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Nutritional therapy in amyotrophic lateral sclerosis: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Amyotrophic lateral sclerosis (ALS) is a complex neurodegenerative disease characterised by the degeneration of motor neurons. Nutritional interventions in ALS are essential and must be based on scientific evidence to provide quality of healthcare, improve the quality of life and increase survival time. Therefore, this protocol of systematic reviews and meta-analyses aims to present a synthesis of evidence-based recommendations to support adequate nutrition therapy for patients with ALS.

Methods and analysis The search will be performed using the following databases: PubMed, Excerpta Medica Database (Embase), Scopus, SciELO, Web of Science, LILACS, Cochrane Central Register of Controlled Trials (CENTRAL), ScienceDirect, ProQuest and Google Scholar. We will include clinical practice guidelines, treatment protocols, systematic reviews and clinical trials according to the three research questions to be answered related to nutrition therapy and interventions in patients with ALS. This protocol will be developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols. To evaluate the methodological quality of the studies, Appraisal of Guidelines, Research and Evaluation II, Cochrane Risk of Bias 2.0 and Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tools will be used. In addition, the Grading of Recommendations Assessment, Development and Evaluation will be used to assess the quality of evidence and the strength of the recommendations. The findings will be summarised and presented descriptively according to the Cochrane Collaboration Handbook and the standard statistical meta-analysis techniques.

Ethics and dissemination Ethical approval and human consent are not required because this is a protocol for systematic review and only secondary data will be used. Findings will be published in a peer-reviewed journal and presented at conferences. In case of any changes in this protocol, amendments will be updated in International Prospective Register of Systematic Reviews (PROSPERO) and the modifications will be explained in the final report of this review.

PROSPERO registration number CRD42021233088.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This protocol encompasses two systematic reviews.
⇒ This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement guidelines.
⇒ The methodological quality of the studies will be performed using the Appraisal of Guidelines, Research and Evaluation II statement.
⇒ The methodological quality and risk of bias of clinical trials will be accomplished using the Cochrane Risk of Bias 2.0 and Risk of Bias in Non-randomized Studies of Interventions tools for randomised and non-randomised studies, respectively.
⇒ Meta-analysis may not be possible for certain outcomes due to a limited number of eligible studies.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a multisystemic neurodegenerative disease characterised by progressive cell death of upper and lower motor neurons.[1 2] Worldwide ALS prevalence varies from 1.57 cases per 100 000 to 9.62 per 100 000. Its incidence varies from 0.42 per 100 000 to 2.76 per 100 000 people/year. Both ALS prevalence and incidence are higher in developed regions.[3] Clinical signs of the disease have a low incidence before age 50 years, with a peak around age 85 years followed by a marked decrease in incidence. However, the onset of this disease is rarely possible in early adulthood.[4] The severity of the disease points to a short median survival of 3–4 years after the initial diagnosis.[5–8]

Malnutrition is a frequent condition in patients with ALS, with prevalence ranging from 16% to 53%.[9] The body mass index (BMI) is an important anthropometric parameter for diagnosing malnutrition among these patients. BMI reduction is related to faster disease progression and increased risk of mortality.[10] Marin *et al*[11] demonstrated that 5% of body weight loss increases the risk of death by 30% in patients with ALS. Thus, nutritional care is essential for maintaining adequate nutritional status, which positively affects these patients' functional capacity, quality of life and survival time.[12–14]

Several risk factors such as dysphagia, anorexia, gastrointestinal disorders, cognitive impairment, apathy, psychological disorders, and inadequate energy and nutrient intake contribute to malnutrition in patients with ALS. In addition, hypermetabolism may be present and can increase the risk of malnutrition or aggravate this condition, especially in the absence of nutritional care.[15 16] Therefore, evidence-based nutritional interventions for ALS are of the utmost importance and must consider the different stages of the disease.[17]

Clinical practice guidelines (CPGs) have been developed to provide scientific evidence to support clinical decision-making of health professionals and establish standards of care for many conditions.[18 19] CPGs focused on all aspects of nutritional therapy for ALS are still lacking. Existent guidelines on this matter only address some nutritional aspects, most of them related to gastrostomy and dysphagia. Many other aspects of nutritional therapy have not been covered, such as energy and nutrient requirements, modified consistency diet, micronutrients and bioactive compounds supplementation, and nutrition advice for comorbidities in patients with ALS.

