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Caregiver burden in amyotrophic lateral sclerosis: A systematic review

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Abstract

Background: Informal caregivers of patients with amyotrophic lateral sclerosis experience increased levels of caregiver burden as the disease progresses. Insight in the factors related to caregiver burden is needed in order to develop supportive interventions.

Aim: To evaluate the evidence on patient and caregiver factors associated with caregiver burden in amyotrophic lateral sclerosis informal caregivers.

Design: A systematic review.

Data sources: Four electronic databases were searched up to 2017. Studies that investigated quantitative relations between patient or caregiver factors and caregiver burden were included. The overall quality of evidence for factors was assessed using the Grading of Recommendations Assessment, Development and Evaluation approach.

Results: A total of 25 articles were included. High quality of evidence was found for the relation between caregiver burden and the factor "behavioral impairments." Moderate quality of evidence was found for the relations between caregiver burden and the factors "feelings of depression" of the caregiver and "physical functioning" of the patient. The remaining rated caregiver factors—"feelings of anxiety," "distress," "social support," "family functioning," and "age"—and patient factors—"bulbar function," "motor function," "respiratory function," "disease duration," "disinhibition," "executive functioning," "cognitive functioning," "feelings of depression," and "age"—showed low to very low quality of evidence for their association with caregiver burden.

Conclusion: Higher caregiver burden is associated with greater behavioral and physical impairment of the patient and with more depressive feelings of the caregiver. This knowledge enables the identification of caregivers at risk for caregiver burden and guides the development of interventions to diminish caregiver burden.

Keywords

Amyotrophic lateral sclerosis, family caregivers, systematic review

What is already known about the topic?

- Informal caregivers of patients with amyotrophic lateral sclerosis (ALS) experience increased caregiver burden during the disease course of the patient.
- Little is known regarding which caregiver factors and which patient factors influence caregiver burden in ALS.

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What this paper adds?

- This systematic review offers a comprehensive overview of both patient and caregiver factors related to caregiver burden in informal caregivers of patients with ALS.
- Higher caregiver burden is associated with greater behavioral and physical impairment of the patient and with more depressive feelings of the caregiver.

Implications for practice, theory, or policy

- This knowledge enables the identification of caregivers of people with ALS who are at risk for caregiver burden.
- This knowledge informs the development of interventions focusing on diminishing burden in caregivers of ALS patients.
- More studies are needed that examine caregiver-related factors (such as feelings of competence in caregiving or self-efficacy) in relation to caregiver burden.

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that causes severe restrictions in physical functioning. Patients suffer from progressive weakness of voluntary muscles and approximately 30%–50% of the ALS patients experience cognitive impairments.[1,2] The disease leads to an increasing need for care; a major role in this care process is fulfilled by informal caregivers (family, friends, and neighbors).

Caring for an ALS patient is a demanding task. During the course of the disease, the patient may require support with all activities of daily living such as eating, transportation, and medical care.[3] Furthermore, caregivers often struggle with accepting this fatal disease, their increased responsibilities, concerns about the future, and feelings of guilt.[4] Findings from longitudinal studies indicate that caregivers of patients with ALS experience increasing levels of physical and emotional distress, often referred to as caregiver burden.[5,6] Caregiver burden is defined as the impact on the emotional health, physical health, social life, and the financial status of the caregiver as a result of adopting the caregiving role.[7]

The well-being of caregivers is essential in ALS care; their capacity proves to be an important factor in enabling ALS patients to remain at home until the end of their lives rather than going into a care facility.[8] Moreover, studies show a high concordance between the well-being of the patient and that of the caregiver, indicating that a reduced well-being of the caregiver can negatively impact the well-being of the patient.[9–11]

Knowledge about which factors relate to caregiver burden is needed in order to develop interventions to support caregivers. During the last decade, three reviews have been published concerning the well-being of ALS caregivers, but a comprehensive overview of both modifiable and non-modifiable patient and caregiver factors influencing caregiver burden is lacking.[12–14] The objective of this study, therefore, was to systematically review published literature to investigate which caregiver and patient factors are related to caregiver burden in informal caregivers of patients with ALS.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[15] see Supplementary Appendix 1. This systematic review has been registered with PROSPERO 2015 CRD42015019842.

Search strategy

The electronic databases PsycINFO, Medline (PubMed), CINAHL, and EMBASE were systematically searched using the following keywords, along with synonyms: "amyotrophic lateral sclerosis," "burden," and "caregiver." A clinical librarian was consulted regarding the search strategy, which is presented in the online Supplementary Appendix 2. No constraint was placed on the year of publication; searches were conducted up to 2017. Additionally, references were checked for relevant publications. To make sure that no relevant papers had been missed, we sent a list of papers identified through the search to researchers in the field of ALS care for their review.

Inclusion criteria

Studies that investigated quantitative relationships between caregiver or patient factors and caregiver burden in informal ALS caregivers were included. Factors had to be explicitly defined and in case of self-reported constructs measured with a validated questionnaire or a clearly described single question. Burden had to be assessed with a total caregiver burden construct. Only full-text articles, published in peer-reviewed journals, in English, Dutch, or German, were considered eligible.

Exclusion criteria

Mixed sample studies—studies where caregivers of patients with different diagnoses are grouped together—were excluded, unless subsample analysis was performed for ALS caregivers. Studies that described the association solely with subscales of burden measures, or studies that combined burden with other outcomes measures into one overarching outcomes measure, were not taken into account. Intervention studies, qualitative studies, reviews, and case reports were excluded.

Study selection

The titles and abstracts of the articles were independently screened for relevance by two reviewers (J.d.W. and A.C.v.G.); relevant publications, potentially eligible for inclusion, were read in full text by two reviewers (J.d.W. and L.A.B.). Disagreements were resolved by discussion until consensus was reached. Authors of the studies in the review were contacted by e-mail when information was missing.

