies with body mass index as a continuous variable

Reference	Year	Country	Study design	Timing of measurement	No. of cases	No. of controls	Mean age (SD)	Male-to-female ratio	Compliance with STROBE (at least 80% of items)
30	2008	France	Retrospective cohort	A	168	—	63.4 (12.0)	0.96	Not applicable
35	2015	France	Prospective case-control	B	117	48	NA	1.66	Yes
33	2015	Italy	Data review from 2 databases	B	2,909	—	NA	1.57	Yes
32	2015	Multicenter	Data review from 6 clinical trials	A	1,322	—	56.1 (11.5)	1.65	Yes
34	2016	US	Retrospective cohort	A	165	161.809	NA	All female	Yes
36	2017	US	Retrospective case-control	A	467	975	60 (53–67)	17.33	Yes

Abbreviations: STROBE = STrengthening the Reporting of OBservational studies in Epidemiology; NA = not available.

Figure 1 Prisma flowchart of the current meta-analysis

0.60–1.01). However, the HR for the comparison of the “normal” subgroup with the “underweight” subgroup was estimated to be as high as 1.94 (95% CI: 1.42–2.65) (figure 3B). The leave-one-out analysis indicated that the most influential study was that of Mariosa et al.³⁶ (figure 3C). The trim-and-fill funnel plot showed that there was no important publication bias, as verified by the Egger linear regression test ($p = 0.09$) (figure 3D). The measurement of BMI in all studies took place before the diagnosis or at the initial assessment.

Discussion

The current meta-analysis concentrated on data from a large number of participants ($n = 6,098$) to investigate the effect of

BMI on the survival of patients with ALS. We report a significant influence of BMI (as measures before the disease diagnosis or progression) on the survival from ALS. More precisely, an increased BMI at diagnosis should be considered among the protective factors in terms of overall survival in patients with ALS, whereas underweight patients are at an increased risk of ALS and death from the disease (HR decreases by 3% per unit of BMI). That was especially true for underweight patients who seemed to have almost twice the risk of death in comparison to normal weight patients (HRs for the “normal” vs “underweight” subgroups were estimated to be as high as 1.94).

A wide spectrum of genetic and exogenous factors has been associated with the risk of developing ALS, including

Figure 2 Body mass index (BMI) as a continuous variable

(A) Baujat plot depicting the influence of each study on the overall result according to the contribution to the overall heterogeneity. Henriques et al. had the major contribution to the overall heterogeneity, whereas the study of Eaglehouse had the major influence on the overall result. BMI is regarded as a continuous variable. (1 = Desport et al.³⁰; 2 = Henriques et al.³⁵; 3 = Lunetta et al.³³; 4 = Paganoni et al.³²; 5, Eaglehouse et al.³⁴; 6 = Mariosa et al.³⁶) (B) Hazard ratio forest plot of the role of BMI in the amyotrophic lateral sclerosis survival. The fixed- and random-effects estimates along with their 95% confidence intervals are also visualized. BMI is regarded as a continuous variable. (C) Influence analysis according to the leave-one-out method. (D) The funnel plot is indicative of a high risk of publication bias.

exposure to heavy metals and organic chemicals, participation in sports, occupation, and physical trauma.¹⁶ BMI is among the exogenous factors associated with the risk of developing ALS.^{16,17} Lower presymptomatic BMI and obesity rates have been documented in individuals who go on to develop ALS^{39,40} consistent with studies indicating an association with BMI before ALS diagnosis.^{41–43}

Consequently, BMI may act as a red flag for ALS in the prediagnostic period.