Considering this gap and aiming to provide broader guidance on nutrition therapy for patients with ALS, it is essential to gather and synthesise recommendations on this subject, based on available scientific evidence of clinical protocols and guidelines; also based on the effectiveness of nutritional interventions verified through clinical trials. We believe that a synthesis of recommendations on nutrition therapy in ALS will help and guide the nutrition care process and benefit the patients.[20 21]

Given the information above, this protocol will seek to answer the following research questions: (*RQ1*)—What are the evidence-based nutritional recommendations to maintain or restore the nutritional status of patients with ALS? *RQ2*—What is the effect of a diet rich in energy and protein in people with ALS? *RQ3*—What are the effects of supplementing isolated micronutrients or bioactive compounds in people with ALS?

Therefore, this protocol aims to build an outline of upcoming systematic reviews and meta-analyses to present a synthesis of evidence-based recommendations to support adequate nutrition therapy and improve the nutritional status of patients with ALS.

METHODS AND ANALYSIS

Protocol registration

This protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database on 12 April 2021 (CRD42021233088). This protocol is in line with international ethical parameters and because it is a study with secondary data, there is no need to seek approval from a research ethics committee. Also, it was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) statement guidelines.[22] The PRISMA-P checklist used to prepare this protocol has been provided as an online supplemental file 1. To report the systematic review, the PRISMA statement with a 27-item checklist and descriptive flow diagram will be used.[23] This present protocol encompasses two systematic reviews and meta-analyses. The first one will be a review of protocols/guidelines aimed to answer the RQ1. The second one will be a review of clinical trials aimed to answer RQ2 and RQ3. The information regarding methods and analysis is described according to the RQs.

Selection criteria

For RQ1, we will include CPGs, treatment protocols and systematic reviews. For RQ2 and RQ3, we will only include clinical trials with control groups.

Participants

For all RQs we will include studies comprising adults (aged 18 and over) and seniors of both sexes with a clinical diagnosis of ALS as definite, probable or possible, according to the revised El Escorial criteria.

Types of interventions

For RQ1, we will include studies involving nutrition therapy recommendations to maintain or restore the nutritional status of patients with ALS. For RQ2, we will include studies implementing a diet rich in energy and/or protein as an intervention. For RQ3, we will include studies supplementing single micronutrients or bioactive compounds as an intervention.

Outcome measures

For RQ1, only the summary of the nutritional recommendations for recovery or maintenance of the nutritional status in patients with ALS will be performed, with no outcomes to be measured. For the RQ2, the outcome will be the change of BMI, percentage of weight loss, progression rate of total Revised ALS Functional Rating Scale (ALSFRS-R) and mortality rate. For the RQ3, the outcome will be the antioxidant effect, ALSFRS-R progression rate and mortality rate.

Inclusion criteria

For RQ1, the inclusion criteria are evidence-based nutritional recommendations to maintain or restore the nutritional status of patients diagnosed with definite, probable or possible ALS. For RQ2 and RQ3, the inclusion criteria are adults and elderly patients of both sexes, diagnosed with definite, probable or possible ALS.

Exclusion criteria

For all RQs we will exclude studies with other neurodegenerative diseases or without nutritional recommendations. No restrictions of time and language will be applied in our search.

Search strategy

A comprehensive electronic search will be performed in the following databases: PubMed, Excerpta Medica Database (Embase), Scopus, SciELO, Web of Science, LILACS, Cochrane Central Register of Controlled Trials (CENTRAL), ScienceDirect, ProQuest and Google Scholar.