Risk of bias assessment

The risk of bias of the included studies was assessed independently by the two researchers who assessed the full-text articles (J.d.W. and L.A.B.). The Methodological Quality Assessment List,[16,17] an 8-point checklist that yields a total score between 0 (low methodological quality) and 8 (high methodological quality), was used (Supplementary Appendix 3). Since this checklist was originally applied to research on patients, the relevant characteristics to score item 3 "external validity" were changed into "caregiver age, gender, type of relationship with patient, physical functioning of the patient and time since patient's diagnosis." Studies with a total score below 3 were excluded from the quality of evidence assessment. In case of disagreement, a third author was consulted.

Data synthesis

Data were independently extracted from eligible papers by two researchers (J.d.W. and L.A.B.) using structured data forms that were developed for this study and included key components of the study characteristics, study results, and methodological quality of the studies. Due to the diversity of outcome measures and factors included in the study, a meta-analysis was not possible. Bivariate and multivariate associations were described separately in terms of correlation coefficients (r) and standardized β-coefficients (β). In studies that applied a logistic regression, the odds ratio (OR) was presented. Factors were grouped into patient and caregiver characteristics and subsequently thematically categorized.

Quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the overall quality of evidence for each factor measured in at least three studies (Supplementary Appendix 4).[18] Two researchers (J.d.W. and L.A.B.) rated the factors on the GRADE criteria study limitations (here we used the Methodological Quality Assessment List), inconsistency, indirectness, imprecision, and publication bias. The criteria "dose effect" and "moderate/large effect" were omitted, since these criteria were not relevant for the quality of evidence in our review. The overall quality of evidence was classified as high, moderate, low, or very low.

Results

Studies selected

The search identified a total of 1126 possibly relevant articles. After the removal of duplicates and the abstract and full-text screening, a total of 25 studies were left for inclusion in the review (Figure 1). Two study samples were described in two articles each.[19–22] Since these articles investigated different factors in relation to burden, they were retained for review.

Risk of bias

The methodological quality scores of the studies ranged from 2 to 7 out of a maximum of 8 (high quality) points (Supplementary Appendix 5). One study scored a low total score, indicating a high risk of bias, and was not incorporated in the quality of evidence assessment.[23] The following items of the Methodological Quality Assessment List were not met by the majority of the studies: study participation, proportion sample size versus factors, and confounding bias.

Description of studies included

The key characteristics of each study are presented in Table 1. The included studies were published in eight different countries between 1998 and 2016 and the majority was published in the last decade. A total of 20 studies used a cross-sectional design and 5 studies used a longitudinal design. A total of 22 studies investigated univariate associations; in 10 studies, associations were explored in multivariate models. The study samples ranged from 19 to 415 caregivers. Among the studies that reported the caregiver's relationship with the patient ($n=22$), partners dominated the sample (range, 63%–100%), with two studies recruiting partners only. Other relationships included children, siblings, parents, friends, neighbors, and other relatives. Caregivers were predominantly female and the mean age

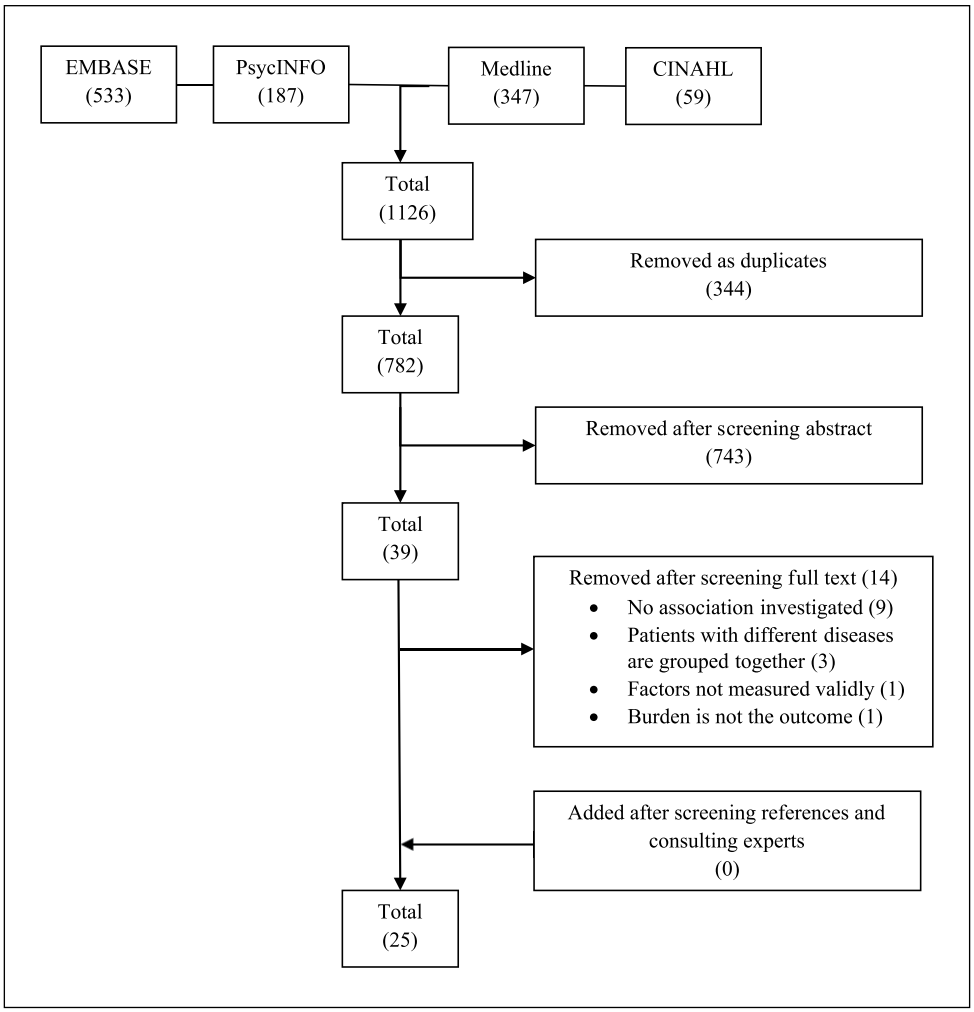

Figure 1. Search flowchart.

of caregivers varied from 48 to 61 years. The mean time since disease onset ranged from 15 to 40 months.

