



## REVIEW

# Burden of caregivers of patients with frontotemporal lobar degeneration – a scoping review

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## ABSTRACT

**Background:** Frontotemporal lobar degeneration (FTLD) is the second-most common cause of young-onset dementia. Personality and behavior changes lead to high caregiver stress and burden, but little support is available. Our aim is to present the evidence on the characteristics, challenges and unmet needs of caregivers as well as on possible interventions.

**Methods:** We conducted a scoping review on caregiver burden using PubMed, Web of Science and Science-Direct. A total of 69 articles were considered eligible and were analyzed in the present study.

**Results:** Through the analysis of 69 empirical articles, our results show that caregivers of patients with FTLD are often younger in age, have children and find behavioral disturbances to be the most burdensome. Nine studies assessed the needs of and support for caregivers. Ten studies compared the burden in different forms of FTLD, 19 compared FTLD to other types of dementia, and one compared the caregiver burden between two countries. Eight studies reported on interventions for caregivers or interventions taking burden into account. One study assessed the support structure for caregivers of FTLD patients. Five case reports, eight research overviews and three reviews addressed specific needs and challenges.

**Conclusions:** Further research should reproduce and validate efficacious interventions and focus on underage children of FTLD patients and findings from non-Western countries. Additionally, support structures for FTLD caregivers should be assessed and extended. Awareness both in the wider population and among healthcare professionals is an urgent need for the future.

**Key words:** frontotemporal dementia (FTD), dementia, early onset dementia, carers, young onset dementia

## Introduction

Frontotemporal lobar degeneration (FTLD) is a neurodegenerative disorder resulting from brain atrophy in the frontal and temporal lobes, leading to changes in personality, behavior, language skills and forward planning (Piguet and Hodges, 2013). A systematic review conducted in 2016 estimated that FTLD cases constitute 15% of all cases of dementia in individuals younger than 65 or 70 years (different cut-offs were used in the reviewed studies), making it

the second-most common form of presenile dementia after Alzheimer's Disease (AD) (Hogan *et al.*, 2016). Factors unique to FTLD that are considered particularly burdensome for caregivers are the young age of onset, behavioral changes such as disinhibition and apathy, and an often prolonged and distressing way of obtaining a correct diagnosis. There is a lack of information as well as appropriate care facilities. Caregiver depression and reduced caregiver well-being can occur as a result of neglecting one's own needs (Piguet and Hodges, 2013).

Consensus criteria differentiate between behavioral variant frontotemporal dementia (bvFTD) and primary progressive aphasia (PPA) (Rascovsky *et al.*, 2011). Primary progressive aphasia can be further divided into three subtypes: the semantic variant

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(sv-PPA, formerly semantic dementia/SD), the non-fluent/agrammatic variant (nfv-PPA, formerly progressive non-fluent aphasia/PNFA) and the logopenic variant (lv-PPA); however, lv-PPA is now widely considered to be a form of Alzheimer's disease rather than belonging to the FTLD entity (Gorno-Tempini *et al.*, 2011). As a third variant, FTLD symptoms are known to overlap with motor neuron disease (MND, mainly amyotrophic lateral sclerosis (ALS)), corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) (Piguet and Hodges, 2013).

Patients with bvFTD typically show behavioral and personality changes, with major symptoms including apathy, disinhibition, perseveration, hoarding, mental rigidity, blunting of affect, changes in eating behavior and loss of empathy (Piguet and Hodges, 2013). Moreover, patients are notably younger at onset, being mainly <65 years (Hogan *et al.*, 2016), but some patients can even be diagnosed in their early twenties (Diehl-Schmid *et al.*, 2013).

Language skills as well as spatial cognition remain relatively preserved in bvFTD. A decline in executive functions is debatable, but its onset appears later during the course of the disease compared to AD. Approximately 10–15% of patients exhibit signs of severe amnesia and deficits in episodic memory that can be compared to those of patients with AD, even though this is atypical for most bvFTD patients. Prevailing neuropsychological findings are changes in social cognition, e.g., the ability to empathize with others, recognize emotions and solve complex problems. Thus, the next of kin of FTLD patients describe 'coldness' and inappropriate behavior in social situations. However, physiological reactions to emotional stimuli (i.e., skin conductance) remain preserved, even though the patients perform poorly in testing. Some of those deficits may be sensitive to retraining (Piguet and Hodges, 2013).

The prevalence of FTLD cases can only be estimated within studies indicating a point prevalence between 0.01 to 4.6 per 1000 persons and an incidence of 0.0 to 0.3 per 1,000 persons per year. Accurate epidemiologic data is hard to determine since studies vary in their methodology. FTLD is associated with a relative loss of remaining life expectancy of 72% to 84%, or an absolute loss of 11.5 to 15.4 years, respectively (Brodaty *et al.*, 2012).

Currently, there are no effective pharmacological treatment options available. Drugs used for AD treatment, such as acetylcholinesterase inhibitors or NMDA receptor antagonists, as well as antipsychotic or antidepressant medications, are estimated to effectively alleviate behavioral symptoms. Aside from pharmacological options, no evidence-based

interventions for patients with FTLD exist, and the burden among those caring for FTLD patients is high (Piguet and Hodges, 2013).

The last comprehensive review examining burden in caregivers of patients with FTLD was conducted by Nunnemann *et al.* (2012) with a similar systematic search strategy (search keywords: "frontotemporal or FT(L)D" and "caregiver or carer"), making no restrictions regarding study design but including non-medical databases (Medline, Cinahl, Embase, Cochrane Library: Cochrane Dementia and Cognitive Improvement Group, Psycindex, PsycINFO, SocINDEX, SOWIPORT, WISO, Social Sciences Citation Index, Periodicals Index Online). At the time their review was conducted, no randomized controlled interventions could be identified for caregiver burden in FTLD, and only one study focused on caregiver needs (Nicolaou *et al.*, 2010). The amount of literature on caregiver burden in FTLD has risen so that new implications for caregiving, especially in the form of interventions, were added, which makes another comprehensive scoping review on the topic reasonable. Thus, the aim of this review is to give an overview on existing literature about factors contributing to caregivers' distress and on interventions that have the potential to decrease the burden of the caregivers of people with FTLD.

## Methods

For the presentation and synthesis of existing knowledge about burden of caregivers of persons with FTLD, we chose the format of a scoping review (Peters *et al.*, 2017; Tricco *et al.*, 2016). The aim of this type of review is to search all existing literature concerning a research question, to summarize it and to map the current knowledge. In consequence, research gaps and implications for future studies can be obtained. In contrast to a systematic review, no quality assessment or meta-analyses are performed (Tricco *et al.*, 2016).

A systematic literature search was conducted in April 2017. The databases PubMed, Web of Science and ScienceDirect were searched for the terms "FTD", "FTLD", "ALS" or "aphasia" and "caregiver burden", respectively. We therefore extended the search terms to cover appropriate research in the overlap between the fields of ALS-FTD and aphasia. No limitations were made regarding the type of study, including posters and congress publications, and publication date; articles were excluded if they were in a language other than English or German. All studies that focused on caregivers that included an FTLD cohort as well as interventions that

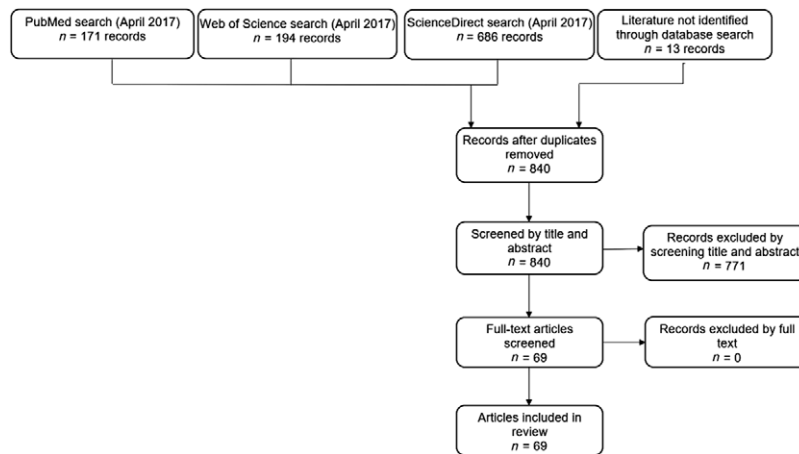


Figure 1. Literature search flow chart.

assessed caregiver burden in the said cohort were included. When we searched the ScienceDirect database, the following filters were applied: for “ALS caregiver burden” and “aphasia caregiver burden”, the topic “dementia” was set to exclude a large number of articles addressing other aspects of these diseases.