The search strategy will include the following descriptors (MeSH): 'Amyotrophic Lateral Sclerosis', 'Motor Neuron Disease', 'Nutrition', 'Nutritional Assessment', 'Nutrition Therapy', 'Diet', 'Dietary Supplements', 'Deglutition Disorders', 'Guideline' and 'Clinical Protocols'. In addition, the Emtree terms 'Diet Therapy', 'Dysphagia' and 'Practice Guideline' will be included for the Embase database. A draft of our search strategy has been provided as an online supplemental file 2.

Searches of other resources

To ensure the comprehensiveness of this research, we will supplement searches by hand-searching in the reference lists of retrieved studies or relevant reviews. To identify unpublished studies and assess publication bias, we will also examine *ClinicalTrials.gov* and *ensaiosclinicos.gov.br* for registered clinical trials using interventions such as high-energy and/or high-protein diet and supplementation of micronutrients or bioactive compounds in people with ALS.

Study selection

For all identified studies, at least two authors (MDdCV and LL-L) will independently select and review titles and abstracts using the Rayyan QCRI tool. Papers that meet the inclusion criteria will be ordered for a full review. Any disagreement will be resolved by discussion with a third reviewer (SHdLV). A manual search will be performed if any relevant studies are found using the defined search strategies. All investigators will then review the full text of all eligible studies. The information on the phases of the selection process will be described through PRISMA flow diagram.[23]

Data extraction

The data extraction will be done in a standardised way using Microsoft Excel by two independent authors (MDdCV and LL-L). Discrepancies between the data extraction will be resolved by consensus. The study characteristics will be collated according to the RQs. For RQ1, the following data will be extracted: general information about the guideline (title, responsible organisation, year of publication and funding); nutritional recommendations addressed; and the stratification of the level of evidence used. For RQ2 and RQ3, the following data will be extracted: general information (title, authors, journal, year, country); study characteristics (study design, study duration); sample characteristics (sample size, mean age, ALS subtype, ALSFRS-R); intervention (type of intervention, duration, diet characteristics, energy and/or protein amount); outcomes (changes in BMI, percentage of weight loss, progression rate of functional status, mortality rate); and statistical results. If study reports are incomplete or missing data, corresponding authors will be contacted. If we do not receive clarification, the requested data will be excluded from our analysis and will be commented in the Discussion section.

Evaluation of methodological quality

Two independent authors (SHdLV and MDdCV) will evaluate the methodological quality of the studies using the Appraisal of Guidelines, Research and Evaluation II statement. This instrument assesses six domains: (1) scope and purpose, (2) stakeholder involvement, (3) rigour of development, (4) clarity of presentation, (5) applicability, and (6) editorial independence.[24] To assess the methodological quality and risk of bias of clinical trials, the Cochrane Risk of Bias 2.0 and Risk of Bias in Non-randomized Studies of Interventions tools will be used for randomised and non-randomised studies, respectively.[25 26]

Data synthesis

For the first systematic review (RQ1), the findings and main recommendations will be narratively summarised. For the second systematic review (RQ2 and RQ3), meta-analysis will be performed, if possible. If meta-analysis is not possible, we will conduct a systematic review with narrative analysis tabling the results.

Assessment of heterogeneity

To assess the heterogeneity, we plan to calculate the standard χ^2 statistic, which is a quantitative measure of inconsistency between the studies. Next, the I^2 index will be calculated to quantify heterogeneity. The I^2 statistic describes the percentage of variation across studies due to heterogeneity rather than chance. No heterogeneity is observed when I^2 is 0%, and the variability can be explained by chance alone. A value of I^2 >50% indicates high heterogeneity.

Meta-analysis

If there is the possibility of meta-analysis, standard statistical techniques will be used. If substantial heterogeneity occurs, we will perform subgroup analysis and meta-regression to identify possible associated cofactors such as disease onset (bulbar or spinal), age at onset, disease duration and clinical stages of ALS (early, middle, late and end). In addition, the random effects model will be used in the synthesis of data from the included studies. Publication bias will be assessed using a funnel plot and its asymmetry will be verified by linear regression.