Measures of burden

Across studies, five different validated measures of caregiver burden were used (Zarit Burden Interview ($n=11$),[40] Caregiver Burden Inventory ($n=6$),[41] Caregiver Strain Index ($n=2$),[42] Burden Scale for Family Caregivers ($n=1$),[43] and Caregiver Burden Scale ($n=1$))[44] and two studies used a number of selected items of the Zarit Burden Interview (see Supplementary Appendix 6). Two studies used a single-item measurement to measure burden.[45]

Studied factors in relation to caregiver burden in ALS caregivers

Overviews of the studied caregiver and patient factors that were investigated in relation to caregiver burden are presented in Tables 2 and 3. Caregiver factors were grouped into the following categories: emotional functioning, social environment, demographics, personal factors, physical health, and caregiving time. Patient factors were categorized into physical health, behavioral impairments, cognitive impairments, emotional functioning, personal factors, demographics, and social environment.

Evidence for factors related to caregiver burden

Caregiver factors. The synthesis of evidence for the caregiver factors using the GRADE criteria resulted in a rating of moderate quality of evidence for the relationship between higher caregiver burden and "feelings of depression" (see Table 4). Low quality of evidence was found for the relations between higher caregiver burden and the factors "anxiety," "distress," and "age." The social environment factors "social support" and "family functioning" showed very low quality of evidence as factors associated with lower caregiver burden.

Table 1. The summary of included studies.

Authors (Year)	Country	Design (follow-up)[a]	Caregiver sample, *n* (% female)	Spouse of the patient (%)	Age in years caregivers, mean (SD)	Time since disease onset (o), time since diagnosis (d) Mean (SD) months	ALSFRS, mean (SD)
Andrews et al. (2016)[24]	Australia	Cross-sectional	40 (78)	n.r.	56 (14.5)	26 (14.2), o	35.3 (8.9)[R]
Bock et al. (2016)[25]	USA	Cross-sectional	86 (n.r.)	n.r.	n.r.	26 (48.6), o*	33.5 (11.1)[R*]
Burke et al. (2015)[26]	Ireland	Cross-sectional	33 (66)	81.3	58 (11.1)	30 (18.2), o	36.6 (7.8)[R]
Chio et al. (2005)[10]	Italy	Cross-sectional	60 (63)	76.7	58 (12.3)	28 (25.2), o	24.6 (10.6)
Chio et al. (2010)[27]	Italy	Cross-sectional	70 (67)	80.0	55 (13.3)	17 (9.3), o	29.2 (6.1)
Creemers et al. (2015)[5]	The Netherlands	Longitudinal (12 months)	126 (66)	85.0	59 (12.5)	25 (n.r.), o*	31.8 (8.2)[R]
Galvin et al. (2016)[28]	Ireland	Cross-sectional	81 (70)	71.6	55 (13.4)	n.r.	n.r.
Gauthier et al. (2007)[6]	Italy	Longitudinal (9 months)	31 (71)	80.6	55 (11.3)	40 (31.5), o	28.7 (7.0)
Geng et al. (2016)[29]	China	Cross-sectional	81 (68)	67.9	48 (14.5)	17.8 (14.9), o	36.5 (8.6)
Goldstein et al. (1998)[20]	UK	Cross-sectional	19 (53)	100	60 (12.6)	34 (23.9), o	n.r.
Goldstein et al. (2000)[19]	UK	Cross-sectional	19 (53)	100	60 (12.6)	34 (23.9), o	n.r.
Hecht et al. (2003)[30]	Germany	Cross-sectional	37 (73)	81.1	57 (13.4)	25 (26.6), d	23.5 (9.1)
Jenkinson et al. (2000)[31]	UK	Cross-sectional	415 (n.r.)	79.6	55 (13.1)	26 (29.5), o	25.9 (28.8)
Lillo et al. (2012)[32]	Australia	Cross-sectional	140 (69)	90.0	61 (12.0)	36 (n.r.), o*	30.4 (9.7)[R]
Pagnini et al. (2010)[22]	Italy	Cross-sectional	40 (70; 78)[b]	82.5	56 (12.3)	15 (n.r.), o	34.9 (7.8)[R]
Pagnini et al. (2011)[33]	Italy	Cross-sectional	37 (62)	86.5	55 (11.4)	21 (4.2), o	27.8 (14.7)[R]
Pagnini et al. (2012)[21]	Italy	Cross-sectional	40 (70; 78)[b]	82.5	56 (12.3)	15 (n.r.), o	34.9 (7.8)[R]
Pagnini et al. (2016)[34]	Italy	Longitudinal (4 months)	114 (70)	82.3	57 (13.5)	32 (50.3), d	30.6 (9.9)
Qutub et al. (2014)[23]	USA	Cross-sectional	50 (66)	n.r.	61 (n.r.)	37 (n.r.), o	34.10 (n.r)[R]
Rabkin et al. (2000)[11]	USA	Cross-sectional	31 (61)	96.7	53 (12.0)	14 (n.r.), d	30.4 (4.7)
Rabkin et al. (2009)[35]	USA	Longitudinal (monthly)[c]	71 (74)	63.0	57 (15.0)	n.r.	23.6 (7.8)[R]
Tramonti et al. (2014)[36]	Italy	Longitudinal (6 months)	19 (68)	68.4	53 (11.6)	<6, d	18.2 (12.0)
Tramonti et al. (2015)[37]	Italy	Cross-sectional	70 (69)	71.4	54 (11.5)	n.r.	n.r.
Tremolizzo et al. (2016)[38]	Italy	Cross-sectional	84 (75)	78.0	n.r.	40 (37.5), n.r.	30.6 (9.0)[R]
Watermeyer et al. (2015)[39]	UK	Cross-sectional	35 (72)	100	58 (10.5)	30 (14.3), o	34.1 (8.2)[R]