ALS survival has been associated with age at disease onset, sex, clinical phenotype, respiratory failure at an early stage, treatment with riluzole, and weight loss.^{44,45} Survival in ALS is also influenced by the functional status and its slope of

Figure 3 Body mass index (BMI) as a categorical variable

(A) Baujat plot depicting the influence of each study on the overall result according to the contribution to the overall heterogeneity. Traxinger et al. had the major contribution to the overall heterogeneity and the major influence on the overall result. (1 = "Normal vs Underweight"/Gallo et al.³¹; 2 = "Normal vs Overweight"/Gallo et al.³¹; 3 = "Normal vs Obese"/Gallo et al.³¹; 4 = "Normal vs Underweight"/Traxinger et al.³⁸; 5 = "Normal vs Overweight"/Traxinger et al.³⁸; 6 = "Normal vs Underweight"/Mariosa et al.³⁶; 7 = "Normal vs Overweight"/Mariosa et al.³⁶; 8 = "Normal vs Obese"/Mariosa et al.³⁶) (B) Hazard ratio forest plot of the role of BMI in amyotrophic lateral sclerosis (ALS) survival. The fixed- and random-effects estimates along with their 95% confidence intervals (CIs) are also visualized. BMI is regarded as a continuous variable. (C) Influence analysis according to the leave-one-out method. (D) The funnel plot is indicative of a high risk of publication bias.

decline.⁴⁶ Desport et al.³⁰ were the first to examine the effect of BMI on the survival of patients with ALS. It was reported that a 5% weight loss at the time of diagnosis increased the risk of death in those patients by as much as 30%, whereas each BMI unit loss could increase the risk of death by 20%.²⁵ A relationship was also reported between mortality and BMI, with the longest survival observed in the patients with BMI between 30 and 35 kg/m². Higher or lower BMI values were correlated with higher mortality.³⁷ Findings from Atassi et al. also supported a relationship between BMI and survival, with overweight (BMI ≥ 25 kg/m²) and obese patients with ALS (BMI ≥ 30 kg/m²) having a 35% and 54%

reduced risk of dying, respectively, compared with patients with BMI <25 kg/m².⁴⁷ Consequently, BMI seems to influence both the development and the survival of patients with ALS.^{44,45,48}

The precise pathophysiologic processes by which BMI may influence ALS development and survival are only partially understood. A reduction in BMI has consistently been reported in patients with ALS during the course of the disease and has been attributed to hypermetabolism or reduced calorie intake secondary to loss of appetite, dysphagia, or hand muscle weakness⁴⁸⁻⁵⁰; nutritional supplements (e.g.,

The precise pathophysiologic processes by which BMI may influence ALS development and survival are only partially understood.

acetylcarnitine) may protect against these symptoms.^{51,52} There is also some evidence to suggest that the entire human body and cellular metabolism may even contribute to ALS development.³⁴ Moreover, endogenous retroviruses (HERVs)—HERV-K in principal—have been causally associated with ALS,⁵³ and their activity in mammals inversely correlates with body size.⁵⁴

This meta-analysis has some limitations. First, because of the rarity of ALS, most data are from retrospective analyses of clinical trials or registries. Also, the majority of studies were conducted in very few developed countries with increased health care awareness. Therefore, the influence of ethnic diversity on BMI and ALS cannot be assessed. Only a few potential confounding factors that may influence weight, BMI, and ALS were included. Finally, our study carries all the inherent limitations of using BMI as a measure of obesity.⁵⁵

In conclusion, this meta-analysis reveals a possible influence for initial BMI on the survival of patients with ALS. Further large-scale collaborative studies, including low- and middle-income countries, would be helpful to elucidate the net effect of BMI on ALS and neurodegeneration. Our findings have important implications for the diagnosis, classification, prognosis, and management of ALS. Monitoring weight and BMI would also help physicians personalize the nutritional needs of patients with ALS.

Author contributions

E. Dardiotis: original idea, study design, investigation, interpretation of results, methodology, project administration, supervision, and writing—original draft preparation and review and editing. V. Siokas: investigation, validation, visualization, resources, methodology, and writing—original draft preparation and review and editing. M. Sokratous: investigation and writing—original draft preparation and review and editing. Z. Tsouris: methodology and writing—original draft preparation. A.-M. Aloizou, D. Florou, M. Dastamani, and A.-F.A. Mentis: writing—review and editing. A.G. Brotis: statistical analysis, software, investigation, interpretation of results, and writing—review and editing.

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Disclosure

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