Subgroup analysis

For the RQ1 the analysis of subgroups is not applicable. If sufficient data are available for the RQ2 and RQ3, the subgroup analysis will consider disease onset (bulbar or spinal), age of onset, disease duration and clinical stages of ALS (early, middle, late and end). These stages are classified as follows: stage 1 for symptom onset or functional involvement of one central nervous system (CNS) region (*early*), stage 2 for diagnosis or functional involvement of two CNS regions (*middle*), stage 3 for functional involvement of three CNS regions (*late*), stage 4 for need for gastrostomy or non-invasive ventilation (*end*) and stage 5 for death.[27 28]

Assessment of quality of evidence (Grading of Recommendations Assessment, Development and Evaluation)

Two independent authors (MDdCV and LL-L) will assess the quality of the evidence and the strength of the recommendations provided by the selected studies. For this purpose, we will use the Grading of Recommendations

Assessment, Development and Evaluation[29] for decision-making in health, which classifies the quality of evidence into four levels (high, moderate, low and very low) and the strength of the evidence into two levels (strong or weak).

Patient and public involvement

No patients or the public will be directly engaged in this research, as it is conducted using secondary data.

DISCUSSION

This study aims to gather and synthesise recommendations for nutritional intervention and treatment based on available scientific evidence from clinical protocols and guidelines. Also, the effectiveness of interventions will be verified through clinical trials.

Weight loss, low BMI and malnutrition are frequent in patients with ALS. According to the guideline conducted by Burgos *et al*,[30] the BMI reduction in patients with ALS is associated with shortened survival and high risk of mortality.

A systematic review states that there is no cure or effective treatment for ALS to date. Multidisciplinary care is the basis for its treatment, including nutritional support as well as respiratory and symptom management during the disease. Furthermore, the review highlights that dietary intervention can help improve nutrition status. For example, gastrostomy is indicated if oral intake is insufficient or is no longer safe.[31]

Dorst *et al* found that high-energy supplementation effectively stabilises the body weight of patients with ALS and no side effects were detected. The authors also observed a positive impact on the survival of the patients. Thus, the use of high-energy supplementation was suggested.[32] In a cohort study, Traynor *et al*[33] demonstrated that patients with ALS who received multidisciplinary care had a better prognosis than patients who received general care through a neurology clinic.

Scientific entities specialised in ALS recognise nutrition as integral part of care during the course of the disease and address some nutritional recommendations.[34 35] Nutrition therapy seeks to prevent malnutrition, maintain adequate nutritional status, promote haemodynamic stability, reduce the rate of disease progression and positively impact the quality of life and survival of patients with ALS.[36] Thus, identifying consistent recommendations for nutrition intervention in ALS is of the utmost importance and will contribute to more assertive patient care.[37–40] Nevertheless, systematic reviews and guidelines about ALS nutritional therapy are scarce and some of them present gaps because they do not discuss specific aspects regarding nutritional treatment and management that should be implemented in this type of patient.

For example, the recommendations by del Olmo García *et al*[41] describe the nutritional aspects of ALS and nutritional management with recommendations for high-energy intake and those related to enteral and parenteral nutrition. However, it does not address percentages of macronutrient distribution, micronutrient requirements or adjuvant nutritional supplements.

In a review paper about nutrition management in ALS, Greenwood[39] prioritises the quantitative recommendation of protein but does not determine recommendations for lipids, carbohydrates, fibres, micronutrients, bioactive compounds and nutritional supplements. The pieces of information we gathered show how these two systematic reviews proposed by our group are needed and can be helpful in assisting the nutrition care of patients with ALS with robust recommendations based on scientific evidence.

In this sense, the development of updated systematic reviews with meta-analyses and synthesised recommendations on nutrition therapy of patients with ALS can reduce the nutritional risk and positively influence their quality of life and survival time. Furthermore, it will support the first Brazilian guideline of nutrition therapy in ALS, which will guide the clinical nutrition practice with greater safety and efficiency. Thus, we believe this protocol is relevant and it will benefit the scientific community, healthcare professionals, caregivers and especially patients with ALS. In addition, the systematic reviews proposed can also help highlight areas that require more research in the subject of nutrition therapy and ALS.

