Aus dem Deutschen Zentrum für Neurodegenerative Erkrankungen Standort Rostock/Greifswald (Prof. Dr. Wolfgang Hoffmann) in Kooperation mit der Universitätsmedizin der Universität Greifswald

Thema:

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

Inaugural - Dissertation
zur
Erlangung des akademischen
Grades
Doktor der Medizin
(Dr. med.)
der
Universitätsmedizin
der
Universität Greifswald
2021

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Tag der Disputation: 23.09.2022

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List of Abbreviations

AD *Alzheimer's Dementia*

ADL *activities of daily living*

ALS *amyotrophic lateral sclerosis*

BPSD *behavioral and psychological symptoms in dementia*

bvFTD *behavioral variant frontotemporal dementia*

CB *caregiver burden*

CBD *corticobasal degeneration*

CBI *Caregiver Burden Index*

CBS *Caregiver Burden Scale*

CDR *Clinical Dementia Rating Scale*

CSF *cerebrospinal fluid*

CSI *Caregiver Strain Index*

DLB *dementia with Lewy bodies*

ECT *electroconvulsive therapy*

FAQ *Functional Activities Questionnaire*

FTD *Frontotemporal Dementia*

FTDC *Frontotemporal Dementia Criteria Consortium*

FTLD *Frontotemporal Lobar Degeneration*

IBM *Intimate Bond Measure*

ICD *International Classification of Diseases*

IRI *Intepersonal Reactivity Index*

LOD *late onset dementia*

LPA *logopenic progressive aphasia → lvPPA*

lvFTD *language variant frontotemporal dementia*

lvPPA *logopenic variant primary progressive aphasia*

MND *motor neuron disease*

MRI *magnetic resonance imaging*

nfvPPA *nonfluent variant primary progressive aphasia*

NPI *Neuropsychiatric Inventory*

PDD *Parkinson's disease dementia*

PET *positron emission tomography*

phFTD *phenocopy of frontotemporal dementia*

PNFA *progressive nonfluent aphasia → nfvPPA*

PPA *primary progressive aphasia*

PSP *progressive supranuclear palsy*

PwD *person with dementia*

QALYs *quality-adjusted life years*

QoL *Quality of Life*

RCT *randomized controlled trial*

RSS *Relatives' Stress Scale*

SCB *Screen for Caregiver Burden*

SD *semantic dementia → svPPA*

SPECT *single-photon emission computed tomography*

svPPA *semantic variant primary progressive aphasia*

sZBI *short form Zarit Burden Interview*

WHO *World Health Organization*

YOD *Young Onset Dementia*

ZBI *Zarit Burden Interview*

1. Introduction

Around 50 million people worldwide are estimated to suffer from dementia, and by 2050, this number is predicted to rise to 135 million. The term ‘dementia’ describes conditions affecting the human brain that lead to neurodegeneration. Thus, a person with dementia usually loses some of their previously intact higher brain functions, such as memory, executive function, language, movement, and social skills. The majority of individuals suffering from dementia are older than 65 (WHO, 2015).

The need for care already within an early stage of dementia is one of the major challenges this disorder imposes on global health. In 2010, an equivalent of 1% of the world’s gross domestic product was estimated to be spent on dementia-related costs. Nevertheless, expenditures on direct healthcare are not the main cost factor. Care is mainly being provided by informal caregivers, such as family members and friends. In low- and middle-income countries, 58% and 65% of costs are spent on informal caregiving, respectively. In high income countries, informal care costs account for 40% of dementia-related expenditures (WHO, 2015). This underlines the worldwide importance of social- and community-based care as a foundation for dementia caregiving.

Young-onset dementia (YOD), i.e. dementia in individuals younger than 65 years of age, however imposes special problems and challenges. After Alzheimer’s Dementia (AD), Frontotemporal Lobar Degeneration (FTLD) appears to be the second-most common cause of YOD (Devineni and Onyike, 2015).

1.1 FTLD: Clinical Presentation and Diagnosis

1.1.1 Classification and Diagnosis

Frontotemporal lobar degeneration, often referred to as frontotemporal dementia (FTD), is the circumscribed atrophy of frontal and temporal brain matter that leads to characteristic changes in behavior and abilities in a person (Olney, Spina and Miller, 2017).

Generally, FTLD can be divided into the two main subgroups of a behavioral-variant (bvFTD), which mainly affects the person’s behavior and character, and the language variants (lvFTD), also referred to as Primary Progressive Aphasias (PPA), which cause

impairments in speech and/or language comprehension as a predominant symptom. PPAs can furthermore be divided into three subtypes: the semantic variant (svPPA), the non-fluent variant (nfvPPA) and the logopenic variant (lvPPA) (Gorno-Tempini *et al.* 2011). The former two variants are generally regarded as FTLD subtypes, whereas lvPPA is considered to be part of the spectrum of Alzheimer's dementia, as biomarker findings indicate (Gorno-Tempini *et al.* 2011). A revised classification as well as diagnostic criteria for PPAs were proposed by Gorno-Tempini *et al.* (2011).

A third group of cases consist of overlap disorders between other neurodegenerative diseases and FTLD. Such presentations have been described for amyotrophic lateral sclerosis (ALS) and other motor neuron diseases (MND), for corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP).

Diagnostic criteria for bvFTD were proposed by the FTD Criteria Consortium (FTDC) which were revised by Rascovsky *et al.* (2011).

Both the criteria as described by Rascovsky *et al.* 2011 and Gorno-Tempini *et al.* (2011) provide the source for the diagnostic criteria that is currently in use according to the German guideline on dementias (Jessen *et al.,* 2017).

Major symptoms in bvFTD comprise of disinhibition, loss of empathy, hyperorality and changes in dietary preferences, as well as apathy, stereotypical or compulsive behavior and a loss of executive functions. However, at least in early stages of the disease episodic memory as well as visuospatial cognitive skills remain relatively spared from the functional decline (Olney, Spina and Miller 2017). Neuropsychological symptoms can be assessed using diagnostic tools such as the Clinical Dementia Rating Scale (CDR) or the Functional Activities Questionnaire (FAQ). Imaging of the brain using MRI, PET or SPECT scans can furthermore underpin the diagnosis when atrophy or hypometabolism in frontal and/or temporal cortical areas is detected.

A definitive diagnosis can only be confirmed histopathologically in a brain biopsy or post-mortem. Common findings in bvFTD are accumulations of Tau, TDP-43, ubiquitin and fused-in-sarcoma (FUS) proteins that can be further subclassified (Olney, Spina and Miller, 2017).

The semantic variant PPA can be detected in patients with anomia and impaired single-word comprehension. Furthermore, impaired object recognition as well as dyslexia and/or dysgraphia especially of words with irregular spelling can occur. Repetition and speech production however remain relatively unaffected in this form of PPA (Gorno-Tempini *et al.* 2011). The clinical diagnosis may be supported by MRI-detected atrophy principally in the anterior temporal lobe, or SPECT/PET hypoperfusion in those areas, respectively. Histopathological findings in svPPA most often include ubiquitin-positive and TDP43-positive cytoplasmic inclusions in neurons (Olney, Spina and Miller, 2017).

In contrast to svPPA, hallmark symptoms in the non-fluent variant PPA are agrammatism and effortful speech production. Errors in sound production and distortions can be subsumed as apraxia of speech. Moreover, the comprehension of complex syntax is impaired, while single-word comprehension and object recognition remain spared (Gorno-Tempini *et al.* 2011). In nfvPPA, atrophy and/or hypoperfusion can be detected mainly in the left posterior fronto-insular region. Histopathalogy in nfvPPA mainly finds tau-positive cytoplasmic inclusions (Olney, Spina and Miller, 2017).

The third variant of PPA, the logopenic variant, is widely associated with AD due to its histopathological findings similar to those seen in AD. For examples, decreased Aβ42 levels and increased tau levels may be found in the cerebrospinal fluid (CSF) (Olney, Spina and Miller 2017). Symptomatically, patients with lvPPA exhibit an impaired single-word retrieval and repetition of sentences. Object recognition, single-word comprehension and motor speech remain relatively unimpaired. Even though there might occur phonologic errors during spontaneous speech production, severe agrammatism is absent. Alterations in brain imaging are mainly found in the left posterior perisylvian or parietal regions (Gorno-Tempini *et al.* 2011).

The Strong *et al.* (2017) revised criteria allow diagnostics and classification of ALS-FTD. These can be summarized as a person having an established diagnosis of ALS/MND and observed behavioral changes, who accordingly meets the Rascovsky *et al.* (2011) or Gorno-Tempini *et al.* (2011) criteria or shows behavioral/cognitive symptoms as well as loss of insight and/or psychotic symptoms (Strong *et al.*, 2017). Furthermore, patients that exhibit either cognitive or behavioral symptoms, but fail to

meet the FTD criteria, are subclassified as ALS with cognitive impairment (ALS-ci) or ALS with behavioral impairment (ALS-bi).

There have been descriptions of patients presenting symptoms consistent with a bvFTD diagnosis but with a slow disease progression. Pathological findings in imaging are usually absent in these cases that are referred to as FTD phenocopies (phFTD), yet differential diagnosis, which is crucial in order to estimate the patient's prognosis, remains difficult. Some findings indicate there might be a connection to the C9orf72 mutation in some of these patients, a mutation that is also estimated to be the most common cause of hereditary FTD (Kipps, Hodges, and Hornberger, 2010).

1.1.2 Genetics of FTLD

A notable family history of FTD can be found in around 30% of cases, where a hereditary component can be assumed. Within bvFTD, genetic mutations might be held accountable for up to 48% of cases and up to >40% in ALS-FTD, whereas only about 12% of PPA cases have a strong family history hinting at a genetic cause (Greaves and Rohrer, 2019).

The three most common genetic mutations associated with the FTD spectrum are C9orf72 – the most common mutation – followed by the progranulin (GRN) and mictrotubule-associated protein tau (MAPT) mutations. Each of these mutations is estimated to cause between 5 and 10% of FTD cases (Greaves and Rohrer, 2019).

The three mutations are each more or less strongly associated with different clinical presentations within the FTD spectrum. Even though bvFTD is the most common subtype observed among all three mutations, an atypical bvFTD with hallucinations or delusions can be exhibited by C9orf72 mutation carriers. GRN mutation carriers may present a form of PPA and CBS, whereas PSP and ALS-FTD cases are extremely rare. ALS-FTD is never seen in MAPT mutations but can quite frequently be found as a phenotype of C9orf72 mutations, the latter of which can also be found in ALS cases without FTD. Typical clinical presentations of MAPT mutations include a semantic speech impairment in PPA, and more seldomly cases of CBS and PSP (Greaves and Rohrer, 2019.

There is ongoing research about modifying genes and epigenetic factors influencing genetic penetrance of the three main mutations, mainly being reflected by the earlier

age of onset. At the present time, reliable predictions on penetrance in positively-tested family members are hard to make (Greaves and Rohrer, 2019).

1.1.3 Epidemiology

Dementias from the FTD spectrum are considered to be the second most common cause of dementia under the age of 65 after AD (Devineni and Onyike, 2015).

A systematic review conducted by Hogan *et al.* (2016) summarized the findings of 26 studies on FTLD epidemiology. Prevalence rates varied widely among the studies which might be attributed to different methodological approaches in the definition of the study population. For individuals <65 years of age, the range of prevalence was given from 0.07 to 0.30 per 1000. Studies including older participants stated prevalence rates between 0.01 to 4.61 per 1000.

Reported incidences ranged from 0.00 to 0.33 per 1000 person-years, with the incidences in studies restricted to participants younger than 65 or 70 years of age ranging between 0.00 to 0.06 per 1000 person-years.

Out of all reviewed studies, males made up 52.5% of all FTD cases and females 47.5%.

In this review conducted by Hogan *et al.* (2016), the proportion of persons with bvFTD was about four times higher at 79.7% than that of persons with different forms of PPA, which made up approximately 20% of the cumulative study population.

1.2 Caregiver Burden

Even though there has long been an understanding of the challenging situation of caregivers - especially those caring for a PwD - Zarit, Reever and Bach-Peterson made a major contribution to caregiver burden research in 1980 by developing the Zarit Burden Interview, comprising 29 questions and originally aimed at spousal caregivers of individuals with “senile dementia” (Zarit, Reever and Bach-Peterson, 1980). Their self-reported questionnaire addresses various aspects of caregiving (e.g., patient-caregiver relationship, involvement of other family members, financial situation) and associated feelings, e.g. anger, guilt, depression, but also positively attributed feelings of being needed or helpful.

Research on caregiver burden in the following decades would test numerous models to identify and quantify factors that influence caregiver burden, usually focusing on

dementia in general or on AD. Influences on burden can generally be divided into two main categories: caregiver-associated factors (e.g. coping skills, social support) and patient-associated factors (e.g. behavioral disturbance, need for assistance) (Clyburn *et al.*, 2000; van der Lee *et al.*, 2014).

1.3 Aims of this Review

In 2012, Nunnemann *et al.* conducted a systematic review on caregiver burden in FTD. A total of 19 publications were considered in this review. In accordance with the main factors contributing to caregiver burden pointed out above, Nunnemann *et al.* (2012) identified the young age at onset, the behavioral disturbance and delayed diagnosis to be burdensome. Moreover, they identified the deteriorating effect of care provision on caregiver health and personal needs. Caregivers found information about the disease to be scarce and suitable care facilities lacking. Moreover, no RCTs for interventional measures could be found. In the years between 2012 and 2017, when the search for the present publication was conducted, forty-two new publications were found and thus underpinned the necessity for an updated overview of the existing knowledge, aimed at obtaining information regarding the following questions:

What are major contributors to caregiver burden in FTLD?
What distinct features are there in caregiver burden in FTLD compared to caregiver burden in other types of dementia?
What strategies or interventions are there to reduce caregiver burden?
What is the caregiver burden situation like in different countries?
What new findings have been made that have not been subject to research before?

2. Methods

2.1 Search Process

The aim of this study is to give an overview of currently available research on caregiver burden in FTLD so as to identify key findings and research gaps. We thus chose the format of a scoping review that allows for different resources of published knowledge to be summarized into a synopsis of existing knowledge (Tricco *et al.* 2016). Scoping reviews are a suitable format four our research question, because they permit inclusion of a wide range of scientific approaches and coverage of different aspects of caregiver burden. Therefore, we made no limitations regarding study type or content, as long as it contributed to knowledge about caregiver burden in FTLD.

Unlike in a systematic review, study quality was not systematically assessed and no meta-analyses were conducted due to the broad approach to gathering all available information instead of comparing distinct features of caregiver burden in FTLD.

After the first literature synopsis had been finished, a modified PRISMA checklist for scoping reviews was released (Tricco *et al.* 2018). After retrospectively comparing our scoping review published in Karnatz *et al.* 2019 (see Appendix 1) with the checklist, we found it to be compliant with the novel guidelines released and continued to adhere to the checklist in the second literature search conducted in November 2019. The reported PRISMA checklist for scoping reviews items for both the original publication and the follow-up review can be found in Appendix 2.

In April of 2017, a literature search was conducted to identify eligible studies for the scoping review. The databases PubMed, Web of Science and ScienceDirect were searched using the detailed search strategy described in Karnatz *et al.* (2019). In a two-step process, a first screening excluded irrelevant articles by scanning their titles and abstracts. Full-text articles were consulted in the remaining publications, excluding those shown to be irrelevant for the review's topic. We used cross-referencing of the included articles to identify articles that met the eligibility criteria, but were not identified through our search strategy. Ambiguities concerning the inclusion or exclusion of publications were resolved by consensus among T. Karnatz and J. R. Thyrian.

A second literature search, using the same search strategy as well as the same databases that were used for the original search in 2017, was conducted in November 2019. A flow-chart documenting the search process for the follow-up search, in analogy to the original search process, can be found in Figure 1.

The present second literature search was undertaken in order to identify additional findings and contributions to the implications that were proposed in Karnatz *et al.* (2019). We therefore included eligible new publications that were released between 2017 and 2019 (some of the publications scheduled to be publicized in 2020) that had not been included in the original publication.

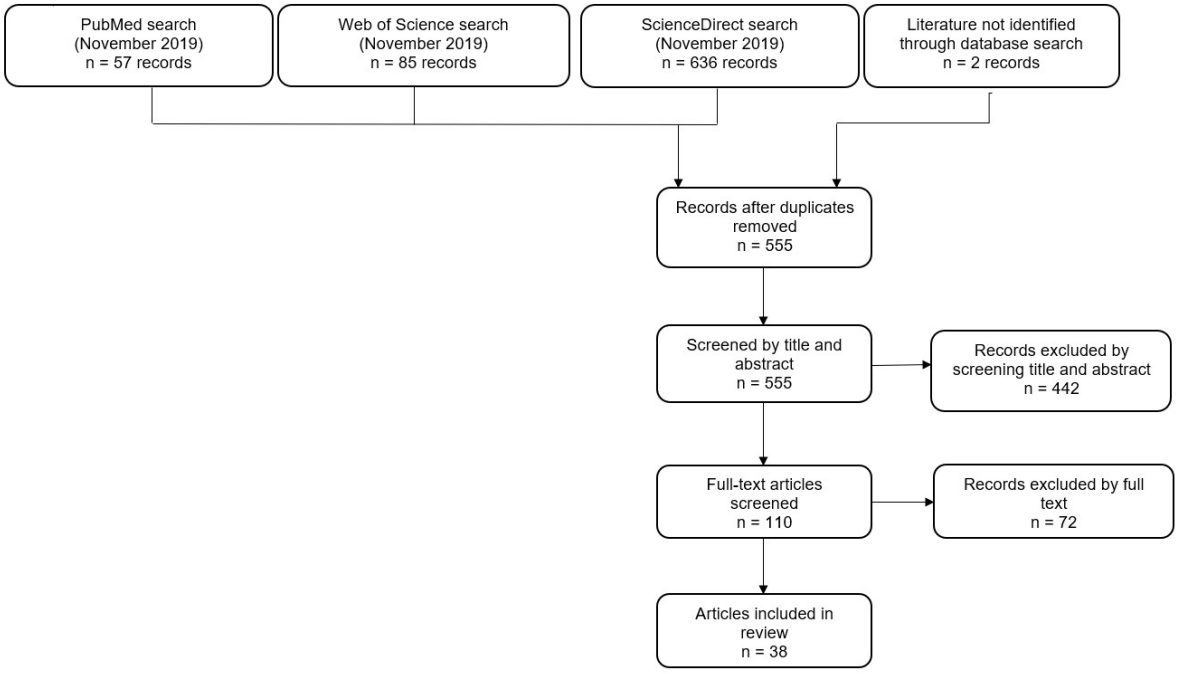

Figure 1 - Literature search flow chart

2.2 Literature Synopsis

After all eligible studies had been identified, a chart was developed to summarize each article's contents (an example can be found in Table 1). Articles were grouped by type (study article, interventions, case reports, educational articles). Sample characteristics such as caregiver country, age, gender, relationship to the patient as well as the patients' diagnoses and situation of living were obtained where available. Comparisons of caregiver burden and distinct challenges were made for the different subtypes among the FTLD spectrum and between FTLD and other forms of dementia. Key topics

of the selected studies were established in order to create a synopsis of the current findings.

Interventions that assessed changes in caregiver burden as a primary or secondary endpoint were presented in a separate section. Moreover, results in the original publication were compared to the findings publicized in the review by Nunnemann *et al.* (2012).

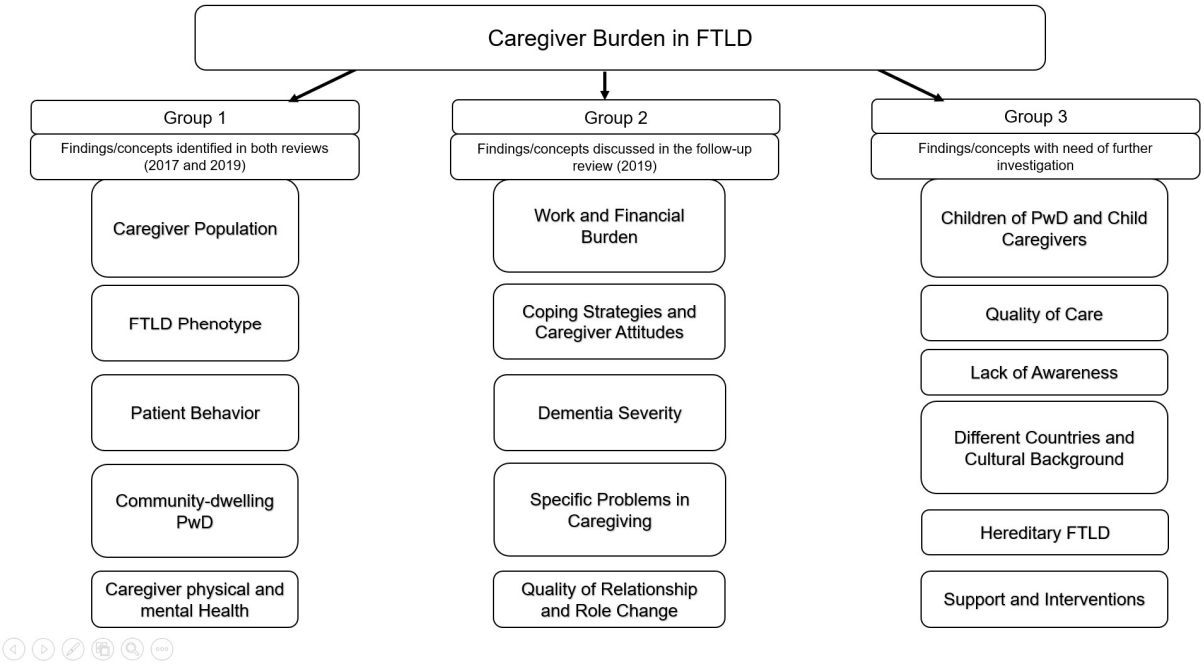

Figure 2 - Concept of Caregiver Burden in FTLD

Using these key findings, we were able to develop a concept of factors inherently important to caregiver burden in FTLD (Figure 2). Comparing the findings from both reviews from 2017 and 2019, we found a partial overlap of the aforementioned key topics, i.e. topics to which both of our reviews provided a considerable amount of information. This group of aspects was labeled as Group 1 in our model. However, the follow-up review also added considerable knowledge in previously scarcely studied aspects of caregiver burden in FTLD, therefore we grouped these findings in Group 2. Research interests that have not been studied extensively or not studied at all to this point remain as Group 3 in our model.

This work will predominantly present the results and implications of the follow-up literature search conducted in November 2019, i.e. model groups 2 and 3, whereas results of the original literature search (Group 1) have already been published in Karnatz *et al.* (2019, Appendix 1). Where appropriate, these results will be referred to for comparison.

3. Results

3.1 Design and Methods of the Included Studies

A total of 69 publications were found eligible for the original review in 2017. This number comprises 44 controlled studies, eight interventions, eight educational articles, five case studies, three reviews and one assessment of support structures.

The second literature search conducted in November of 2019 yielded 38 additional articles that were included into this follow-up review. Of the identified articles, 19 were quantitative studies, four interventions, one educational article, seven reviews, one case study, five qualitative studies, and one cost assessment. Included in these publications are poster abstracts from the 2018 American Association for Geriatric Psychiatry (AAGP) Annual Meeting (Wagner *et al.,* 2018), and the 2019 AAGP Annual Meeting (Nowaskie *et al.,* 2019). Furthermore, abstracts from the 2017 Abstract Supplement of Alzheimer's & Dementia journal were included (Hughes *et al.*, 2017; Ratti *et al.*, 2017; Zahir *et al.*, 2017).

3.2 Outcomes and Measures of Quantitative Studies

We reported the tools used to assess caregiver burden. Among the publications that were included in both literature searches, the most commonly used measure was the Zarit Burden Interview (ZBI; 2017: n=13, 2019: n=5) and its short from (sZBI; 2017: n=10, 2019: n=3). In order to facilitate reading, references for the measures used in the 2019 review can be found in Table 2, and in Table 5 of the original publication for the included studies therein.

The Zarit Burden Interview is a 22-item questionnaire that can be used to quantify and compare caregiver burden, and to assess its changes over time (Bédard et al., 2001). A 12-item short form for easier administration in research as well as a four-item screening version for quick identification of caregiver burden have been developed, sharing the high internal consistency with the long version (Bédard et al., 2001). Items are rated on a scale between 0 (never) to 4 (always), yielding a score range of 0 to 88 (long version), with greater scores indicating higher burden. Different cut-offs have been suggested to identify burden (Bédard et al., 2001).

Another measure commonly used to assess caregiver burden is the distress subscale, a part of the Neuropsychiatric Inventory (NPI). It was used in ten studies that were identified in the 2017 literature search and in two studies identified in 2019.

The Neuropsychiatric Inventory is an instrument to assess twelve behavioral and psychiatric symptoms: delusions, hallucinations, euphoria, dysphoria, apathy, anxiety, agitation/aggression, disinhibition, irritability/lability, aberrant motor behavior, night-time behaviors, and appetite and eating behaviors (Cummings, 1997). After screening for the presence of these symptoms, informants rate the frequency of each symptom on a scale from 1 (occasionally) to 4 (very frequent), and the severity of each symptom on a scale from 0 (symptom not present) to 3 (very severe). Moreover, caregivers rate the distress they experience with each symptom on a scale from 0 (not distressing at all) to 5 (very distressing). A maximum total score of 144 can be reached, with higher scores indicating greater behavioral disturbance (Cummings, 1997). A version applicable for nursing home residents, rated by professional caregivers, was also derived; caregiving staff rate the level of occupational disruptiveness (e.g. need to adjust time management) for each symptom (Wood et al., 2000).

Other tools to assess the construct of caregiver burden were the Caregiver Burden Scale (CBS; 2017: n=2, 2019: n=1), the Caregiver Burden Index (CBI; 2017: n=3, 2019: n=2), the Caregiver Strain Index (CSI; 2017: n=3, 2019: n=2), the Screen for Caregiver Burden (SCB; 2017: n=1), a visual analogue scale (2017: n=4), and the Relatives' Stress Scale (RSS; 2019: n=1).

It is worth noting that the studies used different cut-offs to classify caregiver burden. If provided in the publication, these cut-offs can be found in the summary of each article. Moreover, some publications assessed additional outcomes such as caregiver stress, depression, anxiety, and QoL.

3.3 Sample Characteristics of the Included Studies

We reported the total numbers of patients and caregivers included in quantitative studies in the original publication, and will subsequently report the same data for the newly identified studies in 2019. The overall sample from these publications, excluding data from reviews and educational articles, comprised a total of n = 6290 patients,

thereof n = 3183 with a diagnosis belonging to the FTLD spectrum and n = 217 patients with ALS/MND. The total number of caregivers for persons with FTLD was n = 2729.

Out of the 19 quantitative studies that were included in the 2019 literature search, 14 studies had included participants with a diagnosis based on consensus criteria. The survey studies from Besser and Galvin (2019) and Galvin *et al.* (2017) relied on caregiver report of the diagnosis. The poster abstracts from Hughes *et al.* (2017), Ratti *et al.* (2017), and Zahir *et al.* (2017) did not report their source of diagnosis.

The cost analysis carried out by Chen *et al.* (2019) obtained diagnoses using the ICD coding in Medicare files.

Out of the six qualitative studies and case studies, only the study by Tyrrell *et al.* (2019) reported that the participating patients' diagnoses were made according to consensus criteria.

The interventional studies carried out by Jokel *et al.* (2017) and Spalding-Wilson *et al.* (2018) also relied on consensus criteria for patient inclusion. The aphasia intervention by Armour *et al.* (2019) and the abstract by Wagner *et al.* (2018), however, did not state their source of diagnosis.