ALSFRS: Amyotrophic Lateral Sclerosis Functioning Rating Scale [total score range 0–40 (better functioning)]; d: time since diagnosis; n.r.: not reported; o: time since disease onset; [R]: Amyotrophic Lateral Sclerosis Functioning Rating Scale Revised [total score range 0–48 (better functioning)]; SD: standard deviation; *: median.
[a]Design of caregiver study.
[b]Not consistently reported.
[c]Only cross-sectional data with regard to burden was analyzed.

Factors within the categories personal factors, physical health of the caregiver, and caregiving time were investigated in fewer than three studies and could not, therefore, be rated with the GRADE.

Patient factors. The synthesis of the evidence for the patient factors led to a rating of high quality evidence for the relationship between higher caregiver burden and "behavioral impairments." This factor represents total scores of questionnaires that measure behavioral impairments in patients, which was investigated in six studies. Patients' "physical functioning" was most frequently studied ($n = 11$). There was moderate quality of evidence for the relation between decreased physical functioning and higher caregiver burden. Very low quality of evidence was found for the association with higher caregiver burden and the factors "limb function," "respiratory function," "executive functioning," "cognitive functioning," and "age." Low evidence was found for "bulbar function" and "feelings of depression," and very low quality of evidence for "disease durations" as factors not associated with caregiver burden.

Since each of the factors within the categories personal factors and social environment was studied in one or two studies, no synthesis of evidence could be performed.

Table 2. Associations between caregiver factors and caregiver burden.

	Factor[a]	Measure factor	Outcome caregiver burden	Bivariate association	Bivariate analysis	Multivariate association	*N*	Ref
				r		β/OR (CI)		
Emotional functioning	Feelings of depression	BDI	ZBI-6 items	0.49*	P	–	31	11
		BDI	CBI	0.51***	P	–	82	38
		BDI-II	ZBI	0.43**	P	–	40	21
		BDI-II	ZBI	+n.r.***	R	–	50	23
		ZDS	CBI	0.55***	S	+n.r.*** (n.r.)	60	10
		ZDS	CBI	–	–	n.r.* (n.r.)	70	27
		ZDS	CBI	n.r.*	n.r.	–	31	6
		ZDS (t1)	CBI (t1)	n.r.*	n.r.	–	31	6
		HADS-Depression (t0–t3)	CSI (t0–t3)	–	–	ns	116	5
		HADS-Depression	ZBI	0.57***	P	ns	35	39
		DASS-Depression	ZBI-sv	–	–	ns[OR]	140	32
	Depression-Somatic	BDI-II-Somatic	ZBI	0.84***	S	–	40	22
	Depression-Psychological	BDI-II-Psychological	ZBI	0.57*	S	–	40	22
	Feelings of anxiety	HADS-Anxiety	ZBI	0.37*	P	ns	35	39
		HADS-Anxiety (t0–t3)	CSI (t0–t3)	–	–	0.19*** (0.086, 0.286)	116	5
		DASS-Anxiety	ZBI-sv	–		ns[OR]	140	32
		STAI-Trait	ZBI	0.36*	P	–	40	21
		STAI-Trait	ZBI-6 items	0.40[n.r.]	P	–	31	11
	Distress	HADS-Total	ZBI	0.62***	R	–	33	26
		HADS-Total	ZBI	–	–	+n.r.** (n.r.)	81	28
		DASS-Stress	ZBI-sv	–	–	1.12[OR]* (0.86, 1.00)	140	32
	Mental health	SF-36-MCS	CSI	0.50***	n.r.	–	415	31
	Hopelessness	BHS	ZBI-6 items	ns	P	–	31	11
Social environment	Social support	MQoL-Ss	ZBI	−0.73***	S	–	40	22
		5-point scale	ZBI	ns	P	–	31	11
		No. of friends/relatives seen	Strain Index	ns	S	–	19	19
		No. of close friends	Strain Index	ns	S	–	19	19
		No. of friends that can help	Strain Index	ns	S	–	19	19
		No. of substitute cgs	CBI	ns	S	–	60	10
		Participating in support group	BSFC	ns	S	–	37	30
		Participating in support group	CBI	ns	S	–	60	10
		Outside help received	ZBI	ns	R	–	50	23
		Hours per week help	ZBI	ns	R	–	50	23
	Family functioning	FACES-Real cohesion	CBI	ns	S	–	19	36
		FACES-Real cohesion (t0)	CBI (t1)	–	–	0.53* (n.r.)	19	36
		FACES-Ideal cohesion	CBI	ns	S	–	19	36
		FACES-Real adaptability	CBI	ns	S	–	19	36
		FACES-Ideal adaptability	CBI	ns	S	–	19	36
		MIS	ZBI	−0.45**	P	ns	35	39

Table 2. (Continued)