ETHICS AND DISSEMINATION

Ethical approval and human consent are not required because this is a protocol for systematic review and only secondary data will be used. Findings will be published in a peer-reviewed journal and presented at conferences. In case of any changes in this protocol, amendments will be updated in PROSPERO and explanations of these modifications will be described in the final report of this review.

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Contributors MDdCV, LL-L and GP conceptualised and designed the protocol. The protocol manuscript was written by MDdCV and LL-L. It was critically reviewed by GP, GCBSM, KMDC, SHdLV and JB-N. The search strategy was developed by MDdCV, LL-L, SHdLV, GP and GCBSM. MDdCV, KMDC and LL-L will lead the study selection. MDdCV, LL-L and KMDC will be responsible for data extraction. Statistical analysis will be performed by MDdCV, SHdLV, LL-L, GCBSM and GP. JB-N will be the third party and will host consensus meetings at each stage in case of disagreement. All authors read, reviewed and approved the final protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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REFERENCES

1 Brown RH, Al-Chalabi A. Amyotrophic lateral sclerosis. *N Engl J Med* 2017;377:162–72.
2 Strong MJ. Revisiting the concept of amyotrophic lateral sclerosis as a multisystems disorder of limited phenotypic expression. *Curr Opin Neurol* 2017;30:599–607.
3 Xu L, Liu T, Liu L, *et al*. Global variation in prevalence and incidence of amyotrophic lateral sclerosis: a systematic review and meta-analysis. *J Neurol* 2020;267:944–53.
4 GBD. Motor neuron disease Collaborators. global, regional, and national burden of motor neuron diseases 1990-2016: a systematic analysis for the global burden of disease study 2016. *Lancet Neurol* 2016;17:1083–97.
5 van Es MA, Hardiman O, Chio A, *et al*. Amyotrophic lateral sclerosis. *Lancet* 2017;390:2084–98.
6 Davis DA, Cox PA, Banack SA, *et al*. L-Serine reduces spinal cord pathology in a vervet model of preclinical ALS/MND. *J Neuropathol Exp Neurol* 2020;79:393–406.
7 Kiernan MC, Vucic S, Cheah BC, *et al*. Amyotrophic lateral sclerosis. *Lancet* 2011;377:942–55.
8 Wang Z, Bai Z, Qin X, *et al*. Aberrations in oxidative stress markers in amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Oxid Med Cell Longev* 2019;2019:1712323.
9 Muscaritoli M, Kushta I, Molfino A, *et al*. Nutritional and metabolic support in patients with amyotrophic lateral sclerosis. *Nutrition* 2012;28:959–66.
10 Piquet MA. Approche nutritionnelle des patients atteints de Sclérose Latérale Amyotrophique [Nutritional approach for patients with amyotrophic lateral sclerosis]. *Rev Neurol*;162 Spec No 2:4S177–4S187.
11 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;82:628–34.
12 Roubeau V, Blasco H, Maillot F, *et al*. Nutritional assessment of amyotrophic lateral sclerosis in routine practice: value of weighing and bioelectrical impedance analysis. *Muscle Nerve* 2015;51:479–84.
13 EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis: Andersen PM, Abrahams S, Borasio GD, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)-revised report of an EFNS task force. *Eur J Neurol* 2012;19:360–75.
14 Almeida CS, Stanich P, Salvioni CCS, *et al*. Assessment and nutrition education in patients with amyotrophic lateral sclerosis. *Arq Neuropsiquiatr* 2016;74:902–8.
15 Prado LdeGR, Bicalho ICS, Vidigal-Lopes M, *et al*. Depression and anxiety in a case series of amyotrophic lateral sclerosis: frequency and association with clinical features. *Einstein* 2017;15:58–60.
