Appendix 1 PRISMA Checklist Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Titlepage
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N.A.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group, (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2 and 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N.A.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N.A.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix 2: Literature search

Medline (via PubMed) search strategy d.d. 17 February 2015

Search (((((((((((((als[Title/Abstract]) OR amyotrophic lateral sclerosis[Title/Abstract]) OR mnd[Title/Abstract]) OR motor neuron disease[Title/Abstract]) OR motor neuron diseases[Title/Abstract]) OR motor neurone disease[Title/Abstract]) OR motor neurone diseases[Title/Abstract]) OR lou gehrig's disease[Title/Abstract]) OR lou gehrigs disease[Title/Abstract]) OR charcot disease[Title/Abstract]) OR amyotrophic lateral sclerosis[MeSH Terms])) AND (((caregiver[Title/Abstract]) OR caregivers[Title/Abstract]) OR care giver[Title/Abstract]) OR care givers[Title/Abstract]) OR caretaker[Title/Abstract]) OR caretakers[Title/Abstract]) OR carer[Title/Abstract]) OR carers[Title/Abstract]) OR partner[Title/Abstract]) OR partners[Title/Abstract]) OR next of kin[Title/Abstract]) OR family[Title/Abstract]) OR families[Title/Abstract]) OR parent[Title/Abstract]) OR parents[Title/Abstract]) OR spouse[Title/Abstract]) OR spouses[Title/Abstract]) OR husband[Title/Abstract]) OR husbands[Title/Abstract]) OR wife[Title/Abstract]) OR wives[Title/Abstract]) OR child[Title/Abstract]) OR children[Title/Abstract]) OR brother[Title/Abstract]) OR brothers[Title/Abstract]) OR sister[Title/Abstract]) OR sisters[Title/Abstract]) OR sibling[Title/Abstract]) OR siblings[Title/Abstract]) OR friend[Title/Abstract]) OR friends[Title/Abstract]) OR social support[Title/Abstract]) OR social network[Title/Abstract]) OR social networks[Title/Abstract]) OR significant other[Title/Abstract]) OR significant others[Title/Abstract]) OR relative[Title/Abstract]) OR relatives[Title/Abstract]) OR married person[Title/Abstract]) OR married persons[Title/Abstract]) OR spousal notification[Title/Abstract]) OR stepfamily[Title/Abstract]) OR stepfamilies[Title/Abstract]) OR support system[Title/Abstract]) OR support systems[Title/Abstract]) OR support system[Title/Abstract]) OR support systems[Title/Abstract]) OR neighbor[Title/Abstract]) OR neighbors[Title/Abstract]) OR neighbour[Title/Abstract]) OR neighbours[Title/Abstract]) OR family caregiver[MeSH Terms]) OR social support[MeSH Terms])) AND ((((((burden[Title/Abstract]) OR distress[Title/Abstract]) OR stress[Title/Abstract]) OR strain[Title/Abstract]) OR overload[Title/Abstract]) OR psychological stress[MeSH Terms])

EMBASE search strategy d.d. 17 February 2015

('caregiver':ab,ti OR 'caregivers':ab,ti OR 'care giver':ab,ti OR 'care givers':ab,ti OR 'caretaker':ab,ti OR 'caretakers':ab,ti OR 'carer':ab,ti OR 'carers':ab,ti OR 'partner':ab,ti OR 'partners':ab,ti OR 'next of kin':ab,ti OR 'family':ab,ti OR 'families':ab,ti OR 'parent':ab,ti OR 'parents':ab,ti OR 'spouse':ab,ti OR 'spouses':ab,ti OR 'husband':ab,ti OR 'husbands':ab,ti OR 'wife':ab,ti OR 'wives':ab,ti OR 'child':ab,ti OR 'children':ab,ti OR 'brother':ab,ti OR 'brothers':ab,ti OR 'sister':ab,ti OR 'sisters':ab,ti OR 'sibling':ab,ti OR 'siblings':ab,ti OR 'friend':ab,ti OR 'friends':ab,ti OR 'social support':ab,ti OR 'social network':ab,ti OR 'social networks':ab,ti OR 'significant other':ab,ti OR 'significant others':ab,ti OR 'relative':ab,ti OR 'relatives':ab,ti OR 'married person':ab,ti OR 'married persons':ab,ti OR 'spousal notification':ab,ti OR 'step family':ab,ti OR 'step families':ab,ti OR 'supportsystem':ab,ti OR 'supportsystems':ab,ti OR 'support system':ab,ti OR 'support systems':ab,ti OR 'neighbor':ab,ti OR 'neighbors':ab,ti OR 'neighbour':ab,ti OR 'neighbours':ab,ti OR 'caregiver'/exp) AND (als:ab,ti OR 'amyotrophic lateral sclerosis':ab,ti OR 'mnd':ab,ti OR 'motor neuron disease':ab,ti OR 'motor neuron diseases':ab,ti OR 'motor neurone disease':ab,ti OR 'motor neurone diseases':ab,ti OR 'lou gehrig/s disease':ab,ti OR 'lou gehrigs