	Factor[a]	Measure factor	Outcome caregiver burden	Bivariate association	Bivariate analysis	Multivariate association	*N*	Ref
				r		*β*/OR (CI)		
		MIS (change)	ISS-I	0.50*	n.r.	–	19	20
	Quality of care cgs	Numerical scale (t0–t3)	CSI (t0–t3)	–	–	−0.45*** (−0.672, −0.232)	116	5
Demographics	Age	Years	CBI	ns	S	–	60	10
		Years	CBI	ns	n.r.	–	31	6
		Years	CBI	0.24*	S	–	70	37
		Years	ZBI	ns	P	–	35	39
		Years	ZBI	–	–	ns	81	28
		Years	ZBI	−n.r.**	R	–	50	23
		Years	ZBI	–	–	0.19* (n.r.)	81	29
	Gender	Male/female	CBI	ns	n.r.	–	31	6
		Male/female	ZBI	–	–	ns	81	28
	Years married	Years	ZBI	ns	P	–	35	39
	Relationship patient	Spouse/child/parent/..	ZBI	–	–	ns	81	28
	Living with patient	Yes/no	ZBI	–	–	ns	81	28
	Household income	Dollars	ZBI	ns	R	–	50	23
Personal factors	State of mindfulness	LMS	ZBI	−0.27**	P	–	140	34
		LMS (t1)	ZBI (t1)	−0.29*	P	–	140	34
		LMS (t0 + t1)	ZBI (t0 + t1)	–	–	−n.r.* (n.r.)	140	34
	Religiosity	RBI	ZBI-6 items	ns	P	–	31	11
		Not-very religious	ZBI	ns	R	–	50	23
	Positive meaning in caring	FM-4 items	ZBI-6 items	0.49**	P	–	31	11
	Passive coping	UCL-PA (t0–t3)	CSI (t0–t3)	–		0.15* (0.015, 0.289)	116	5
	Illness affects life areas	ISS-4	ISS-I	0.50*	n.r.	–	19	20
	Attribution style	Globality attribution measure	Strain Index	0.58**	S	–	19	19
	Control over reactions	Control over reactions measure	Strain Index	−n.r.*	S	–	19	19
Physical health	Physical functioning	SF-36-PCS	CSI	0.28***	n.r.	–	415	31
	Physical fatigue	CFS-physical fatigue	ZBI-6 items	0.36[n.r.]	P	–	31	11
Caregiving time	Time caring	Hours per day	ZBI	ns	R	–	33	26
		Hours per week	ZBI	–		n.r.* (n.r.)	81	28
		Hours per day	ZBI	+n.r.*	R	–	50	23
		Time with patient	Hours per day	ZBI	ns	–	50	23
		% time caring	% time of day	ZBI	ns	–	50	23

BDI: Beck Depression Inventory; BHS: Beck Hopelessness Scale; BSFC: Burden Scale for Family Caregivers; CBI: Caregiver Burden Inventory; CFS-physical fatigue: Chalder Fatigue Scale, Physical Fatigue subscale; cgs: caregivers; CI: confidence interval; CSI: Caregiver Strain Index; DASS: Depression, Anxiety, Stress Scale; FACES: Family Adaptation and Cohesion Evaluation Scale; FM: Folkman's 4-item measure of finding positive meaning in caregiving; HADS: Hospital Anxiety and Depression Scale; ISS: Item Strain Scale; LMS: Langer Mindfulness Scale; MIS: Marital Intimacy Scale; MQoL-Ss: McGill Quality of Life social support subscale; n.r.: not reported; no.: number; ns: not significant; OR: Odds Ratio; P: Pearson's product moment correlation; R: univariate regression analysis; RBI: Religious Beliefs Inventory; S: Spearman's rank order correlation; SF-36: 36-item Short Form Health Survey Questionnaire; SF-36-MCS: 36-item Short Form Health Survey Questionnaire Mental Component; SF-36-PCS: 36-item Short Form Health Survey Questionnaire Physical Component; STAI: State-Trait Anxiety Inventory; UCL-PA: Utrecht Coping List Passive Approach subscale; ZBI: Zarit Burden Interview; ZBI-sv: Zarit Burden Interview-short version; ZDS: Zung Depression Scale.

[a]Factors and outcomes are measured at t0 unless mentioned otherwise.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 3. Associations between patient factors and caregiver burden.

	Factor[a]	Measure factor	Outcome caregiver burden	Bivariate association	Bivariate analysis	Multivariate association	*N*	Ref
				r		β/OR (CI)		
Physical health	Physical functioning	ALSFRS	CBI	−0.61***	S	−n.r.*** (n.r.)	60	10
		ALSFRS	CBI	−0.61***	n.r.	–	31	6
		ALSFRS (t1)	CBI (t1)	−0.64***	n.r.	–	31	6
		ALSFRS	CBI	−0.44**	S	–	70	37
		ALSFRS-R	CBI	−0.52***	P	–	84	38
		ALSFRS	BSFC	−0.47**	S	–	37	30
		ALSFRS-R	ZBI	−0.46*	S	–	40	22
		ALSFRS-R	ZBI	ns	R	–	33	26
		ALSFRS-R	ZBI	ns	S	–	40	24
		ALSFRS-R	ZBI	ns	R	–	50	23
		ALSFRS-R	ZBI-5 items	ns	P	–	71	35
		ALSFRS-R	CGBS	–	–	−0.58* (−1.1, −0.01)	86	25
		ALSFRS-R (t0–t3)	CSI (t0–t3)	–	–	−0.13*** (−0.170, −0.092)	116	5
	Bulbar function	ALSFRS-Bulbar	CBI	ns	n.r.	–	31	6
		ALSFRS-Bulbar	ZBI-sv	–	–	ns[OR]	140	32
		ALSFRS-R-Bulbar	ZBI	ns	P	–	35	39
	Motor function	ALSFRS-R-Limb	ZBI	−0.66***	P	−0.51** (n.r.)	35	39
		ALSFRS-R-Upper limb	CBI	n.r.*	n.r.	–	31	6
		ALSFRS-Lower limb	CBI	n.r.*	n.r.	–	31	6
		ALSFRS-Fine motor	ZBI-sv	–	–	ns[OR]	140	32
		ALSFRS-Gross motor	ZBI-sv	–	–	ns[OR]	140	32
		ALSFRS-R Fine & Gross	ZBI	–	–	−0.52*** (n.r.)	81	29
	Respiratory function	ALSFRS-Respiration	CBI	ns	n.r.	–	31	6
		ALSFRS-Respiration	ZBI-sv	–	–	ns[OR]	140	32
		ALSFRS-R-Respiration	ZBI	ns	P	–	35	39
		FVC	ZBI	−0.42**	P	–	40	21
		PCF	ZBI	−0.35*	P	–	40	21
	Disease progression	Progression index[b]	CBI	0.27*	P	–	84	38
	Physical health	SF-36-PCS	CSI	0.51***	n.r.	–	415	31
	Self care	CBI-R-Self care	ZBI	ns	S	–	40	24
	Everyday skills	CBI-R-Everyday skills	ZBI	0.41**	S	–	40	24
	Disease duration	Years	CBI	–	–	n.r.* (n.r.)	60	10
		Months	ZBI	ns	P	–	35	39
		Months	CBI	ns	P	–	84	38
Behavioral impairments	Behavioral impairments	FrSBe-Total	CBI	0.38***	P	+n.r.* (n.r.)	70	27
		FrSBe-Total	ZBI	0.69***	P	0.69** (n.r.)	35	39
		CBI-R-Total	ZBI	0.66***	S	–	40	24
		FrSBe-Total (change)	ZBI	0.56*	R	–	33	26
		ALS-CBS-Behavior	CGBS	−0.76***	R	−0.69*** (−0.98, −0.41)	86	25
		ALS-CBS-Behavior	CBI	−0.22*	P	−n.r.* (n.r.)	84	38