Search results were screened for eligibility in a two-step process, excluding articles by title and by abstract. The flow chart is illustrated in Figure 1. Fifty-six full-text articles were identified. Another 13 applicable articles that could be identified from references — but had not appeared as results in the database search — were added to the list of literature sources to be reviewed, yielding a total of 69 publications. Ambiguities concerning the inclusion of articles were resolved by consensus.

Following the inclusion of articles, a table was developed for summarizing articles. An example can be found in Table 1, the comprehensive summary of all articles is available as supplementary material published online attached to the electronic version of this paper. The country of origin was assessed to determine any bias that may be associated with certain countries or regions contributing the majority of research findings and identify the need for cross-cultural validation of results. The characteristics of participants are given, as are the methods and measures used. In interventional studies, the intervention procedure is presented separately. The main findings are outlined with a focus on results concerning FTLN patients and their caregivers in studies that also include other types of dementia. Self-reported biases are included in the summary, but no systematic quality assessment was performed due to the nature of a scoping review. In the analysis, findings were grouped based on the methods of the studies; the socioeconomic and demographic characteristics of

the study populations; the needs, problems and challenges for caregivers; and interventions. Findings from quantitative and qualitative studies alike are presented together within these categories to outline key findings of the research.

## Results

### Design and methods of the included studies

Of the 69 papers included in this review, 42 were published between 2012 and 2017, underpinning the implication for a comprehensive review. Forty-four out of 69 articles are quantitative studies of an observational, descriptive nature. Their results will be summarized in order to give an overview about the prevalence of caregiver burden, its causes and influencing variables. Among those studies are three poster presentations from the Alzheimer’s Association International Conference on Alzheimer’s Disease 2010 (Merrilees *et al.*, 2010), the Alzheimer’s Association International Conference 2012 (Ng *et al.*, 2012) and the 2015 American Association for Geriatric Psychiatry (AAGP) Annual Meeting (Uflacker *et al.*, 2015).

Eight publications are intervention studies for caregivers or for FTLN patients with consideration of caregiver burden and are presented in Table 2. Another eight papers were research overviews, summarizing knowledge about caregiver-related topics; additionally, three systematic or integrative reviews were found. Properties of reviews and research articles can be found in Table 3. The remaining articles consist of five case reports (for a detailed description, see Table 4) and one study reporting on structural support provision for caregivers of persons with FTLN (Ibach *et al.*, 2004).

**Table 1.** Exemplary summary table

Reference	Armstrong, Nicole; Schupf, Nicole; Grafman, Jordan; Huey, Edward D. (2013): Caregiver burden in frontotemporal degeneration and corticobasal syndrome. In <i>Dementia and geriatric cognitive disorders</i> 36 (5–6), pp. 310–318. DOI: 10.1159/000351670.
Type	Controlled cohort study, descriptive study
Location/country	USA
Aim/subject	To assess the association between behavioral symptoms and caregiver burden in patients with frontotemporal dementia (FTD) and corticobasal syndrome (CBS)
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	267 caregivers of FTD/CBS patients in total who received questionnaires ( $n = 180$ FTD caregivers, $n = 87$ CBS caregivers) FTD/CBS diagnosis confirmed at National Institutes of Health according to published consensus criteria 102 caregivers completed FrSBe and ZBI ( $n = 61$ FTD caregivers, $n = 41$ CBS caregivers) Age of patient: FTD $60 \pm 9$ years; CBS: $66 \pm 8$ years; total: $63 \pm 9$ years Gender of patient: FTD 30 male/31 female; CBS 21 male/20 female; (total 51 male/51 female) Race of patient: FTD, 60 white/Caucasian, 1 other; CBS, 37 white/Caucasian, 2 African American, 2 Asian/Pacific Islanders Caregiver relationship to patient: FTD 53 significant other, 8 family members; CBS 34 significant other, 5 family members, 1 friend, 1 paid caregiver
Methods/measures	FrSBe – T-score used as main predictor variable, representing frontal lobe dysfunction ( $\geq$ cutoff score 65), adjusted for gender, level of education and age ZBI – total score used as main outcome variable, representing caregiver burden ( $>$ cutoff score 24) Multivariate regression model using T-score, ZBI score, relationship to patient and diagnosis T-scores from apathy and disinhibition subscales of the FrSBe examined separately as independent predictors Associations between groups of (1) caregivers of patients with apathy and disinhibition, (2) caregivers of patients with only apathy, (3) caregivers of patients with only disinhibition and (4) caregivers of patients without either apathy or disinhibition, examined by one-sample t-test Associations regarding type of diagnosis examined by between-group two-sample t-test Relationship to patient and type of diagnosis considered to be potential confounders
Interventions (where applicable)	None
Outcomes (variables, main findings)	Caregiver burden=ZBI scores Frontal lobe dysfunction=FrSBe T-scores Caregivers of patients with frontal lobe dysfunction had 13.0 times the odds of experiencing caregiver burden than caregivers of patients without frontal lobe dysfunction Association between the apathy and disinhibition subscales of the FrSBe and caregiver burden – 57 patients exhibited both apathy and disinhibition Executive dysfunction subscale of the FrSBe not considered a covariate since sample was homogenous in attaining scores $\geq 65$ Apathy and disinhibition can co-occur; apathy can occur without disinhibition, whereas disinhibition without apathy is very rare
Limitations	FTD subtypes were not considered separately due to small patient numbers FrSBe narrow in scope – some symptoms that are included in the NPI are not measured No information available about dementia severity in patients No information about caregiver characteristics (e.g., age, gender) available No control/comparison group

Armstrong *et al.* (2013) – Caregiver burden in frontotemporal degeneration and corticobasal syndrome.

**Table 2. Interventions**

REFERENCE	AIM	PROCEDURE	PARTICIPANTS	RESULTS
<b>Pharmacological interventions</b>				
Boxer <i>et al.</i> (2013)	Effect of memantine (NMDA receptor antagonist) in FTD	RCT with intention-to-treat analysis; behavior, cognition, and caregiver burden among other outcomes	IG: 31 bvFTD, 8 SD CG: 33 bvFTD, 9 SD	No difference in caregiver burden and cognition; only transient improvement in behavior
Vercelletto <i>et al.</i> (2011)	Effect of memantine (NMDA receptor antagonist) in bvFTD	RCT with intention-to-treat analysis; behavior, cognition, and caregiver burden among other outcomes	IG: 23 bvFTD CG: 26 bvFTD	No differences in caregiver burden and cognition; slightly quicker increase in behavioral disturbances in CG
Moretti <i>et al.</i> (2004)	Effect of rivastigmine (acetylcholinesterase and butyrylcholinesterase inhibitor) in FTD	Intervention (not blinded, not randomized); behavior, cognition, caregiver stress among other outcomes	IG: 20 FTD CG: 20 FTD	Behavioral disturbances decreased in IG and increased in CG; no changes in cognition; caregiver stress decreased in IG compared to CG
<b>Caregiver interventions</b>				
Diehl <i>et al.</i> (2003)	Effect of a caregiver support group	7 structured sessions moderated by an expert providing FTD-specific information (legal, social, coping); unmoderated sessions followed; evaluation	8 caregivers of patients with FTD, SD and frontal Binswanger's disease	Intervention was rated as helpful; knowledge increased and mutual support was sought; new contacts were developed
O'Connell <i>et al.</i> (2014)	Effect of a video-conference telehealth support group in Saskatchewan	Monthly moderated open-agenda sessions attended in a telehealth center nearest to the participant; one in-person workshop; evaluation	11 spouses of patients with PNFA, SD, bvFTD, secondary dementia, or frontal strokes	Intervention was rated as helpful due to exclusivity to spouses and FTD patients in openly discussing specific problems; technical difficulties and long travel to telehealth sites were problematic.
Dowling <i>et al.</i> (2014)	Effect of the Life Enhancing Activities for Family Caregivers Intervention (LEAF) in FTD caregivers	RCT; IG completed 5 skill-building sessions for positive affect and coping; affect, mood, stress, distress and burden measured	IG: 12 caregivers CG: 12 caregivers (sessions without skill-building)	Positive affect increased, negative affect and stress decreased, and caregiver burden significantly improved in the IG compared to the CG. The risk for depression decreased in the IG, and the intervention was highly recommended.
Mioshi <i>et al.</i> (2013b)	Effect of an intervention for improving cognitive reappraisal and coping skills in FTD caregivers	Not randomized; IG completed 15 group sessions for training (e.g., problem solving, reframing); psychological assessment	IG: 9 caregivers CG: 12 caregivers	Caregiver burden and reaction to disruptive behavior improved in IG and remained unchanged in CG.
<b>Patient intervention</b>				
O'Connor <i>et al.</i> (2016)	Effect of the Tailored Activities Program (TAP) for patients on caregiver situation	Activities tailored to the two patients' abilities implemented; assessment of patient behavior, cognition, caregiver confidence and time spent caring	Case 1: 51-year-old woman with bvFTD, husband and two children; Case 2: 62-year-old man with svPPA and daughter	Case 1: Patient ADLs and behavior improved, cognition declined, less time spent caring, more confidence Case 2: Vigilance times but also confidence decreased, some symptoms produced less distress.