disease':ab,ti OR 'charcot disease':ab,ti OR 'amyotrophic lateral sclerosis'/exp) AND (burden:ab,ti OR strain:ab,ti OR distress:ab,ti OR stress:ab,ti OR overload:ab,ti OR 'caregiver burden'/exp) AND [embase]/lim AND ([dutch]/lim OR [english]/lim OR [german]/lim)

Appendix 3: Methodological Quality Assessment List

Item	Outcome Strategy	Criteria (positive=1, otherwise=0)
1.	*Internal validity:* Were the main outcome measures valid and reliable?	Positive, if the study tests the validity and reliability of the measurements used, or refers to other studies which have established the validity and reliability.
2.	*Study participation:* Is the sample representative for the target group?	Positive, if specified how many persons were approached, how many persons participated, and a nonresponse analysis is done to compare participants and nonparticipants.
3.	*External validity:* Were the relevant patient characteristics specified (in- and exclusion criteria)?	Positive, if caregiver age, -gender, type of relationship with patient, time since patients' diagnosis and the physical functioning of the patient is reported.
4.	*Statistical validity:* Was the relationship between dependent and independent variables statistically valid?	Positive, if the relationship between a dependent and independent variable is tested for statistical significance.
5.	*Proportion sample size vs factors*: Was the sample size (n) adequate in relation to the number of factors (K)?	Positive, if univariate ratio [n:K] exceeds [20:1] and if multivariate ratio [n:K] exceeds [10:1].
6.	*Multicollinearity* : Was there a control for multicollinearity?	Positive, if specified that multicollinearity between variables has been tested.
7.	*Confounding bias:* Were potentially confounding variables controlled?	Positive, if specified that the design accounts for and analyses are corrected for confounders.
8.	*Reporting:* Are the main findings of the study clearly described?	Positive, if purpose is described, results are related to the purpose, statistical analyses are clearly reported, and data tables are explained in the results.

Appendix 4: GRADE factors

Item	GRADE factor	Criteria **(No serious limitation = ✓, serious limitation=×)**
1.	Study limitations	No serious limitation, if at least 75% of the studies are moderate- (total score 3-5) to high quality (total score 6-8) studies based on the Methodological Quality Assessment List.
2.	Inconsistency	No serious limitation, if the point of effect estimates are not on either side of the line of no effect.
3.	Indirectness	No serious limitation, if at least 75% of the studies used a study sample that fully represents the review question.
4.	Imprecision	No serious limitation, if 75% of the studies applied the rule of thumb: univariate ratio [n:K] exceeds [20:1] and if multivariate ratio [n:K] exceeds [10:1]. In which n represents the sample size and K the number of studied factors.
5.	Publication bias	No serious limitation, if the factor is investigated in 3 or more studies.