Table 3. (Continued)

	Factor[a]	Measure factor	Outcome caregiver burden	Bivariate association	Bivariate analysis	Multivariate association	*N*	Ref
				r		*β*/OR (CI)		
	Apathy	FrSBe-Apathy	ZBI	0.63***	P	ns	35	39
		FrSBe-Apathy (change)	ZBI	0.39*	R	–	33	26
	Disinhibition	FrSBe-Disinhibition	CBI	ns	P	–	70	27
		FrSBe-Disinhibition	ZBI	0.51**	P	ns	35	39
		FrSBe-Disinhibition (change)	ZBI	0.53**	R	–	33	26
	Executive functioning	FrSBe-Executive dysfunction	CBI	0.44***	P	ns	70	27
		FrSBe-Executive dysfunction	ZBI	0.51**	P	ns	35	39
		FrSBe-Executive dysfunction (change)	ZBI	0.37*	R	–	33	26
		Battery of tests	ZBI	ns	P	–	35	39
	Behavior abnormalities	CBI-R-Abnormal behavior	ZBI-sv	–	–	1.44[OR]** (1.13, 1.85)	140	32
		CBI-R-Abnormal behavior	ZBI	0.38*	S	–	40	24
	Eating habits	CBI-R-Eating habits	ZBI-sv	–	–	ns[OR]	140	32
		CBI-R-Eating habits	ZBI	0.36*	S	–	40	24
	Stereotypic and motor behaviors	CBI-R-Stereotypical motor behavior	ZBI-sv	–	–	ns[OR]	140	32
		CBI-R-Stereotypical motor behavior	ZBI	0.32*	S	–	40	24
	Motivation	CBI-R-Lack of motivation	ZBI-sv	–	–	ns[OR]	140	32
		CBI-R-Lack of motivation	ZBI	0.43**	S	–	40	24
	Odd beliefs	CBI-R-Odd beliefs	ZBI	ns	S	–	40	24
Cognitive impairments	Overall cognitive functioning	Neuropsychological tests	ZBI	ns	R	–	33	26
		MMSE	CBI	ns	P	–	84	38
		FAB	CBI	ns	P	–	84	38
		ALS-CBS-Cognition	CBI	ns	P	–	84	38
		ALS-CBS-Cognition	CGBS	−1.4*	R	−1.42* (−2.8, −0.05)	86	25
	Attention	ALS-CBS-Attention	CGBS	–0.25*	R	–	86	25
	Concentration	ALS-CBS-Concentration	CGBS	–0.25*	R	–	86	25
	Fluency	ALS-CBS-Fluency	CGBS	ns	R	–	86	25
	Memory/orientation	CBI-R Memory/orientation	ZBI	0.63***	S	–	40	24
	Executive functioning	WST	CBI	ns	P	–	84	38
	Social cognition	Battery of tests	ZBI	ns	P	–	35	39
Emotional functioning	Feelings of depression	HADS-Depression (t0–t3)	CSI (t0–t3)	–	–	ns	116	5
		HADS-R-Depression	ZBI	ns	P	–	35	39
		BDI	CBI	ns	P	–	79	38
	Anxiety	HADS-R-Anxiety	ZBI	ns	P	–	35	39
	Emotional functioning	ALSAQ-40Se (t0–t3)	CSI (t0–t3)	–	–	0.02* (0.022, 0.042)	116	5
	Lability	ELQ	ZBI	ns	P	–	35	39
	Mental health	SF-36-MCS	CSI	0.28***	n.r.	–	415	31
	Mood	CBI-R-Mood	ZBI	0.38*	S	–	40	24

(Continued)

Table 3. (Continued)