Taking the qualitative, quantitative, and case studies as well as the intervention studies and the cost analysis into account, 27 studies reported figures for diagnostic groups. The largest proportion of FTLD patients had no specified diagnosis reported (n = 1390, n = 13 studies). Of those with a specified FTLD phenotype, the largest group was that of bvFTD patients (n = 1066, in n = 11 studies). Three studies included patients with PPA, but without further specification (n = 291 patients). For the two PPA phenotypes that belong to the FTLD spectrum, n = 154 patients were diagnoses with svPPA/SD (reported in n = 8 studies) and n = 91 patients were diagnosed with nfvPPA/PNFA (reported in n = 5 studies).

Studies focusing on neurodegenerative diseases that overlap with FTLD were also included. Four studies included patients with CBD (n = 112 patients), with the study by Southi *et al.* (2019) focusing solely on this patient group. A total of n = 79 patients, reported in n = 3 studies, were diagnosed with PSP.

The largest group of overlapping syndromes is that of MND/ALS and FTLD. Study cohorts including these patients were reported in n = 5 studies, with a total of n = 217 patients. All references to the aforementioned studies can be found in Table 2.

3.4 Country/Region of Origin

Both in the original publication as well as in the follow-up literature search, we grouped publications by their country of origin. Similar to the findings from the 2017 literature search, the majority of publications identified in 2019 originate from Europe (2017: n = 22, 2019: n = 12), the US/Canada (2017: n = 24, 2019: n = 18), and Australia (2017: n = 16, 2019: n = 5), see Table 2 for references.

We argued that more studies from newly industrialized countries (NIC) and developing countries are needed to add different cultural aspects of caregiving and the possible burden associated with them. In the present literature search, three studies out of the 38 newly identified studies were not conducted in traditional Western industrialized countries: the study by Liu *et al.*(2018) from China, by Mukherjee *et al.*(2017) from India, and by Kücükgüclü *et al.*(2017) from Turkey, even though Turkey might be considered as a European and thus Western industrialized country.

Contrary to our findings from 2017, the novel literature search could not identify a study that compared burden between two countries and/or cultural backgrounds.

3.5 Setting

We examined the included articles for reports on the patient's living situation (at home vs. institutionalized). Out of the quantitative studies identified in 2019, three gave accounts on the living situation (Besser and Galvin, 2018; Sani *et al.,* 2019, van Duinen-van den IJssel *et al.,* 2018). The study conducted by Sani *et al.* (2019) assessed sleep difficulties (see Section "Need for Care") and thus required all patient participants to live at home and have a bed partner.

The study by van Duinen-van den IJssel *et al.* (2018) was the only study to focus on nursing home residents, and, moreover, the only study to assess burden in nursing staff (see Section "Type of Relationship").

The majority (78.1%) of the patients in the Besser and Galvin (2018) survey were reported to live at home, either independently or with assistance. Out of the qualitative

and case studies, four gave accounts of the patients' living situation (Bryant and Miller, 2018; Damianakis *et al.*, 2018; Johannessen *et al.*, 2017; Tyrrell *et al.*, 2019), with the study by Johanessen *et al.* 2017 being the only one of these including seven patients – out of a total of 16 patients - living in a nursing home.

The lack of appropriate care facilities for persons with FTLD was a remarkable finding that we argued to be a major contributor to burden in the original publication (see Karnatz *et al.*, 2019), and a concern that was often voiced by caregivers in other studies (Nowaskie *et al.*, 2019). This can be illustrated by the example of the patient presented in the Bryant and Miller (2018) case study: The patient, after several hospital inpatient stays and emergency room visits, was transferred to a residential nursing home, but asked to leave two days later because of his challenging behavior (aggression, wandering, agitation). This exemplary story reflects the frequent difficulty of caregivers finding appropriate support and care facilities. Tyrrell *et al.* (2019) added in their case study the concern for consistency from outside care providers and the necessary understanding for the patient's situation, because in some cases, the need for assisted care was overlooked or underestimated by healthcare professionals.

3.6 Type of Relationship

In both literature searches, we took the relationship between the caregiver and the person with FTLD into consideration. In the second literature search, thirteen studies quantified the type of relationship between informal caregivers and the person with FTLD (for references, see Table 2). The sample of these 13 studies comprised a total of 1067 caregivers, with the majority of them being a spouse or partner of the PwD (78.3%), followed by children (15.7%). These findings are similar to those from the original publication (spouses/partners: 76.4%, children: 18.5%; Karnatz *et al.*, 2019). Other caregiver groups included siblings (2019: 0.28% vs. 2017: 0.19%), unspecified family members (2019: 0.66% vs. 2017: 0.62%), friends (2019: 0.28% vs. 2017: 0.19%), and other caregivers not specified (2019: 4.7% vs. 2017: 3.9%). However, no parents were named as caregivers in the newly identified studies (2019: 0.00% vs. 2017: 0.04%),

Making up the largest proportion of caregivers, spouses have been the focus of three studies (Damianakis *et al.*, 2018: Johannessen *et al.*, 2017; Jokel *et al.*, 2017). All three were qualitative studies, one with members recruited from a support group

(Damianakis *et al.*, 2018), and one newly initiated group as an intervention for caregivers of persons with PPA (Jokel *et al.*, 2017).

Our review based on the literature search from 2017 yielded only two studies that focused specifically on the children of individuals with FTLD. We pointed out a lack of research in this area. However, we could not identify any newer publications in the second literature search. Nevertheless, Besser and Galvin (2019) found a trend for higher burden in caregivers who are children of FTLD patients, and the topic remains to be relevant for caregivers, as an example from Johannessen *et al.* (2017) shows: One couple, comprising a 62-year-old male with FTLD and his 61-year old wife, had children living with them, and the severity of the patient's dementia affected the children's well-being over time. Eventually, the burden of this situation led to the institutionalization of the patient into a nursing home.

Similar to our findings in 2017, ten studies explicitly focused on family caregivers (see Table 2) and the study by Caga *et al.* (2018), examining cognitive and behavioral symptoms in ALS patients, excluded paid caregivers from participation.

As already mentioned above, the study by van Duinen-van den IJssel *et al.* (2018) specifically assessed burden in nursing home staff, caring for people with YOD. For them, caring for residents with YOD was perceived as more distressing than for residents with LOD. This was partly explained by the better physical health younger residents with dementia had, with need for more supervision due to wandering and potentially dangerous activities.

Apart from that, no paid caregivers were explicitly reported to be included as study participants in quantitative studies.

3.7 Gender

In both literature searches, we quantified caregiver gender and summarized any findings on gender differences in caregiving.

In the second literature search in 2019, nine quantitative studies and four qualitative/case studies reported exact numbers of caregiver gender (see Table 2 for references). Summarizing the nine quantitative studies, comprising a total of 1,696 caregivers, it was found that the majority of 77.8% were female caregivers, an even

higher percentage than that of the sample found in 2017 (66.4%, see Karnatz *et al.*, 2019).

Three studies gave account of gender differences in caregiving. Contrary to our findings in 2017, we could only find one study that showed female caregivers to be more severely affected by caregiving (Besser and Galvin, 2019).

In contrast, the study by Hvidsten *et al.* (2019), found female caregiver gender to be significantly associated with a higher QoL. It was argued that this might be attributable to women traditionally finding it easier to adapt to their caregiver role, and thus feeling a higher sense of self-efficacy.

The study by Galvin *et al.* (2017) assessed quality-adjusted life years (QALYs) for caregivers of FTLD patients, which reflect life expectancy adjusted for quality of living. Negative QALYs would indicate a survival time in a health state being "worse than death". In this study, QALYs were highest for constellations comprising a female caregiver and a male patient, but lowest for constellations where both caregiver and patient are female.

3.8 Patient Behavioral Changes as a Burden Factor

In both literature searches, we sought to identify main patient factors associated with caregiver burden. Our follow-up review in 2019 supported the findings that a high number and severity of behavioral and psychological symptoms in dementia (BPSD) is associated with higher caregiver burden (Besser and Galvin, 2019; Koyama *et al.*, 2018; Kücükgüclü *et al.*, 2017, Mukherjee *et al.*, 2017). Apathy was an especially high contributor to caregiver burden in FTLD (Koyama *et al.*, 2018; Kücükgüclü *et al.*, 2017, Liu *et al.*, 2018), and, similar to our findings from the original publication, aberrant motor behavior was also stated as burdensome (Mukherjee *et al.*, 2017). Quantitative studies on FTLD patients did not state a significantly higher frequency or impact of disinhibition, however, this behavioral symptom was described to be burdensome by caregivers in three case studies (Damianakis *et al.*, 2018; Johannessen *et al.*, 2017; Tyrrell *et al.*, 2019).

Case studies also gave an account of possible criminal and hazardous behaviors exhibited by the patient, such as dangerous driving, and inappropriate behavior towards strangers, sometimes leading to police intercalations (Rasmussen *et al.*, 2019; Tyrrell *et al.*, 2019). In the Galvin *et al.* (2018) survey, six percent of participants

reported costs related to police interventions, and 9.6% reported costs associated to legal spending, including criminal cases and civil lawsuits.

Apart from behavioral changes, sometimes leading as far as delinquency, we identified empathy changes in the patient to be another burdensome factor for caregivers (see Karnatz *et al.*, 2019), a finding that was supported in the review about empathy changes in neurocognitive disorders by Bartochowski *et al.* (2019), that included mainly the same studies that we also included in our original publication. The study by Takeda *et al.* (2019) examined the association between patient empathy and their relationship status. It was found that patients with bvFTD and nfvPPA had significantly lower empathy ratings compared to other FTLD subtypes, FTLD overlap syndromes and AD patients. In the follow-up review, we furthermore found two studies assessing empathy changes for PNFA patients (Hazelton *et al.*, 2017) and CBD (Southi *et al.*, 2019), respectively. Both studies showed that patients with PNFA and CBD had deficits in emotion recognition, taking the perspective of others and empathic concern. Moreover, for both patient groups, a decline of empathy when compared to time before disease onset was associated with increased caregiver burden. An interesting contribution, however, was made by the study by Wells *et al.* (2019), assessing the association between patient empathy and caregiver well-being and its moderation by the caregiver's 5-HTTLPR genotype. The 5-HTTLPR gene is a candidate gene coding for a serotonin transporter, and individuals possessing two short alleles have been linked to possibly experiencing higher stress, anxiety, and depression when facing adversity. It could be shown that in this study, too, that being a caregiver with two short alleles of the 5-HTTLPR gene moderated the positive association of patient empathy and caregiver well-being.

The gradual loss of the well-known and beloved patient's personality was described as particularly hurtful, and thus burdensome, in qualitative and case studies (Bryant and Miller, 2018; Damianakis *et al.,* 2018; Johannessen *et al.*, 2017; Nowaskie *et al.*, 2019; Rasmussen *et al.*, 2019; Tyrrell *et al.*, 2019; see also Table 3).

Another aspect that was frequently expressed in case and qualitative studies: The lengthiness of obtaining a correct diagnosis. While early personality changes were often dismissed as results of stress or frustration, and patients refused to acknowledge those changes (Damianakis *et al.*, 2018; Johannessen *et al.*, 2017; Rasmussen *et al.*,

2019; Tyrrell *et al.*, 2019), caregivers often felt helpless regarding the absence of an appropriate professional to seek help at, and some of them felt they were not being taken seriously with their concerns (Johannessen *et al.*, 2017; Rasmussen *et al.*, 2019; Tyrrell *et al.*, 2019). Rasmussen *et al.* (2019) focused their qualitative interviews on the experiences before the FTLD diagnosis had been established. Six of the 14 participants had observed symptoms for five years or more - up to 12 years in one case – before the diagnosis was made. A similar finding could be seen in the participants in the Johanessen *et al.* (2017) study: Here, eight out of 16 patients had had exhibited symptoms for five years or longer before having been diagnosed with FTD, with one case having had experienced symptoms for 15 years prior to diagnosis. Both studies highlight the difficulty of pinpointing the behavioral changes and drawing the conclusion of a possible underlying FTLD as a cause.

3.9 Type of Dementia

We searched publications for differences in caregiver burden depending on the type of dementia.

Out of the 19 quantitative studies, four studies (Besser and Galvin, 2019; Galvin *et al.,* 2018; Hughes *et al.,* 2017; Koyama *et al.,* 2018) included only participants with some form of FTLD or overlap syndromes. Caregiver burden was highest for caregivers with bvFTD (Besser and Galvin, 2019; Koyama *et al.,* 2018) and PSP (Besser and Galvin 2019), while it was lowest for caregivers of patients with CBD and PPA (Besser and Galvin, 2019).

In the follow-up review, a total of eleven quantitative studies (Hazelton *et al.*, 2017; Hvidsten *et al.*, 2019; Kücükgüclü *et al.*, 2017; Liu *et al.*, 2018; Mukherjee *et al.*, 2017; Sani *et al.*, 2019; Takeda *et al.*, 2019; van Duinen-van den IJssel *et al.*, 2018; Wells *et al.*, 2019; Wu *et al.*, 2018; Zahir *et al.*, 2017) included samples with patients with a diagnosis of the AD spectrum. Similar to our findings in the original publication, AD is thus the type of dementia most frequently compared to FTLD, being as well the most common type of dementia in general. FTLD patients had significantly higher NPI scores than AD patients (Kücükgüclü *et al.*, 2017, Liu *et al.*, 2018, Mukherjee *et al.*, 2017, for bvFTD: Takeda *et al.*, 2019), which Kücükgüclü *et al.* (2017) found to be associated with higher CB in both patient groups. Liu *et al.* (2018) furthermore found levels of

depression and anxiety, as well low sleep quality, to be significantly higher in FTLD caregivers compared to AD caregivers.

Examining the capability to live well in patients and caregivers, a construct derived from QoL, satisfaction with life, and well-being, Wu *et al.* (2018) showed that there were no significant differences in scores for AD and FTD caregivers. Nevertheless, within the FTLD group, bvFTD caregivers reported lower scores for living well than caregivers of other FTLD patients, however with the sample being too small for in-group comparisons.

The study by Hvidsten *et al.* (2019) even found QoL in FTD caregivers to remain stable over time, but to decline significantly in AD caregivers. When examining empathy changes in patients with PNFA, neuropathologically considered an FTLD phenotype, and lvPPA, neuropathologically considered an AD phenotype, both patient groups had significant impairments in their empathy abilities compared to healthy controls, but caregiver burden was not significantly different, neither were depression and anxiety levels (Hazelton *et al.*, 2017).

Five quantitative studies (Liu *et al.*, 2018; Mukherjee *et al.*, 2017; van Duinen-van den IJssel *et al.,* 2018; Wu *et al.,* 2018; Zahir *et al.,* 2017) included dementia diagnoses other than AD or FTLD in their samples. Although the study by Liu *et al.* (2018) did not compare FTLD and DLB directly, but either group with AD, respectively, it was shown than both caregiver groups in FTLD and DLB had similarly high ZBI mean scores (FTLD: 23.63 ± 15.91; DLB: 22.58 ± 16.46), both ranging significantly higher than in AD caregivers (12.26 ± 9.74) (Liu *et al.*, 2018). Likewise, the study showed behavioral disturbance in DLB to be significantly higher than in AD, a finding that was supported by Mukherjee *et al.* (2017), where DLB patients exhibited the second-highest magnitude in BPSD after FTLD. Moreover, caregivers of patients with DLB and PDD had a significantly lower ability to live well compared to AD caregivers, in a study that also included FTLD caregivers, who scored similar to AD caregivers (Wu *et al.*, 2018).

3.10 The ALS-FTD Overlap and Caregiver Burden

In our original publication, derived from the literature search in 2017, we included six quantitative studies including patients with ALS/MND. From the second literature search in 2019, two quantitative studies (Bock *et al.*, 2017; Caga *et al.*, 2018) focusing

on ALS were identified, as well as five reviews addressing cognitive and behavioral changes in ALS and their effect on caregivers (Baumann *et al.*, 2019; Benbrika *et al.*, 2019; Caga *et al.*, 2019; Linse *et al.*, 2018; de Wit *et al.*, 2018). Moreover, three quantitative studies included ALS/MND patients in their samples (Besser and Galvin, 2019; Galvin *et al.*, 2018; Wells *et al.*, 2019). The two quantitative studies focusing solely on ALS patients included a total of n = 100 patients, of whom n = 9 met the consensus criteria for ALS-FTD. Bock *et al.* (2017) classified n =23 (46.9%) patients as cognitively impaired (ALS-Ci), whereas 33% of patients in the Caga *et al.* (2018) cohort were cognitively impaired. Another 53% were behaviorally impaired, and 18% showed impairment both in cognitive and in behavioral testing (Caga *et al.*, 2018). Interestingly, Bock *et al.* 2017 found that caregiver burden remained relatively stable in caregivers of cognitively impaired ALS patients or ALS-FTD patients, but only changed significantly with cognitive or behavioral decline in the patient over time. The authors discussed this might be due to little change in the patients' established deficits causing a relatively unchanged level of burden in caregivers, or due to floor effects in caregiver burden measures (Bock *et al.*, 2017). Similar to the findings in FTLD in general, Caga *et al.* (2018) found apathy to be the most frequent behavioral symptom in their ALS cohort, which they examined further. Behavioral symptoms of apathy, often requiring the caregiver to provide extended supervision, prompting, and re-checking in patient's activities, was a significant predictor of caregiver burden in ALS patients in general as well as in ALS-FTD patients (Caga *et al.*, 2018).

The reviews focusing on ALS patients (see Table 4) underpin the importance of behavioral changes in the patient as a major contributor to caregiver burden (Baumann *et al.*, 2019; Benbrika *et al.*, 2019; Caga *et al.*, 2019; de Wit *et al.*, 2018). Moreover, the article by Linse *et al.* (2018) highlighted the negative impact cognitive and behavioral changes in ALS have on the use of communication devices for patients, an aspect that furthermore increases caregiver burden.

3.11 Dementia Severity

All included studies were assessed for associations between dementia severity and caregiver burden.

Similar to our findings in the original publication, Besser and Galvin (2019) found a higher disease severity to be significantly associated with increasing caregiver burden.

Along those lines, Mukherjee *et al.* (2017) found significant associations between the number and severity of BPSD and dementia severity, as well as the association between BPSD and impaired ADL. Caregiver burden, in turn, was found to be associated with a high magnitude of BPSD.

Other studies' findings supported the association between impairment in ADL and higher caregiver burden (for bvFTD and right-sided SD: Koyama *et al.*, 2018; Kücükgüclü *et al.*, 2017). The limited data presented in the abstract by Hughes *et al.* (2017) showed a longitudinal trend for increasing burden particularly in caregivers of mildly symptomatic FTD patients, where the increase over time was more pronounced than in the severely impaired FTD group. The abstract by Ratti *et al.* (2017) presents the study protocol for investigating cognitive measures and their possible predictability of rates of change in patient characteristics and caregiver burden. However, no resulting data was available for this study protocol as of November 2019.

The studies by Besser and Galvin (2019) and Galvin *et al.* (2018) showed an association between higher dementia severity and increased financial burden for caregivers, which will be presented more in detail in the section "Financial aspects and employment". Moreover, Besser and Galvin (2019) found out that the percentage of caregivers who experienced a patient-related crisis in the past year was significantly higher in caregivers of FTLD patients with more severe dementia.

3.12 Need for Care

The general need for provision of care and the associated role shift was a concern found to be perceived as burdensome in the original publication. Moreover, studies were identified that addressed specific patient-related problems caregivers frequently encounter in everyday life.

In our second literature search conducted in 2019, those specific problems of caregiving were mainly addressed in the qualitative and case studies. An overview of those can be found in Table 3. Caregivers regularly expressed the need for constant surveillance of the patient and were concerned about the patient's and other people's safety if this could not be provided (Johannessen *et al.*, 2017; Rasmussen *et al.*, 2019; Tyrrell *et al.*, 2019). This demand on their time was perceived as overwhelming and often left caregivers feeling isolated and without time for their own needs and interests (Damianakis *et al.*, 2018; Johannessen *et al.*, 2017; Rasmussen *et al.*, 2019).

The quantitative study by Besser and Galvin (2019) identified three main factors in caregiver burden: role strain, personal strain, and performance strain (i.e. worries about their performance in caregiving duties). The strain associated with the role of a caregiver was the most prominent of these three factors, followed by performance strain, which was experienced as more burdensome by male caregivers (Besser and Galvin, 2019). Adapting to the new role as a caregiver was perceived to be a factor of burden in qualitative studies and case studies, too (Damianakis *et al.*, 2018; Johannessen *et al.*, 2017; Nowaskie *et al.*, 2019; Rasmussen *et al.*, 2019; Tyrrell *et al.*, 2019).

However, as we had already pointed out in the original publication, no study assessed quality of care provided to the patient and its possible relationship with caregiver burden.

The quantitative study by Sani *et al.* (2019) included 40 FTD patients, as well as 39 AD patients and 25 healthy controls. It studied sleep disturbances in patients with dementia, as reported by caregivers (bed partners). Patients with some form of FTD were more likely to experience difficulty sleeping, with especially bvFTD patients spending more time in bed than healthy controls, and experiencing excessive daytime sleepiness (Sani *et al.*, 2019). Loss of sleeping patterns, when experienced by a bed partner, can cause severe sleep disturbance in caregivers (Bryant and Miller, 2018; Liu *et al.*, 2018; Kücükgüclü *et al.*, 2017) and may require the caregiver to activate the patient more during daytime (Johannessen *et al.*, 2017).

The review by Lewis *et al.* (2018) summarized findings about problematic mealtime behavior in patients with FTLD. These behaviors mainly include overeating (hyperphagia, see Tyrell *et al.*, 2019), mouthing of inedible objects, swallowing difficulties that can lead to aspiration, and changes in food preferences, leading to an unbalanced diet with subsequent diseases and nutritional deficiencies (Lewis *et al.*, 2018). These predominantly behavioral changes were most pronounced in bvFTD and can lead to excessive wandering when looking for food and agitation, while patients with PPA or overlap syndromes experience more difficulties swallowing (as a result of oropharyngeal weakness or apraxia) and must thus be closely monitored to prevent or detect aspiration. Moreover, possible treatment strategies, including environmental modification and appetite-reducing drugs, are presented in this article (Lewis *et al.*, 2018).

We identified one article with anecdotal data and suggestions for managing problematic behavior in FTD patients, directed mainly at nursing staff (Mulkey, 2019). These include strategies for aggressive, sexualized, and roaming behaviors. A shorter summary of this article can be found in Table 4.

3.13 Financial Aspects and Employment

Due to the younger age of onset in FTD on average, we examined studies for reports on employment and caregivers' financial situation. In the original publication, we identified this aspect to be a topic for further future research.

Three quantitative studies included financial burden and/or employment in their caregiver assessments (Besser and Galvin, 2019; Galvin *et al.*, 2017; Kücükgüclü *et al.*, 2017). Moreover, one study analyzed the dementia-related cost of the US Medicare system in California (Chen *et al.*, 2019).

The survey by Galvin *et al.* (2017) was directed entirely at the assessment of socioeconomic burden in FTD caregivers in the US, and to compare the results with previous findings for AD caregivers. Forty-five percent of caregivers were employed, and of those, 74% worked full-time. Thirty-seven percent of caregivers were no longer employed after the patient's FTD diagnosis. Among the patients, 3.3% still worked. Lost days of work due to patient-related issues were reported by 25.6% of caregivers, and the median loss of working days due to an FTD-related cause was 7 days within the previous 4 weeks. Due to own health issues, 21.6% of caregivers lost working days. Annual household income, when compared between the time before and after diagnosis, decreased substantially from a range of $75,000-99,000 before diagnosis to $50,000-59,999 after diagnosis. These findings were found to be relatively independent from FTD subtype, caregiver relationship to the patient or patient gender.

Fifty-three percent of caregivers reported increased personal healthcare costs, 31.6% hired a paid private caregiver several times a week. Apart from regular medical, emergency medical, and care costs, 6% of caregivers reported to have faced costs associated with police interventions and 6% for a lawyer. Moreover, 9.6% of caregivers spent financial resources on legal costs, both for administrative reasons (legal guardianship), criminal cases and civil lawsuits, as well as for bankruptcy and loss of home or business (Galvin *et al.*, 2017).

The estimate of total direct cost was $47,916 p.a., being higher in older and more severely diseased patients, as well as in women, who often lived in nursing homes or assisted living. Average indirect costs were estimated at $71,737 p.a., and were higher for male patients. This total estimate of $119,654 was found to be 53% higher than overall costs for caregiving in AD, even though different methodological approaches make comparisons difficult.

From a public funding perspective, the average annual cost generated by an FTD patient in the US Medicare system in California is $14,853 (Chen *et al.*, 2019), generating a total cost volume of $11 mio./year. Even though costs for FTD were higher than for AD, it was below average for all dementia patients ($16,867 per annum). Authors argued, however, that FTD, as a young-onset dementia with specific behavioral disturbances, may require more out-of-the-pocket payments by caregivers (e.g. for residential care) that are not paid for by Medicare, thus explaining the relatively low cost for public funding found in this study (Chen *et al.*, 2019).

The survey conducted by Besser and Galvin (2019) asked participating caregivers to rate how care-associated costs were affecting their ability to make ends meet. The biggest group of respondents (46.5%) rated these costs as a “major impact”, while 30.4% rated the impact as “just a little”. A percentage of 15.6% of caregivers said caregiving costs did not influence them in making ends meet at all, while in contrast 7.5% of caregivers were not able to make ends meet at all (Besser and Galvin, 2019). Adjusted regression analyses showed that higher financial burden was associated with worse caregiver burden and higher strain associated with fulfilment of the caregiver role (Besser and Galvin, 2019).

As the only study investigating the situation outside of the US, Kücükgüclü *et al.* (2017) asked their Turkish caregiver cohort to rate whether household income was less than expenditure (FTD: 9.1% of caregivers), equaled expenditure (FTD: 61.4%), or exceeded expenditure (FTD: 29.5%). In this sample, 29.5% of FTD caregivers were working, vs. 21.1% of AD caregivers.

The qualitative aspects of caregivers working and economic situations were discussed in qualitative and case studies. Except for the abstract by Nowaskie *et al.* (2019), all of the following presented studies originated from Scandinavian countries.

Five of the 16 caregivers in the Johannessen *et al.* (2017) study were still working, and another six were still employed, but currently on sick leave, with the remaining number of caregivers being either retired or receiving disability benefits for own health conditions. This study highlighted the experiences spouses and partners made when having to balance work and their caregiving duties: Patients would sometimes try to initiate contact with their spouse at work, and caregivers would often worry about the patient when not being able to care for them. Nevertheless, caregivers stressed their wish to continue to work because it was seen as "time off" from their caregiving and a way to sustain some their own lives, at least partly. However, reduced working time resulted in decreased household income. Usually, the patient had to quit working because of their symptoms and eventually their diagnosis, which resulted in a lack of contribution of income – which was sometimes diminished even more by excessive spending on the patient's part. Moreover, loss of employment led to decreased self-esteem in patients and the need for suitable activities and surveillance during the daytime, when the patient was home alone. Obtaining financial benefits was sometimes regarded as difficult if the patient was lacking insight into their own condition, with some of them refusing to apply for financial support.

The preliminary findings from the Nowaskie *et al.* (2019) abstract highlighted "experiencing significant financial and legal challenges" as a main concern of caregivers. Some caregivers interviewed by Rasmussen *et al.* (2019) claimed to have been forced to take sick leave or go into early retirement because of the patient's condition. Moreover, some caregivers in the Tyrrell *et al.* (2019) study claimed to have lost money as a result of the patient's behavior.