**Table 3.** Reviews and research overviews

REFERENCE	TOPIC/TYPE	FINDINGS	IMPLICATIONS FOR CAREGIVING
<i>Reviews</i>			
Caceres <i>et al.</i> (2016)	Integrative review: Burden and problems of family caregivers in FTD (non-primary settings and studies including other non-FTD dementias excluded)	8 quantitative/3 qualitative articles, assessed using the Crowe Critical Appraisal Tool.	See text
Nunnemann <i>et al.</i> (2012)	Systematic review: caregiver burden in FTLD	10 publications focusing on burden/16 publications focusing on problems; no RCTs could be identified; eight interventions.	
Shinagawa <i>et al.</i> (2015)	Systematic review: non-pharmacological management of behavioral symptoms in FTD; exclusion of publications focusing on, e.g., language impairments and articles focusing on ALS/MND management	4 clinical trials/5 case reports; higher evidence for interventions aimed at caregivers than for patient interventions/environmental strategies.	
<i>Educational articles</i>			
Houseman <i>et al.</i> (2013)	Practical suggestions for nurses caring for a patient with FTD	Main problems occur with cognitive impairment and behavioral disturbances, e.g., impaired interactions with others.	Nurses should provide education about the disease and clarify the difference between FTD and AD; they should address safety and environmental issues such as medication management, driving, financial resources and the use of potentially dangerous objects and tools.
Massimo <i>et al.</i> (2014)	Apathy in FTD	Lack of goal-directed behavior; the initiation, planning or motivation for an action can be impaired.	Often overlooked in care because it usually does not cause distress; determining the subtype of apathy can help provide specific interventions, e.g., rewards for motivational problems or restructuring complex activities for patients with planning difficulties.
McCarter <i>et al.</i> (2016)	Sleep disturbances in FTD	The most common sleep disturbances observed are sleep disordered breathing, i.e., apnea, insomnia and excessive daytime sleepiness; REM sleep behavior disorder has been observed.	No guidelines for the treatment of sleep disturbances were available at that time; sleep disturbances were found to greatly contribute to caregiver burden.

Table 3. Continued

REFERENCE	TOPIC/TYPE	FINDINGS	IMPLICATIONS FOR CAREGIVING
Merrilees (2007)	A model to manage behavioral disturbances in FTD	Understanding the underlying pathology as a cause for erratic behavior is crucial to enable modification.	The antecedent-behavior-consequence (ABC) model is presented to approach and react to such behaviors. For instance, frontal lobe atrophy (A) causes disinhibition in the patient, which makes others feel uncomfortable (B). Caregivers could react by explaining the behavior using a business card format and limiting contact with others (C). Behaviors could also be modified by a substitution of potentially dangerous or disruptive behaviors. Causes other than frontotemporal degeneration, e.g., infections as a cause for changes in toilet habits, must be ruled out first.
O'Connor <i>et al.</i> (2014)	Functional disabilities in different subtypes of aphasia	Caregivers of svPPA patients report lower burden levels than those of bvFTD patients; impairments in ADLs can occur as a result of patients' strict routines and inability to understand complex instructions.	Professionals are advised to educate caregivers about the disease and to enable them to accept and adapt to constant changes; specific recommendations for modifying the patient's environment and management of everyday life are provided. For example, using images instead of written instructions and using familiar products can enable the patient to carry out tasks independently.

### Outcomes and measures of quantitative studies

The most frequently used measures to assess caregiver burden and distress in the 44 quantitative articles were the Zarit Burden Interview (ZBI,  $n = 10$ ), the short ZBI ( $n = 11$ ) and the Neuropsychiatric Inventory (NPI,  $n = 9$ ). Other assessments used were the Caregiver Burden Scale (CBS,  $n = 2$ ), the Caregiver Burden Index (CBI,  $n = 3$ ), the Caregiver Strain Index (CSI,  $n = 3$ ), the Screen for Caregiver Burden (SCB,  $n = 1$ ) and a Visual Analogue Scale ( $n = 4$ ). References to the respective studies can be found in Table 5. The studies used different cut-offs to determine and categorize caregiver burden and distress. Cut-off values as well as other assessments (e.g., depression, social network, stress) are stated in the summary of each article (see supplementary material) where applicable.

### Sample characteristics of the studies

A total of  $n = 3355$  patients and  $n = 3365$  caregivers were included in the quantitative studies, with at least 1453 thereof suffering from some kind of frontotemporal lobar degeneration. Of the  $n = 44$  quantitative studies, all but ten studies relied on diagnoses according to consensus criteria or diagnoses confirmed by a specialized healthcare professional, the others did not report how the diagnoses were obtained (Brioschi Guevara *et al.*, 2015; Bristow *et al.*, 2008; Chow *et al.*, 2011; Cosseddu *et al.*, 2013; Denny *et al.*, 2012; Merrilees *et al.*, 2010; Ng *et al.*, 2012; Uflacker *et al.*, 2015; Wong and Wallhagen, 2012, 2014). All participants in case studies were diagnosed according to consensus criteria, as well as participants in four intervention studies; the other four, however, relied on self-report or did not state the source of diagnosis (Dowling *et al.*, 2014;

**Table 4.** Case reports

REFERENCE	PARTICIPANTS	SYMPTOMS AND PROBLEMS	IMPLICATIONS FOR CAREGIVER BURDEN
Chemali <i>et al.</i> (2010)	39-year-old female	Participant experienced symptoms 20 months prior to diagnosis; divorce, homelessness, unemployment and loss of custody for her adopted children occurred. Her main symptoms were confabulation and inappropriate and labile affect at first neurology visit, but she was not hospitalized. Following a police arrest on charges of fraud, neurology and psychiatric clinics declined her admission; the patient was referred to a tertiary psychiatric facility. She underwent imaging and genetic testing (her mother died from an unnamed neuropsychiatric disorder at age 52). She was discharged into a shelter home — no relatives were willing to care for her — on antipsychotic medication, and no nursing home was willing to accept her. Free care is provided since she had lost insurance coverage.	Behavioral changes can lead to isolation of the patient; friends and relatives are still needed to initiate diagnosis and treatment.
Kindell <i>et al.</i> (2014)	71-year-old retired lecturer of engineering and his two primary caregivers: his wife (71 years old) and his nearby-living son	The patient was diagnosed with semantic dementia five years ago; The patient developed numerous routines such as wearing the same set of clothes and rubbing his hands on all kinds of objects around the house. He performed potentially dangerous activities and increased the use of hand gestures. He experienced changes in personality and new preferences (TV programs, etc.).	Four major themes in the daily life with the patient were described: living with the patient's routines; policing and protecting, i.e., the way caregivers kept the patient from potentially dangerous activities and possibly inappropriate interactions with others; engaging in conversations and topics with the patient that might be interesting for him; and trying to understand his use of hand gestures in making connections. Caregivers adapted to the changed personality of the patient and his new preferences.