	Factor[a]	Measure factor	Outcome caregiver burden	Bivariate association	Bivariate analysis	Multivariate association	*N*	Ref
				r		*β*/OR (CI)		
Personal factors	Existential well-being	MQol-Ewbs	ZBI	−0.60***	P	–	37	33
	Religion is source of strength	ALSSQoL-R statement (0–10)	ZBI	−0.43***	P	–	37	33
	Consider self as religious/spiritual	ALSSQoL-R statement (0–10)	ZBI	−0.49***	P	–	37	33
	Self perceived as burden	SPBS	CBI	0.33*	S	ns	60	10
		SPBS	CBI	0.41*	n.r.	–	31	6
		SPBS (t1)	CBI (t1)	0.38*	n.r.	–	31	6
	Burden cg rated by patient	Visual analogue scale	ZBI-5 items	0.29*	P	–	71	35
	Active coping	UCL-AA (t0–t3)	CSI (t0–t3)	–	–	ns	116	5
Demographics	Age	Years	ZBI	ns	R	–	33	26
		Years	ZBI	0.35*	P	ns	35	39
		Years	CSI (t0–t3)	–	–	ns	116	5
	Gender	Male/female	ZBI	ns	R	–	33	26
		Male/female	CGBS	–	–	8.1* (1.0, 15.2)	86	25
Social environment	Social support	MQoL-Ss	ZBI	−0.53**	P	–	40	21
	Quality of care	n.r. (t0–t3)	CSI (t0–t3)	–	–	ns	116	5
	Family functioning	FACES-Ideal cohesion	CBI	−0.59**	S	–	19	36
	Reimbursement costs care	Yes/no	ZBI	–	–	−0.19* (n.r.)	81	29

ALSAQ-40Se: Amyotrophic Lateral Sclerosis Assessment Questionnaire 40-item subscale emotional functioning; ALS-CBS: Amyotrophic Lateral Sclerosis Cognitive-Behavioral Screen; ALSFRS: Amyotrophic Lateral Sclerosis Functional Rating Scale; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; ALSSQoL-R: Amyotrophic Lateral Sclerosis Specific Quality of Life-Revised questionnaire; BDI: Beck Depression Inventory; BSFC: Burden Scale for Family Caregivers; CBI: Caregiver Burden Inventory; CBI-R: Cambridge Behavioural Inventory Revised; CGBS: Caregiver Burden Scale; CI: confidence interval; CSI: Caregiver Strain Index; ELQ: Emotional Lability Questionnaire; FAB: Frontal Assessment Battery; FACES: Family Adaptation and Cohesion Evaluation Scale; FrSBe: Frontal Systems Behavior Scale; FVC: Forced Vital Capacity; HADS: Hospital Anxiety and Depression Scale; HADS-R: Hospital Anxiety and Depression Scale Revised; MMSE: Mini-Mental State Examination; MQoL-Ewbs: McGill Quality of Life existential well-being subscale; MQoL-Ss: McGill Quality of Life social support subscale; n.r.: not reported; ns: not significant; ^{OR}: Odds Ratio; P: Pearson's product moment correlation; PCF: Peak Cough Flow; R: univariate regression analysis; S: Spearman's rank order correlation; SF-36-MCS: 36-item Short Form Health Survey Questionnaire Mental Component; SF-36-PCS: 36-item Short Form Health Survey Questionnaire Physical Component; SPBS: Self-Perceived Burden Scale; UCL-AA: Utrecht Coping List Active Approach subscale; WST: Weigl's Sorting test; ZBI: Zarit Burden Interview; ZBI-sv: Zarit Burden Interview-short version.
[a]Factors and outcomes are measured at t0 unless mentioned otherwise.
[b]Calculated as ([48-ALSFRS-R]/disease duration in months).
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 4. Adapted GRADE table for narrative systematic reviews of prognostic studies.

Potential factors	Participants (*n*)	No. of studies	Bivariate[a]				Multivariate				Grade factors					
			+	0	−	n.r.	+	0	−	n.r.	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality
Caregiver																
Feelings of depression	605	9	5	–	–	1	1	3	–	1	✓	✓	✓	×	✓	Moderate
Feelings of anxiety	362	5	2	–	–	1	1	2	–	–	✓	✓	✓	×	✓	Low
Distress	254	3	1	–	–	–	2	–	–	–	✓	✓	✓	×	✓	Low
Social support	187	5	–	7	1	–	–	–	–	–	✓	✓	✓	×	✓	Very low
Family functioning	73	3	–	4	2	–	1	1	–	–	✓	×	✓	×	✓	Very low
Age	474	7	1	3	–	–	1	2	–	–	✓	✓	✓	×	✓	Low
Patient																
Physical functioning	668	11	–	3	6	–	–	–	3	–	✓	✓	✓	×	✓	Moderate
Bulbar function	206	3	–	2	–	–	–	1	–	–	✓	✓	✓	×	✓	Low
Motor function	287	4	–	–	1	2	–	2	2	–	✓	✓	✓	×	✓	Very low
Respiratory function	246	4	–	2	2	–	–	1	–	–	✓	✓	✓	×	✓	Very low
Disease duration	179	3	–	2	–	–	–	–	–	1	✓	✓	✓	×	✓	Very low
Behavioral impairments	348	6	6	–	–	–	4	–	–	–	✓	✓	✓	×	✓	High
Disinhibition	138	3	2	1	–	–	–	1	–	–	✓	✓	✓	×	✓	Very low
Executive functioning	138	3	3	1	–	–	–	2	–	–	✓	✓	✓	×	✓	Very low
Cognitive functioning	203	3	1	4	–	–	1	–	–	–	✓	✓	✓	×	✓	Very low
Feelings of depression	230	3	–	2	–	–	–	1	–	–	✓	✓	✓	×	✓	Low
Age	184	3	1	1	–	–	–	2	–	–	✓	✓	✓	×	✓	Very low

For uni- and multivariate analyses: +: number of significant associations with a positive value; 0: number of non-significant associations; −: number of significant associations with a negative value; n.r.: number of associations of which the direction was not reported. For GRADE factors: ✓: no serious limitations; ×: serious limitations. For overall quality of evidence: very low, low, moderate, high.
[a]Bivariate associations that are measured twice in one study on different measuring points are counted as one association.