16 Campos CF, Gromicho M, Uysal H, *et al*. Family history of neurodegenerative disorders in patients with amyotrophic lateral sclerosis: population-based case-control study. *J Neurol Neurosurg Psychiatry* 2020;91:671–2.
17 Van Damme P, Bogaert E, Dewil M, *et al*. Astrocytes regulate GluR2 expression in motor neurons and their vulnerability to excitotoxicity. *Proc Natl Acad Sci U S A* 2007;104:14825–30.
18 Brouwers MC, Florez ID, McNair SA, *et al*. Clinical practice guidelines: tools to support high quality patient care. *Semin Nucl Med* 2019;49:145–52.
19 Kredo T, Bernhardsson S, Machingaidze S, *et al*. Guide to clinical practice guidelines: the current state of play. *Int J Qual Health Care* 2016;28:122–8.
20 Ghorob A, Bodenheimer T. Sharing the care to improve access to primary care. *N Engl J Med* 2012;366:1955–7.
21 Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. *Lancet* 1993;342:1317–22.
22 Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.
23 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
24 Brouwers MC, Kho ME, Browman GP, *et al*. Agree II: advancing Guideline development, reporting and evaluation in health care. *CMAJ* 2010;182:E839–42.
25 Sterne JAC, Savović J, Page MJ, *et al*. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
26 Sterne JA, Hernán MA, Reeves BC, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
27 Roche JC, Rojas-Garcia R, Scott KM, *et al*. A proposed staging system for amyotrophic lateral sclerosis. *Brain* 2012;135:847–52.
28 Balendra R, Jones A, Jivraj N, *et al*. Estimating clinical stage of amyotrophic lateral sclerosis from the ALS functional rating scale. *Amyotroph Lateral Scler Frontotemporal Degener* 2014;15:279–84.
29 Guyatt GH, Oxman AD, Vist GE, *et al*. Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
30 Burgos R, Bretón I, Cereda E, *et al*. ESPEN guideline clinical nutrition in neurology. *Clin Nutr* 2018;37:354–96.
31 Masrori P, Van Damme P. Amyotrophic lateral sclerosis: a clinical review. *Eur J Neurol* 2020;27:1918–29.
32 Dorst J, Cypionka J, Ludolph AC. High-caloric food supplements in the treatment of amyotrophic lateral sclerosis: a prospective interventional study. *Amyotroph Lateral Scler Frontotemporal Degener* 2013;14:533–6.
33 Traynor BJ, Alexander M, Corr B, *et al*. Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: a population based study, 1996-2000. *J Neurol Neurosurg Psychiatry* 2003;74:1258–61.
34 Miller RG, Jackson CE, Kasarskis EJ, *et al*. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009;73:1218–26.
35 Kellogg J, Bottman L, Arra EJ, *et al*. Nutrition management methods effective in increasing weight, survival time and functional status in ALS patients: a systematic review. *Amyotroph Lateral Scler Frontotemporal Degener* 2018;19:7–11.
36 Chiò A, Logroscino G, Hardiman O, *et al*. Prognostic factors in ALS: a critical review. *Amyotroph Lateral Scler* 2009;10:310–23.
37 Genton L, Viatte V, Janssens J-P, *et al*. Nutritional state, energy intakes and energy expenditure of amyotrophic lateral sclerosis (ALS) patients. *Clin Nutr* 2011;30:553–9.
38 España GMde, Sanidad Mde. Servicios Sociales E Igualdad. Estrategia en Enfermedades neurológicas del Sistema Nacional de Salud. *Abril* 2016.
39 Greenwood DI. Nutrition management of amyotrophic lateral sclerosis. *Nutr Clin Pract* 2013;28:392–9.
40 National Clinical Guideline Centre (UK). *Motor neurone disease: assessment and management*. London: National Institute for Health and Care Excellence (UK), 2016.
41 Del Olmo García M [a] Dolores, Virgili Casas N, Cantón Blanco A, *et al*. [Nutritional management of amyotrophic lateral sclerosis: summary of recommendations]. *Nutr Hosp* 2018;35:1243–51.