**Table 4. Continued**

REFERENCE	PARTICIPANTS	SYMPTOMS AND PROBLEMS	IMPLICATIONS FOR CAREGIVER BURDEN
Kumamoto <i>et al.</i> (2004)	Case 1: 69-year-old patient and her 77-year-old husband caregiver. Case 2: 69-year-old male with his 62-year-old wife and one son living nearby.	Case 1: She had symptoms for 15 years and attended day care for four years. She lost her job as a shop assistant due to her symptoms. Case 2: He developed symptoms at age 63 and was diagnosed four years later. Both patients were driving dangerously and, after their licenses were revoked, were walking around restlessly around the house and the neighborhood. Both patients were forcing large amounts of food into their mouths without proper chewing and swallowing. Inappropriate and stereotypic behavior led to refusal of admission by hospitals and other institutions. Patients were reported to be able, to some extent, to understand what was being said to them and to perform certain activities, e.g., slicing vegetables.	Patients require constant vigilance; grooming and bathing were entirely carried out by caregivers and complicated by patients' unpredictable behavior. Urinary and fecal incontinence required a large amount of cleaning; eating behavior caused the need for feeding and resulted in dental problems.
Massimo <i>et al.</i> (2013)	Two wives in their mid-fifties to early sixties caring for their husbands (diagnosed with FTD for <2 years).	Emotionally cold patients, described as 'inconsiderate', lacked insight about the disease. They experienced personality changes, loss of memory, and reduced functioning in everyday life.	Five recurring themes are described: Identity and role change — the wives needed to adapt to their new roles as caregivers while the marital relationship was gradually lost; isolation — both caregivers were unable to speak to the patient about the situation since they were lacking insight; anger — caused by erratic behavior, emotional coldness and lack of reciprocated feelings by the patient; facing the future and building ideas for a good day; and reframing — the separation of the disease from the patient and reminding themselves of the pathology that causes the symptoms.

Table 4. Continued

REFERENCE	PARTICIPANTS	SYMPTOMS AND PROBLEMS	IMPLICATIONS FOR CAREGIVER BURDEN
Oyebode <i>et al.</i> (2013)	Six family caregivers of fvFTD patients — three husbands, a wife, a daughter (living with the patient) and a brother (patient living in residential care).	Changes in appetites and drives, lack of forward planning, and loss of inhibition lead to socially embarrassing and risky behaviors caused by impaired judgement. Overeating or walking excessively may occur. In other patients, a lack of motivation leads to problems with personal hygiene, following urges in public or invading other people's personal space; injuries, declines in communication abilities, loss of affection toward their partner, wandering, and repetitive questions may occur.	Eleven recurring themes in three clusters were determined: witnessing bizarre and strange changes; managing erratic behaviors and taking on tasks and roles as a caregiver; defending, asserting and explaining, i.e., finding appropriate services and explaining the disease in public; promoting the patient's quality of life; working around a lack of awareness in the patient; having an impact on the relationship and the person with FTD — loss of the relationship and the person with FTD who was connected with heartbreak; and being a source of support and hope, both for themselves and the patient.

Mioshi *et al.*, 2013b; O'Connell *et al.*, 2014; O'Connor *et al.*, 2016). Eighteen studies did not further specify the FTLT diagnosis. Diagnoses of patients suffering from an illness belonging to the entity of FTLT included behavioral and frontal variant FTLT (16 studies), semantic dementia (10 studies), non-fluent aphasia (6 studies) or a type of aphasia not specified (4 studies). References about the studies reporting diagnoses can be found in Table 5. It should be noted that the literature is inconsistent in terminology, with older publications using the abbreviations SD and PNFA rather than the nomenclature suggested by Gorno-Tempini *et al.* (2011). Overlapping syndromes were found in 17 studies: corticobasal syndrome (4 studies) and progressive supranuclear palsy (2 studies), these studies can be found in Table 5.

The largest group of overlapping types of FTLT are patients with MND, mostly ALS (six studies, see Table 5). Referring to measurements, five of the six studies examining ALS-FTD (all except Lillo *et al.*, 2012) stated that the El Escorial criteria were used for determining the ALS diagnosis. It should be noted that the online survey by Chow *et al.* (2011) allowed participants to report more than one diagnosis. The studies of Mourik *et al.* (2004) and Riedijk *et al.* (2006, 2008, 2009) used data from the same cohort, as did Diehl-Schmid *et al.* (2013) and Roche *et al.* (2015), as well as Wong and Wallhagen (2012, 2014), respectively.

### Country/region of origin

The vast majority of the observed population are cohorts from Europe (22 studies), the US/ Canada (24 studies) and Australia (16 studies), see Table 5 for references. The only study to compare caregiver burden between two countries — India and Australia — was conducted by Mekala *et al.* (2013). Indian caregivers were found to provide a significantly higher number of hours of care to more severely impaired patients. This arrangement did not result in a higher burden than in Australian caregivers, but in significantly higher levels of anxiety, implying that caregiving might affect people from different cultures in different aspects of life. Mekala *et al.* (2013) argued that the higher level of anxiety in India might on the one hand be caused by the cultural variation of emotional expression, with symptoms like anxiety prevailing in Asian and Indian cultures over depressive symptoms. Moreover, a lack of supportive healthcare, home-based care and the symptoms regarded as being “normal” in the ageing process contribute to anxiety because problems and concerns cannot be adequately addressed.

**Table 5.** Study characteristics

CHARACTERISTIC	NUMBER OF STUDIES	REFERENCES
Measures to assess caregiver burden in quantitative studies		
Zarit Burden Interview	10	Andrews <i>et al.</i> (2017), Armstrong <i>et al.</i> (2013), Boutoleau-Bretonniere <i>et al.</i> (2008), Brodaty <i>et al.</i> (2014), Davis and Tremont (2007), Kaiser and Panegyres (2006), Knutson <i>et al.</i> (2008), Liu <i>et al.</i> (2017), Nicolaou <i>et al.</i> (2010), Uflacker <i>et al.</i> (2015)
Short Zarit Burden Interview	11	Hsieh <i>et al.</i> (2013), Hsieh <i>et al.</i> (2016), Kaizik <i>et al.</i> (2017), Kumfor <i>et al.</i> (2014), Kumfor <i>et al.</i> (2016), Lillo <i>et al.</i> (2012), Lima-Silva <i>et al.</i> (2015), Mekala <i>et al.</i> (2013), Miller <i>et al.</i> (2013), Mioshi <i>et al.</i> (2013a), Uflacker <i>et al.</i> (2016)
Neuropsychiatric Inventory	9	Lima-Silva <i>et al.</i> (2015), Mourik <i>et al.</i> (2004), Ng <i>et al.</i> (2012), Riedijk <i>et al.</i> (2006), Riedijk <i>et al.</i> (2008), Riedijk <i>et al.</i> (2009), Uflacker <i>et al.</i> (2015), Vugt <i>et al.</i> (2009), Wong and Wallhagen (2012)
Caregiver Burden Scale	2	Bock <i>et al.</i> (2016), Bristow <i>et al.</i> (2008)
Caregiver Burden Index	3	Chio <i>et al.</i> (2010), Cosseddu <i>et al.</i> (2013), Cui <i>et al.</i> (2015)
Caregiver Strain Index	3	Diehl-Schmid <i>et al.</i> (2013), Merrilees <i>et al.</i> (2010), Roche <i>et al.</i> (2015)
Screen for Caregiver Burden	1	Ng <i>et al.</i> (2012)
Visual Analogue Scale	4	Riedijk <i>et al.</i> (2006, 2008, 2009), de Vugt <i>et al.</i> (2006)
FTLD diagnoses in quantitative studies		
Not specified	18	Ascher <i>et al.</i> (2010), Brodaty <i>et al.</i> (2014), Davis and Tremont (2007), Kaizik <i>et al.</i> (2017), Mekala <i>et al.</i> (2013), Merrilees <i>et al.</i> (2010), Mioshi <i>et al.</i> (2009), Mourik <i>et al.</i> (2004), Nicolaou <i>et al.</i> (2010), Ng <i>et al.</i> (2012), Riedijk <i>et al.</i> (2006), Riedijk <i>et al.</i> (2008), Riedijk <i>et al.</i> (2009), Rosness <i>et al.</i> (2008), Uflacker <i>et al.</i> (2015), de Vugt <i>et al.</i> (2006), Wong and Wallhagen (2012), Wong and Wallhagen (2014)
bvFTD/fvFTD	16	Armstrong <i>et al.</i> (2013), Boutoleau-Bretonniere <i>et al.</i> (2008), Brioschi Guevara <i>et al.</i> (2015), Bristow <i>et al.</i> (2008), Chow <i>et al.</i> (2011), Cosseddu <i>et al.</i> (2013), Diehl-Schmid <i>et al.</i> (2013), Hsieh <i>et al.</i> (2013), Hsieh <i>et al.</i> (2016), Knutson <i>et al.</i> (2008), Kumfor <i>et al.</i> (2016), Lima-Silva <i>et al.</i> (2015), Liu <i>et al.</i> (2017), Miller <i>et al.</i> (2013), Mioshi <i>et al.</i> (2013a), Uflacker <i>et al.</i> (2016)
Aphasia not specified	4	Armstrong <i>et al.</i> (2013), Cosseddu <i>et al.</i> (2013), Diehl-Schmid <i>et al.</i> (2013), Kaiser and Panegyres (2006)
SD	10	Armstrong <i>et al.</i> (2013), Bristow <i>et al.</i> (2008), Chow <i>et al.</i> (2011), Hsieh <i>et al.</i> (2013), Hsieh <i>et al.</i> (2016), Kumfor <i>et al.</i> (2016), Liu <i>et al.</i> (2017), Miller <i>et al.</i> (2013), Mioshi <i>et al.</i> (2013a), Riedl <i>et al.</i> (2014)
PNFA	6	Chow <i>et al.</i> (2011), Kumfor <i>et al.</i> (2014), Liu <i>et al.</i> (2017), Miller <i>et al.</i> (2013), Mioshi <i>et al.</i> (2013a), Riedl <i>et al.</i> (2014)
Overlap syndromes in quantitative studies		
CBS	4	Armstrong <i>et al.</i> (2013), Chow <i>et al.</i> (2011), Knutson <i>et al.</i> (2008), Kaizik <i>et al.</i> (2017)
PSP	3	Chow <i>et al.</i> (2011), Davis and Tremont (2007), Kaizik <i>et al.</i> (2017)
MND	6	Andrews <i>et al.</i> (2017), Bock <i>et al.</i> (2016), Chio <i>et al.</i> (2010), Cui <i>et al.</i> (2015), Hsieh <i>et al.</i> (2016), Lillo <i>et al.</i> (2012)