Discussion

In our systematic review, we focused on both patient factors and caregiver factors in relation to burden in caregivers of ALS patients. Moderate to high quality of evidence was found for "behavioral impairments" of the patient, "physical functioning" of the patient, and "feelings of depression" of the caregiver as factors related to caregiver burden. These results indicate that there is a specific group of caregivers that is vulnerable to caregiver burden. For the relations between caregiver burden and the remaining caregiver and patient factors, the quality of evidence was low to very low and no general conclusions could be drawn.

We found high quality of evidence for the relation between caregiver burden and behavioral impairments of the patient. Behavioral impairments such as apathy or disinhibition occur in a substantial proportion of ALS patients and 5%–15% of patients meet the criteria for frontotemporal dementia (FTD), which is associated with more severe behavioral impairments.[46,47] The findings of this review highlight the impact of behavioral impairments in patients on caregiver burden, whereas cognitive impairments in patients are less likely to result in caregiver burden. This underscores the relevance of the distinction between pure ALS, ALS with behavioral impairment, ALS with cognitive impairment, and ALS with FTD.[48]

Moderate quality of evidence was found for the relation between caregiver burden and the level of physical functioning of the patient. Caregiver burden seems to increase parallel to the disease severity of the patient, which is in line with conclusions in other progressive neurological diseases.[49,50] Low to very low quality of evidence was found for the relation between caregiver burden and factors measuring functioning in specific physical areas (e.g. respiratory function, motor function), indicating that burden seems to be related to the overall physical functioning but not to specific functions. The increase in burden may be the result of the fact that ALS leads to rapid decline in physical functioning, as this constantly requires physical and emotional adjustments from both patient and caregiver.[51,52] Furthermore, as the disease progresses, worsening of symptoms and physical concerns may lead to increased stress, worries, and burden of caregivers, taking a toll on their time and energy for leisure activities and time to fulfill their own needs.[10,22]

Moderate quality of evidence was found for the relation between caregiver burden and feelings of depression of the caregiver; in other words, caregivers, who experience depressive symptoms, are more likely to experience high caregiver burden. This association between caregiver burden and depressive symptoms experienced by the caregiver is consistent with findings in other neurological diseases, such as dementia and stroke.[50,53] Caregivers who experience feelings of depression may find it even more challenging to cope with the caregiving demands placed on them, which influences caregiver burden. Although research seems to indicate that caregiver burden and depression are distinct constructs,[54,55] there might be conceptual overlap between the measures of depressive symptoms and caregiver burden.[56] Questions related to depressive feelings are often included in burden measures (e.g. I feel emotionally drained due to caring for him or her. Caregiver Burden Inventory item 9; Do you feel tired and worn out? Caregiver Burden Scale item 1). However, in this review, we conceived caregiver burden and depression as two separate concepts because caregiver burden represents outcomes specific to the caregiving situation, while measurements of depression represent a more general outcome.

In previous systematic reviews, the suggestion was made that social support might be a protective factor for caregiver burden,[12,57] but this result could not be confirmed in our review. This difference might be attributed to the inclusion of both quantitative and qualitative studies. An alternative explanation could be that only specific subtypes of social support (i.e. emotional, instrumental, informational, or appraisal support)[58] mitigate caregiver burden. For example, the benefits of receiving social support in caregiving (instrumental support) may be overestimated in ALS care, as taking over caregiving tasks is complicated, especially in later stages of the disease. Family members and friends are often not equipped to offer this specialized care to the patient.[4] Hence, relieving the burden of the caregiver by providing physical support in caregiving seems to be a difficult task for their social environment, while relieving caregiver burden with emotional support may be more feasible. However, it was impossible to make this differentiation in our review due to scarcity of research in this topic.

This systematic review offers insight into factors related to caregiver burden and guides the development of interventions aiming to reduce caregiver burden, but more additional research into factors related to caregiver burden is needed. Personal factors of ALS caregivers are possible modifiable factors but are currently understudied. Only 6 out of 25 of the studies included in this review paid attention to these factors. More knowledge about personal caregiver factors, such as feelings of competence in caregiving or self-efficacy, is needed since these personal factors seem to play a protective role in the development of burden in caregivers of patients with dementia.[59]

Strengths and limitations

This review was carried out in accordance with the PRISMA guidelines; the quality of the evidence was judged by assessing the risk of bias, and the GRADE approach was used, which are strengths of this review.

There were also some limitations of the review. First, it was not possible to perform a meta-analysis because of the heterogeneity of both the measures used to assess caregiver burden and the measures used to assess the associated factors.

Second, the instruments used to assess caregiver burden represented different interpretations of the concept, caregiver burden. Therefore, we only included studies which assessed a total score on burden as this represents a general concept of burden. Others have suggested, however, that the use of multidimensional measures of caregiver burden might provide different information.[60] For the interpretation of results on caregiver burden, and the comparison of intervention effects, a gold standard for the measurement of burden in ALS caregivers would be preferable.

Third, we only included full-text, peer-reviewed published studies and therefore might have missed evidence about relationships between patient and caregiver factors and caregiver burden.

Finally, the overwhelming majority of studies was cross-sectional and does not, therefore, allow any causal inferences between caregiver burden and factors. Longitudinal data are required to understand the temporal pattern of caregiver burden, its determinants, and the optimal time to deliver an intervention to diminish caregiver burden.

Conclusion

This review presents the current knowledge on associations between both patient factors and caregiver factors which are related to caregiver burden in ALS caregivers. There is moderate to high quality of evidence for the relation between behavioral impairments of the patient and caregiver burden, physical functioning of the patient and caregiver burden, and feelings of depression of the caregiver himself or herself and caregiver burden. This is important knowledge in order to identify those caregivers who are at risk of caregiver burden and to inform the development of interventions focusing on diminishing burden in caregivers of ALS patients.

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