3.14 Consequences of burden on caregiver health and well-being

We sought to summarize findings on the consequences burden can have on caregiver health. In the survey conducted by Galvin *et al.* (2017), 67% of caregivers reported a decline in their own health. Five out of 23 caregivers caring for patients with PNFA reported moderate to severe depression, and two reported moderate to severe anxiety (Hazelton *et al.*, 2017). Similarly, Chinese FTLD caregivers in the Liu *et al.* (2018) study reported of high levels of sleep disturbance, anxiety, and depression. Wells *et al.* (2019) showed the association between caregiver well-being, which was regarded as a construct of low depression and anxiety levels, and low negative affect, and the

caregiver's genotype in the 5-HTTLPR receptor. Even though this sample did not solely contain FTD patients, this association was moderated by the patients' empathy.
Well-being as a construct was furthermore assessed by Wu *et al.* (2018), with bvFTD caregivers reporting a lower ability to live well than other FTD caregivers (see also "Type of dementia").
The case study by Johannessen *et al.* (2017) listed caregiver's employment status, which revealed that four of the 16 caregivers were receiving disability benefits for their own health conditions. However, it was not reported more in detail how these conditions affected their caregiving or vice versa.

3.15 Relationship Quality

In the original publication, we found a change of relationship between the caregiver and the care recipient, i.e. the person with FTLD, often to be addressed as a major concern by caregivers.

Presently, we found two quantitative and five qualitative studies addressing a change in relationships.

The study by Hazelton *et al.* (2017) assessed the quality of relationship using the Intimate Bond Measure (IBM) when studying empathy in patients with PNFA and LPA (lvPPA), using the Interpersonal Reactivity Index (IRI). However, no significant differences between the groups or significant associations between empathy impairment and relationship quality were established.

Takeda *et al.* (2019) also assessed associations between patient empathy (as measured by the IRI) and patient's relationship, but by investigating relationship status and relationship-related problems. It was found that 9.80% of bvFTD patients had experienced the dissolution of a relationship, which was significantly higher than in AD, and was associated with significantly lower empathy scores as well as higher dementia severity. It is of note that in most of the cases, the dissolution of a relationship preceded the diagnosis.

Another significant difference was found for infidelity on the patient's part (bvFTD: 11.54%), while there was no infidelity in AD or svPPA patients. Again, infidelity was associated with lower empathy scores on the empathic concern and perspective taking

subscales. Moreover, bvFTD patients experienced the highest rate of estrangement from family members (2.54%).

Caregivers in qualitative studies consistently reported of a change of personality in the patient, which led to estrangement and growing distance, or were described as a gradual loss (Damianakis *et al.*, 2018, Johannessen *et al.*, 2017; Nowaskie *et al.*, 2019; Rasmussen *et al.*, 2019; Tyrrell *et al.*, 2019). Caregivers had to adapt to their new roles, which focused on providing care and assistance, instead of that as a spouse or romantic partner (Damianakis *et al.*, 2018, Johannessen *et al.*, 2017; Nowaskie *et al.*, 2019; Tyrrell *et al.*, 2019) or from a beloved child to providing care to a now emotionally cold, indifferent parent (Rasmussen *et al.*, 2019). Moreover, caregivers had to take on responsibilities their care recipient used to take care of before their disease, i.e. repairs around the house, doing household chores, and managing the household finance situation (Johannessen *et al.*, 2017).

3.16 Coping Processes

Studies that gave accounts on how caregivers coped with their burden were identified and summarized. In the second literature search in 2019, no studies quantitatively assessing caregiver coping strategies were identified. However, indirect conclusions about coping processes can be made using qualitative analysis of the identified studies. Caregivers attending interventions or support groups (Damianakis *et al.*, 2018; Jokel *et al.*, 2017; Wagner and Taylor, 2018) described the mutual understanding and a place to share their experiences as helpful. The group sessions described by Damianakis *et al.* (2018) were focused on spirituality as a way to cope with caregiving-related stress, and showed that many caregivers tried to find a deeper sense within their caregiving task. Moreover, caregivers tried to appreciate the positive moments and what they could learn from the situation, as a means to be able to support others going through the same difficulties (Damianakis *et al.*, 2018).

Tyrrell *et al.* (2019) described how caregivers found brain imaging of the patient as a visual correlate for the neurodegenerative process causing the disturbing behavior to be reassuring of the fact that the patient was not responsible for their condition. Interestingly, the abstract by Zahir *et al.* (2017) assessed whether these types of thoughts might lead to objectification of patients (i.e. “They can’t control the way they

act", "They don't understand what's important or unimportant") and how this attitude might impact the relationship between caregiver and patient. Their preliminary results showed that the newly developed latent variable of an "objectifying attitude" negatively influences relationship closeness and mediates the association between disease severity and caregiver burden. Therefore, objectifying attitudes do not protect the caregiver from burden, but rather worsen the relationship to the patient. These findings might thus be useful in order to identify objectifying attituded and create suitable interventions. (Zahir *et al.*, 2017).

3.17 Support and Interventions for Caregivers of Individuals with FTLD

We examined all publications for accounts they gave about support for caregivers. Apart from Galvin *et al.* (2017), that reported 31.6% of caregivers to have hired a paid caregiver, none of the qualitative studies explicitly reported about help for caregivers.

The caregivers in the Bryant and Miller (2018) case study remarked that navigating the healthcare system to find appropriate care services was frustrating, as they had encountered different care settings such as a geriatric inpatient unit, mental health inpatient unit, memory inpatient unit, and nursing home, but none of them being able to find or provide long-term care for the patient. A similar concern was raised in the qualitative study by Tyrrell *et al.* (2019), explaining that patients were reluctant to accept help, and that social care planners were often unaware of the specific challenges associated with care for an FTLD patient. Rasmussen *et al.* (2019) supported the problem of some patients not accepting help, either from their family or from professional caregivers, as some patients "left the house before health services came to visit" or were aggressive towards care providers.

Preliminary data from the Nowaskie *et al.* (2019) identified two conflicting themes: One was the difficulty of finding appropriate and knowledgeable care providers, the other one was finding support in disease-specific programs.

Johannessen *et al.* (2017) assessed support for both caregivers and patients in their 16 caregiver/patient dyad cohort. Fourteen caregivers received support from the hospital they visited for FTLD follow-ups, three caregivers received support from their municipality. Nine caregivers attended support groups. Reflections of caregivers in a video-conferenced support group are presented in the qualitative study by Damianakis

et al. (2018). They outlined recurring themes from three AD caregiver groups and two FTD caregiver groups. Mutual understanding and exchanges of experiences – both of a practical nature, when discussing caregiving challenges, as well as emotional struggles – were perceived as helpful by the participants.

The abstract of the intervention by Wagner and Taylor (2018) underlined this perceived helpfulness of support groups, and furthermore supports the need for educated doctors and other experienced healthcare professionals. A community event in order to raise awareness about FTD and to exchange experiences and resources was organized.

The intervention by Spalding-Wilson *et al.* (2018) included patients with FTD and their caregivers among other dementia patient/caregiver dyads, mostly AD. The intervention consisted of a session including psychoeducation about dementia, self-care for caregivers, communication with PwD (which was practiced in workshops with the dementia patient), emotion recognition, and management of difficult behaviors. Compared to a control group that did not attend the session, perceived stress was the only parameter to be positively influenced by this intervention, whereas no significant differences in depression, anxiety, self-efficacy, helplessness, and caregiver burden were found. However, caregivers perceived the intervention as helpful and continued to use their newly acquired skills, and an FTD caregiver pointed out the need for a specialized intervention of this kind directed specifically at FTD caregivers and patients (Spalding-Wilson *et al.*, 2018).

The two other interventions were aimed at individuals with aphasia. Jokel *et al.* (2017) included patients with PPA and their spousal caregivers into ten weekly 2h group sessions, where patients engaged in general discussions and language skill training in the first hour, while caregivers worked on communication skills and shared experiences. The second hour was spent jointly in educational sessions, and two sessions practicing the newly acquired skills. The score of successfully conveyed messages increased from the first to the second practice session, and caregivers reported increased levels of preparedness, knowledge about PPA, awareness of progression, management of psychological issues, communication challenges, daily problem solving, and talking about the spouse's PPA, when compared to before the intervention. No such changes were observed in the control group that did not attend the intervention. Moreover, the intervention was the first interactive source of

information for most caregivers, who usually obtained information on the internet. Qualitatively, caregivers rated the received information and mutual understanding in the group as helpful and would have liked to have more practice time and to continue the program (Jokel *et al.*, 2017).

Another intervention mainly aimed at persons with aphasia, but also their caregivers, was provided in an aphasia center and did not specify the etiology of their participants' aphasia (Armour *et al.*, 2019). Patients attended one or up to three eleven-week programs with group sessions using the life participation approach. Caregivers showed a significant reduction in burden after completion of the program, and the reduction sustained after each eleven-week session.

4. Discussion

The analysis of 107 publications in total yields a comprehensive overview of the current state of research in FTLD caregiver burden. Apart from identifying and summarizing aspects of caregiver burden that have been studied relatively extensively thus far, this scoping review also identifies implications for future points of interests in research.

4.1 Current Fields of Interest in Research (Group 2)

Analyzing and grouping the new findings in some aspects of caregiver burden enabled us to identify research areas where most contributions have been made in the past two years.

In the original publication, we pointed out financial burden and the caregiver's work situation as a field for future research, which is the topic that has gained the highest increase in new data during the follow-up period. We identified three new quantitative studies and one cost analysis that assessed the financial aspect of care for persons with FTLD. Moreover, four qualitative interview studies added the caregiver's perspectives on their financial situation. Even though private expenses related to caregiving were estimated to be significantly higher in FTLD than in AD, caregivers were generally able to make up for that cost. Nevertheless, the problem of high out-of-pocket costs, mostly for private care and monitoring, was addressed, and studies should assess how their country-specific healthcare system is currently covering costs related to FTLD caregiving.

While many studies included in both reviews assessed caregiver burden and distress factors, only a few studies in the original literature search examined the coping strategies caregivers use. The 2019 follow-up was able to add qualitative findings on coping strategies. Some of those findings are direct results of intervention studies, since caregivers used support groups and educational meetings as a way of coping. Another interesting topic that could be newly identified were the preliminary findings on the adverse effects on caregivers that exhibited objectifying attitudes towards PwD. Objectifying attitudes can thus be assumed to constitute a destructive coping mechanism, of which only few have been described to date in the field of caregiving in FTLD.

In consistence with previous findings, our results confirmed that caring for a patient with more severe dementia is more demanding for caregivers and thus associated with higher burden. Additionally, newly identified studies focused on three specific problems caregivers caring for a person with FTLD have to manage: sleep, motivational and mealtime disturbances.

However, the process of study selection in these educational articles is often not addressed, and the quality of evidence regarding these strategies can thus not be assessed since they are often based on the author's own professional experience.

The role change for caregivers from an intimate partner or loving family member into a care provider was repeatedly pointed out as burdensome. Moreover, numerous studies presented a deterioration of the relationship between patient and caregiver as an important factor of distress. In FTLD, this aspect of caregiving may be particularly burdensome due to the averagely younger age of both the PwD and their primary caregivers, with the role shift occurring at a stage of life where adults are expected to - aside from being a part of the workforce - fulfil roles as romantic partners, parents or as caregivers for older generations (Svanberg *et al.*, 2011)

4.2 Understudied Components of Caregiver Burden in FTLD (Group 3)

In contrast to the elements of caregiver burden discussed previously, we found other areas of research to still be understudied or to be standing at the very beginning of becoming a research interest.

Research about child caregivers in FTLD was one of those areas lacking reports. Even though children of individuals with FTLD were included in the studies, no publication we identified for the follow-up research focused on this topic or added relevant new findings. Knowledge about child caregivers in FTLD is still very limited. Specific challenges for caregiving children were previously addressed elsewhere, e.g. for children administering medication to their parents (Nickels *et al.,* 2018). Safety concerns that arise from this responsibility may also apply to FTLD child caregivers. Other interesting aspects lie in the coping strategies those young caregivers use with regard to the problematic behavior some patients with FTLD exhibit and that typically differ from other forms of YOD, e.g. apathy, emotional coldness, or aggression, among

others. Future research should focus on this particular group of affected relatives or caregivers and their situation.

Only a small number of studies, and none of those addressing FTLD specifically, have assessed the effect of caregiver burden on quality of care. We argued in the 2017 publication that high burden is not only distressing for the caregivers themselves, but may also result in inappropriate care provision to the PwD as a result of excessive demand on the caregiver. An association between elevated caregiver burden and elder abuse was established previously (Johannessen and LoGiudice, 2013). More research in this field would help to tackle the most problematic aspects of the patient-caregiver relationship in a condition as challenging as FTLD. It is conceivable that behavioral disturbances including coldness or aggression on the PwD's side could provoke negative reactions from the caregiver. Along those lines, research on coping mechanisms should focus on the identification of destructive coping mechanisms in caregivers as a possible target for future interventions.

Additionally, we established the lack of awareness about FTLD to be a key factor contributing to caregiver burden. This finding was strongly supported by the experiences that family caregivers described in qualitative studies. The abstract by Wagner *et al.* (2018) was the only publication to describe attempts to raise public awareness through an event about FTLD. It is nevertheless necessary to point out the importance of knowledgeable health professionals, foremost doctors and nurse practitioners, in order to obtain a correct diagnosis as early as possible. Previous research indicated that the time to diagnosis in YOD is on average 4.5 years from symptom onset, which was found to be 1.6 years longer than for older onset PwD (van Vliet *et al.*, 2013). These numbers are coherent with the duration of diagnostic delay as reported by caregivers in qualitative interviews.

With regard to the origin of the studies included in both reviews, we found that the vast majority of studies originates from Western industrialized countries. Since the percentage of cost associated to informal care is even higher in low- and middle-income countries (WHO, 2015), it can be hypothesized that care provided by family, friends and other members of the community plays an even more important part in developing and newly industrialized countries than it does in Western-industrialized countries. Thus, there is likely to be a large population of caregivers that has been only

scarcely studied so far. The access to professional healthcare in this group of caregivers is mostly unknown. Apart from these caregivers' levels of burden, investigating their country- or community-specific support, e.g. through the healthcare system, social benefits or welfare, is an additional aspect warranting further investigation. Our review does feature insights on country-specific support structures, but exclusively from Western-industrialized societies such as the US or Scandinavia.

An entirely new point of interest can be found in the rising amount of research of hereditary causes of FTLD and its impact on caregivers, often family members of the person with FTLD. The LEFFTDS cohort studies the three main genetic mutations causing FTD spectrum dementias – C9orf72, GRN and MAPT (Boeve, 2015). Factors that have an impact of genetic penetrance of these mutations and thus their influence on the age of onset are not yet fully understood (Greaves and Rohrer, 2019). The risk of hereditary dementia and its probable affection of children and other offspring could be assumed to be another factor causing distress in caregivers. The preliminary data from this cohort does however not specify whether the knowledge about hereditability itself is being investigated as a potential cause of burden.

The influence of the hereditary component in FTD on caregiver burden should be studied both quantitatively and qualitatively to assess concrete concerns especially children and child caregivers of FTD patients have. Aside from psychological distress, a confirmed genetic mutation in the family history might disadvantage relatives of persons with FTLD when trying to obtain insurance or employment, a problem that has already been observed for genetic testing in other hereditary diseases (Bélisle-Pipon *et al.*, 2019).

4.3 Intervention Research as a Key Interest of Future Investigation (Group 3)

The identification of any interventions for caregivers or for PwD with the effect of decreased burden for those caring for the person with FTD played a major part in both reviews, and the lack of high-quality evidence can still be regarded as a predominant need for future research.

The most efficacious interventions to alleviate burden were targeted at the caregivers themselves. Support groups were almost universally considered to be helpful. The opportunity to share experiences and reflections with others in the same situation, as

well as practical support, were the main aspects caregivers appreciated about those groups. Some of those studies were held using video-conferencing software, which makes this form of intervention a relatively easily accessible one, since it can be utilized by caregivers in remote areas and without the need to leave their homes.

Interventions that were aimed at patients were either investigating pharmacological treatment and examining caregiver burden as a secondary endpoint, or sought to find non-pharmacological strategies to alleviate symptoms exhibited by the PwD. No RCT for the latter type of interventions could be identified. Interventions aimed at patients with types of PPA were more common and were aimed at improving communication skills. It must be of note that patients with aphasia are more likely to have insight into their language impairment and thus are more willing to participate in activities that could ameliorate their symptoms. Since patients with bvFTD often do not acknowledge any behavioral problems, a modification of their environment and creating activities that are appropriate for the PwD often is the only way for caregivers to prevent hazardous situations and gain more time for themselves. Articles providing an overview of management strategies like Mulkey (2019) allow care providers, possibly including informal caregivers, to obtain an overview about the disease and suggestions for dealing with erratic behavior.

Most of the time, the management strategies presented in the articles remain to be reports of professionals from their own clinical experience without further validation.

Even though this review has shown that disease-modifying strategies are less effective in decreasing caregiver burden than interventions directly aimed at the caregiver, numerous mostly experimental therapy options have been proposed to alleviate symptom burden in patients with FTLD, but did not yet investigate the impact on caregiver burden. To give one example, the administration of oxytocin showed short-term improvement of behavioral and neuropsychiatric symptoms, but due to lack of data this cannot be recommended to regular use yet (Trampi *et al.*, 2017). Moreover, the effect of electroconvulsive therapy (ECT) on agitated and aggressive behavior in PwD was assessed in some studies, including persons with FTLD. However, even though ECT might be effective in these behavioral disturbances, RCTs are still lacking (van den Berg *et al.*, 2017).

When assessing these new options, not only patient-related outcomes such as dementia severity or ADL performance should be taken into account, but caregiver burden should be considered and assessed as a secondary endpoint in those studies. Since patients might probably not subjectively notice changes in their behavior, an ameliorating effect on caregiver burden would provide a practical marker to assess treatment effectiveness in everyday life. It however needs to be considered that patient-directed pharmacological or physical interventions are difficult to conduct from an ethical perspective, since patients often lack insight into the necessity of treatment and thus might be unable to provide informed consent, to participate in treatment or to adhere to treatment plans.

4.4 Strengths and Limitations

The present qualitative analysis of a total of 107 articles in two literature searches provides a comprehensive overview of the current state of available knowledge on caregiver burden in FTLD. Using the methodology of a scoping review, we were able to consider a wide array of different sources, originating from different professional backgrounds including medical, psychological, nursing and biostatistical sciences. Both the search process and the reporting were conducted in adherence to the PRISMA checklist for scoping reviews. Moreover, having established key topics of interest in the analyzed publications enabled us to develop a model of different aspects of caregiver burden in FTLD at the current state of research. This model in turn could be used as a reference for the formulation of future research questions, since there remain key aspects of caregiver burden specific to FTLD that have only constituted side-notes until now. The format of a scoping review enabled us to identify these latter aspects specifically, since the risk of preemptively excluding minor, but relevant contributions is relatively low compared to a more circumscribed type of review (Tricco *et al.*, 2016).

However, several limitations regarding this review have to be considered. Our search algorithm might have not identified eligible studies if differing nomenclature was used. It is noteworthy that concepts such as caregiver burden, strain, or distress are sometimes being used synonymously, while at other times being used to describe distinct aspects of caregiver problems. The same applies for the inconsistent use of nomenclature to label the underlying diseases, especially in the field of primary

progressive aphasias. However, we are confident that our search keywords were selected with sufficient scope to approach the topic.

Only publications in English or German were included, and other relevant contributions might have thus been missed, altogether limiting the extent to which our results can be generalized and compared. Possibly, this might also explain the small number of studies from non-Western Industrialized Countries. Moreover, we did not make limitations whatsoever regarding study type, nor did we systematically assess study quality, in accordance with scoping review guidelines (Tricco *et al.*, 2016). Therefore, no account of study quality or quality of evidence can be given and studies notably vary in scope, ranging from abstracts reporting preliminary data to meta-analyses. However, the lack of RCTs in this field of research furthermore reduces validity. Next steps into a more detailed and therefore valid synopsis of knowledge about caregiver burden could consist of systematic reviews, tackling specific aspects of caregiver burden or distinct sub-groups of caregivers and/or PwD.

In both literature searches, we found a relatively big disparity in methodology. In total, eight different tools were used to assess caregiver burden, and different cut-offs were applied for the same tool (e.g. ZBI), rendering reliable comparisons problematic. This aspect again could be overcome in a review or meta-analysis of a narrower scope.

4.5 Outlook

Having identified 69 publications in 2017 for the original publication, and 38 more articles for the follow-up review in 2019, this increase in publications by more than 50% shows the vast importance of caregiver burden in FTLD for research and is likely to continue to do so in the future. Study results with a focus on burdened caregiver groups and interventions aiming at them are expected to find implementation in a context where findings can be applied by healthcare providers in everyday practice. The extensive knowledge about caregiver burden, its causes and characteristics is crucial in order to identify those at the highest risk of adverse effects both on mental and

physical well-being, which in turn is very likely to exert a notable influence on the care situation of persons with FTLD.

5. Summary

Frontotemporal lobar degeneration (FTLD) is likely to be the second-most common cause of dementia in individuals under 65 years of age. Pathognomonic changes in personality, behavior and motivation are known to lead to high caregiver stress and burden, with little support being available. The aim of this work is to present the current state of knowledge on the characteristics, challenges and unmet needs of caregivers as well as on possible interventions.

Two scoping reviews on caregiver burden using the PRISMA checklist for scoping reviews were conducted using PubMed, Web of Science and ScienceDirect in April 2017 and November 2019, respectively. A total of 107 articles were considered eligible and were analyzed qualitatively and summarized.

Our results show that caregivers of patients with FTLD are often female, spouses of the PwD, younger in age, have underage children and provide care at home. Behavioral and motivational disturbances in the PwD are perceived to be the most burdensome aspects of caregiving. Those caring for an individual with the bvFTD subtype thus report higher levels of burden than caregivers of an individual with a form of PPA. With rising dementia severity, caregivers report higher levels of burden. Many caregivers experience a decline in their own physical and mental health as well as a significant financial burden resulting from care duties. The deterioration of the relationship between the PwD and their caregivers is a main burdensome aspect. Only few interventions were conducted so far, and none of those that were identified were designed as an RCT. The most efficacious interventions were those aimed directly at caregivers, whereas interventions aiming at the amelioration of symptoms in the PwD showed little effect.

Further research should reproduce and validate efficacious interventions and establish new interventional approaches. Another focus should be set on the situation of underage children of individuals with FTLD and relatives of a person with hereditary FTD. More research from non-Western countries is needed in order to identify culture-specific factors of caregiver burden. Along those lines, support structures for FTLD caregivers should be assessed on a local basis and extended accordingly. So far, no study has assessed the relationship between caregiver burden and possible consequences for the quality of care provided to the PwD in FTLD specifically. Awareness both in the wider population and among healthcare professionals is an urgent need for the future since FTLD is often misdiagnosed, leading to a delay in obtaining the correct diagnosis and access to suitable support.

6. Literature

1. **Armour, M., Brady, S., Sayyad, A., and Krieger, R.** (2019). Self-Reported Quality of Life Outcomes in Aphasia Using Life Participation Approach Values. 1-Year Outcomes. Archives of Rehabilitation Research and Clinical Translation, 100025. Available from: http://www.sciencedirect.com/science/article/pii/S2590109519300278 doi:10.1016/j.arrct.2019.100025.
2. **Bartochowski, Z., Gatla, S., Khoury, R., Al-Dahhak, R., and Grossberg, G. T.** (2018). Empathy changes in neurocognitive disorders. A review. Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists, 30 (3), 220–232.
3. **Baumann, L., Klosch, M., Greger, M., Dieplinger, A., and Lorenzl, S.** (2019). Amyotrophic Lateral Sclerosis - Challenges of Family Caregivers. Fortschritte der Neurologie-Psychiatrie, 87 (9), 476–482 doi:10.1055/a-0934-6163.
4. **Bédard, M., Molloy, D. W., Squire, L., Dubois, S., Lever, J. A., and O'Donnell, M.** (2001). The Zarit Burden Interview. A new short version and screening version. The Gerontologist, 41 (5), 652–657 doi:10.1093/geront/41.5.652.
5. **Bélisle-Pipon, J.-C., Vayena, E., Green, R. C., and Cohen, I. G.** (2019). Genetic testing, insurance discrimination and medical research. What the United States can learn from peer countries. Nature medicine, 25 (8), 1198–1204 doi:10.1038/s41591-019-0534-z.
6. **Benbrika, S., Desgranges, B., Eustache, F., and Viader, F.** (2019). Cognitive, Emotional and Psychological Manifestations in Amyotrophic Lateral Sclerosis at Baseline and Overtime. A Review. FRONTIERS IN NEUROSCIENCE, 13 doi:10.3389/fnins.2019.00951.
7. **Besser, L. M., and Galvin, J. E.** (2019). Perceived burden among caregivers of patients with frontotemporal degeneration in the United States. International psychogeriatrics, 31 (8), 1191–1201 doi:10.1017/S104161021800159X.
8. **Bock, M., Duong, Y.-N., Kim, A., Allen, I., Murphy, J., and Lomen-Hoerth, C.** (2017). Progression and effect of cognitive-behavioral changes in patients with amyotrophic lateral sclerosis. Neurology. Clinical practice, 7 (6), 488–498 doi:10.1212/CPJ.0000000000000397.
9. **Boeve, B.** (2015). Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects [online]. Available from: https://ClinicalTrials.gov/show/NCT02372773 [Accessed 9 February 2020].
10. **Bryant, R., and Miller, C.** (2018). Challenges of a frontotemporal dementia patient. Geriatric nursing (New York, N.Y.), 39 (6), 716–718. Available from: http://www.sciencedirect.com/science/article/pii/S019745721830555X doi:10.1016/j.gerinurse.2018.10.009.
11. **Caga, J.*, et al.*** (2018). The burden of apathy for caregivers of patients with amyotrophic lateral sclerosis. Amyotrophic lateral sclerosis & frontotemporal degeneration, 19 (7-8), 599–605 doi:10.1080/21678421.2018.1497659.
12. **Caga, J., Hsieh, S., Lillo, P., Dudley, K., and Mioshi, E.** (2019). The Impact of Cognitive and Behavioral Symptoms on ALS Patients and Their Caregivers. Frontiers in neurology, 10, 192 doi:10.3389/fneur.2019.00192.
13. **Chen, Y.*, et al.*** (2019). The costs of dementia subtypes to California Medicare fee-for-service, 2015. Alzheimer's & Dementia, 15 (7), 899–906. Available from: http://www.sciencedirect.com/science/article/pii/S1552526019300901 doi:10.1016/j.jalz.2019.03.015.
14. **Clyburn, L. D., Stones, M. J., Hadjistavropoulos, T., and Tuokko, H.** (2000). Predicting caregiver burden and depression in Alzheimer's disease. The journals of

gerontology. Series B, Psychological sciences and social sciences, 55 (1), S2-13 doi:10.1093/geronb/55.1.s2.
15. **Cummings, J. L.** (1997). The Neuropsychiatric Inventory. Assessing psychopathology in dementia patients. Neurology, 48 (5 Suppl 6), S10-6 doi:10.1212/wnl.48.5_suppl_6.10s.
16. **Damianakis, T., Wilson, K., and Marziali, E.** (2018). Family caregiver support groups. Spiritual reflections' impact on stress management. Aging & mental health, 22 (1), 70–76 doi:10.1080/13607863.2016.1231169.
17. **Devineni, B., and Onyike, C. U.** (2015). Young-onset dementia epidemiology applied to neuropsychiatry practice. The Psychiatric clinics of North America, 38 (2), 233–248 doi:10.1016/j.psc.2015.02.003.
18. **Galvin, J. E., Howard, D. H., Denny, S. S., Dickinson, S., and Tatton, N.** (2017). The social and economic burden of frontotemporal degeneration. Neurology, 89 (20), 2049–2056 doi:10.1212/WNL.0000000000004614.
19. **Gorno-Tempini, M. L.*, et al.*** (2011). Classification of primary progressive aphasia and its variants. Neurology, 76 (11), 1006–1014 doi:10.1212/WNL.0b013e31821103e6.
20. **Greaves, C. V., and Rohrer, J. D.** (2019). An update on genetic frontotemporal dementia. Journal of neurology, 266 (8), 2075–2086 doi:10.1007/s00415-019-09363-4.
21. **Hazelton, J. L., Irish, M., Hodges, J. R., Piguet, O., and Kumfor, F.** (2017). Cognitive and Affective Empathy Disruption in Non-Fluent Primary Progressive Aphasia Syndromes. Brain Impairment, 18 (1), 117–129 doi:10.1017/BrImp.2016.21.
22. **Hogan, D. B.*, et al.*** (2016). The Prevalence and Incidence of Frontotemporal Dementia. A Systematic Review. Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques, 43 (S1), S96-S109 doi:10.1017/cjn.2016.25.
23. **Hughes, S. R.*, et al.*** (2017). Caregiver burden in familial frontotemporal dementia subjects. Preliminary data in the LEFFTDS cojort. Alzheimer's & Dementia, 13 (7, Supplement), P722 - P723. Available from: http://www.sciencedirect.com/science/article/pii/S1552526017311676 doi:10.1016/j.jalz.2017.06.934.
24. **Hvidsten, L., Engedal, K., Selbaek, G., Wyller, T. B., Benth, J. S., and Kersten, H.** (2019). Quality of life of family carers of persons with young-onset dementia. A Nordic two-year observational multicenter study. PLOS ONE, 14 (7) doi:10.1371/journal.pone.0219859.
25. **Jessen, F. *et al.*** (2017). S3-Leitlinie Demenzen. Berlin, Heidelberg: Springer Berlin Heidelberg.
26. **Johannesen, M., and LoGiudice, D.** (2013). Elder abuse. A systematic review of risk factors in community-dwelling elders. Age and ageing, 42 (3), 292–298 doi:10.1093/ageing/afs195.
27. **Johannessen, A., Helvik, A.-S., Engedal, K., and Thorsen, K.** (2017). Experiences and needs of spouses of persons with young-onset frontotemporal lobe dementia during the progression of the disease. Scandinavian journal of caring sciences, 31 (4), 779–788 doi:10.1111/scs.12397.
28. **Jokel, R.*, et al.*** (2017). Group intervention for individuals with primary progressive aphasia and their spouses. Who comes first? Journal of Communication Disorders, 66, 51–64. Available from: http://www.sciencedirect.com/science/article/pii/S0021992417300746 doi:10.1016/j.jcomdis.2017.04.002.