**Table 5.** Continued

CHARACTERISTIC	NUMBER OF STUDIES	REFERENCES
Country/region of origin (all studies)		
USA/Canada	24	Armstrong <i>et al.</i> (2013), Ascher <i>et al.</i> (2010), Bock <i>et al.</i> (2016), Boxer <i>et al.</i> (2013), Brioschi Guevara <i>et al.</i> (2015), Caceres <i>et al.</i> (2016), Chemali <i>et al.</i> (2010), Chow <i>et al.</i> (2011), Davis and Tremont (2007), Denny <i>et al.</i> (2013), Dowling <i>et al.</i> (2014), Houseman <i>et al.</i> (2013), Knutson <i>et al.</i> (2008), Massimo <i>et al.</i> (2013, 2014), McCarter <i>et al.</i> (2016), Merrilees <i>et al.</i> (2007, 2013b), Morhardt (2011), O'Connell <i>et al.</i> (2014), Uflacker <i>et al.</i> (2015), Uflacker <i>et al.</i> (2016), Wong and Wallhagen (2012, 2014)
Europe	22	Boutoleau-Bretonniere <i>et al.</i> (2008), Chow <i>et al.</i> (2011), Chio <i>et al.</i> (2010), Cosseddu <i>et al.</i> (2013), Diehl <i>et al.</i> (2003, 2004), Diehl-Schmid <i>et al.</i> (2013), Ibach <i>et al.</i> (2004), Kindell <i>et al.</i> (2014), Mioshi <i>et al.</i> (2013b), Moretti <i>et al.</i> (2004), Mourik <i>et al.</i> (2004), Nunnemann <i>et al.</i> (2012), Oyebode <i>et al.</i> (2013), Riedijk <i>et al.</i> (2006) Riedijk <i>et al.</i> (2008), Riedijk <i>et al.</i> (2009), Riedl <i>et al.</i> (2014), Roche <i>et al.</i> (2015), Rosness <i>et al.</i> (2008), Vercelletto <i>et al.</i> (2011), de Vugt <i>et al.</i> (2006)
Australia	16	Andrews <i>et al.</i> (2017), Brodaty <i>et al.</i> (2014), Hsieh <i>et al.</i> (2013), Hsieh <i>et al.</i> (2016), Kaiser and Panegyres (2006), Kaizik <i>et al.</i> (2017), Kumfor <i>et al.</i> (2014), Kumfor <i>et al.</i> (2016), LoGiudice and Hassett (2005), Mekala <i>et al.</i> (2013), Miller <i>et al.</i> (2013), Mioshi <i>et al.</i> (2009), Mioshi <i>et al.</i> (2013a), Nicolaou <i>et al.</i> (2010), O'Connor <i>et al.</i> (2014, 2016)
Caregiver characteristics in quantitative studies		
Setting (patient living at home vs. institutionalized)	13	Boutoleau-Bretonniere <i>et al.</i> (2008), Brodaty <i>et al.</i> (2014), Davis and Tremont (2007), Diehl-Schmid <i>et al.</i> (2013), Kaiser and Panegyres (2006), Mekala <i>et al.</i> (2013), Mioshi <i>et al.</i> (2009), Mourik <i>et al.</i> (2004), Nicolaou <i>et al.</i> (2010), Riedijk <i>et al.</i> (2006), Riedijk <i>et al.</i> (2008), Riedijk <i>et al.</i> (2009), Uflacker <i>et al.</i> (2016)
Relationship to patient	27	Armstrong <i>et al.</i> (2013), Ascher <i>et al.</i> (2010), Bristow <i>et al.</i> (2008), Brodaty <i>et al.</i> (2014), Chio <i>et al.</i> (2010), Cosseddu <i>et al.</i> (2013), Cui <i>et al.</i> (2015), Diehl-Schmid <i>et al.</i> (2013), Hsieh <i>et al.</i> (2013), Hsieh <i>et al.</i> (2016), Kaiser and Panegyres (2006), Kaizik <i>et al.</i> (2017), Kumfor <i>et al.</i> (2016), Lillo <i>et al.</i> (2012), Lima-Silva <i>et al.</i> (2015), Liu <i>et al.</i> (2017), Miller <i>et al.</i> (2013), Mioshi <i>et al.</i> (2013a), Mourik <i>et al.</i> (2004), Nicolaou <i>et al.</i> (2010), Riedijk <i>et al.</i> (2007), Riedijk <i>et al.</i> (2008), Riedijk <i>et al.</i> (2009), Riedl <i>et al.</i> (2014), Rosness <i>et al.</i> (2008), de Vugt <i>et al.</i> (2006), Wong and Wallhagen (2012)
Gender	33	Andrews <i>et al.</i> (2017), Ascher <i>et al.</i> (2010), Bristow <i>et al.</i> (2008), Brodaty <i>et al.</i> (2014), Chiò <i>et al.</i> (2010), Chow <i>et al.</i> (2011), Cosseddu <i>et al.</i> (2013), Davis and Tremont (2007), Denny <i>et al.</i> (2012), Diehl-Schmid <i>et al.</i> (2013), Hsieh <i>et al.</i> (2013, 2016), Kaiser and Panegyres (2006), Kaizik <i>et al.</i> (2017), Kumfor <i>et al.</i> (2016), Lillo <i>et al.</i> (2012), Lima-Silva <i>et al.</i> (2015), Liu <i>et al.</i> (2017), Mekala <i>et al.</i> (2013), Merrilees <i>et al.</i> (2010), Miller <i>et al.</i> (2013), Mioshi <i>et al.</i> (2009, 2013a), Mourik <i>et al.</i> (2004), Nicolaou <i>et al.</i> (2010), Riedijk <i>et al.</i> (2006, 2008, 2009), Riedl <i>et al.</i> (2014), Roche <i>et al.</i> (2015), de Vugt <i>et al.</i> (2006), Wong and Wallhagen (2012, 2014)

## Setting

Thirteen studies (references can be found in Table 5) gave accounts of the residency of the person with FTLD, the majority of them living in the community, i.e. living in their own home with assistance or with non-professional caregivers but not being admitted to care homes or hospitals.

Differences in the burden of caregivers of community-dwelling versus institutionalized patients have already been discussed in Nunnemann *et al.* (2012).

In the study of Rosness *et al.* (2008), 43% of FTLD patients and 22% of AD patients were institutionalized in some way, but only 17% of FTLD long-term care residents lived in specialized care facilities. When also taking temporary admissions into short-term care into account, significantly more FTLD than early-onset AD patients had been admitted into care at some point during their disease. In a PPA cohort examined by Riedl *et al.* (2014), 40% of patients were institutionalized. However, 12% of patients had been denied admission to or had been discharged from a nursing home because staff members were not able to manage the symptoms exhibited by patients.