Appendix 5. Risk of bias

	Item [a, b]								
References	*1.Internal validity*	*2.Study participation*	*3.External validity*	*4.Statistical validity*	*5.Proportion sample size vs factors*	*6.Multi collinearity*	*7.Confounding bias*	*8.Reporting*	*Total*
Andrews (2016) [46]	1	0	0	1	0	NA	0	1	3
Bock (2016) [47]	1	0	0	1	0	1	1	1	5
Burke (2015) [48]	1	0	1	1	0	NA	0	1	4
Chio (2005) [10]	1	0	1	1	1	0	1	0	5
Chio (2010) [49]	1	0	1	1	1	0	1	0	5
Creemers (2015) [5]	1	0	1	1	1	0	1	1	6
Galvin (2016) [50]	1	0	0	1	1	0	0	0	3
Gauthier (2007) [6]	1	0	1	1	0	NA	0	0	3
Geng (2016) [51]	1	0	1	1	1	1	1	1	7
Goldstein (1998) [20]	0	1	1	1	0	NA	0	0	3
Goldstein (2000) [19]	0	1	1	1	0	NA	0	1	4
Hecht (2003) [52]	1	0	1	1	0	NA	0	1	4
Jenkinson (2000) [24]	1	0	0	1	1	NA	0	0	3
Lillo (2012) [53]	1	0	1	1	1	0	1	1	6
Pagnini (2010) [22]	1	0	1	1	0	NA	0	1	4
Pagnini (2011) [54]	1	0	1	1	0	NA	0	1	4
Pagnini (2012) [21]	1	0	1	1	0	NA	0	1	4
Pagnini (2016) [55]	1	0	1	1	1	0	1	1	6
Qutub (2014) [23]	1	0	0	1	0	NA	0	0	2
Rabkin (2000) [11]	0	0	1	1	0	NA	0	1	3
Rabkin (2009) [56]	0	1	0	1	1	NA	0	1	4
Tramonti (2014) [57]	1	0	1	1	0	0	1	1	5
Tramonti (2015) [58]	1	0	0	1	0	NA	0	1	3
Tremolizzo (2016) [59]	1	0	0	1	1	0	1	0	4
Watermeyer (2015) [60]	1	0	1	1	0	0	1	1	5

Notes .[a]0 = negative; 1 = positive; NA = not applicable

[b]1. Positive if the study tests the validity and reliability of the outcome measures used, or refers to other studies which have established the validity and reliability; 2. Positive if specified how many persons were approached, how many persons participated, and a non-response analysis is done to compare participants and non-participants; 3.Positive if caregiver age, -gender, type of relationship with patient, and time since diagnosis or onset and physical functioning

of the patient are specified; 4. Positive if the relationship between a dependent and independent variable is tested for statistical significance; 5. Positive if univariate ratio [n:K] exceeds [20:1] and if multivariate ratio [n:K] exceeds [10:1]; 6. Positive if specified that multicollinearity between variables has been tested; 7. Positive if specified that the design accounts for and analyses are corrected for confounders; 8. Positive, if purpose is described, results are related to the purpose, statistical analyses and results are clearly reported, and data tables are explained in the results.

Appendix 6. Caregiver burden instruments

Instrument	*Description*	*Number of Items*	*Applied by studies in this review*
Zarit Burden Interview (ZBI) [25]	This instrument is a measurement for the degree of caregiver burden. It covers areas mentioned by caregivers as problems including health, psychological wellbeing, finances, social life and relationship with the patient. Caregivers indicate how much discomfort each topic causes, choosing answer option from "not at all" to extremely. The range of possible scores is 0-88, with a higher score indicating a greater level of burden.	22	[46,48,50,53,22,54,21,55,11,56,60,51,23] [1,2,3]
Caregiver Burden Inventory (CBI) [26]	This instrument measures the impact of burden on caregivers. It is a multidimensional measure that permits distinction between five dimensions of burden (time dependence, developmental, physical, social and emotional). Scores for each item are evaluated using a 5-point scale ranging from 0 (not at all disruptive) to 4 (very disruptive). Total scores range from 0 (lowest level) to 96 (highest level).	24	[10,49,6,57-59]
Caregiver Strain Index (CSI) [27]	This is a screening instrument for the detection of caregiver strain. The CSI contains 13 items, each scored on a dichotomous (yes/no) scale. CSI examines both subjective [e.g. feeling completely overwhelmed] and objective elements [e.g. there have been work adjustments] of caregiver strain. Total scores range from 0-13, higher scores reflect higher caregiver burden.	13	[5,24]
Burden Scale for Family Caregivers (BSFC) [28]	This scale is a global measure of perceived burden. Its purpose is to cover all the relevant aspects which can contribute to caregiver burden. Every item is scored from 0 to 3 points (`quite correct', `correct on the whole', `correct in part', `not correct') resulting in a total score from 0 (lowest) to 84 (highest).	28	[52]
Caregiver Burden Scale (CGBS) [29]	This scale measures subjective burden and contains five indices; general strain, isolation, disappointment, emotional involvement and environment. Items are scored on a four point scale and total scores range from 22 (lowest) to 88 (highest).	22	[47]
Strain scale [30]	''I feel no strain because of the way my partner is nowadays'' [1] to ''I feel severe strain because of the way my partner is nowadays'' [7]	1	[20,19]

[1] Lillo, 2012 used the validated short 12 item version

[2] Rabkin, 2000 used 6 items of this instrument

[3] Rabkin, 2009 used 5 items of this instrument