29. **Karnatz, T.*, et al.*** (2019). Burden of caregivers of patients with frontotemporal lobar degeneration - a scoping review. International psychogeriatrics, 1–21 doi:10.1017/S1041610219000176.
30. **Kipps, C. M., Hodges, J. R., and Hornberger, M.** (2010). Nonprogressive behavioural frontotemporal dementia. Recent developments and clinical implications of the 'bvFTD phenocopy syndrome'. Current opinion in neurology, 23 (6), 628–632 doi:10.1097/WCO.0b013e3283404309.
31. **Koyama, A.*, et al.*** (2018). Caregiver Burden in Semantic Dementia with Right- and Left-Sided Predominant Cerebral Atrophy and in Behavioral-Variant Frontotemporal Dementia. Dementia and geriatric cognitive disorders extra, 8 (1), 128–137 doi:10.1159/000487851.
32. **Kucukguclu, O., Soylemez, B. A., Yener, G., Barutcu, C. D., and Akyol, M. A.** (2017). Examining Factors Affecting Caregiver Burden. A Comparison of Frontotemporal Dementia and Alzheimer's Disease. American journal of Alzheimer's disease and other dementias, 32 (4), 200–206 doi:10.1177/1533317517703479.
33. **Lewis, C., Walterfang, M., Velakoulis, D., and Vogel, A. P.** (2018). A Review. Mealtime Difficulties following Frontotemporal Lobar Degeneration. Dementia and geriatric cognitive disorders, 46 (5-6), 285–297 doi:10.1159/000494210.
34. **Linse, K., Aust, E., Joos, M., and Hermann, A.** (2018). Communication Matters-Pitfalls and Promise of Hightech Communication Devices in Palliative Care of Severely Physically Disabled Patients With Amyotrophic Lateral Sclerosis. Frontiers in neurology, 9, 603 doi:10.3389/fneur.2018.00603.
35. **Liu, S.*, et al.*** (2018). Caregiver burden, sleep quality, depression, and anxiety in dementia caregivers. A comparison of frontotemporal lobar degeneration, dementia with Lewy bodies, and Alzheimer's disease. International psychogeriatrics, 30 (8), 1131–1138 doi:10.1017/S1041610217002630.
36. **Mukherjee, A., Biswas, A., Roy, A., Biswas, S., Gangopadhyay, G., and Das, S. K.** (2017). Behavioural and Psychological Symptoms of Dementia. Correlates and Impact on Caregiver Distress. Dementia and geriatric cognitive disorders extra, 7 (3), 354–365 doi:10.1159/000481568.
37. **Mulkey, M.** (2019). Understanding Frontotemporal Disease Progression and Management Strategies. Nursing Clinics of North America, 54 (3), 437–448. Available from: http://www.sciencedirect.com/science/article/pii/S0029646519300337 doi:10.1016/j.cnur.2019.04.011.
38. **Nickels, M., Siskowski, C., Lebron, C. N., and Belkowitz, J.** (2018). Medication administration by caregiving youth. An inside look at how adolescents manage medications for family members. Journal of Adolescence, 69 (1), 33–43 doi:10.1016/j.adolescence.2018.09.001.
39. **Nowaskie, D., Austrom, M., and Morhardt, D.** (2019). Understanding the challenges, needs, and qualities of frontotemporal dementia family caregivers. The American Journal of Geriatric Psychiatry, 27 (3, Supplement), S139 - S140. Available from: http://www.sciencedirect.com/science/article/pii/S1064748119300594 doi:10.1016/j.jagp.2019.01.047.
40. **Nunnemann, S., Kurz, A., Leucht, S., and Diehl-Schmid, J.** (2012). Caregivers of patients with frontotemporal lobar degeneration. A review of burden, problems, needs, and interventions. International psychogeriatrics, 24 (9), 1368–1386 doi:10.1017/S104161021200035X.
41. **Olney, N. T., Spina, S., and Miller, B. L.** (2017). Frontotemporal Dementia. Neurologic clinics, 35 (2), 339–374 doi:10.1016/j.ncl.2017.01.008.
42. **Rascovsky, K.*, et al.*** (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain, 134 (9), 2456–2477 doi:10.1093/brain/awr179.

43. **Rasmussen, H., Hellzen, O., Stordal, E., and Enmarker, I.** (2019). Family caregivers experiences of the pre-diagnostic stage in frontotemporal dementia. Geriatric nursing (New York, N.Y.), 40 (3), 246–251 doi:10.1016/j.gerinurse.2018.10.006.
44. **Ratti, E.*, et al.*** (2017). A study to model rates of change on neuropsychological test measures in subjects diagnosed with behavioral variant frontotemporal dementia and healthy subjects. Alzheimer's & Dementia, 13 (7, Supplement), P1259 - P1260. Available from: http://www.sciencedirect.com/science/article/pii/S1552526017321155 doi:10.1016/j.jalz.2017.06.1880.
45. **Sani, T. P.*, et al.*** (2019). Sleep symptoms in syndromes of frontotemporal dementia and Alzheimer's disease. A proof-of-principle behavioural study. eNeurologicalSci, 100212. Available from: http://www.sciencedirect.com/science/article/pii/S240565021930036X doi:10.1016/j.ensci.2019.100212.
46. **Southi, N., Honan, C. A., Hodges, J. R., Piguet, O., and Kumfor, F.** (2019). Reduced capacity for empathy in corticobasal syndrome and its impact on carer burden. INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY, 34 (3), 497–503 doi:10.1002/gps.5045.
47. **Spalding-Wilson, K. N., Guzmán-Vélez, E., Angelica, J., Wiggs, K., Savransky, A., and Tranel, D.** (2018). A novel two-day intervention reduces stress in caregivers of persons with dementia. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 4, 450–460. Available from: http://www.sciencedirect.com/science/article/pii/S2352873718300465 doi:10.1016/j.trci.2018.08.004.
48. **Strong, M. J.*, et al.*** (2017). Amyotrophic lateral sclerosis - frontotemporal spectrum disorder (ALS-FTSD). Revised diagnostic criteria. Amyotrophic lateral sclerosis & frontotemporal degeneration, 18 (3-4), 153–174 doi:10.1080/21678421.2016.1267768.
49. **Svanberg, E., Spector, A., and Stott, J.** (2011). The impact of young onset dementia on the family. A literature review. International psychogeriatrics, 23 (3), 356–371 doi:10.1017/S1041610210001353.
50. **Takeda, A., Sturm, V. E., Rankin, K. P., Ketelle, R., Miller, B. L., and Perry, D. C.** (2019). Relationship Turmoil and Emotional Empathy in Frontotemporal Dementia. Alzheimer Disease and Associated Disorders, 33 (3), 260–265 doi:10.1097/WAD.0000000000000317.
51. **Tampi, R. R., Maksimowski, M., Ahmed, M., and Tampi, D. J.** (2017). Oxytocin for frontotemporal dementia. A systematic review. Therapeutic advances in psychopharmacology, 7 (1), 48–53 doi:10.1177/2045125316672574.
52. **Tricco, A. C.*, et al.*** (2016). A scoping review on the conduct and reporting of scoping reviews. BMC medical research methodology, 16, 15 doi:10.1186/s12874-016-0116-4.
53. **Tricco, A. C.*, et al.*** (2018). PRISMA Extension for Scoping Reviews (PRISMA-ScR). Checklist and Explanation. Annals of internal medicine, 169 (7), 467–473 doi:10.7326/M18-0850.
54. **Tyrrell, M., Fossum, B., Skovdahl, K., Religa, D., and Hilleras, P.** (2019). Living with a well-known stranger. Voices of family members to older persons with frontotemporal dementia. INTERNATIONAL JOURNAL OF OLDER PEOPLE NURSING doi:10.1111/opn.12264.
55. **van den Berg, J. F., Kruithof, H. C., Kok, R. M., Verwijk, E., and Spaans, H.-P.** (2018). Electroconvulsive Therapy for Agitation and Aggression in Dementia. A Systematic Review. The American journal of geriatric psychiatry : official journal of the

American Association for Geriatric Psychiatry, 26 (4), 419–434 doi:10.1016/j.jagp.2017.09.023.

56. **van der Lee, J., Bakker, T. J. E. M., Duivenvoorden, H. J., and Dröes, R.-M.** (2014). Multivariate models of subjective caregiver burden in dementia. A systematic review. Ageing research reviews, 15, 76–93 doi:10.1016/j.arr.2014.03.003.
57. **van IJssel, J. C. L. D.-v. d.*, et al.*** (2018). Nursing Staff Distress Associated With Neuropsychiatric Symptoms in Young-Onset Dementia and Late-Onset Dementia. Journal of the American Medical Directors Association, 19 (7), 627–632. Available from: http://www.sciencedirect.com/science/article/pii/S1525861017305789 doi:10.1016/j.jamda.2017.10.004.
58. **van Vliet, D.*, et al.*** (2013). Time to diagnosis in young-onset dementia as compared with late-onset dementia. Psychological medicine, 43 (2), 423–432 doi:10.1017/S0033291712001122.
59. **Wagner, E. B., and Taylor, W. D.** (2018). Poster Number. EI 38 - Community Awareness Model for Frontotemporal Dementia: Improving Recognition of Illness and Amplifying Support for Caregivers. The American Journal of Geriatric Psychiatry, 26 (3, Supplement), S105 - S106. Available from: http://www.sciencedirect.com/science/article/pii/S1064748118301313 doi:10.1016/j.jagp.2018.01.129.
60. **Wells, J. L.*, et al.*** (2019). Neurodegenerative Disease Caregivers' 5-HTTLPR Genotype Moderates the Effect of Patients' Empathic Accuracy Deficits on Caregivers' Well-Being. The American Journal of Geriatric Psychiatry, 27 (10), 1046–1056. Available from: http://www.sciencedirect.com/science/article/pii/S1064748119303434 doi:10.1016/j.jagp.2019.04.009.
61. **WHO** (2015). The epidemiology and impact of dementia: current state and future trends [online]. World Health Organizaton. Available from: www.who.int/mental_health/neurology/dementia/dementia_thematicbrief_epidemiology.pdf [Accessed 11 February 2020].
62. **Wit, J.** de*, et al.* (2018). Caregiver burden in amyotrophic lateral sclerosis. A systematic review. PALLIATIVE MEDICINE, 32 (1), 231–245 doi:10.1177/0269216317709965.
63. **Wood, S.*, et al.*** (2000). The use of the neuropsychiatric inventory in nursing home residents. Characterization and measurement. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry, 8 (1), 75–83 doi:10.1097/00019442-200002000-00010.
64. **Wu, Y.-T.*, et al.*** (2018). Dementia subtype and living well. Results from the Improving the experience of Dementia and Enhancing Active Life (IDEAL) study. BMC MEDICINE, 16 doi:10.1186/s12916-018-1135-2.
65. **Zahir, A., Rojas-Martinez, J., and Chiong, W.** (2017). Caregiver objectifying attitudes toward dementia patients. Consequences for caregiver strain and relationship closeness. Alzheimer's & Dementia, 13 (7, Supplement), P835. Available from: http://www.sciencedirect.com/science/article/pii/S1552526017313997 doi:10.1016/j.jalz.2017.06.1166.
66. **Zarit, S. H., Reever, K. E., and Bach-Peterson, J.** (1980). Relatives of the impaired elderly. Correlates of feelings of burden. The Gerontologist, 20 (6), 649–655 doi:10.1093/geront/20.6.649.

7. Table 1 – Exemplary summary table

Reference	Besser, Lilah M.; Galvin, James E. (2019): Perceived burden among caregivers of patients with frontotemporal degeneration in the United States. In *International psychogeriatrics* 31 (8), pp. 1191–1201. DOI: 10.1017/S104161021800159X.
Type	Cross-sectional cohort study
Location/Country	USA
Aim/subject	To assess self-reported burden in caregivers of patients with FTD in the US
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	Recruitment via Association for Frontotemporal Degeneration – e-mail newsletter, social media, website n=675 (70.5% out of n=956 who initiated survey) completed online survey with full ZBI data diagnoses: n=360 (53.7%) bvFTD, n=145 (21.6%) PPA, n=52 (7.8%) ALS, n=32 (4.8%) PSP or CBS, n=82 (12.2%) other/non-specified dementia stages: n=43 mild, n=314 moderate, n=267 severe, n=48 terminal (deceased in the past 6 months) overall patients (mean/SD): age 65.8 (8.6) years, 467 male (69.4%), disease duration 4.7 (3.5) years, independent living 472 (70.1%), assisted living 121 (18.0%), nursing home 80 (11.9%), (QDRS, FAQ, NPI, eNPI, combined NPI+eNPI mean scores reported) data for disease stages (mild, moderate, severe, terminal) reported overall caregivers (mean/SD): age 60.8 (9.9) years (range 22-88 years), 533 female (79.3%), education level less than high school 5 (0.7%), high school 66 (9.8%), at least some college 602 (89.5%), spouses 552 (82.0%), children 78 (11.6%), other 43 (6.4%), 97% white race mean ZBI 27.8 (8.0) living with patient 461 (68.6%), living in rural location 124 (18.5%) caregiving cost affecting the ability to make ends meet: not at all 83 (15.6%), just a little 162 (30.4%), major impact 248 (46.5%), unable to make ends meet 40 (7.5%) Crisis in past year 351 (54.4%), school-age children 91 (13.5%) data for disease stages (mild, moderate, severe, terminal) reported
Methods/measures	250-question online survey, 1-2 h to complete by caregiver (multiple sessions possible), containing validated scale and newly developed questions Patients (obtained by caregiver report): demographic data, diagnosis, Quick Dementia Rating scale (QDRS) for dementia severity (score range 0-30, higher scores indicating greater impairment), Functional Activities Questionnaire (FAQ) for instrumental AdL (score range 0-30, higher scores indicating greater impairment), NPI for neuropsychiatric symptoms (score range 0 to 36, higher scores indicating greater disturbance), extended NPI (eNPI) with 11 added items for FTD-specific behavior and symptoms (score range 0-33, higher scores indicating greater disturbance)

	Caregivers: demographic data, living situation, financial situation, ZBI for caregiver burden (score range 0-48, higher scores indicating higher burden) Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Percentage of female caregivers, caregivers with school-age children, and living in rural locations declined significantly with increasing disease severity; financial burden (ability to make ends meet) and having experienced a patient-related crisis in the past year increased significantly with increasing disease severity Percentage of patients living independently decreased with increasing disease severity, still 53% of severely diseased patients lived independently (e.g. in an apartment or house); worse cognitive and neuropsychiatric symptoms, higher functional limitations with increasing disease severity Mean ZBI at 27.8 (SD 8.0), no significant variance between disease severity groups; stratified by diagnosis worst CB was found for bvFTD and PSP caregivers, least for CBS and PPA caregivers Females had significantly higher ZBI scores, higher burden indicated in child caregivers; identification of three major burden factors: role strain, personal strain, and performance strain; role strain received highest mean endorsement per item, followed by performance strain and then personal strain Unadjusted analyses – predictors of CB (total ZBI): patient age, patient gender, NPI, eNPI, FAQ, QDRS, diagnosis, caregiver age, caregiver gender, caregiver-patient relationship, financial costs, experiencing a crisis Predictors of Role strain: patient age, patient gender, NPI, eNPI, FAQ, QDRS, diagnosis, caregiver age, caregiver gender, caregiver-patient relationship, financial costs, experiencing a crisis, disease severity, caregiver living with the patient Predictors of Personal strain: caregiver gender, NPI, eNPI, FAQ, QDRS, disease severity, diagnosis, patient's housing, caregiver age, caregiver gender, caregiver living with patient, experiencing a crisis Predictors of Perfomance strain: patient age, patient gender, NPI, eNPI, disease severity, patient's housing, caregiver age, caregiver education, caregiver-patient relationship, caregiver living with patient, experiencing a crisis Adjusted analyses – association of worse CB with higher total NPI + eNPI scores, younger caregiver age, financial costs, experiencing a crisis Higher role strain associated with higher total NPI + eNPI scores, worse FAQ scores, female caregivers, non-spouse/child caregivers, financial costs, experiencing a crisis Higher personal strain associated with higher total NPI + eNPI scores Higher performance strain associated with higher total NPI + eNPI scores, younger caregiver age, male caregivers, experiencing a crisis

	Caregiver age and NPI scores strongest significant predictors;
Limitations	Self-reported: no information about amount of time spent caregiving, almost exclusively white participants, caregiver self-reports might lack accuracy, PSP and CBS may be underrepresented

8. Table 2 – Study Characteristics

Characteristic	**Number of studies**	**References**
Measures to assess caregiver burden in quantitative studies		
Zarit Burden Interview (ZBI)	5	Besser and Galvin (2019), Galvin *et al.* (2018), Hughes *et al.* (2017), Koyama *et al.* (2018), Liu *et al.* (2018)
Short Zarit Burden Interview (sZBI)	3	Caga *et al.* (2018), Hazelton *et al.* (2017), Southi *et al.* (2019)
Neuropsychiatric Inventory (NPI)	2	Mukherjee *et al.* (2017, NPI-D), van Duinen-van den IJssel *et al.*(2018, NPI-NH)
Caregiver Burden Scale (CBS)	1	Bock *et al.* (2017)
Caregiver Burden Index (CBI)	2	Kücükgüclü *et al.* (2017), Spalding-Wilson *et al.* (2018)
Caregiver Strain Index (CSI)	2	Armour *et al.* (2019), Zahir *et al.* (2017)
Relatives' Stress Scale (RSS)	1	Hvidsten *et al.* (2019)
FTLD diagnoses in quantitative studies		
Not specified	13	Chen *et al.* (2019), Damianakis *et al.* (2018), Galvin *et al.* (2018), Hughes *et al.* (2017), Hvidsten *et al.* (2019), Johannessen *et al.* (2017), Liu *et al.* (2018), Mukherjee *et al.* (2017), Rasmussen *et al.* (2019), Tyrrell *et al.* (2019), van Duinen-van den IJssel *et al.* (2018), Wells *et al.* (2019), Wu *et al.* (2018)
bvFTD	11	Besser and Galvin (2019), Galvin *et al.* (2018), Koyama *et al.* (2018), Kücükgüclü *et al.* (2017), Nowaskie *et al.* (2019), Ratti *et al.* (2017), Sani *et al.* (2019), Takeda *et al.* (2019), Tyrrell *et al.*

		(2019), Wu *et al.* (2018), Zahir *et al.* (2017)
Aphasia not specified	3	Besser and Galvin (2019), Galvin *et al.* (2018), Nowaskie *et al.* (2019)
svPPA/SD	8	Bryant and Miller (2018), Jokel *et al.* (2017), Koyama *et al.* (2018), Kücükgüclü *et al.* (2017), Sani *et al.* (2019), Takeda *et al.* (2019), Tyrrell *et al.* (2019), Zahir *et al.* (2017)
nfvPPA/PNFA	5	Hazelton *et al.* (2017), Jokel *et al.* (2017), Kücükgüclü *et al.* (2017), Sani *et al.* 2019, Takeda *et al.* (2019)
Overlap syndromes in quantitative studies		
CBS	4	Besser and Galvin (2019), Galvin *et al.* (2018), Southi *et al.* (2019), Takeda *et al.* (2019)
PSP	3	Besser and Galvin (2019), Galvin *et al.* (2018), Takeda *et al.* (2019)
MND	5	Besser and Galvin (2019), Bock *et al.* (2017), Caga *et al.* (2019), Galvin *et al.* (2018), Wells *et al.* (2019)
Country/region of origin (all studies)		
USA/Canada	18	Armour *et al.* (2019), Bartochowski *et al.* (2018), Besser and Galvin (2019), Bock *et al.* (2017), Bryant and Miller (2018), Chen *et al.* (2019), Damianakis *et al.* (2018), Galvin *et al.* (2018), Hughes *et al.* (2017), Jokel *et al.* (2017), Mulkey *et al.* (2019), Nowaskie *et al.* (2019), Ratti *et al.* (2017), Spalding-Wilson *et al.* (2018), Takeda *et al.* (2019), Wagner *et al.* (2018), Wells *et al.* (2019), Zahir *et al.* (2017)
Europe	12	Baumann *et al.* (2019), Benbrika *et al.* (2019), de Wit *et al.* (2018), Hvidsten *et al.* (2019), Johannessen *et al.* (2017), Kücükgüclü *et al.*

		(2017), Linse *et al.* (2018), Rasmussen *et al.* (2019), Sani *et al.* (2019), Tyrrell *et al.* (2019), van Duinen-van den IJssel *et al.* (2018), Wu *et al.* (2018)
Australia	5	Caga *et al.* (2018), Caga *et al.* (2019), Hazelton *et al.* (2017), Lewis *et al.* (2018), Southi *et al.* (2019)
Caregiver characteristics		
Relationship to patient (informal caregivers)	13	Besser and Galvin (2019), Bryant and Miller (2018), Caga *et al.* (2018), Damianakis *et al.* (2018), Hazelton *et al.* (2017), Johannessen *et al.* (2017), Jokel *et al.* (2017), Koyama *et al.* (2018), Kücükgüclü *et al.* (2017), Liu *et al.* (2018), Rasmussen *et al.* (2019), Southi *et al.* (2019), Tyrrell *et al.* (2019)
Focused on family caregivers	10	Caga *et al.* (2018), Damianakis *et al.* (2018), Hughes *et al.* (2017), Hvidsten *et al.* (2019), Johannessen *et al.* (2017), Jokel *et al.* (2017), Kücükgüclü *et al.* (2017), Nowaskie *et al.* (2019), Rasmussen *et al.* (2019), Tyrrell *et al.* (2019)
Gender	13	Besser and Galvin (2019), Caga *et al.* (2018), Damianakis *et al.* (2018), Galvin *et al.* (2018), Hazelton *et al.* (2017), Johannessen *et al.* (2017), Jokel *et al.* (2017), Koyama *et al.* (2018), Kücükgüclü *et al.* (2017), Liu *et al.* (2018), Rasmussen *et al.* (2019), Southi *et al.* (2019), Tyrrell *et al.* (2019)

9. Table 3 – Case Study and Qualitative Studies

Reference	Participants	Symptoms and Problems	Implications for Caregiver Burden
Bryant and Miller, 2018	62-year old male with svPPA, his wife, and three adult children	Behavioral disturbances made first home visits and then hospitalization necessary; treatment with antipsychotic and mood stabilizing drugs; disruptive behavior caused major distress in family (e.g. lack of sleep; symptoms could not be managed in nursing home; several ER and inpatient treatments	Caregivers found it difficult to navigate through different providers in the healthcare system and would have appreciated support doing this; caregivers would need more education about disease and (limited) treatment options; lack of appropriate care facilities for FTD patients
Damianakis *et al.* (2018)	6 spouses of FTD patients (+ 18 spouses of AD patients)	Reflections from a support group; discussed reactions to patient's behavior and changing relationship; making sense of their new role as a caregiver; finding support in religion and spirituality; experiencing gratitude and coping in the moment	Spouses found mutual understanding in the support group; improved self-esteem in group; video-technology for conferencing perceived as useful to connect caregivers from their homes
Johannessen *et al.* (2017)	16 spouses/partners from patients with yo-FTLD	Identification of themes with different importance during different stages of dementia; early signs, turmoil and distress providing care in more severe dementia; interference with workplace both in the patient and the caregiver; difficult process of obtaining a diagnosis, need for assistance, transition into nursing homes	Need for educated healthcare professionals to facilitate diagnostic process and finding adequate support; support with administrative tasks and ensure economic stability

Nowaskie *et al.* (2019)	4 caregivers of patients with PPA, 5 caregivers of patients with bvFTD	Identification of main themes: difficulty in obtaining a diagnosis, lack of education about diagnosis, adapting to changing roles, financial and legal challenges, grieving, lack of disease-specific services	(abstract with limited data)
Rasmussen *et al.* (2019)	14 caregivers of FTD patients	Focus on experiences in pre-diagnostic stage; feelings of distance and insecurity, increasing distress and devastation facing the patient's situation; estrangement from patient	Need for healthcare professionals to obtain a correct diagnosis; support in care when patients get into potentially dangerous or self-threatening situations
Tyrrell *et al.* (2019)	9 caregivers of FTD patients	Main themes "living with a well-known stranger" and "coping and overstepping social norms"; gradual loss of a loved person; living with offensive and abusive behavior; finding solutions to make things work (e.g. tracking devices for patients), constant preoccupation about patient's safety	Need for caregiving and financial support, continuity and reliability in care providers, thorough education about diagnosis and what to expect from it, precautions for patient's safety