## Type of relationship

Twenty-seven articles reported the type of caregiver-patient relationship and can be found in Table 5. The studies of Mekala *et al.* (2013), Merrilees *et al.* (2010), Riedijk *et al.* (2006, 2008, 2009), Riedl *et al.* (2014), Rosness *et al.* (2008) and Wong and Wallhagen (2012, 2014) focused on family caregivers. Four studies (Ascher *et al.*, 2010; Bristow *et al.*, 2008; de Vugt *et al.*, 2006; Kaiser and Panegyres, 2006) reported specifically on spousal caregivers. In these samples, spouses constitute 76.4% of all caregivers. The second-largest group of caregivers were children of any age (18.5%), and other studies included siblings (0.19%), friends (0.19%), a parent (0.04%), unspecified family members (0.62%) and other caregivers not specified (3.9%). In four cases, a paid caregiver was reported; however, these caregivers were excluded in other studies (Chio *et al.*, 2010; Cui *et al.*, 2015; Liu *et al.*, 2017). Depression rates were significantly higher among spouses than among caregiving children (Cosseddu *et al.*, 2013). The study of Kaizik *et al.* (2017) also compared the burden of spousal and child caregivers. Both groups reported similar levels of burden, stress and depression regardless of dementia severity. Child caregivers tended to report clinically significant anxiety levels and had significantly smaller social networks. The quality of the relationship was reported as suboptimal by both children and spouses. Moreover, children felt a significantly

more controlling relationship towards them from their FTLD parent than spouses did. Younger caregiver age was associated with worse outcomes (Kaizik *et al.*, 2017; Nicolaou *et al.*, 2010; Wong and Wallhagen, 2012, 2014).

The only study to focus solely on children of FTLD patients was conducted by Denny *et al.* (2012) and will therefore be presented more in detail. A seven-person task force assessed the needs of children who were living with an FTLD patient when they were younger than 18 years of age. Therefore, Denny *et al.* conducted a literature search on child caregivers and anticipatory grief and an online search for support programs. For further insight, Denny *et al.* (2012) included anecdotal data from the Association for Frontotemporal Degeneration (AFTD) support groups and telephone services, and two postal and online surveys among affected children were conducted. It was found that existing support specified for children of FTLD parents is extremely limited. Some children provided hands-on help with personal care. Most participants found the most difficult aspect of the disease to be embarrassing behavior and the patient losing their role as a parent. Some children nevertheless stated that the care experience raised their responsibility and awareness of their own lives, but they were also concerned for their well parent. A portion of the respondents wished for interaction with other affected children and teenagers; however, the Internet was not found to be the most helpful resource compared to in-person support services.

## Gender

Thirty-three studies reported caregiver gender (see Table 5 for references). Out of 3,090 total caregivers in these samples, the majority (66.4%) were female.

Female caregivers were found to be more affected by problematic aspects of caregiving (Diehl-Schmid *et al.*, 2013; Merrilees *et al.*, 2010; Mourik *et al.*, 2004; Nicolaou *et al.*, 2010).

## Burden, challenges and unmet needs of caregivers of persons with FTLD

Caregiver burden was found to be significantly associated with patients' behavioral changes (Armstrong *et al.*, 2013; Boutoleau-Bretonniere *et al.*, 2008; Cosseddu *et al.*, 2013; Davis and Tremont, 2007; Diehl-Schmid *et al.*, 2013; in SD and ALS-FTD: Hsieh *et al.*, 2016; in bvFTD: Knutson *et al.*, 2008; Liu *et al.*, 2017; Ng *et al.*, 2012; Uflacker *et al.*, 2016). Frequently reported behavior changes were apathy (Armstrong *et al.*, 2013; Boutoleau-Bretonniere *et al.*, 2008; de Vugt *et al.*, 2006; Lima-Silva *et al.*, 2015; Riedijk *et al.*, 2009; Uflacker *et al.*, 2016; Wong and Wallhagen, 2012), disinhibition (Armstrong *et al.*,



2013; Boutoleau-Bretonniere *et al.*, 2008; de Vugt *et al.*, 2006; Lima-Silva *et al.*, 2015; Liu *et al.*, 2017; Uflacker *et al.*, 2016), aberrant motor behavior (Boutoleau-Bretonniere *et al.*, 2008; Liu *et al.*, 2017; Riedijk *et al.*, 2006) and changes in appetite and eating behavior (Boutoleau-Bretonniere *et al.*, 2008; Wong and Wallhagen, 2012). Some patients exhibited criminal behavior as a result of their disease, which Wong and Wallhagen (2012) found in 9.8% of their FTLD cohort. Thirty-five percent of FTLD patients in a study conducted by Rosness *et al.* (2016) had conflicts with local authorities or police, compared to 8% of AD patients. Such problems were also described for participants in the Chemali *et al.* (2010), Kumamoto *et al.* (2004) and Oyeboode *et al.* (2013) case studies. FTLD patients performed significantly worse on an empathy (faux-pas) test than healthy peer group subjects, indicating that they experience difficulties in taking another person's viewpoint, when Brioschi Guevara *et al.* (2015) examined theory of mind (ToM) in FTLD patients. Impairments in ToM as well as atrophy in the left lateral premotor cortex, an area involved in ToM, were associated with higher caregiver burden.

All patient groups (bvFTD, SD, and AD) performed worse in emotion recognition than healthy controls when empathy loss was examined by Hsieh *et al.* (2013). In bvFTD, empathy loss was associated with a less-caring relationship between patient and caregiver. In SD patients, there was a trend of association between a lower empathy score and higher caregiver burden.

### Type of dementia

Within the FTLD spectrum, caregiver burden was found to be significantly higher in bvFTD when compared to the language variants of FTLD and CBS (Cosseddu *et al.*, 2013; Hsieh *et al.*, 2016; Knutson *et al.*, 2008; Liu *et al.*, 2017; Mioshi *et al.*, 2013a; Uflacker *et al.*, 2016). Moreover, depression levels were higher in caregivers of bvFTD patients compared to PPA, AD and other dementias (Kaiser and Panegyres, 2006). Levels of burden and a controlling type of relationship in bvFTD and SD were found to be equal by Bristow *et al.* (2008) and Kumfor *et al.* (2014).

It is estimated that 8% of ALS patients meet criteria for bvFTD (Raaphorst *et al.*, 2012). Seven studies (including the research overview by Houseman *et al.*, 2013) reported on patients with overlapping ALS/FTD and their caregivers, a total of 429 patients. Of those, 32 had a confirmed diagnosis of ALS-FTD.

Behavioral disturbances similar to those seen in bvFTD predicted caregiver burden in all examined ALS cohorts (Andrews *et al.*, 2017; Bock *et al.*,

2016; Chio *et al.*, 2010; Cui *et al.*, 2015; Hsieh *et al.*, 2016; Lillo *et al.*, 2012). Two studies also highlighted that those disturbances were more frequent in patients with a bulbar (vs. limb) onset of symptoms (Chio *et al.*, 2010; Cui *et al.*, 2015); however, this difference was not found by Lillo *et al.* (2012).

The papers of Uflacker *et al.* (2015, 2016) compared caregivers of bvFTD patients to those of patients with AD and sporadic Creutzfeldt-Jakob disease (sCJD) or Prion disease. NPI distress and severity scores were comparably high between patients with FTLD and sCJD or Prion disease, respectively, in both papers and were both predictors of caregiver burden. Nineteen studies compared caregivers of FTLD patients to those providing care for AD patients, the most frequent type of dementia (Sacuiu, 2016). Eleven studies found the burden that caregivers of FTLD patients experience to be significantly higher than that of AD patients' caregivers (Boutoleau-Bretonniere *et al.*, 2008; Brodaty *et al.*, 2012; de Vugt *et al.*, 2006; Hsieh *et al.*, 2013; Kumfor *et al.*, 2014; Liu *et al.*, 2017; Miller *et al.*, 2013; Mioshi *et al.*, 2009, 2013a; Riedijk *et al.*, 2006; Uflacker *et al.*, 2016). Nevertheless, six studies could not find a difference in burden (Davis and Tremont, 2007; Kumfor *et al.*, 2016; Lima-Silva *et al.*, 2015; Merrilees *et al.*, 2010; Nicolaou *et al.*, 2010; Uflacker *et al.*, 2015).