10. Table 4 – Reviews and Educational Articles

Reference	**Topic/Type**	**Findings**
FTD		
Bartochowski *et al.* (2018)	To review empathy changes in neurocognitive disorders	Lower empathy in FTD patients, mostly both cognitive and emotional empathy impaired (conflicting study results)
Lewis *et al.* (2018)	To review mealtime difficulties in FTD	Mostly behavioral changes (hyperphagia, tachyphagia, inedible items, wandering, agitation) in bvFTD, swallowing difficulties (oropharyngeal weakness, apraxia, coordination) in PPA and overlap syndromes; change in

		food preferences leading to unbalanced diet and associated conditions
Mulkey, 2019	Educational article	Presentation of FTD progress and treatment options
ALS/MND		
Baumann *et al.* (2019)	To review caregiver burden in ALS family caregivers	Four main themes: 1) burden due to patient behavioral changes (making up to 1/3 of perceived burden) 2) burden due to patient cognitive changes 3) burden due to caregiver anxiety 4) burden due to caregiver depression
Benbrika *et al.* (2019)	To review the longitudinal development of cognitive, emotional, and psychological manifestations in ALS	Description of Cognition, Emotion Perception/Social Cognition, Behavior, and Psychological Reactions over time; description of apathy as a major behavioral symptom, general importance of behavioral disturbance as a CB predictor
Caga *et al.* (2019)	To review the impact of cognitive and behavioral changes in ALS on patients and their caregivers	Description of impact on patient's psychological well-being and treatment adherence; inconsistent findings about the magnitude of impact of behavioral and cognitive symptoms on CB; little research about motor symptoms' impact on CB
Linse *et al.* (2018)	To review the factors to consider in using high-tech communication devices for ALS patients	Description of communication devices and their way of functioning; devices decrease CB and help in making decisions; changes in ALS-Ci, ALS-Bi or ALS-FTD can impair use of the devices, especially language impairments
De Wit *et al.* (2018)	To review factors contributing to CB in ALS and evaluate their evidence	Caregiver factors: depression (moderate quality of evidence), anxiety, distress, age (low quality), social support, family functioning (very low quality); Patient factors: behavioral impairments (high quality), physical functioning (moderate), limb function, respiratory function, executive functioning, cognitive functioning, age (very low)

11. Appendix I - Tabular Summary of Included Publications

1. Cohort and epidemiological studies
1.1 FTLD

1.1.1 Besser and Galvin 2019

Reference	Besser, Lilah M.; Galvin, James E. (2019): Perceived burden among caregivers of patients with frontotemporal degeneration in the United States. In *International psychogeriatrics* 31 (8), pp. 1191–1201. DOI: 10.1017/S104161021800159X.
Type	Cross-sectional cohort study
Location/Country	USA
Aim/subject	To assess self-reported burden in caregivers of patients with FTD in the US
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	Recruitment via Association for Frontotemporal Degeneration – e-mail newsletter, social media, website n=675 (70.5% out of n=956 who initiated survey) completed online survey with full ZBI data diagnoses: n=360 (53.7%) bvFTD, n=145 (21.6%) PPA, n=52 (7.8%) ALS, n=32 (4.8%) PSP or CBS, n=82 (12.2%) other/non-specified dementia stages: n=43 mild, n=314 moderate, n=267 severe, n=48 terminal (deceased in the past 6 months) overall patients (mean/SD): age 65.8 (8.6) years, 467 male (69.4%), disease duration 4.7 (3.5) years, independent living 472 (70.1%), assisted living 121 (18.0%), nursing home 80 (11.9%), (QDRS, FAQ, NPI, eNPI, combined NPI+eNPI mean scores reported) data for disease stages (mild, moderate, severe, terminal) reported

	overall caregivers (mean/SD): age 60.8 (9.9) years (range 22-88 years), 533 female (79.3%), education level less than high school 5 (0.7%), high school 66 (9.8%), at least some college 602 (89.5%), spouses 552 (82.0%), children 78 (11.6%), other 43 (6.4%), 97% white race mean ZBI 27.8 (8.0) living with patient 461 (68.6%), living in rural location 124 (18.5%) caregiving cost affecting the ability to make ends meet: not at all 83 (15.6%), just a little 162 (30.4%), major impact 248 (46.5%), unable to make ends meet 40 (7.5%) Crisis in past year 351 (54.4%), school-age children 91 (13.5%) data for disease stages (mild, moderate, severe, terminal) reported
Methods/measures	250-question online survey, 1-2 h to complete by caregiver (multiple sessions possible), containing validated scale and newly developed questions Patients (obtained by caregiver report): demographic data, diagnosis, Quick Dementia Rating scale (QDRS) for dementia severity (score range 0-30, higher scores indicating greater impairment), Functional Activities Questionnaire (FAQ) for instrumental AdL (score range 0-30, higher scores indicating greater impairment), NPI for neuropsychiatric symptoms (score range 0 to 36, higher scores indicating greater disturbance), extended NPI (eNPI) with 11 added items for FTD-specific behavior and symptoms (score range 0-33, higher scores indicating greater disturbance) Caregivers: demographic data, living situation, financial situation, ZBI for caregiver burden (score range 0-48, higher scores indicating higher burden) Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Percentage of female caregivers, caregivers with school-age children, and living in rural locations declined significantly with increasing disease severity; financial burden (ability to make ends meet) and having experienced a patient-related crisis in the past year increased significantly with increasing disease severity Percentage of patients living independently decreased with increasing disease severity, still 53% of severely diseased patients lived independently (e.g. in an apartment or house); worse cognitive and neuropsychiatric symptoms, higher functional limitations with increasing disease severity Mean ZBI at 27.8 (SD 8.0), no significant variance between disease severity groups; stratified by diagnosis worst CB was found for bvFTD and PSP caregivers, least for CBS and PPA caregivers Females had significantly higher ZBI scores, higher burden indicated in child caregivers; identification of three major burden factors: role strain, personal strain, and performance strain; role strain received highest mean endorsement per item, followed by performance strain and then personal strain

	Unadjusted analyses – predictors of CB (total ZBI): patient age, patient gender, NPI, eNPI, FAQ, QDRS, diagnosis, caregiver age, caregiver gender, caregiver-patient relationship, financial costs, experiencing a crisis Predictors of Role strain: patient age, patient gender, NPI, eNPI, FAQ, QDRS, diagnosis, caregiver age, caregiver gender, caregiver-patient relationship, financial costs, experiencing a crisis, disease severity, caregiver living with the patient Predictors of Personal strain: caregiver gender, NPI, eNPI, FAQ, QDRS, disease severity, diagnosis, patient's housing, caregiver age, caregiver gender, caregiver living with patient, experiencing a crisis Predictors of Perfomance strain: patient age, patient gender, NPI, eNPI, disease severity, patient's housing, caregiver age, caregiver education, caregiver-patient relationship, caregiver living with patient, experiencing a crisis Adjusted analyses – association of worse CB with higher total NPI + eNPI scores, younger caregiver age, financial costs, experiencing a crisis Higher role strain associated with higher total NPI + eNPI scores, worse FAQ scores, female caregivers, non-spouse/child caregivers, financial costs, experiencing a crisis Higher personal strain associated with higher total NPI + eNPI scores Higher performance strain associated with higher total NPI + eNPI scores, younger caregiver age, male caregivers, experiencing a crisis Caregiver age and NPI scores strongest significant predictors;
Limitations	Self-reported: no information about amount of time spent caregiving, almost exclusively white participants, caregiver self-reports might lack accuracy, PSP and CBS may be underrepresented

1.1.2 Chen et al. 2019

Reference	Chen, Yingjia; Wilson, Leslie; Kornak, John; Dudley, R. Adams; Merrilees, Jennifer; Bonasera, Stephen J. et al. (2019): The costs of dementia subtypes to California Medicare fee-for-service, 2015. In *Alzheimer's & Dementia* 15 (7), pp. 899–906. DOI: 10.1016/j.jalz.2019.03.015.
Type	Retrospective cost analysis
Location/Country	California, USA
Aim/subject	To assess dementia-related costs for different dementia subtypes in California
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to	n=247,007 Persons with dementia, n=57,225 AD (23.2%), n=10,869 DLB (4.4%), n=9911 VaD (4.0%), n=728 FTD (0.3%), n=513 other (0.2%), n=8816 mixed dementia (3.6%), n=11,618 classified elsewhere (4.7%), n=147,327 not otherwise specified (59.6%) All beneficiaries: mean age 73.4 (SD 10.2), 43.8% male, 63% white, 5% black, 17% Asian, 12% Hispanic, 0% North American Native, 3% other/unknown Metropolitan area 95%, rural area 5%, unknown 0% 0 comorbidities 79%, 1 comorbidity 7%, 2+ comorbidities 14%

patient, initial scores)	History of falls 40.9%, delirium 3.4%, depression 3.3%, anxiety 2.6%, hallucinations 0.0%, delusions 0.0%, dehydration 2.1%, urinary incontinence or infection 4.0%, orthostasis 0.3%, sleep disorders 0.8%, full year coverage 85% All dementia patients: mean age 83.0 (SD 9.5), 37% male, 65% white, 6% black, 15% Asian, 11% Hispanic, 0% North American Native, 2% other/unknown Metropolitan area 96%, rural area 4%, unknown 0% 0 comorbidities 55%, 1 comorbidity 8%, 2+ comorbidities 37% History of falls 63.5%, delirium 14.5%, depression 10.3%, anxiety 6.8%, hallucinations 0.3%, delusions 0.3%, dehydration 10.5%, urinary incontinence or infection 19.4%, orthostasis 1.1%, sleep disorders 2.1%, full year coverage 74% FTD patients: mean age 76.7 (SD 10.2), 45% male, 77% white, 4% black, 9% Asian, 7% Hispanic, 0% North American Native, 2% other/unknown Metropolitan area 95%, rural area 5%, unknown 0% 0 comorbidities 56%, 1 comorbidity 9%, 2+ comorbidities 35% History of falls 54.1%, delirium 12.1%, depression 10.4%, anxiety 5.9%, hallucinations 0.3%, delusions 0.9%, dehydration 8.5%, urinary incontinence or infection 15.9%, orthostasis 2.0%, sleep disorders 3.6%, full year coverage 73% Data reported for all non-dementia beneficiaries, LBD, VaD, AD, and other/classified elsewhere/NOS/mixed
Methods/measures	Data of the Medicare & Medicaid aidministrative enrollment and claims data for 100% of Medicare beneficiaries enrolled in the fee-for-service (FFS) program in 2015 n=3,001,987 beneficiaries with positive claims included, 85% with Plan A and B coverage Data used in accordance with data use and privacy regulations Using ICD-9-CM and ICD-10-CM diagnostic codes related to dementia, all persons with at least one diagnosis of dementia considered as PwD, all other beneficiaries as controls Identification of potential cost drivers: falls, delirium, depression, anxiety, delusions, hallucinations, dehydration, urinary incontinence or infection, orthostasis, sleep disorder Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	(mainly results for FTD reported) n=247,007 (8.2%) of all beneficiaries had a dementia diagnosis, higher mean age and proportion of females in dementia patients, more female AD patients, more male DLB patients 77% of FTD patients identified as white, lower percentages of other races than in any other dementia subtype Total cost for all beneficiaries with dementia $4.2 billion, $16,867 per beneficiary (vs. $6070 per beneficiary without dementia); total cost for AD $798 million, DLB $245 million, VaD $208 million, FTD $11 million

	All dementia patients per person ($, mean/SD): total cost 16,867 (28,712), inpatient cost 8522 (21,670), outpatient cost 488 (1764), carrier cost 4726 (7262), home health agency cost 2431 (4963), Hospice cost 119 (638), Skilled nursing facility cost 580 (2734) FTD patients per person ($, mean/SD): total cost 14,853 (26,540), inpatient cost 8160 (20,721), outpatient cost 584 (2602), carrier cost 3663 (5006), home health agency cost 1782 (4658), Hospice cost 144 (841), Skilled nursing facility cost 521 (3019) Data reported for non-dementia patients, DLB, VaD, AD and Other/classified elsewhere/NOS/mixed Substantially higher costs for dementia patients for hospitalization, physician visits, ER visits, ambulance services, long-term care services, hospice; dementia costs by subtype mainly driven by hospitalization cost; FTD cost higher than AD cost (AD had the lowest annual costs); subsequent analyses for DLB (LBD and PDD), the costliest subtype Medicare does not cover expenses for long-term care or out-of-pocket costs; higher rate of behavioral disturbances in FTD might result in higher out-of-pocket costs that are not represented in this study
Limitations	Self-reported: costs not covered by Medicare are not being represented in the present study, limited sensitivity of dementia diagnosis identification in claims (likely to be underestimated), subtype diagnosis relying on clinical phenomenology instead of biological disease, no meaningful inferences of association between codes and costs

1.1.3 van Duinen–van den IJssel et al. 2017

Reference	van IJssel, Jeannette C. L. Duinen-van den; Mulders, Ans J. M. J.; Smalbrugge, Martin; Zwijsen, Sandra A.; Appelhof, Britt; Zuidema, Sytse U. et al. (2018): Nursing Staff Distress Associated With Neuropsychiatric Symptoms in Young-Onset Dementia and Late-Onset Dementia. In *Journal of the American Medical Directors Association* 19 (7), pp. 627–632. DOI: 10.1016/j.jamda.2017.10.004.
Type	Controlled cross-sectional study
Location/Country	Netherlands
Aim/subject	To assess distress in nursing staff caring for patients with YOD and LOD
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver	Participants recruited in Behavior and Evolution of Young-onset Dementia (Beyond) Parts I and II studies and WAAL Behavior in Dementia-II study Beyond I and II studies: YOD nursing home residents (dementia with symptom onset <65 years, residence at least 1 month); exclusion criteria: lack of informed consent, HIV dementia, traumatic brain injury, Down syndrome, Korsakow syndrome, alcohol-related dementia, Huntington's disease

relationship to patient, initial scores)	Waalbed-II study: LOD comparison group, identical inclusion and exclusion criteria (dementia diagnosis >65 years, or older than 70 years at time of institutionalization or at time of study inclusion) Informed consent and ethical approval obtained n=382 YOD residents, n=261 LOD residents YOD total (n/%): mean age at inclusion 62.7 (SD 6.9) years, age range 39.3-78.2 years; 193 male (50.5%), AD 41.9%, VaD and mixed dementia 16.5%, FTD 24.6%, other 17%; mild dementia 16%, moderate dementia 21.5%, severe dementia 35.9%, very severe dementia 26.7% (NPI-NH F×S scores for separate symptoms provided) LOD total (n/%): mean age at inclusion 84.9 (SD 5.9) years, age range 70.4-102.2; 59 male (22.6%), AD 43.7%, VaD and mixed dementia 16.9%. FTD 3.1%, other 36.4%; mild dementia 5.7%, moderate dementia 23.4%, severe dementia 42.9%, very severe dementia 28% (NPI-NH F×S scores for separate symptoms provided)
Methods/measures	Nursing staff: Occupational disruptiveness scale from the NPI-Nursing home scale (NPI-NH), Dutch edition to assess distress (disruptiveness scores 0-5, higher scores indicating higher disruptiveness; total distress score range 0-60) Independent variables: NPI-NH frequency (F) x severity (S) scores for symptom severity (score range 0-12, higher scores indicating higher symptom severity), Global Deterioration Scale (GDS) for dementia severity (score range 0-7, higher scores indicating higher severity) Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Baseline data from Beyond I and II & Waalbed-II studies More male participants in YOD group; both groups with predominantly severe dementia; FTD more prevalent in YOD group Agitation/aggression, apathy, and irritability were the most common NPS in both YOD and LOD groups; all separate NPS caused medium or high distress in a majority of nurses caring for YOD residents; YOD: ~45% of nurses rated sleep and nighttime behavior disorders, agitation/aggression, and delusions as highly distressing, nearly equally often rated as medium distressing More than half of nurses experienced some level of distress because of euphoria, but it was most often rated as not distressing Distress because of hallucinations most often rated as absent or minimal, but nearly equally high percentage experienced medium distress All other symptoms most often rated as medium distressing LOD:

	All symptoms cause at least some level of distress, absolute rates of no/low distress higher than in YOD, absolute rated of high distress lower than in YOD Symptoms most often rated as medium distressing More than 50% of nurses rated anxiety, irritability, and appetite and eating changes to be medium distressing More than 50% of nurses experienced no/low distress related to hallucinations, euphoria, and apathy Nurses caring for YOD residents experienced significantly more distress than those caring for LOD residents Logistic regression analyses: odds for experiencing distress related to sleep and nighttime behavior disorders significantly higher for YOD nurses than for LOD nurses; no significant differences for all other symptoms After controlling for group (YOD vs. LOD), gender, dementia subtype, and dementia severity; nurses were likely to experience more distress for every 1-point increase on the NPI-NH F×S scale for every symptom except for apathy, OR highest for irritability, lowest for aberrant motor behavior Odds of experiencing distress related to irritability increased when the resident was male compared to female residents; no significant effects for dementia severity and distress or dementia subtype and distress Additional subgroup analyses: no interaction effects between group and gender, dementia subtype, dementia severity, and NPI-NH F×S score
Limitations	Dichotomization of distress scores, collapsing dementia severity into two groups; some symptoms only present in few residents; distress ratings might influence frequency and severity ratings; Beyond-II cohort newer than Beyond-I and Waalbed-II cohorts, demographic data Subgroup analyses for FTD: included into “other” dementia diagnoses group together with DLB, PDD, neurosyphilis, and dementia not otherwise specified Number of nurses, nurses caring for both LOD and YOD patients?

1.1.4 Galvin et al. 2017

Reference	Galvin, James E.; Howard, David H.; Denny, Sharon S.; Dickinson, Susan; Tatton, Nadine (2017): The social and economic burden of frontotemporal degeneration. In *Neurology* 89 (20), pp. 2049–2056. DOI: 10.1212/WNL.0000000000004614.
Type	Controlled, cross-sectional study
Location/Country	USA
Aim/subject	To assess and quantify the socioeconomic burden of FTD compared to previous findings for AD
Participants (number, patient diagnosis, gender, age range, race,	956 participants recruited, 674 completed 52.9% bvFTD, 21.1% PPA, 7.3% MND-FTD, 5.4% PSP or CBS, 13.3% undefined FTD (caregiver did not know subtype)

ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	Mild stage caregivers (mean/SD): age 58.7 (9.2) years, 88.9% female, 79.6% spouses, 9.3% children; ZBI 25.4 (10.9) Mild stage patients (mean/SD): age 64.5 (10.5) years, 22.6% female, 63.0% bvFTD, 13.0% PPA, 7.4% MND-FTD, 7.5% PSP or CBS, 9.3% other or unspecified (disease duration, Quick Dementia Rating, Functional Activities and NPI reported) Moderate stage caregivers (mean/SD): age 60.9 (9.8) years, 82.4% female, 84.1% spouses, 8% children; ZBI 27.7 (7.6) Moderate stage patients (mean/SD): age 65.6 (8.1) years, 27.0% female, 55.7% bvFTD, 19.1% PPA, 7.7% MND-FTD, 4.1% PSP or CBS, 13.4% other or unspecified (disease duration, Quick Dementia Rating, Functional Activities and NPI reported) Severe stage caregivers (mean/SD): age 61.5 (10.0) years, 73.2% female, 80.0% spouses, 13.1% children; ZBI 28.3 (7.9) Severe stage patients (mean/SD): age 66.2 (8.8) years, 37.3% female, 47.9% bvFTD, 24.9% PPA, 7.3% MND-FTD, 5.8% PSP or CBS, 14.1% other or unspecified (disease duration, Quick Dementia Rating, Functional Activities and NPI reported) Terminal stage caregivers (mean/SD): age 61.0 (11.1) years, 74.2% female, 74.2% spouses, 17.7% children; ZBI 28.1 (7.6) Terminal stage patients (mean/SD): age 67.9 (8.1) years, 40.3% female, 54.1% bvFTD, 21.3% PPA, 4.9% MND-FTD, 6.6% PSP or CBS, 13.1% other or unspecified (disease duration, Quick Dementia Rating, Functional Activities and NPI reported)
Methods/measures	Online 250-question survey for the primary caregiver of FTD patient, no identifiable personal data collected, app. 2 hours to complete survey Patient clinical characterization: Quick Dementia Rating Scale (10 questions), Neuropsychiatric Inventory (NPI, 12 questions), Functional Activities Questionnaire (10 questions), Zarit Burden Inventory (ZBI, 12 questions); caregiver-rated disease severity based on opinion and observation of the past 6 months (mild, moderate, severe, terminal) Patient health utility and resource use: Health Utilities Index 3-(HUI3) for HRQoL, estimated quality-adjusted life years (QALYs), Resource Utilization Inventory (RUI) for dementia-associated costs, use of care, loss of paid employment; calculations and estimations for costs described Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	674/956 completed (70.5%); patients divided into four groups based on caregiver rating: mild, moderate, severe or terminal (characteristics see “participants”) No significant demographic differences between completers and non-completers, staging scales and disease duration matched well with

	caregiver severity rating, caregiver burden not different across disease stages Changes in household income and lost days of work: 45% of caregivers worked (74% full-time), 37% not employed after patient's FTD diagnosis; 3.3% of patients worked; 25.6% reported lost days of work due to patient health issues and 21.6% due to caregiver health issues; in full-time workers, median loss of 7.0 FTD-related working days in the previous 4 weeks; household income 12 months before and 12 months after diagnosis: significant decline from range of $75,000-99,000 to $50,000-59,999 after diagnosis; no differences between FTD subtype, caregiver type or patient sex Patient and caregiver health costs: 67% of caregivers reported decline in health, 53% increased personal health costs, average of 7 clinician visits, slightly less than 1 inpatient admission/year; patients had an average of 6 overnight respite stays, 16 daytime respite stays, 35 clinician visits, 2 hospital or ER visits/year; 31.6% had to hire a paid caregiver several times a week Estimates of annual per patient costs: direct costs were $47,916; indirect costs $71,737 (total $119,654); higher direct costs: patients ≥65 years, women (mainly living in nursing homes or assisted living), severe or terminal disease stage, bvFTD; higher indirect costs: men, lower indirect costs: patients ≥65 years Other costs associated with FTD; 19% required ER visits, 11% emergency medical services, 8% urgent psychiatric care, 6% police intervention, 6% lawyer; poor financial decisions by FTD patient reported by 58%, 9.6% reported spending on legal costs for reasons of legal guardianship, bankruptcy, loss of home, loss of business, criminal cases and civil lawsuits Changes in HRQoL: HUI3 and QALYs lower for patients in severe and terminal disease stages (significantly indicating that QoL is worse than death); HRQoL declined across all stages; QALYs highest in female caregiver-male patient dyads, lowest in female caregiver-female patient dyads; no HRQoL or QALY differences by FTD subtypes Comparison to economic costs of AD: costs greater in the US than in other countries; difficult comparability across studies due to different methodology; costs unadjusted for coexisting conditions and replacement costs comparable to the present study; overall estimated costs were 53% lower than the estimated FTD total of $119,654
Limitations	Self-reported: - self-reported data of respondents willing to participate in research - Cross-sectional, no longitudinal data

1.1.5 Hazelton et al. 2017

Reference	Hazelton, Jessica L.; Irish, Muireann; Hodges, John R.; Piguet, Olivier; Kumfor, Fiona (2017): Cognitive and Affective Empathy

	Disruption in Non-Fluent Primary Progressive Aphasia Syndromes. In *Brain Impairment* 18 (1), pp. 117–129. DOI: 10.1017/BrImp.2016.21.
Type	Controlled cross-sectional study
Location/Country	Australia
Aim/subject	To assess empathy in patients with PNFA & LPA and its effects on caregivers
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	n=23 PNFA (nfvPPA) patient/caregiver dyads, n=16 logopenic progressive aphasia (LPA/lvPPA) patient/caregiver dyads, n=24 healthy controls (CG) Patient recruitment from FRONTIER YOD clinic in Sydney, Exclusion criteria: current or prior history of psychiatric illness, significant head injury, alcohol or substance abuse, presence of another neurological disorder, limited proficiency in English Informed consent and ethical approval obtained PNFA patients (mean/SD): age 68.5 (11.0) years, 11 male, years of education 12.2 (3.0), years of disease duration 3.3 (2.2), FRS (Rasch score) 1.8 (1.7) LPA patients (mean/SD): age 67.3 (7.6) years, 6 male, years of education 13.3 (3.7), years of disease duration 4.3 (2.8), FRS (Rasch score) 1.6 (1.6) CG (mean/SD): age 67.9 (6.8) years, 14 male, years of education 13.8 (1.7) Caregivers: 30 spouses (76.9%), 4 children (10.3%), 2 children's spouses (5.1%), 2 patient's friends (5.1%), 1 patient's sibling (2.6%); 24 female (61.5%)
Methods/measures	Patients: ACE-R or ACE-III for cognition; Digit Span and Trail Making Test for attention and working memory; Rey Complex Figure Test (RCF) for visuo-constructional skills and non-verbal episodic memory; Sydney Language Battery (SYDBAT) for language functioning; Letter fluency for word generativity; Emotion Selection Task for emotion recognition; Frontotemporal dementia Rating Scale (FRS) for everyday functioning and behaviors (higher scores indicating higher functional capabilities) Empathy measures: Interpersonal Reactivity Index (IRI) for cognitive and affective empathy (Fantasy, Personal Distress, Perspective Taking subscales); completed by informant for two periods of time: before the illness and at present time; controls completed IRI for present time Caregivers: ZBI (sZBI) for caregiver burden (score range 0-48, cut-off ≥ indicating high burden); Intimate Bond Measure (IBM) for perceived relationship quality with the patient (score range 0-36 for Care and Control subscales); Depression Anxiety Stress Scale (DASS-21) for psychological well-being (converted to DASS-42 scores, total score calculated) Statistical data analyses
Interventions (where applicable)	n/a

Outcomes (variables, main findings)	No significant group differences between patients and CG for age, sex, or education; patients did not differ significantly PNFA patients showed significantly worse cognition, attention, verbal working memory, language function, and emotion recognition ability than CG; visuo-spatial abilities and non-verbal episodic memory remained relatively intact LPA patients showed significantly worse cognition, language, verbal attention, verbal working memory, visuomotor processing speed, mental flexibility, and emotion recognition performance than CG; single-word repetition similar to CG PNFA patients performed significantly worse in single-word repetition than LPA patients; LPA patients had worse non-verbal episodic memory and single-word naming than PNFA patients Burden, Relationship Quality and Caregiver DASS: no significant differences between PNFA and LPA group in burden; 36% of caregivers reported high burden; no differences in DASS between PNFA and LPA groups; six caregivers reported moderate to severe depression; three caregivers reported moderate to severe anxiety; 5 caregivers reported moderate to severe stress; no IBM subscale differences between PNFA and LPA IRI: PNFA patients rated significantly lower on the perspective taking subscale, LPA patients rated similarly to CG; both PNFA and LPA groups scored lower on Fantasy subscale compared to CG; no significant effect of diagnoses on Empathic Concern and Personal Distress subscales PNFA patients had decreased Perspective Taking and Empathic Concern scores as well as increased Personal Distress compared to before disease onset, no changes in Fantasy subscale compared to pre-morbid situation LPA patients had decreased Perspective Taking and increased Personal distress compared to before disease onset, trend for decreased Empathic concern, no changes on Fantasy subscale Relationship between Empathy and Cognition, Emotion Recognition, and Caregiver Well-being: in PNFA, reduced Perspective taking was associated with worse emotion recognition; in LPA, reduced Perspective taking was associated with lower visuo-spatial abilities, reduced Empathic concern was associated with increased caregiver burden; no other significant correlations Controlling for disease severity (FRS scores): trend between reduced Empathic concern and increased CB; association between Empathic concern and CB remained significant in LPA Non-language features of PPA are significant contributors to caregiver burden and should thus be addressed when educating caregivers about the disease
Limitations	Self-reported: No direct measure of empathy deficits in patients; small power

1.1.6 Hughes et al. 2017

Reference	Hughes, Samantha R.; Boeve, Brad F.; Rosen, Howard J.; Boxer, Adam L.; Calvert, Kendrick J.; Dheel, Christina et al. (2017): CAREGIVER BURDEN IN FAMILIAL FRONTOTEMPORAL DEMENTIA SUBJECTS. PRELIMINARY DATA IN THE LEFFTDS COHORT. In *Alzheimer's & Dementia* 13 (7, Supplement), P722 - P723. DOI: 10.1016/j.jalz.2017.06.934.
Type	Controlled longitudinal cohort-study (abstract)
Location/Country	USA
Aim/subject	To assess longitudinal development of caregiver burden in caregivers of subjects with familial FTD
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	188 participants upon visit 1, 43 upon visit 2 LEFFTDS cohort: 8 North American centers, subjects carrying one of the 3 most common genetic mutations of familial FTD and exhibiting symptomatic FTD and their caregivers; annual evaluation
Methods/measures	Patients: modified Clinical Dementia Rating (CDR) – 0 normal neurologic function, 0.5 – minimally symptomatic FTD, ≥1 overtly symptomatic FTD Caregivers: Zarit Caregiver Interview (ZCI) - 0-21 little to no burden, 21-40 mild to moderate burden, 41-60 moderate to severe burden Annual evaluation, statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Baseline (188 participants, mean/SD): CDR 0 – ZCI 6.1 (8.8), CDR 0.5 – ZCI 8.5 (8.3), CDR ≥1 – ZCI 27.8 (14.7) Follow-up (43 participants, 23% follow-up rate, mean/SD): CDR 0 – ZCI 5.5 (5.5), CDR 0.5 – ZCI 17.2 (14.6), CDR ≥1 – ZCI 30.2 (15.0) Median (Q1, Q3) ZCI at Visit 1: 11 (2, 24), Visit 2: 13 (4, 26) Trends for increasing burden among CDR 0.5 (p=0.078) and all subjects (0.077) – mostly low burden range
Limitations	- Preliminary data from abstract - No caregiver/patient characteristics

1.1.7 Hvidsten et al. 2019

Reference	Hvidsten, Lara; Engedal, Knut; Selbaek, Geir; Wyller, Torgeir Bruun; Benth, Jurate Saltyte; Kersten, Hege (2019): Quality of life of family carers of persons with young-onset dementia. A Nordic two-year

	observational multicenter study. In *PLOS ONE* 14 (7). DOI: 10.1371/journal.pone.0219859.
Type	Controlled longitudinal cohort study
Location/Country	Norway, Denmark, Iceland
Aim/subject	To assess burden, QoL and depression in family caregivers of persons with YOD
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	88 family caregivers recruited from nine memory clinics in Norway, Denmark and Iceland between 02/2014 and 07/2015; PwD diagnoses: n=50 AD, n=38 FTD Family caregiver: unpaid informal help, face-to-face contact to the PwD at least once a week Mean caregiver age: 57 years (SD 11.7, range 25-75), Relationship to patient: 70% spouses, 18% adult children, 12% sibling or friend Baseline caregivers (mean/SD): n=88, age 57 (11.7) years, 36 male (41%), 61 (70%) spouses, 26 (30%) other (MADRS, GDS, RSS, QoL-AD, ADL-assistance reported) Baseline patient (mean/SD): n=88, age 63.0 (4.8) years, 48 male (55%), AD n=50, FTD n=38 (CDR, MMSE, symptom duration, Cornell, Awareness, ADL, QoL-AD reported) 1-year follow-up caregivers: n=68, 28 male (41%), 50 (74%) spouses, 18 (26%) other (MADRS, GDS, RSS, QoL-AD, ADL-assistance reported) 1-year follow-up patients: n=68, 34 male (50%), *AD n=49, FTD n=37* (CDR, MMSE, symptom duration, Cornell, Awareness, ADL, QoL-AD reported) 2-year follow-up caregivers: n=64, 25 male (39%), 48 (74%) spouses, 16 (25%) other (MADRS, GDS, RSS, QoL-AD, ADL-assistance reported) 2-year follow-up patients: n=64, 33 male (48%), AD n=40, FTD n=24 (CDR, MMSE, symptom duration, Cornell, Awareness, ADL, QoL-AD reported) Informed consent provided
Methods/measures	Patients: NorCog for sociodemographic, clinical and functional characteristics, AD diagnosis ICD-10 criteria, bvFTD diagnosis Neary or Consensus criteria, PPA diagnosis Mesulam criteria Clinical Dementia Rating scale sum-of-boxes score (CDR) for dementia severity, Cornell Scale for Depression in Dementia, Reed anosognosia scale for disease awareness QoL-AD proxy version for QoL Caregivers: NorCog for sociodemographic and clinical characteristics, Relatives' Stress Scale (RSS) for burden (score 0-60, higher scores indicate higher burden), Montgomery-Åsberg Depression Rating Scale (MADRS) for depression (score 0-60, ≥7 indicates depression), Resource Utilization in Dementia Lite (RUD Lite) for hours of informal assistance, QoL-AD for QoL

	Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	88 caregivers, 70 (80%) completed 2-year follow-up (thereof five newly introduced upon follow-up), no significant difference in QoL-AD scores or sex distribution between AD and FTD groups Baseline: 2-year follow-up: 34% of patients had become nursing home residents, two main trajectories of QoL development: one group with higher initial QoL and stable pattern (“better QoL”) and other group with lower initial QoL and significant linear decline (“lesser QoL”), only higher burden in RSS significantly associated with lesser QoL group Significant decline in QoL in AD caregivers, stable in FTD caregivers – no difference in QoL change in time trend Significantly higher mean QoL at follow-ups in FTD caregivers; in AD significantly higher QoL when caring for a woman, no differences in both groups for patient gender over time Lower QoL scores significantly associated with high burden and depressive symptoms in caregivers Higher QoL scores significantly associated with female caregiver gender
Limitations	Self-reported: - limited sample size - Limited follow-up time - Mixed caregiver population (spousal/other) - QoL-AD questionnaire used for caregivers (originally designed for PwD) - Proxy reports for PwD Possible wrong number in Tab. 2 representing FTD and AD diagnoses of patients

1.1.8 Koyama et al. 2018

Reference	Koyama, Asuka; Hashimoto, Mamoru; Fukuhara, Ryuji; Ichimi, Naoko; Takasaki, Akihiro; Matsushita, Masateru et al. (2018): Caregiver Burden in Semantic Dementia with Right- and Left-Sided Predominant Cerebral Atrophy and in Behavioral-Variant Frontotemporal Dementia. In *Dementia and geriatric cognitive disorders extra* 8 (1), pp. 128–137. DOI: 10.1159/000487851.
Type	Controlled cross-sectional cohort study
Location/Country	Japan
Aim/subject	To assess caregiver burden in three types of FTD
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment,	n=43 patient/caregiver dyads: n=20 bvFTD, n=13 SD [L>R], n=10 SD [R>L] first-visit outpatients in dementia clinic in Kumamoto, atrophy focus diagnosed through MRI and SPECT, left-handed and ambidextrous SD patients excluded

caregiver relationship to patient, initial scores)	bvFTD patients (mean/SD): age 66.3 (9.9) years, 10 male, 10 female, education 11.7 (2.5) years, illness duration 2.8 (2.2) years (MMSE, PSMS, IADL, NPI and CDR severity reported) bvFTD caregivers: 14 spouses, 6 children, 5 male, 15 female SD [L>R] patients (mean/SD): age 71.2 (6.9) years, 4 male, 9 female, education 10.6 (2.4) years, illness duration 2.8 (3.3) years (MMSE, PSMS, IADL, NPI and CDR severity reported) SD [L>R] caregivers: 6 spouses, 6 children, 1 other, 4 male, 9 female SD [R>L] patients (mean/SD): age 66.4 (6.8) years, 6 male, 4 female, education 12.4 (4.2) years, illness duration 2.6 (1.7) years SD [R>L] caregivers: 7 spouses, 3 children, 3 male, 7 female
Methods/measures	Patients: Mini Mental State Examination (MMSE) for cognitive function, Clinical Dementia Rating (CDR) scale for dementia severity, Physical Self- Maintenance Scale (PSMS) for ADL, Lawton IADL scale for instrumental ADL (three domains excluded for gender differences), Neuropsychiatric Inventory (NPI) for BPSD Caregivers: Japanese Zarit Burden Interview (J-ZBI), score range 0-88, higher scores indicate higher burden Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Significant difference in MMSE scores between diagnostic groups (SD L>R lower scores than SD R>L); significant differences in PSMS and IADL (lower scores for bvFTD than SD); no significant differences between demographic features, illness duration, NPI, CDR; no significant differences in caregiver characteristics No significant differences in BPSD; apathy especially high in bvFTD Significantly higher ZBI scores in bvFTD group; no significant difference between SD [L>R] and SD [R>L] groups No significant ZBI correlation with age, education or illness duration; Significant ZBI correlation with PSMS and IADL scores in bvFTD group; Significant ZBI correlation with IADL in SD [R>L] group; Significant ZBI correlation with NPI in all groups Significant ZBI correlation with depression/dysphoria in SD [L>R] group
Limitations	Self-reported: relatively small sample size, no longitudinal study, no PNFA patients

1.1.9 Kücükgüclü et al. 2017

Reference	Kucukguclu, Ozlem; Soylemez, Burcu Akpinar; Yener, Gorsev; Barutcu, Canan Demir; Akyol, Merve Aliye (2017): Examining Factors Affecting Caregiver Burden. A Comparison of Frontotemporal Dementia and Alzheimer's Disease. In *American journal of Alzheimer's disease and other dementias* 32 (4), pp. 200–206. DOI: 10.1177/1533317517703479.
Type	Controlled cross-sectional comparative study

Location/Country	Turkey
Aim/subject	To compare caregiver burden between FTD and AD caregivers and its influencing factors
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	n=134 patient/caregiver dyads, n=90 AD patients, n=44 FTD → n=25 bvFTD, n=14 nfvPPA, n=6 svPPA Patient exclusion criteria: psychiatric disorders (severe depression, schizophrenia, bipolar disorder), other neurological diseases, other type of dementia Caregiver inclusion criteria: family member of patient, primary caregiver, minimum of 3h/daily care; exclusion criteria: visual, hearing, or speech impairments AD patients: 56 female (62.6%), education level literate 18 (20.0%), primary school 27 (41.1%), high school 19 (21.1%), university 16 (17.8%); age (mean/SD) 76.70 (8.62) years AD caregivers: 60 female (66.7%), education level primary school 18 (20%), high school 34 (37.8%), university 38 (42.2%); spouse 33 (36.7%), patient being the mother 42 (46.7%), the father 12 (13.3%), relatives 3 (3.3%); income < expenditure 21 (23.3%), = expenditure 53 (58.9%), > expenditure 16 (17.8%); working 19 (21.1%), not working 71 (78.9%); caregiving <1 year 12 (13.3%), 1 to 5 years 45 (50.0%), ≥6 years 33 (36.7%); age (mean/SD) 57.41 (11.60) years FTD patients: 20 female (45.5%), education level literate 5 (11.4%), primary school 15 (34.1%), high school 7 (15.9%), university 17 (38.6%); age (mean/SD) 67.28 (9.30) years FTD caregivers: 38 female (86.4%), education level primary school 7 (15.9%), high school 17 (38.6%), university 20 (45.5%); spouse 21 (47.7%), patient being the mother 14 (31.8%), the father 4 (9.1%), relatives 5 (11.4%); income < expenditure 4 (9.1%), = expenditure 27 (61.4%), > expenditure 13 (29.5%); working 13 (29.5%), not working 31 (70.5%); caregiving <1 year 5 (11.4%), 1 to 5 years 20 (45.5%), ≥6 years 19 (43.2%); age (mean/SD) 52.68 (14.86) years
Methods/measures	Patients: sociodemographic characteristics questionnaire, NPI for neuropsychiatric symptoms, FAQ for everyday life task performance, MMSE for cognitive function Caregivers: Sociodemographic characteristics questionnaire, Caregiver Burden Inventory (CBI) Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	CBI: more burden on time dependence subscale than on emotional subscale in both groups; time dependency subscale significantly higher in FTD caregivers Total FAQ and NPI scores correlated significantly with CB in AD and FTD; no significant correlation between MMSE scores and CB; NPI and FAQ scores higher in FTD than in AD, MMSE scores lower in FTD than in AD

	Factors affecting CB in AD: total FAQ and NPI scores correlated significantly with CB; delusion most frequent BPSD but not strongest CB correlation; aberrant motor behavior correlated significantly with CB Factors affecting CB in FTD: total FAQ and NPI scores correlated significantly with CB; apathy most frequent BPSD but not strongest CB correlation; hallucinations, euphoria, and sleep disturbances correlated significantly with CB
Limitations	- Caregivers restricted to family members

1.1.10 Liu et al. 2018

Reference	Liu, Shuai; Liu, Jing; Wang, Xiao-Dan; Shi, Zhihong; Zhou, Yuying; Li, Jing et al. (2018): Caregiver burden, sleep quality, depression, and anxiety in dementia caregivers. A comparison of frontotemporal lobar degeneration, dementia with Lewy bodies, and Alzheimer's disease. In *International psychogeriatrics* 30 (8), pp. 1131–1138. DOI: 10.1017/S1041610217002630.
Type	Controlled cross-sectional comparative study
Location/Country	China
Aim/subject	To compare caregivers of AD, FTLD, and DLB patients in their caregiver situation
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	n=492 patient/caregiver dyads from Tianjin Huanhu outpatient clinic (03/2011-01/2014), informed consent provided n=131 FTLD, n=36 DLB, n=325 AD FTLD patients (mean/SD): age 68.00 (8.83) years, 47 male (35.88%), dementia duration 63.44 (17.95) months FTLD caregivers (mean/SD): age 58.27 (13.46) years, 32 male (62.60%)?, 87 spouses (66.67%), children 44 (33.33%) DLB patients (mean/SD): age 72.73 (9.33) years, 19 male (52.75%), dementia duration 53.58 (25.72) months DLB caregivers (mean/SD): age 61.31 (11.09) years, 12 male (33.33%), 21 spouses (57.69%), 15 children (42.31%) AD patients (mean/SD): age 70.67 (8.96) years, 132 male (40.62%), dementia duration 45.28 (20.51) months AD caregivers (mean/SD): age 60.58 (12.69) years, 175 male (53.85%), 194 spouses (59.55%), 131 children (40.45%)
Methods/measures	Patients: socio-demographic characteristics, MMSE for cognitive function, ADL questionnaire for ADL (as per caregiver observation), Chinese NPI for neuropsychiatric disturbance (range 0-144, higher scores indicating higher disturbance) Caregivers: sociodemographic characteristics, ZBI for caregiver burden (range 0-88, higher scores indicating higher burden), Patient Health Questionnaire-9 (PHQ-9) for depression (range 0-27, higher scores indicating higher depression), Generalized Anxiety Disorder

	scale (GAD-7) for anxiety (range 0-21, higher scores indicating greater anxiety), Pittsburgh Sleep Quality Index (PSQI) for sleep quality (range 0-21, higher scores indicating poorer sleep quality) Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	No significant differences in socio-demographic characteristics, however FTLD disease duration significantly longer compared to AD FTLD patients exhibited significantly higher neuropsychiatric disturbances than AD patients, no significant differences in MMSE and ADL scores FTLD caregivers had significantly higher burden, depression, and anxiety scores and had significantly poorer sleep quality than AD caregivers – in linear regression, delusions, apathy, GAD-7 scores, and PHQ-9 scores accounted for 72.0% of the variance of ZBI scores No significant differences in socio-demographic characteristics and disease duration between DLB and AD groups DLB patients had significantly higher NPI scores than AD patients, no significant differences in MMSE and ADL scores DLB caregivers had significantly higher burden, depression, and anxiety scores and had significantly poorer sleep quality than AD caregivers – in linear regression, NPI and GAD-7 scores accounted for 66.9% of variance in ZBI scores Higher burden in FTLD and DLB caregivers might be related to lacking support structures, because prevalence is lower than AD Caregivers might need more psychological treatment
Limitations	Self-reported: no complete characterization of caregivers, cross-sectional instead of longitudinal design - Possible faulty percentage at FTLD caregiver gender rate - No comparison of FTLD and DLB

1.1.11 Mukherjee et al. 2017

Reference	Mukherjee, Adreesh; Biswas, Atanu; Roy, Arijit; Biswas, Samar; Gangopadhyay, Goutam; Das, Shyamal Kumar (2017): Behavioural and Psychological Symptoms of Dementia. Correlates and Impact on Caregiver Distress. In *Dementia and geriatric cognitive disorders extra* 7 (3), pp. 354–365. DOI: 10.1159/000481568.
Type	Controlled cross-sectional study
Location/Country	India
Aim/subject	To assess behavioral and psychological symptoms in different types of dementia and their impact on caregiver distress
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home,	n=107 patients recruited in cognitive tertiary care clinic and their caregivers (= person that provided regular care/management and spent most of the time with the patient), informed consent and ethics approval provided

care facility], initial treatment, caregiver relationship to patient, initial scores)	AD 61.7%, FTD (all bvFTD) 17.8% (n=19), VaD 10.3%, mixed dementia 6.5%, DLB 3.7% Total patients (mean/SD): age 66.6 (9.36) years, 70 male (65.42%), 37 female (34.58%), education level illiterate 15 (14.02%), primary 32 (29.91%), secondary 27 (25.23%), graduate 33 (30.84%), residence rural 31 (28.97%), urban 76 (71.03%) (dementia severity as per CDR-G, CDR-SOB and IADL-E CDI provided) FTD patients (mean/SD): age 59.32 (9.26) years, 17 male (89.47%), 2 female (18.18%), education level illiterate 3 (15.79%), primary 3 (15.79%), secondary 7 (36.84%), graduate 6 (31.58%), residence rural 10 (52.63%), urban 9 (47.37%), CDR G 0.5 – 0 (0%), 1 – 9 (47.37%), 2 – 6 (31.58), 3 – 4 (21.05%) (CDR-SOB and IADL-E CDI provided) Characteristics for AD, VaD, mixed dementia, and DLB groups provided
Methods/measures	Patients: Clinical Dementia Rating Scale (CDR) for dementia severity → CDR global score (CDR-G, stages 0.5, 1, 2, 3) and CDR sum-of-boxes score (CDR-SOB), Instrumental Activities of Daily Living in the elderly (IADL-E) for ADL → IADL Cognitive Disability Index used (IADL CDI) derived from disability ratings NPI for BPSD assessment (12-item score) Caregivers: NPI-Distress (NPI-D) for caregiver distress Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	- no significant differences in education or residence between groups, however significantly more female AD patients - CDR-G and IADL impairments similar in all groups - 99.1% of patients hat at least 1 BPSD, 71% had 4 or more BPSD - Magnitude of BPSD significantly higher in FTLD (followed by DLB) - Aberrant motor behavior significantly more frequent in FTLD (68.42%) - Non-significant higher frequency of disinhibition - Predominant BPSD: agitation, apathy, appetite and eating disorders, aberrant motor behavior, sleep disorders, and irritability - Overall number of BPSD correlated strongly with CDR-SOB score – all individual symptoms except for anxiety and elation showed a significant positive correlation with increasing dementia severity and dementia duration (except for hallucinations, aberrant motor behavior, anxiety, and elation) - All BPSD except for anxiety and elation showed significant positive correlation with IADL CDI scores - Caregiver distress increased significantly with increasing number and magnitude of BPSD - In multiple linear regression, all individual BPSD symptoms were predictors of caregiver distress, except for elation

	- Relatively higher number of VaD and FTD and younger age of onset compared to Western countries, but similar to data from India
Limitations	Self-reported: - referral bias (study conducted in tertiary care clinic) - Small sample size, distorted proportions of diagnoses - Cross-sectional design does not allow to establish causal relationships - No autoptic confirmation of diagnoses (diagnostics where however made according to current consensus criteria) No caregiver characteristics, separate comparison of caregiver distress between groups

1.1.12 Ratti et al. 2017

Reference	Ratti, Elena; Jaeger, Judith; Huang, Ellen; Petrillo, Jennifer; Wager, Carrie; Boxer, Adam et al. (2017): A STUDY TO MODEL RATES OF CHANGE ON NEUROPSYCHOLOGICAL TEST MEASURES IN SUBJECTS DIAGNOSED WITH BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA AND HEALTHY SUBJECTS. In *Alzheimer's & Dementia* 13 (7, Supplement), P1259 - P1260. DOI: 10.1016/j.jalz.2017.06.1880.
Type	Poster abstract, controlled comparative longitudinal study
Location/Country	USA
Aim/subject	To identify cognitive measures to predict progression in bvFTD and to predict changes symptoms, QoL, function, and caregiver burden
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	n=70 participants, n=40 early-stage bvFTD and their caregivers, n=30 healthy volunteer controls matched by age and education, enrolled in 10 FTD centers in the US
Methods/measures	13 monthly visits to undergo cognitive testing, patient/caregiver group: behavioral, functional, QoL and caregiver burden assessment Quarterly site visits to undergo further testing with a clinician (Modified CDR, NPI, Clinical Global Impression of Change) Voluntary blood samples for DNA/RNA and biomarker testing Expected minimal "standardized effect size" 0.76 SD unjts Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Study design – results to be reported in the future
Limitations	- Only study design with no data

1.1.13 Sani et al. 2019

Reference	Sani, Tara P.; Bond, Rebecca L.; Marshall, Charles R.; Hardy, Chris J. D.; Russell, Lucy L.; Moore, Katrina M. et al. (2019): Sleep symptoms in syndromes of frontotemporal dementia and Alzheimer's disease. A proof-of-principle behavioural study. In *eNeurologicalSci*, p. 100212. DOI: 10.1016/j.ensci.2019.100212.
Type	Controlled cross-sectional cohort study
Location/Country	United Kingdom
Aim/subject	To assess sleep disturbances in FTD patients and their consequences
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	n=40 FTD (n=19 bvFTD, n=11 SD, n=10 PNFA), n=39 AD (n=27 typical AD [tAD], n=12 posterior cortical atrophy [PCA]), n=25 healthy controls (CG) relatively young AD cohort selected to facilitate comparison with FTD group all patients with mild to moderate cognitive impairment and living at home bed partner (primary caregiver) to provide information about sleeping behavior, informed consent and ethical approval provided genetic mutations in FTD group: n=3 GRN, n=2 MAPT, n=4 C9orf72 all FTD patients (mean/SD): age 65.5 (8.1) years, 25 male, years since symptom onset 5.0 (3.2) years, MMSE 23.2 (7.1), 2 AChEI users, 19 antidepressant users, 1 benzodiazepine user bvFTD patients (mean/SD): age 65.3 (7.9) years, 13 male, years since symptom onset 5.1 (4.0), MMSE 21.0 (6.0), 1 acetylcholine esterase inhibitor user (AChEI), 8 antidepressant users SD patients (mean/SD): age 63.0 (6.3) years, 8 male, years since symptom onset 5.5 (2.3), MMSE 23.1 (7.9), 7 antidepressant users, 1 benzodiazepine user PNFA patients (mean/SD): age 69.9 (8.9) years, 4 male, years since symptom onset 4.3 (2.2), MMSE 21.8 (8.7), 1 AChEI user, 4 antidepressant users all AD patients (mean/SD): age 62.9 (7.0) years, 16 male, years since symptom onset 5.1 (2.9), MMSE 21.0 (4.9), 36 AChEI users, 6 memantine users, 12 antidepressant users tAD patients (mean/SD): age 64.4 (7.9) years, 14 male, years since symptom onset 4.9 (2.7), MMSE 19.7 (4.8), 25 AChEI users, 4 memantine users, 7 antidepressant users PCA patients (mean/SD): age 62.7 (4.6) years, 2 males, years since symptom onset 5.5 (3.3), MMSE 14.0 (3.7), 11 AChEI users, 4 memantine users, 7 antidepressant users
Methods/measures	Caregiver reports; domains relevant to sleep from Cambridge Behavioral Inventory (Revised) and Pittsburgh Sleep Quality Index

	Newly created sleep questionnaire: time of retiring and rising, calculated time spent in bed, difficulty sleeping (frequent arousals, delay in falling asleep), excessive daytime somnolence, disruptive sleep events (e.g. nightmares) in healthy CG, disruptive behavior as reported by caregivers Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	No significant demographic differences between AD and FTD groups, more AChEI users in AD group, lower MMSE score in FTD and AD groups compared to CG Time overnight in bed: combined AD group spent significantly more time in bed than CG, no significant difference between combined FTD group and CG, combined AD group significantly longer in bed than combined FTD group; no significant differences in comparisons between syndromic subgroups and CG Time of retiring to bed significantly earlier in AD and FTD combined groups than CG, no differences in time of rising, no differences in syndromic subgroups; different timespans in bed – bvFTD and tAD on average 13h, SD range from 2 to 12 h (4 to 11 h in healthy CG), FTD and AD groups retiring earlier than CG Difficulty sleeping: odds for experiencing difficulty sleeping significantly higher in FTD and AD combined groups compared to CG, no difference between AD and FTD groups, most pronounced odds increase in bvFTD group compared to CG; SD and PNFA did not show difference; both tAD and PCA groups had significantly higher odds for sleeping difficulty than CG, 80% of bvFTD and 60% in other syndromic subgroups experienced sleeping difficulties compared to 27% in CG Excessive daytime somnolence: combined FTD and AD groups as well as all syndromic subgroups showed significantly more daytime somnolence than CG, combined FTD group significantly more likely to experience excessive daytime somnolence than AD group, 80% of FTD patients and 50% of AD patients experienced excessive daytime sleepiness Disruptive sleep events: no significant difference in disruptive sleep events in AD and FTD combined groups compared to CG, significantly higher odds of experiencing disruptive sleep events in FTD group compared to AD group Genetic mutation cases: all patients with genetic mutations experienced difficulty sleeping, six experienced excessive daytime somnolence, all patients with C9orf72 mutations experienced disruptive sleep events, the other patients with genetic mutations did not Sleep symptom correlates: over combined patient cohort, difficulty sleeping and excessive daytime somnolence were strongly associated, no other significant associations; disease duration was

	not significantly correlated with sleep symptoms in either the FTD or the AD groups Genetic associations with sleep disruptions might be relevant, sleep disturbances as a major contributor to caregiver burden
Limitations	Self-reported: small sample size, need for validation of the newly created sleep survey, broad approach with general questions (e.g. time spent in bed not equal to time spent sleeping, sleep disruptions), second-hand reports from caregivers, longitudinal data missing - No caregiver characteristics