Moreover, three studies found caregiver depression to be higher in FTLD than in AD (Kaiser and Panegyres, 2006; Mioshi *et al.*, 2009, 2013a). However, two studies (Kumfor *et al.*, 2016; Nicolaou *et al.*, 2010) could not find a difference.

Similarly, the study of Brodaty *et al.* (2014) found the burden to be highest in the FTLD group when also compared to that of caregivers of patients with vascular and mixed dementia.

### Dementia severity

Other significant predictors of caregiver burden were dementia severity and a declining functional status, measured by impairments in activities of daily living (Davis and Tremont, 2007; Diehl-Schmid *et al.*, 2013; Kaizik *et al.*, 2017; in CBS: Knutson *et al.*, 2008; Lima-Silva *et al.*, 2015; Miller *et al.*, 2013; (Mioshi *et al.*, 2013a; Ng *et al.*, 2012). Some papers also cited memory problems as significant contributors to caregiver burden (Chow *et al.*, 2011; Kumfor *et al.*, 2014; Miller *et al.*, 2013); however, these problems tend to occur during later stages of the disease (Piguet and Hodges, 2013). When Kumfor *et al.* (2016) examined the memory retrieval of recent and remote events, no direct associations between bvFTD and SD memory performance and caregiver burden were found;



however, there was a significant correlation between worse memory in SD patients and a more controlling relationship towards their caregivers. A worse memory of emotionally enhanced stories was associated with depression and stress in caregivers of PNFA patients (Kumfor *et al.*, 2014). Atrophy in the anterior portions of the left inferior and medial temporal gyrus, involved in semantic memory, was found to be significantly correlated with caregiver burden in CBS patients (at  $p < 0.01$ ) (Knutson *et al.*, 2008). The relationship between atrophy of the right orbital gyrus and caregiver burden in the frontal variant of FTD (fvFTD) was found to be less significant and could be explained by a higher level of aggression associated with lesions in this area (at  $p < 0.05$ ) (Knutson *et al.*, 2008).

### Need for care

The need for care and dependence of the patient was also a concern expressed by caregivers (Chow *et al.*, 2011; Diehl-Schmid *et al.*, 2013; Kaiser and Panegyres, 2006; Riedijk *et al.*, 2009). Specific care challenges, such as hyperorality, sleep disorders and risky behavior, are described in Tables 3 and 4.

### Financial aspects and employment

As reported by Rosness *et al.* (2008), 61% of FTLT patients versus 92% of AD patients were employed at the time of disease onset. Both women presented in the Chemali *et al.* (2010) and Kumamoto *et al.* (2004) case reports had lost their jobs as a result of disease symptoms. Not only is the patient's contribution to the household income lacking, but caregivers are also forced to reduce their paid working time. In the Bristow *et al.* (2008) study, 12% of caregivers were working full-time, 16% worked part-time, 68% were retired and 4% were unemployed. In the sample of Kaiser and Panegyres (2006), 25% of spousal caregivers were employed. Of the concerns expressed by caregivers, "feeling stressed between caring for their spouse and trying to meet other responsibilities for their family or work" was the third-most frequently named. In the Mioshi *et al.* (2013a) interventional study, 56% of intervention caregivers and 34% of control group caregivers were employed. Among the participants of the Diehl *et al.* (2003) support group intervention, three out of eight were employed, one of them part-time. The difficulties of employment and caregiving at the same time are supported by reviews and research articles (Caceres *et al.*, 2016; Diehl *et al.*, 2004; LoGiudice and Hassett 2005; Morhardt 2011; Nunnemann *et al.*, 2012; Shinagawa *et al.*, 2015). Adapting to the role of a caregiver – not that of a spouse – which is inconsistent with the younger age, is described as burdensome in the studies of LoGiudice and Hassett (2005), Caceres

*et al.* (2016) and Shinagawa *et al.* (2015). Financial issues can become a problem not only due to the loss of employment but also by the person with FTLT excessively spending money (LoGiudice and Hassett 2005; Morhardt, 2011) and because social benefits can be hard to obtain, as described for the US Medicare system by Morhardt (2011). Lower financial resources were found to partially predict caregiver strain in the study of Roche *et al.* (2015).

In a survey conducted among 30 members of an FTLT support group, in 35.7% of the sample, monthly care for the patient cost between \$5,000 and \$9,999, and in 21.5% of the sample, care expenses exceeded \$10,000 a month (Chemali *et al.*, 2010).

### Consequences of burden

Caregiving was shown NN), using the Mental Component Summary (MCS) of the Short Form 36 (SF-36) health survey and the SF-12, respectively. The MCS comprises self-ratings concerning emotional role limitations, social functioning, mental health and general health perceptions (Riedijk *et al.*, 2006). In one study, caregiving was also shown to negatively influence the physical health of caregivers of bvFTD patients as represented by the Physical Component Summary (PCS) of the SF-36 (Cosseddu *et al.*, 2013). Bristow *et al.* (2008) hypothesized that spousal caregivers of persons with FTLT suffer from chronic stress and distress and exhibit lower levels of IgA in saliva samples, indicating a suppressed immunity. However, no significant difference in the IgA levels was found between caregivers and healthy control subjects (also compare Nunnemann *et al.*, 2012).

### Quality of relationship

Another issue occurring during the process of caregiving is the deterioration of the relationship between the caregiver and patient (de Vugt *et al.*, 2006; Kumfor *et al.*, 2014; Mioshi *et al.*, 2013a; Riedijk *et al.*, 2008). The study of Ascher *et al.* (2010) found couples comprising an FTLT patient and a caregiver to be significantly less satisfied with their marriage and to be using more negative emotional language than healthy couples and couples comprising AD patients and their spouses. Participants of a telehealth support group comprising exclusively spouses of FTLT patients pointed out that relationships changed fundamentally, with a loss of affection and sexuality and a shift from the role as a spouse to that of a caregiver (O'Connell *et al.*, 2014).

Patients with bvFTD had a less caring relationship to their caregivers, and SD patients showed a relationship with more control towards their

caregivers (Hsieh *et al.*, 2013; Mioshi *et al.*, 2013b). Kumfor *et al.* (2016) found the level of control in the patient-caregiver relationship to be equal in SD and bvFTD.

However, no study assessed the quality of care provided to the person with dementia and a possible correlation to caregiver burden.

### Coping processes

Four studies gave accounts of caregiver coping strategies and their effects. Active coping, acceptance, reassuring thoughts and problem- and emotion-focused coping were the most commonly used strategies (Riedijk *et al.*, 2006; Roche *et al.*, 2015; Wong and Wallhagen, 2014). Seeking distraction and dysfunctional coping were associated with increased caregiver burden, and the use of passive coping strategies — which were used the least — was correlated to worse mental health (Riedijk *et al.*, 2006; Roche *et al.*, 2015). Riedijk *et al.* (2008) determined that depressive reaction as a coping strategy increased significantly within a 24-month time span. Women used emotion- and problem-focused coping significantly more than men, the first being associated with better relationship quality. The use of dysfunctional coping strategies was related to younger age and greater dissatisfaction with the relationship (Wong and Wallhagen, 2014).

### Support and Interventions for caregivers of persons with FTLD

Nine studies reported on the needs and support provided for caregivers of patients with FTLD. Bristow *et al.* (2008) assessed the provision of emotional and practical support and the satisfaction with these forms of support. Satisfaction with the first person in the network – i.e., the partner cared for – was significantly lower than in healthy control participants. The neurologist, information from the Internet and help from their own children were the most helpful resources, as stated in an online survey conducted by Chow *et al.* (2011). Other healthcare professionals and interventions, such as support groups, were cited less often.

Diehl-Schmid *et al.* (2013) asked caregivers to rate a variety of suggested support services and interventions for their perceived helpfulness. Caregivers most frequently found a greater provision of information and knowledge helpful in raising awareness not only for themselves but also for healthcare professionals. This lack of knowledge among healthcare professionals is supported by research overviews (Diehl *et al.*, 2004; Morhardt, 2011; Nunnemann *et al.*, 2012; Shinagawa *et al.*, 2015) and was also described in Caceres *et al.* (2016). Since a portion of the Diehl-Schmid cohort reported

a worsening of their financial situation, financial support was also rated as helpful, while pharmacological treatment for the patient and safety measures, e.g., monitoring devices, were not. Furthermore, caregivers wished for an all-inclusive information resource, e.g., trained staff that can provide counseling for legal, financial and social issues.

The study of Nicolaou *et al.* (2010) found caregivers of FTLD patients to have more needs than caregivers of AD patients and to require and receive more overall help, but receiving the same amount of help in formal care. Older caregivers had fewer overall needs and received less help but were more satisfied with the help received. Rosness *et al.* (2008) found that caregivers in FTLD, in comparison to those caring for an AD patient, were significantly less satisfied with the counseling, follow-up visits and information given to them.

Examining the care situation in patients with PPA, Riedl *et al.* (2014) determined that 58% of caregivers did not receive any kind of support. In 31%, formal care help was provided, and 75% received financial support through the German care insurance system. Apart from support groups, which were utilized by 26% of caregivers, no other types of caregiver support were in use.

Diehl *et al.* (2004) and Morhardt (2011) sum up the problems that caregivers of FTLD patients frequently encounter. They mention difficulties in obtaining a correct diagnosis, which is supported by Nunnemann *et al.* (2012) and Shinagawa *et al.* (2015). A paucity of appropriate care facilities and interventions for the patient is described, not least due to the patients often being significantly younger than other dementia patients (Diehl *et al.*, 2004; Caceres *et al.*, 2016; LoGiudice and Hassett 2005; Morhardt, 2011; Nunnemann *et al.*, 2012; Shinagawa *et al.*, 2015). Uniquely, Ibach *et al.* (2004) assessed structural support offers for caregivers of people with FTLD in Germany in a survey conducted in 36 clinics for geriatric psychiatry, covering an area of >20 million inhabitants. Disease-specific counseling for caregivers was provided in 75% of clinics. Additionally, 61% offered support groups; however, it was not stated whether these support groups were aimed specifically at caregivers of FTLD patients. Eighty-nine percent of caregivers were referred to local Alzheimer's societies and 61% to other initiatives. Fewer referrals were correlated with a high proportion of dementia patients. However, 89% of clinics pointed out that there are fundamental deficits in the support provision for caregivers of FTLD patients. Clinics providing for a larger area had worse support offers, and more closed-ward beds were associated with less specific counseling.

Three studies (Boxer *et al.*, 2013; Moretti *et al.*, 2004; Vercelletto *et al.*, 2011) assessed changes in

caregiver burden in pharmacological studies for anti-dementia drugs in FTLD. Two studies reported on support groups (Diehl *et al.*, 2003; O'Connell *et al.*, 2014), two studies reported on interventional activities (Dowling *et al.*, 2014; Mioshi *et al.*, 2013b) for caregivers, and one study (O'Connor *et al.*, 2016) examined the effect of an activity program for patients on caregiver burden.

Intervention procedures and results are summarized in Table 2.

Only the pharmacological study examining the effect of an acetylcholine receptor antagonist (Moretti *et al.*, 2004) showed an improvement in caregiver stress and patient behavior; the other studies did not show significant effects.

Non-pharmacological caregiver interventions were generally reviewed as favorable and helpful, with an emphasis on the establishment of social contacts and mutual support from people in a similar situation.

The intervention aimed at the patient (O'Connor *et al.*, 2016) was helpful in decreasing care time and easing the situation due to improved behavior and higher caregiver confidence.

## Discussion

Our results revealed that during the past five years, the amount of literature on caregiver burden in FTLD has risen substantially. However, knowledge is still lacking data from specific fields of research, such as available support in different countries and the situation of child caregivers. Numerous studies comparing AD and FTLD have been conducted. Our results show that burden and depression are higher in caregivers of FTLD patients than those of AD patients. Reasons for this significant difference are likely to be found in the more burdensome set of behavioral symptoms developed by FTLD patients – apathy, disinhibition, loss of empathy, aberrant motor behavior and changes in appetite and eating behavior – as opposed to the mainly cognitive decline, as exhibited with memory problems in AD (Sacuiu, 2016). Only two studies focusing on child caregivers of FTLD patients could be identified in the present review, even though the young age of onset of some patients with underage children is frequently stated as burdensome. Financial problems are another major challenge that caregivers of persons with FTLD must face. Not only is the patient no longer able to contribute to the family income, but the need for constant care and surveillance also requires the caregiver to reduce their working time or to pay for professional care. Another main concern for caregivers of FTLD patients is the lack of appropriate support and

care services. Medical institutions and healthcare facilities are often not equipped to handle erratic behavioral disturbances, even leading to rejection of the patient. Not only relatives and friends but also a large number of healthcare professionals seem to be unaware of FTLD as a cause for behavioral change and cognitive deficits at a relatively young age. National associations for dementia should therefore intensify their actions in FTLD when educating both professionals and laypersons and highlight the existence of young-onset dementias and how they differ from well-known AD symptoms. Since data concerning the awareness of FTLD is lacking, a first step could be to assess awareness and knowledge about FTLD among family doctors, neurologists, psychiatrists and staff in dementia care facilities in order to provide advanced information tailored to existing levels of knowledge.

While some caregivers expressed hope in drug trials for pharmacological treatment in FTLD (Oyebode *et al.*, 2013), previous studies found that therapies for patients with FTLD were less helpful in relieving the burden than strategies targeting caregivers directly (Diehl-Schmid *et al.*, 2013). Two out of three pharmacological trials could not find a significant improvement in the caregiver's situation, nor were sufficient effects on the patient's symptoms shown.

Interventions aimed directly at the caregiver, however, led to a significant relief in burden. This review found that constructive coping techniques and mutual support, organized in caregiver support groups, were most helpful. It can therefore be concluded that the most efficacious measure when tackling caregiver burden are strategies for improving the caregiver's situation rather than trying to change the patient's behavior. Nevertheless, management strategies for erratic behaviors to reduce caregiver burden have been proposed. However, these strategies remain as reports of the clinical experiences of individual professionals. Randomized controlled trials are needed to assess the efficacy of these strategies.

Of the 69 papers considered in this review, 65 articles originated from Western industrialized countries. Only four articles included data from emerging countries, namely, China, Brazil and India. In a literature search investigating the epidemiology of FTLD, Onyike and Diehl-Schmid (2013) found that all studies reporting the prevalence or incidence of FTLD were conducted in Western industrialized countries, with preliminary studies only emerging from India and China. The study from Mekala *et al.* (2013) was the only paper to explicitly compare cross-cultural caregiver burden and found that the differing attitudes towards caregiving and ageing in societies of different cultural

backgrounds as well as different healthcare structures influence the caregiving experience. More studies from emerging or developing countries would be helpful in addressing the caregiver burden specific to different cultural, social and economic backgrounds.

### Limitations and future research

However, some limitations must be considered regarding the present review. Relevant articles could have been excluded if they were written in a language other than English or German, which may explain the publication bias for the country of origin. Especially studies from the Spanish-speaking world that could contribute findings from non-Western countries might have been missed by our search strategy. Studies that did not specifically provide information on persons with FTLD and their caregivers were also not included, so that more general aspects about caregiver burden in dementia might have been missed in this review. Moreover, the scope of the selected studies varies, and the quality of the studies was not assessed systematically to provide an overview of available research (Tricco *et al.*, 2016). Thus, the quality of evidence reported here cannot be provided and could be assessed in systematic reviews focusing on specific aspects of burden in caregivers of persons with FTLD. Since nomenclature is not always used consistently and some studies fail to report exact numbers of diagnoses, comparisons might be distorted.

Future research should especially assess the situation of underage children in the context of symptoms unique to FTLD and possible interventions. The caregivers' financial and work situation, especially in comparison with the time before care became necessary, is another aspect that should be assessed in the future. Furthermore, the provision of care and support services specific to frontotemporal degeneration should be assessed in each country individually in order to recognize support gaps and lack of community support through health benefits.

Moreover, future research should assess whether the quality of care provided to the persons with dementia is affected by high levels of caregiver burden. This research question was already tackled for persons with dementia in general with a finding of good mental health being associated with a high quality of care (Morlett Paredes *et al.*, 2017), but a special focus should be set on the distinct problems described above caregivers for persons with FTLD encounter.

### Conflict of interest

None.

### Description of authors' roles

T. Karnatz, M. Halek and J. R. Thyrian formulated the research question and designed the study. T. Karnatz carried out the study. T. Karnatz, J. Monsees, D. Wucherer, B. Michalowsky, I. Zwingmann, M. Halek, W. Hoffmann and J. R. Thyrian contributed to analyzing and interpreting the data and assisted in writing the article.

### Supplementary material

To view supplementary material for this article, please visit <https://doi.org/10.1017/S1041610219000176>.

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