1.1.14 Southi et al. 2019

Reference	Southi, Natalie; Honan, Cynthia A.; Hodges, John R.; Piguet, Olivier; Kumfor, Fiona (2019): Reduced capacity for empathy in corticobasal syndrome and its impact on carer burden. In *INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY* 34 (3), pp. 497–503. DOI: 10.1002/gps.5045.
Type	Controlled cross-sectional study
Location/Country	Australia
Aim/subject	To assess empathy functions in CBS patients and its effect on caregiver burden
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	n=29 CBS patients with their caregivers, n=28 healthy age- and education-matched controls (CG) recruited from FRONTIER dementia research clinic in Sydney between 01/2008 and 05/2016; inclusion of CBS patients with completed IRI scale Exclusion criteria: prior mental illness, significant head injury, cerebrovascular disease, substance abuse, use of psychotropic medication, limited proficiency of English language, lack of reliable informant Informed consent and ethical approval provided Caregivers: 26 spouses/partners, 2 children, 1 sibling; 15 male, 14 female CBS patients (mean/SD): age 67.4 (7.4) years, 12 male, education 11.8 (3.5) years, disease duration 3.8 (2.2) years, FRS 0.4 (1.2) Control group (mean/SD): age 67.9 (6.1) years, 13 male, education 13.2 (1.8) years
Methods/measures	Patients/CG: Frontotemporal Dementia Rating Scale (FRS) for patients, CDR for CG; Addenbrooke's Cognitive Examination-Revised (ACE-R) or ACE-III for cognitive function, Trail Making Test and Digit Span for attention, Digit Span for Working Memory, SYDBAT for language, Rey Complex Figure Test for episodic memory and visuospatial abilities, Trail Making Test and Hayling Sentence Completion Test for executive function, Facial Affect and Identity Discrimination Task for emotion processing skills Interpersonal Reactivity Index (IRI) for empathy assessment; four subscales: perspective taking, fantasy, empathic concern, personal

	distress – at present time and before disease for patients, completed by caregivers; self-report by CG Caregivers: short ZBI, score range 0-48, cutoff ≥12 for high levels of burden Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	No significant difference in age and education between CBS and CG groups, on average CBS patients showed moderate functional impairment Neuropsychological assessment: CBS patients with impaired overall cognitive ability, attention, working memory, episodic memory, language, executive function, facial identity and emotion processing when compared to CG Empathy: CBS diagnosis had significant effect on IRI scores, CBS patients rated lower in perspective taking and fantasy than CG, trend for lower ratings in empathic concern, higher levels of personal distress in CBS patients than CG, no effect of gender; significant difference in perspective taking, empathic concern, and personal distress between time before disease onset and present time in CBS group; marginally significant increase of fantasy subscale in CBS group compared to time before disease onset Caregiver burden: mean ZBI 14.0 (SD 9.2) with 58.6% scoring ≥12 → high level of burden, no gender differences; correlation with total ACE score, empathic concern subscale, and perspective taking subscale In regression analysis, ACE total score predicted 11.1% of variance in caregiver burden, perspective taking and empathic concern predicted 14.9% of variance, empathic concern trended towards being a significant predictor with a prediction of 9.7% of unique variance in caregiver burden
Limitations	Self-reported: proxy IRI ratings by caregivers, retrospective report, cross-sectional design

1.1.15 Takeda et al. 2019

Reference	Takeda, Akitoshi; Sturm, Virginia E.; Rankin, Katherine P.; Ketelle, Robin; Miller, Bruce L.; Perry, David C. (2019): Relationship Turmoil and Emotional Empathy in Frontotemporal Dementia. In *ALZHEIMER DISEASE & ASSOCIATED DISORDERS* 33 (3), pp. 260–265. DOI: 10.1097/WAD.0000000000000317.
Type	Controlled retrospective cross-sectional study
Location/Country	USA
Aim/subject	To assess relationship problems in FTD and their connection to emotional empathy
Participants (number, patient diagnosis, gender,	n=483 patients (n=156 bvFTD, n=72 svPPA, n=38 nfvPPA, n=49 CBS, n=45 PSP-S, n=123 AD) recruited from the Memory and Aging Center of the University of California in San Francisco

age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	bvFTD patients (mean/SD): age 60.94 (8.50) years, 94 male, MMSE 21.84 (7.51), CDR 1.33 (0.74), CDR-SB 7.50 (3.63), NPI 45.76 (21.39), IRI-EC 18.78 (6.53), IRI-PT 12.21 (5.34) nfvPPA patients (mean/SD): age 66.47 (9.93) years, 14 male, MMSE 23.53 (7.32), CDR 0.51 (0.41), CDR-SB 2.17 (2.04), NPI 12.58 (13.68), IRI-EC 25.47 (5.02), IRI-PT 21.44 (5.44) svPPA patients (mean/SD): age 63.50 (6.58) years, 36 male, MMSE 22.17 (7.54), CDR 0.78 (0.52), CDR-SB 4.34 (3.12), NPI 31.49 (19.95), IRI-EC 22.92 (7.68), IRI-PT 15.42 (6.72) CBS patients (mean/SD): age 65.51 (8.57) years, 21 male, MMSE 24.33 (4.99), CDR 0.72 (0.59), CDR-SB 3.57 (3.29), NPI 22.96 (16.47), IRI-EC 23.78 (7.07), IRI-PT 19.27 (6.32) PSP-S patients (mean/SD): age 68.82 (7.29) years, 22 male, MMSE 25.42 (4.73), CDR 0.87 (0.67), CDR-SB 4.84 (3.78), NPI 29.26 (18.80), IRI-EC 23.95 (7.07), IRI-PT 20.29 (7.13) AD patients (mean/SD): age 66.93 (10.78) years, 56 male, MMSE 20.80 (5.98), CDR 0.89 (0.42), CDR-SB 4.95 (2.50), NPI 19.07 (16.03), IRI-EC 26.79 (5.16), IRI-PT 19.05 (6.14)
Methods/measures	Patient: NPI for behavioral symptoms, MMSE for global cognitive function, CDR for and CDR-sum of boxes (CDR-SB) score for functional impairment (higher scores indicating higher impairment), Interpersonal Reactivity Index (IRI) empathic concern (IRI-EC) and perspective taking (IRI-PT) subscales for empathy, higher scores indicate greater empathy; IRI subscales completed by caregiver proxy report (caregivers with close contact to the patient, may or may not have been patients' romantic partners), all variables derived from first available time point in patient's history Relationship status: obtained by reviewing visit notes, demographic forms, caregiver and patient reports; marital status at disease onset, current marital or relationship status, age at most recent marriage, lifetime number of marriages, recent changes (since time 5 years preceding disease onset) in relationship status, infidelity (attempting to engage or participating in sexual activity with another) on part of the patient or their partner, estrangement from family Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Group differences: AD and bvFTD groups had lowest MMSE scores, bvFTD group showed greater functional impairment compared to other groups in CDR and CDR-SB scores, bvFTD group had highest behavioral disturbance as measured by NPI scores; bvFTD and nfvPPA groups had significantly lower IRI-EC and IRI-PT scores than other groups IRI ratings: in 77.2% of all cases, informant was the romantic partner; informant type did not differ significantly across groups; no significant difference in IRI ratings in informant groups (partner vs. non-partner)

	Relationship status: - age and sex differed significantly → covariates in comparisons; no significant differences in currently married, currently in a relationship, currently widowed, number of years in current marriage, lifetime number of marriages; no reported infidelity on partners' side - relationship dissolution (separation or divorce within 5 years from disease onset) and infidelity on patient's part higher in bvFTD, relationship dissolution preceded the neurodegenerative diagnosis in 16 out of 19 patients, of the 16 patients who experienced separation or divorce with an IRI, 5 informants were ex-partners, their ratings did not differ significantly with the ratings from the other 11 - in bvFTD, frequency of relationship dissolution (9.80%) was significantly higher than in AD (0.81%); martial infidelity was significantly higher in bvFTD (11.54%) than in AD or svPPA (both 0%); highest frequency of estrangement from family in bvFTD (2.56%) but no significant difference to other groups Regression analysis: IRI-EC scores were a significant predictor for relationship dissolution, no significant predictors of infidelity across all diagnoses; all patients with infidelity had bvFTD; bvFTD patients who experienced relationship dissolution had significantly lower IRI-EC scores than those who did not, bvFTD patients who exhibited infidelity had lower IRI-EC and IRI-PT scores; bvFTD patients who experienced relationship dissolution had significantly higher CDR scores (in contrast to findings across all diagnoses); MMSE, CDR-SB and NPO scores did not differ significantly between bvFTD patients who experienced relationship dissolution or infidelity and those who did not
Limitations	Self-reported: reliance on clinical documentation to assess relationship status history, empathy and behavior ratings by caregivers, underestimation of relationship issues in a cohort with an informant (estranged patients are more unlikely to participate in this kind of study) Small sample size especially for PPA and PSP-S groups No caregiver/informant characteristics

1.1.16 Wells et al. 2019

Reference	Wells, Jenna L.; Brown, Casey L.; Hua, Alice Y.; Soyster, Peter D.; Chen, Kuan-Hua; Dokuru, Deepika R. et al. (2019): Neurodegenerative Disease Caregivers' 5-HTTLPR Genotype Moderates the Effect of Patients' Empathic Accuracy Deficits on Caregivers' Well-Being. In *The American Journal of Geriatric Psychiatry* 27 (10), pp. 1046–1056. DOI: 10.1016/j.jagp.2019.04.009.
Type	Controlled cross-sectional study
Location/Country	USA
Aim/subject	To assess the association between 5-HTTLPR genotype and patient's empathic accuracy and caregiver well-being in neurodegenerative diseases
Participants (number, patient diagnosis, gender,	n=54 patient/caregiver dyads, recruited from the Memory and Aging Center of the University of California, San Francisco Informed consent and ethical approval obtained

age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	Short/short allele group (S/S), n=14 Caregivers (mean/SD): age 61.44 (8.25) years; 8 male; 10 White/European American, 4 Non-white; 13 spouses, 1 other relative (CES-D, BAI, PANAS positive, PANAS negative scores reported) Patients (mean/SD): age 61.89 (11.58) years; 6 male; 9 White/European American, 5 Non-white; 2 AD, 3 FTD, 2 MCI, 4 Motor neurodegenerative disease, 2 other neurodegenerative disease, 1 primary relative of FTD patient (empathic accuracy and CDR-Box scores reported) Short/long allele group (S/L), n=26 Caregivers (mean/SD): age 59.82 (10.40) years; 6 male; 23 White/European American, 3 Non-white; 24 spouses, 1 other relative, 1 friend (CES-D, BAI, PANAS positive, PANAS negative scores reported) Patients (mean/SD): age 62.98 (9.96) years; 18 male; 17 White/European American, 9 Non-White; 2 AD, 11 FTD, 0 MCI, 10 Motor neurodegenerative disease, 0 other neurodegenerative disease, 3 primary relatives of FTD patient (empathic accuracy and CDR-Box scores reported) Long/long allele group (L/L), n=14 Caregiver (mean/SD): age 62.05 (11.96) years; 7 male; 12 White/European American, 2 Non-White; 12 spouses, 2 other relatives (CES-D, BAI, PANAS positive, PANAS negative scores reported) Patients (mean/SD): age 64.41 (8.39) years, 7 male; 13 White/European-American, 1 Non-White; 3 AD, 6 FTD, 2 MCI, 2 Motor neurodegenerative disease, 1 other neurodegenerative disease, 0 primary relatives of FTD patient (empathic accuracy and CDR-Box scores reported)
Methods/measures	Background: previous studies showed associations between 5-HTTLPR genotype (=short alleles) and increased risk for depression, anxiety, and suicide in presence of adversity; greater sensitivity to positive and negative environmental aspects 5-HTTLPR = serotonin-transporter-linked polymorphic region Patients: Empathic Accuracy test using a patient-rating of feelings in a character depicted by an actress CDR (box score range 0-18, higher scores indicating greater disease severity) for disease severity Caregivers: latent variable indicated by low levels of anxiety, depression, and negative affect to conceptualize well-being; Center for Epidemiologic Studies Depression Scale (CES-D; higher scores indicating greater level of depressive symptoms) for depression; Beck Anxiety inventory (BAI; higher scores indicating greater level of anxiety symptoms) for anxiety; Positive and Negative Affect Schedule for caregiver affect (PANAS), positive and negative affect subscores

	5-HTTLPR genotyping → caregivers grouped into participants with two short alleles (S/S), one short and one long allele (S/L), and two long alleles (L/L) Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Preliminary analyses: Lower patient's empathic accuracy associated with higher caregiver depression, anxiety, and negative affect levels; no association with caregiver's positive affect; association between lower empathic accuracy and greater disease severity High reliability among caregiver's depression, anxiety, and negative affect Inequality of variances of depressive symptoms across groups, but not for the other measures Structural Equation Modeling: patient empathic accuracy as a predictor of caregiver well-being Multi-Group Modeling: including 5-HTTLPR genotype improved model fit; Genotype moderated association between patient empathic accuracy and caregiver well-being Lower patient empathic accuracy predicted lower caregiver well-being only for S/S group Inclusion of patients' dementia severity, caregiver's age, sex, and race indicated suboptimal model fit; still, patient empathic accuracy was positively correlated with caregiver well-being in the S/S group only Future research needed (e.g. for effect of serotonin reuptake inhibitors), genotyping might help identify most vulnerable caregivers and provide suitable interventions
Limitations	Small sample size, inclusion of multiple covariates in the model, generalizability limited; candidate gene approach

1.1.17 Wu et al. 2018

Reference	Wu, Yu-Tzu; Clare, Linda; Hindle, V. John; Nelis, Sharon M.; Martyr, Anthony; Matthews, Fiona E.; Enha, Improving Experience Dementia (2018): Dementia subtype and living well. Results from the Improving the experience of Dementia and Enhancing Active Life (IDEAL) study. In *BMC MEDICINE* 16. DOI: 10.1186/s12916-018-1135-2.
Type	Controlled cross-sectional study
Location/Country	United Kingdom
Aim/subject	To assess the ability to live well across different dementia subtypes in PwD and their caregivers
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of	n=1283 PwD/caregiver dyads from the Improving the Experience of Dementia and Enhancing Active Life (IDEAL) study cohort – community-dwelling PwD and their caregivers from England, Scotland, and Wales; recruitment through 29 NHS sites between

residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	07/2014 and 08/2016; clinical dementia diagnosis and MMSE ≥15; informed consent and ethical approval provided Total patients (n/%): age 80+ years 482 (37.6), age 75-79 years 306 (23.9), age 70-74 years 232 (18.1), age 65-69 years 160 (12.5), age <65 years 103 (8.0); median 77 (IQR 12.0) Male 755 (58.9), female 528 (41.1) AD 715 (55.7), VaD 142 (11.1), Mixed AD and VaD 263 (20.5), FTD 45 (3.5), Parkinson's disease dementia (PDD) 43 (3.4), LBD 43 (3.4), other/unspecified 32 (2.5) Chronic conditions (89 missing): 1-2 present 611 (51.2), 3-4 present 426 (35.7), 5+ present 157 (13.1), 35% report fair or poor health Median MMSE 23.0 (IQR 6.0), 27% with no educational qualification Total caregivers: age 80+ years 216 (16.8), age 75-79 years 223 (17.4), age 70-74 years 267 (20.8), age 65-69 years 208 (16.2), age <65 years 369 (68.7), median 71 (IQR 14.0) Male 402 (31.3), female 881 (68.7); 22% with no educational qualification, 30% report fair or poor health Spouse/partner 1039 (81.0), family/friend 244 (12 friends) (19.0)
Methods/measures	Capability to live well = QoL, life satisfaction, and well-being for PwD and caregiver measures Patients: Satisfaction with Life Scale (SwLS) for life satisfaction (score range 5-35), World Health Organization 5 Well-being Index (WHO-5) for well-being (score range 0-100), Quality of Life in Alzheimer's Disease (QOL-AD) for QoL (score range 13-52), demographic data, Charlson Comorbidity Index for comorbidities Caregivers: SwLS for life satisfaction, WHO-5 for well-being, World Health Organization Quality of Life-Brief (WHOQOL-BREF) Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Patients generally reported higher scores for life satisfaction and well-being than caregivers, patterns across subtypes similar in patients and caregivers; mean scores higher in AD, lower in PDD and LBD Patients with non-AD reported lower capability to live well than AD patients; significantly lower in VaD, mixed AD/VaD, PDD, LBD, and other; significantly lower scores remained in PDD and LBD also after adjusting for chronic comorbidities, Relatively little variation between subtypes for caregivers, but lower capability to live well found in PDD and LBD caregivers Association between subtype and capability to live well relatively similar for patients with or without caregivers Caregivers had systematically lower scores in all three measures than patients, except for SwLS and WHO-5 estimates in those with PDD and LBD, that were similar No difference in AD and FTD caregivers in capability to live well – within the FTD group, bvFTD caregivers reported lower scores than those of other FTD variants, sample size too small to make comparisons within group, only mildly to moderately affected FTD patients included

Limitations	Self-reported: exclusion of patients with severe dementia, focus on patients with caregivers, diagnostics conducted by different clinicians countrywide, QoL scores between patients and caregivers not directly comparable - No information about group matching in terms of age, gender, etc.

1.1.18 Zahir et al. 2017

Reference	Zahir, Ali; Rojas-Martinez, Julio; Chiong, Winston (2017): CAREGIVER OBJECTIFYING ATTITUDES TOWARD DEMENTIA PATIENTS. CONSEQUENCES FOR CAREGIVER STRAIN AND RELATIONSHIP CLOSENESS. In *Alzheimer's & Dementia* 13 (7, Supplement), P835. DOI: 10.1016/j.jalz.2017.06.1166.
Type	Controlled cross-sectional study (poster abstract)
Location/Country	USA
Aim/subject	To assess objectifying attitudes towards dementia patients from caregivers
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	Caregivers of patients with n=76 bvFTD, n=37 svPPA, n=38 AD, and n=94 assorted other neurodegenerative syndromes
Methods/measures	Patients: Clinical Dementia Rating Scale (CDR) for disease severity Caregivers: novel questionnaire to measure hypothesized construct of objectifying attitudes towards patient, including questions like "Because my relative has a brain disease, he/she can't fully control the way he/she acts" "While my relative may like or enjoy certain things, he/she no longer understands what is important or unimportant") Factor analysis to group variables into a single latent variable Caregiver Strain Index (CSI) for caregiver strain, Relationship Closeness Scale for relationship closeness Structural equation modelling to measure relationships between latent variable, patients' disease severity, caregiver strain, and relationship closeness
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	10 variables reflected latent factor = interpreted as objectifying attitude towards patient – latent factor exhibited high reliability, with indication of model fit

	Objectifying attitude by caregivers mediates association between disease severity and caregiver strain; negatively influences relationship closeness → objectifying attitudes do not protect against caregiver strain and worsen relationship closeness
Limitations	- Poster abstract without detailed data

1.2 ALS/MND

1.2.1 Bock et al. 2017

Reference	Bock, Meredith; Duong, Y-Nhy; Kim, Anthony; Allen, Isabel; Murphy, Jennifer; Lomen-Hoerth, Catherine (2017): Progression and effect of cognitive-behavioral changes in patients with amyotrophic lateral sclerosis. In *Neurology. Clinical practice* 7 (6), pp. 488–498. DOI: 10.1212/CPJ.0000000000000397.
Type	Controlled cohort study
Location/Country	USA
Aim/subject	To assess cognitive and behavioral functions in ALS patients over time and their association with disease progression, patient QoL and caregiver burden
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	86 participants recruited at the University of San Francisco ALS center or 2 associated clinics, 49 completed follow-up (19 participants had died, 1 had underwent mechanical ventilation), additionally 43 caregivers Exclusion criteria: premorbid non-FTD dementia, comorbid neurologic diagnosis, new ALS diagnosis on day of enrolment, lack of caregiver knowing them before symptom onset Patient age: 64.8 (±11.1) years, Years of education: 16.2 (±3.1), Months of symptom duration: 62.1 (SD 63.7), 28 male, 21 female, Region of onset: Arm 16, Leg 21, Trunk 5, Bulbar 7; Use of riluzole: 30 (61.2%)
Methods/measures	Patients. - ALS Cognitive-Behavioral Screen (ALS CBS) for cognitive function (initiation and retrieval, concentration, attention, tracking/monitoring) - ALS Functional Rating Scale-Revised (ALSFRS-R) for disease severity - Center for Neurologic Study Lability Scale for Pseudobulbar affect - Geriatric depression scale (GDS) for depression - McGill QoL Single-Item Scale (MQOL-SIS) for QoL Caregiver burden: - Caregiver Burden Scale (CBS) for strain, isolation, disappointment, emotional involvement, environment Assessed at baseline and after 7 months Statistical data analyses

Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Cognitive impairment in patients: classification into three categories – normal (n = 21), cognitive impairment ALS-Ci (n = 23), frontotemporal dementia ALS-FTD (n = 5) Stratified by baseline categories, the ALS-Ci group showed a significant improvement of scores over time; normal patients tended to experience a decline compared to ALS-Ci; 15% of baseline normal patients were re-classified as ALS-Ci upon follow-up; no predictors for cognitive change found Behavioral changes in patients: stratified by behavioral normal or impaired groups; patients in the baseline normal group worsened in behavior, no significant change or trend in ALS-Ci and ALS-FTD groups; 16% of baseline normal patients were re-classified as behaviorally impaired upon follow-up; longer disease duration was associated with improved behavior Disease severity; Decline in disease stage and functional vital capacity (FVC); no difference between cognitive groups; FVC decrease was greater in behaviorally impaired groups Patient QoL: no change in QoL in cognitive groups; decline in patients with FTD-level behavioral impairment; correlation with apathy and irritability Caregiver burden: overall increase, burden of caregivers of patients with normal behavior and cognition and baseline increased significantly; no significant change in impaired groups; worsening in behavior and decline in cognition were associated with increased CB
Limitations	Self-reported: - Participants may not represent entire ALS population due to recruitment setting - Possible ceiling or floor effects in Caregiver burden evaluation - Patients without caregiver excluded - No caregiver characteristics

1.2.2 Caga et al. 2018

Reference	Caga, Jashelle; Hsieh, Sharpley; Highton-Williamson, Elizabeth; Zoing, Margaret C.; Ramsey, Eleanor; Devenney, Emma et al. (2018): The burden of apathy for caregivers of patients with amyotrophic lateral sclerosis. In *Amyotrophic lateral sclerosis & frontotemporal degeneration* 19 (7-8), pp. 599–605. DOI: 10.1080/21678421.2018.1497659.
Type	Controlled cross-sectional cohort study
Location/Country	Australia
Aim/subject	To assess the effect of apathy on caregiver burden in ALS
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home,	n=51 patient/caregiver dyads; recruitment from the ALS/FTD Clinic at the Brain and Mind Centre in Australia between 2014 and 2017; patient/main informal caregiver; paid caregivers excluded Informed consent and ethical approval provided

care facility], initial treatment, caregiver relationship to patient, initial scores)	ALS diagnosed according to El Escorial criteria, n=4 (8%) of patients with comorbid FTD according to consensus criteria Patients (mean/SD): age 62.5 (1.5) years, 34 (66.7%) male, years of education 11.6 (0.4), symptom duration 19.9 (13.1-39.0) months, limb onset 37 (72.5%), (ALS-FRS, M-ACE, MiND-B, HADS-Anxiety, and HADS-Depression total scores provided) Caregivers (mean/SD): age 60.2 (1.5) years, 14 male (27.5%), years of education 12.0 (10.0-15.0), spouse/partner 44 (86.3%), (DASS-21-Stress, DASS-21-Depression, and DASS-21-Anxiety total scores provided) Patient and caregiver data separately presented for lower burden (n=25) and higher burden (n=26) groups
Methods/measures	Patients: ALS Functional Rating Scale-Revised (ALSFRS-R) for physical status (maximum score of 48 indicating normal function), Mini-Addenbrooke's Cognitive Examination (M-ACE) for cognitive status (score range 0-30, scores ≤25 indicating cognitive impairment, motor or speech deficits accounted for); Motor Neuron Disease Behavioral Scale (MiND-B) for behavioral status (informant-completed, score range 9-36, scores ≤33 identify ALS plus patients, apathy cut-off ≤8, disinhibition ≤12, stereotypical behavior ≤4; total scores converted into percentage of impairment: 0% absent, 1%-25% mild, 26-50% moderate, 51-75% severe, 76%+ very severe) Hospital Anxiety and Depression Scale (HADS) for anxiety and depression (sub-scores range 0-21, cut-off ≥11 indicating significant levels of anxiety and depression) Apathy Evaluation Scale (AES) for apathy (informant-rated, score range 18-72, cut-off ≥41) Caregivers: sZBI for caregiver burden (score range 0-48, cut-off ≥17 for significant burden) ; Depression, Anxiety, and Stress-Scale 21 (DASS-21) for depression, anxiety, and stress (sub-scores range 0-42, depression cut-off >9, anxiety cut-off >7, stress cut-off >14 Statistical data analyses
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	One outlier with extremely high burden excluded from analysis Median M-ACE at 27.0 (24.0-29.0) and median MiND-B at 33.0 (30.0-35.0) indicate overall intact cognition and subtle behavioral impairment in the cohort; 18% below cut-off for M-ACE and MiND-B, 33% with cognitive impairment only, 53% with behavioral impairment only Apathy as the most prominent behavioral symptom (18%), followed by disinhibition (10%) and stereotypical behavior (10%); mostly mild behavioral changes ZBI median at 11 (6.0-15.0), lower and higher burdened groups relatively well matched for demographic and clinical characteristics, but higher burdened caregivers cared for patients with higher anxiety levels;

	Higher burdened caregivers cared for patients with greater behavioral and non-specific symptoms of apathy compared to lower burdened caregivers Multiple regression analysis: patient anxiety at step 1 of regression analysis explained 2% of variance in CB, step 2 added cognitive, behavioral, emotional, and nonspecific symptoms of apathy, total variance explained by the model at 35%; after controlling for patient anxiety, these symptoms of anxiety explained an additional 33% of CB variance; final model: only behavioral symptoms of apathy significant Positive association between patient depression and behavioral symptoms of apathy; strong positive partial correlation between behavioral symptoms of apathy and caregiver burden (controlling for patient depression, little effect), behavioral symptoms of apathy remained significantly associated with CB also after excluding ALS-FTD patients Behavioral symptoms similar to initiation apathy, requiring the caregiver to provide more supervision, prompting
Limitations	Self-reported: recruitment bias from specialist clinic and thus better clinical status, caregivers of severely disabled patients being unable to attend the clinic, small number of ALS-FTD patients, methodological difficulties of applying AES in this study, no verbal fluency component in M-ACE might influence results of cognitive status

2. Case reports and qualitative studies

2.1 Bryant and Miller 2018

Reference	Bryant, Rebecca; Miller, Charman (2018): Challenges of a frontotemporal dementia patient. In *Geriatric nursing (New York, N.Y.)* 39 (6), pp. 716–718. DOI: 10.1016/j.gerinurse.2018.10.009.
Type	Case study
Location/Country	USA
Aim/subject	To illustrate the challenges of caring for a community-dwelling FTD patient
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	One patient: age 62 years, male, Caucasian, living on a farm with his wife, three adult children living nearby Diagnosis: at age 58 by neurologist, initial symptoms: anomia, impaired word comprehension Baseline situation: seen by nurse practitioner at home; repetitive clucking, reduced empathy, sleep disturbances, apathy, repetitive behaviors, obsessive behaviors and aggression; did not recognize family members or friends, not able to participate in dementia screenings continent of bowel and bladder functions; feeding without assistance, unremarkable physical examination 50 mg quetiapine and 100 mg trazodone at night; little knowledge of family members ➔ Diagnosis consistent with svPPA

Methods/measures	Education of spouse and family about disease, progression monthly house call visits
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	App. 7 months after baseline visit, patient expressed more behavioral disturbances and aggression, became incontinent and experienced hallucinations; increase of quetiapine dose and added valproic acid, family members were unable to control behavior at home, no medical issue as a trigger could be identified; patient was transferred to a geriatric inpatient unit – replacement of valproic acid with gabapentine; after home period with uncontrollable behavior patient was taken to ER and subsequently to a nursing home where his symptoms could not be managed, after another transfer to the ER he was admitted to an inpatient mental health center; after treatment in an outpatient center and an inpatient memory clinic, the patient died shortly after ➔ Navigation through healthcare system was perceived as frustrating by the family members ➔ Disruptive behavior caused major sleep disturbance in family members ➔ Lack of education about the disease and (limited) treatment options ➔ Lack of support structures (e.g. nursing home places) appropriate to cater for FTD patients
Limitations	- Single case - No baseline assessment of dementia severity possible

2.2 Damianakis, Wilson and Marziali 2018

Reference	Damianakis, Thecla; Wilson, Kimberley; Marziali, Elsa (2018): Family caregiver support groups. Spiritual reflections' impact on stress management. In *Aging & mental health* 22 (1), pp. 70–76. DOI: 10.1080/13607863.2016.1231169.
Type	Qualitative study
Location/Country	Canada
Aim/subject	To present thoughts and reflections of a dementia caregiver support group
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	n=24 (n=18 AD, n=6 FTD) spousal caregivers of patients with AD or FTD, six caregivers attending one of four online video conferencing support groups, referrals from professional staff at a large urban long-term care facility, informed consent provided AD group 1: mean age 79.8 years, 4 males, 2 females AD group 2: mean age 73.3 years, 2 males, 4 females AD group 3. mean age 80.5 years, 2 males, 4 females FTD group: mean age 55.8 years, 2 males, 4 females, Spouses mean age 65.3 All community-dwelling
Methods/measures	10 weekly 1-h sessions of an online video conferencing support group, experienced facilitator (social worker), video sessions archived for analysis

	Qualitative content analysis: transcription and line-by-line coding, followed by hierarchical coding and thematic comparisons, identification of manifest and latent content and underlying themes, independent coding by two research assistants, 90% consistency in coding, specific look for content about spiritual beliefs, consensus on final themes
Interventions (where applicable)	See Methods/measures
Outcomes (variables, main findings)	Two main themes with sub-themes identified: 1) Emotional, physical, and social impact of caring for a person with AD or FTD: Personal reactions to care recipient's behavior with caregivers experiencing sadness, helplessness, frustration, confusion, loss of self and own needs, need to adapt to constantly changing behavior and abilities; Changing relationship between caregiver and care recipient: constant redefinition of relationship, in the beginning mainly empathy and compassion, later discussing negative behaviors and reactions more openly such as frustration, embarrassment at inappropriate behavior, less visitors and friends, lack of reciprocal relationship, loss of the patient's former personality and characteristics that defined relationships 2) Spirituality and meaning making: Search for meaning in caregiving with caregivers looking for something good and of value in their situation; Spiritual and religious community support with caregivers meeting helpful and supportive individuals in their religious communities (discussed in middle and later stages of the support group); Personal faith beliefs with caregivers making sense of their situation using beliefs like the ability to become stronger and learn experience something new, the need to aid another person and not solely focus on oneself, to find comfort in religious beliefs; Coping in the moment with caregivers focusing on the present time they can spend with their loved ones to cope with the uncertainty of the future, faith in the ability to manage in the future; Gratitude in relation to the care recipient with caregivers appreciating moments of love with the patient and using them as a source of strength for the future, the feeling of returning support after lifelong devotion, Refocus on sense of self with caregivers expressing the importance of starting to pay more attention to their selves again in order to provide good care, some participants willing to volunteer to help others going through the same experience Participants identified with each other's struggles, mutual understanding and validation, leading to the discussion of more individual experiences, thoughts, and coping strategies; feeling of self-esteem improved, generally perceived as helpful and important; video technology can be used effectively
Limitations	Analysis did not include demographic factors, gender, race, and income, or religious affiliation and their possible impact on

	responses; spontaneous and unsolicited discussions instead of formalized intervention - No report of group differences or similarities between AD and FTD groups

2.3 Johannessen et al. 2017

Reference	Johannessen, Aud; Helvik, Anne-Sofie; Engedal, Knut; Thorsen, Kirsten (2017): Experiences and needs of spouses of persons with young-onset frontotemporal lobe dementia during the progression of the disease. In *Scandinavian journal of caring sciences* 31 (4), pp. 779–788. DOI: 10.1111/scs.12397.
Type	Qualitative Interview study
Location/Country	Norway
Aim/subject	To illustrate the situation of spouses of patients with young onset FTLD
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	16 spouses or partners of patients with young onset (yo-) FTLD recruited from seven memory clinics, informed consent and ethical approval obtained Caregiver 1: wife, 51 y/o, working (sick leave), hospital support/psychological support Patient 1: age at diagnosis 48 y, 3 y since diagnosis, 1y/6 months with symptoms before diagnosis, working (sick leave) at diagnosis, died four months ago Caregiver 2: wife, 60 y/o, disability benefits, hospital support/support group Patient 2: age at diagnosis 61 y, 4 months since diagnosis, 3 y with symptoms before diagnosis, sick leave at diagnosis, hospital support Caregiver 3: wife, 54 y/o, disability benefits, hospital support Patient 3: age at diagnosis 57 y, 1 y since diagnosis, 3 y with symptoms before diagnosis, retired at diagnosis, day care 1×/week Caregiver 4: wife, 56 y/o, working (sick leave), hospital support/support group Patient 4: age at diagnosis 57 y, 1 y/5 months since diagnosis, 5 y with symptoms before diagnosis, sick leave at diagnosis, hospital support/day care Caregiver 5: wife, 56 y/o, working, hospital support Patient 5: age at diagnosis 59 y, 6 months since diagnosis, 9 y with symptoms before diagnosis, no work/disability benefits at diagnosis, no formal services Caregiver 6: wife, 58 y/o, working (disability benefits), hospital support/support groups Patient 6: age at diagnosis 63 y, 1 y since diagnosis, 10 y with symptoms before diagnosis, disability benefits at diagnosis, part time nursing home/day care

	Caregiver 7: wife, 61 y/o, working (sick leave), municipality and hospital support Patient 7: age at diagnosis 62 y, 2 y since diagnosis, 5-6 y with symptoms before diagnosis, sick leave at diagnosis, nursing home Caregiver 8: wife, 60 y/o, working, municipality support/support group Patient 8: age at diagnosis 54 y, 11 y since diagnosis, 2-4 y with symptoms before diagnosis, sick leave at diagnosis, nursing home Caregiver 9: wife, 63 y/o, working (sick leave), hospital support/support group Patient 9: age at diagnosis 67 y, 1 y since diagnosis, 4-5 y with symptoms before diagnosis, working at diagnosis, hospital support Caregiver 10: wife, 64 y/o, working (sick leave), hospital support/support groups Patient 10: age at diagnosis 64 y, 1 y/6 months since diagnosis, 11 y with symptoms before diagnosis, no work/disability benefits at diagnosis, nursing home Caregiver 11: husband, 57 y/o, working, municipality support Patient 11: age at diagnosis 55 y/o, 4 months since diagnosis, 2-3 y with symptoms before diagnosis, disability benefits at diagnosis, nursing home Caregiver 12: husband, 60 y/o, working, hospital support/support group Patient 12: age at diagnosis 55 y/o, 5 y since diagnosis, 4 y with symptoms before diagnosis, sick leave at diagnosis, nursing home Caregiver 13: husband, 60 y/o, disability benefits, hospital support Patient 13: age at diagnosis 58 y, 2 y since diagnosis, 6 y with symptoms before diagnosis, disability benefits at diagnosis, part time nursing home/day care Caregiver 14: husband, 62 y/o, working (sick leave), hospital support Patient 14: age at diagnosis 58 y, 3 y since diagnosis, 2 y with symptoms before diagnosis, working (sick leave) at diagnosis, day care Caregiver 15: partner, 62 y/o, working, hospital support Patient 15: age at diagnosis 60 y, 5 y since diagnosis, 7-8 y with symptoms before diagnosis, working (sick leave) at diagnosis, hospital support/day care Caregiver 16: husband, 69 y/o, retired, hospital support/support groups Patient 16: age at diagnosis 63 y/o, 6 months since diagnosis, 15 y with symptoms before diagnosis, disability benefits at diagnosis, day care
Methods/measures	Interviews in 2014 and 2015 with first author, between 31 and 79 mins (mean = 57 mins); recording and transcription of interviews Six open-ended questions about experience and needs with yo-FTLD Demographical and disease data

	Qualitative content analysis by two authors, identifying themes, subthemes and variations
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Three main themes with subthemes were identified: 1) Sneaking signs at the early stage of dementia: Incomprehensible early signs: Change of personality, neglect of appearance and hygiene, breaking social norms, losing manners, offensive behavior, difficulty driving; often interpreted as stress, tiredness or distraction Lack of self-insight: patients did not accept diagnosis, avoided the topic, covered up their mistakes and blamed others for it 2) Life turning upside down at the later stage of dementia: The torment: patients need constant surveillance and attention, lose their sleeping patterns and energy, some become restless and wander around, caregivers have little time for their own needs Interference with work: patients would contact spouses at work and distract them from it; however, spouses continued to work if possible because that was time away from their home responsibilities; some patients lost work due to their behavioral disturbances, lowered self-esteem and need for surveillance during the daytime hours at home; lack of income to due reduced working time from the spouse, lack of contribution from the patient, excessive spending, reluctance to apply for benefits (lack of insight), some spouses had own health problems they received disability benefits for Vanishing social relations: Loss of spouse as an intimate partner, co-parent, having to take on new roles for the partner (caregiving, supervising) and around the household (repairing, chores) and organizing the economic situation; loss of friendships due to unpleasant contact with the patient, social isolation 3) Needs for assistance through all stages of dementia Relief of the diagnosis: most spouses were shocked, but also relieved upon receiving the diagnosis and an explanation for the observed changes; some patients did not accept diagnosis, others were relieved for an explanation; difficult and prolonged diagnostic process with doctors (mainly GPs) not taking the spouse seriously, not knowing about FTLD, patient unwilling to participate in diagnostics; some stories of fast and supportive diagnostic process and support structures Support at home: many spouses attended support groups, sometimes with patients, support groups were generally seen as helpful if they were tailored to persons/caregivers with YOD, no real helpfulness in AD caregiver support groups; day care and tailored activities for the patient were appreciated in order to allow caregivers time off from caregiving or to go to work; wish for professionals to take care of administrative problems, such as applying for benefits and services The path to nursing home: difficult but often necessary process to move the patient into a nursing home because day care and home support is limited; only some institutions offer care tailored

	to the need of YOD patients and caregivers; patients sometimes reluctant to move but necessary when it affected children's well-being; for some spouses, the social contacts did not return and they felt lonely
Limitations	Self-reported: small sample size, lack of longitudinal observations, exclusion of other family members - No FTLD phenotype given

2.4 Nowaskie, Austrom and Morhardt 2019

Reference	Nowaskie, Dusitn; Austrom, Mary; Morhardt, Darby (2019): UNDERSTANDING THE CHALLENGES, NEEDS, AND QUALITIES OF FRONTOTEMPORAL DEMENTIA FAMILY CAREGIVERS. In *The American Journal of Geriatric Psychiatry* 27 (3, Supplement), S139 - S140. DOI: 10.1016/j.jagp.2019.01.047.
Type	Qualitative interview study (poster abstract) 2019 AAGP annual meeting
Location/Country	USA
Aim/subject	To allow caregivers to describe their caregiving situation for a patient with FTD from early symptoms to diagnosis and throughout the caregiving process
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	n=9 caregivers of n=5 bvFTD and n=4 PPA patients recruited from Indiana University and Northwestern university
Methods/measures	Individual in-depth interviews, recorded and transcribed Content analysis and discussion for emerging themes
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Seven themes were identified: 1) Obtaining an accurate diagnosis was a difficult and lengthy process 2) Finding lack of available information and misunderstanding the diagnosis 3) Adapting to changing roles 4) Experiencing significant financial and legal challenges 5) Grieving losses, particularly developmentally non-normative losses due to younger age of onset 6) Finding lack of disease-specific services and knowledgeable providers 7) Receiving support in disease specific programs
Limitations	Abstract without detailed data

2.5 Rasmussen et al. 2019

Reference	Rasmussen, Hege; Hellzen, Ove; Stordal, Eystein; Enmarker, Ingela (2019): Family caregivers experiences of the pre-diagnostic stage in frontotemporal dementia. In *Geriatric nursing (New York, N.Y.)* 40 (3), pp. 246–251. DOI: 10.1016/j.gerinurse.2018.10.006.
Type	Qualitative interview study
Location/Country	Norway/Sweden
Aim/subject	To explore the experiences of caregivers of persons with FTD in the time before diagnosis was made
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	14 caregivers of patients from two hospital psycho-geriatric units and one neurological unit, informed consent and ethical approval provided - Participant 1: daughter of male FTD patient, earliest symptoms age 55, diagnosed age 67 → 12 years symptoms – diagnosis - Participant 2: husband of female FTD patient, earliest symptoms age 45, diagnosed age 47 → 2 years symptoms-diagnosis - Participant 3: wife of male FTD patient, earliest symptoms age 65, diagnosed age 69 → 4 years symptoms-diagnosis - Participant 4: husband of female FTD patient, earliest symptoms age 67, diagnosed age 67 → 0 years symptoms-diagnosis - Participant 5: husband of female FTD patient, earliest symptoms age 64, diagnosed age 67, 3 years symptoms-diagnosis - Participant 6: husband of female FTD patient, earliest symptoms age 61, diagnosed age 64. 3 years symptoms-diagnosis - Participant 7: husband of female FTD patient, earliest symptoms age 45, diagnosed age 55 → 10 years symptoms-diagnosis - Participant 8: brother of female FTD patient, earliest symptoms age 65, diagnosed age 70 → 5 years symptoms-diagnosis - Participant 9: daughter of male FTD patient, earliest symptoms age 62, diagnosed age 63 → 1 year symptoms-diagnosis - Participant 10: wife of male FTD patient, earliest symptoms age 64, diagnosed age 68 → 4 years symptoms-diagnosis - Participant 11: wife of male FTD patient, earliest symptoms age 57, diagnosed age 67 → 10 years symptoms-diagnosis - Participant 12: close friend/former cohabitant of male FTD patient, earliest symptoms age 68, diagnosed age 76 → 8 years symptoms-diagnosis - Participant 13: daughter of male FTD patient, earliest symptoms age 66, diagnosed age 70 → 4 years symptoms-diagnosis

	- Participant 14: daughter of female FTD patient, earliest symptoms age 60, diagnosed age 68 → 8 years symptoms-diagnosis 35.72% husband, 21.43% wife, 7.14% close friend/cohabitant, 7.14% sibling, 28.57% children (daughters)
Methods/measures	Interview design based on Gadamerian hermeneutic tradition analyzing understanding Interviews face-to-face, semi-structured interview guide Questions about first time the loved one change and what it meant to the caregiver and sub-questions, duration 60-120 mins, all interviews recorded and transcribed Text analysis according to four steps to identify themes and passages
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Pre-diagnostic experience regarded as a process of change in the relationship to the patient with FTD; four sub-themes were established: a) becoming distant, b) becoming insecure, c) becoming devastated, and d) becoming a stranger These four steps occur in different orders among participants a) becoming distant: increasing silence and apathy in the patient, feeling of disconnection, patient easily irritable or uninterested, signs often misinterpreted as effects of stress or aging, or as symptoms of other psychiatric conditions b) becoming insecure: irritation and fright about changed situation, more noticeable withdrawal from the patient and loss of abilities and activities; noticed something was not right but hard to pinpoint or find professional help, sometimes denial of changes in the patient, patient unaware of changes, many participants talked to close friends or relatives although they sometimes felt ashamed c) becoming devastated: increased worry about the patient's safety, first step of change for some participants – especially when latency between first symptoms and diagnosis was short, noticed lack of personal hygiene and housekeeping noticeable, patients got into dangerous situations (fire, food poisoning, no heating) or committed crimes such as hazardous driving, theft, some became aggressive and abusive; leading to taking sick leave or early retirement for caregivers d) becoming a stranger: important personality traits, skills, abilities, and interests were lost in the patient, caregivers felt them to be like a stranger; tremendous feelings of guilt and helplessness; shift of roles e.g. from a beloved daughter to a caregiver to a rude mother, no insight from patients, feelings of exhaustion and depression, conflict between need for personal space and duty to provide care
Limitations	Self-reported: - caregivers in different situations of their own lives (e.g. age, relationship to the patient) and patients in different stages of disease

	- Current situation (e.g. grieving) might overshadow experiences in the pre-diagnostic shade - Text analysis may lead to different possible interpretations

2.6 Tyrrell et al. 2019

Reference	Tyrrell, Marie; Fossum, Bjoorn; Skovdahl, Kirsti; Religa, Dorota; Hilleras, Pernilla: Living with a well-known stranger. Voices of family members to older persons with frontotemporal dementia. In *INTERNATIONAL JOURNAL OF OLDER PEOPLE NURSING. DOI:* 10.1111/opn.12264.
Type	Qualitative interview study
Location/Country	Sweden
Aim/subject	To allow caregivers to describe neuropsychiatric symptoms and their experience in patients with FTD
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	Recruitment from urban geriatric outpatient clinic and urban older adult health-care center, interviews from 06/2016 to 01/2019 Inclusion criteria: family members of a person over 65 years with FTD living in a community setting Informed consent and ethical approval obtained Participant 1: 43 y/o, male, son, PwD: 73 y/o, female, semantic variant FTD, with home help Participant 2: 65 y/o, male, husband, PwD: 65 y/o, female, FTD, with home help Participant 3: 71 y/o, female, wife, PwD: 70 y/o, male, semantic variant FTD, no home help Participant 4: 76 y/o, female, wife, PwD: 74 y/o, male, FTD, no home help Participants 5 & 6: 70 y/o, female, partner & 34 y/o, female, daughter, PwD: 67 y/o, male, FTD, with home help Participant 7: 74 y/o, male, husband, PwD: 75 y/o, female, bvFTD, no home help Participant 8: 70 y/o, female, wife, PwD: 74 y/o, male, semantic variant FTD, no home help Participant 9: 70 y/o, female, wife, PwD: 70 y/o, male bvFTD, no home help
Methods/measures	Eight in-person interviews, one telephone interview; NPI-Nursing Home (NPI-NH) in the Swedish language version to assess patients' behavioral and psychiatric symptoms (questions were modified to cater for the community-dwelling environment); interview guide; Recording (45 min to 150 min) of interviews, transcriptions, NPI data integrated into responses from interviews but not analyzed separately; qualitative content analysis to identify meaning units, which were then categorized and subsumed into sub-themes and themes
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Two main themes in the responses were identified: "Living with a well-known stranger" and "Coping and overstepping social norms" Three sub-themes were identified and presented more in detail:

	1) Losing a loved one to a progressive, debilitating disease: Communication challenges due to language impairment, lack of meaningful conversations; Lacking self-insight with the patient refusing to discuss their situation and leaving them in vulnerable situations; A changed personality with the loss of the person the patient used to be before the disease and presently living a mere co-existence; Self-neglect causing the patient to neglect personal hygiene and appearance; Suicidal thoughts from the patient; Diagnosis before person leaving the caregivers unsure what to expect (e.g. patients becoming apathetic instead of disinhibited, as told by the physician) and difficulty finding FTD-specific care and support 2) Living with disinhibition and loss of control: Anti-social behavior with the patient behaving inappropriately especially in public, leading to intercalations with the police or strangers, fear of misconduct when the patient is not supervised; Loss of impulse control with the patient saying hurtful or offending things to other people or forcing their way around; Childlike behavior with the patient playing children's games or with toys, often causing irritation and embarrassment; Breaching social norms with the patient seeking contact to strangers and talk about intimate subjects in inappropriate situations, developing a gluttonous eating behavior 3) Trying hard to make things work despite struggles: Coping and problem-solving with the caregivers finding solutions to monitor or intervene in problematic behavior, e.g. tracking devices (the patient often being unaware, raising ethical concerns), monitoring their social media activities, discreetly informing others about FTD and associated behavior, some, however, regarded their situation as unsustainable unless changes occurred, some participants lost money due to the patient's behavior; Support and unmet needs with the caregivers expressing the need for more personalized approaches since social care planners are unaware of the situation, discontinuity in home assistance and a reluctance and insecurity in the patient to accept help; Fears for safety with the caregivers addressing traffic safety, disturbed eating behavior and an aphasic patient to be unable to call for help while residing alone
Limitations	Self-reported: small sample size, mixed diagnoses, some participants were uncomfortable with audio recording of the interview

3. Interventions

3.1 Armour et al. 2019

Reference	Armour, Michelle; Brady, Susan; Sayyad, Anjum; Krieger, Richard (2019): Self-Reported Quality of Life Outcomes in Aphasia Using Life Participation Approach Values. 1-Year Outcomes. In *Archives of Rehabilitation Research and Clinical Translation*, p. 100025. DOI: 10.1016/j.arrct.2019.100025.
Type	Controlled intervention study
Location/Country	USA

Aim/subject	To assess QoL and caregiver burden in participants of an aphasia care program and their caregivers
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	41 clients with aphasia - 22 male, 19 female - Mean age 65.2 (±10.5) years, age range 33-84 - 41% <1 year post onset, 47% 1-4 years, 12% >5years (range 3 months – 37 years) - Nonfluent aphasia (4 mild, 5 mild-moderate, 8 moderate, 5 moderate-severe, 8 severe) Fluent aphasia (4 mild, 1 mild-moderate, 1 moderate-severe, 5 severe) - No information on aphasia etiology 40 caregivers
Methods/measures	Patients: Stroke and Aphasia Quality of Life Scale (SAQOL-39) - Dichotomic yes/no questions on program satisfaction Caregivers: Modified caregiver strain index (MCSI)
Interventions (where applicable)	11-week aphasia center program - 27 clients/17 caregivers completed second session - 12 clients/9 caregivers completed third session - 8 clients/3 caregivers completed fourth session 3 hours of group sessions/1 time per week; targeted activities (music, technology, books, games, math, fitness); therapist facilitators
Outcomes (variables, main findings)	SAQOL-39 overall scores and physical/communication/psychosocial/energy subscores improved significantly after one session; improved scores were sustained or improved after each following session - All clients reported improved happiness or satisfaction with life - Average of 89.75% reported improved language after 1 year MCSI score pre-intervention at 10.025 (±5.04) reduced to 8.325 (±5.784) post-intervention (lower scores reflect lower caregiver burden) → significant reduction, mean reduction of 16.96%; reduction sustained after each following session
Limitations	- no information on aphasia etiology - no caregiver characteristics - no control group

3.2 Jokel et al. 2017

Reference	Jokel, Regina; Meltzer, Jed; R, J. D.; M, L. D.; C, J. J.; N, E. A.; T, C. D. (2017): Group intervention for individuals with primary progressive aphasia and their spouses. Who comes first? In *Journal of Communication Disorders* 66, pp. 51–64. DOI: 10.1016/j.jcomdis.2017.04.002.
Type	Controlled intervention study
Location/Country	Canada
Aim/subject	To present the facilitation and outcome of a group intervention for persons with PPA and their spouses
Participants (number, patient diagnosis, gender, age range, race,	n=5 patient/spouse dyads in intervention group (IG), n=5 patient/spouse dyads in control group (CG), recruited from three memory clinics in Toronto, inclusion made on first-come-first-serve basis, diagnosis of PPA according to consensus criteria

ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	IG: Participant 1: Patient 80 y/o female, lvPPA, 15 y education, generalized atrophy in MRI; spouse 85 y/o, 22 y education Participant 2: Patient 77 y/o male, nfvPPA, 12 y education, frontal atrophy and pituitary adenoma in MRI; spouse 74 y/o, 10 y education Participant 3: Patient 59 y/o male, lvPPA, 18 y education, unremarkable MRI; spouse 56 y/o, 18 years education Participant 4: Patient 75 y/o female, nfvPPA, 12 y education, unremarkable CT & MRI; spouse 79 y/o, 12 y education Participant 5: Patient 71 y/o male, nfvPPA, 12 y education, unavailable neuroimaging; spouse 58 y/o, 15 y education Mean patient age: 72.4 y/o, mean patient education: 13.8 y; mean spouse age: 70.4 y/o, mean spouse education: 15.4 y CG: Participant 1: Patient 73 y/o female, lvPPA, 19 y education, unavailable neuroimaging; spouse 75 y/o, 17 y education Participant 2: Patient 69 y/o male, nfvPPA, 12 y education, mild left frontal atrophy in CT; spouse 66 y/o, 14 y education Participant 3: Patient 55 y/o male, nfvPPA, 10 y education, unremarkable SPECT; spouse 53 y/o, 12 years education Participant 4: Patient 64 y/o male, nfvPPA, 18 y education, benign cyst in left frontal region in MRI; spouse 59 y/o, 14 y education Participant 5: Patient 67 y/o male, svPPA, 13 y education, biltateral frontal hypoperfusion in SPECT; spouse 65 y/o, 10 y education Mean patient age: 65.5 y/o, mean patient education: 14.4 y; mean spouse age: 63.6 y/o, mean spouse education: 13.4 y
Methods/measures	1) ASHA-Quality of Communication Life Scale (ASHA QCLS) for quality of communication in adults with communication disorders 2) spousal questionnaire assessing level of knowledge and coping abilities 3) Use of communication strategies as practiced in sessions 5 and 10 rated by instructor and unbiased volunteer (per video recording) 4) Qualitative feedback based on participant comments Statistical data analyses
Interventions (where applicable)	IG: 10 weekly 2h group sessions; patients engaged in general discussions during the first hour, and worked on retrieval tasks and cueing tasks with a facilitator; spouses worked on communication skills, engaged in group discussions with the other participants; the second hour was spent jointly by patients and caregivers for communication sessions or education sessions with healthcare professionals; communication strategies were practiced in session 5 and 10 of the 10 sessions; completion of outcome measures before and after the program CG: completed the same questionnaires as IG in on two occasion 10 weeks apart, no treatment or contact during this time
Outcomes (variables, main findings)	Both groups relatively matched for age and education Quality of Communication: pre-post comparison showed positive changes in IG in Participants 1, 2, and 3; no changes in either

	direction in CG – group comparison showed significant score improvement in IG only Spousal questionnaire: significant improvements in IG participants in pre-post comparisons, biggest in levels of preparedness (52% difference), knowledge of PPA (36%), awareness of progression (32%), managing psychological issues (30%) and communication challenges (29%), daily problem solving (28%), and comfort level talking about the spouse's PPA (22%); most spouses before the intervention finding information on the internet with no interactive resource; no significant changes in CG; no difference in initial knowledge and coping abilities at baseline between IG and CG, significant difference post-treatment Communication strategies: rating of successfully conveyed messages from PPA patient to caregiver in the two practice sessions (one full point per message, half points for partially conveyed messages); average score at first session 1.9, at second session 3.3 Qualitative outcomes: valuable aspects named were learning about nature and types of PPA, about PPA research, getting information on nutrition supporting brain health, information on managing stress and depression, feeling understood by other in the group during difficulties in verbal communication, multidisciplinary support Participants would have liked more time to practice communication strategies and continue the program (e.g. on a bi-weekly basis) Further speech and language training suggested
Limitations	Self-reported: no randomization, only inclusion criterion PPA diagnosis, small sample size, more objective outcome measures - no report on consent/ethical approval - no report on validation of communication strategy rating

3.3 Spalding-Wilson et al. 2018

Reference	Spalding-Wilson, Kelsey N.; Guzmán-Vélez, Edmarie; Angelica, Jade; Wiggs, Kelsey; Savransky, Anya; Tranel, Daniel (2018): A novel two-day intervention reduces stress in caregivers of persons with dementia. In *Alzheimer's & Dementia: Translational Research & Clinical Interventions* 4, pp. 450–460. DOI: 10.1016/j.trci.2018.08.004.
Type	Intervention study
Location/Country	USA
Aim/subject	To assess the effect of a 2-day intervention for caregivers of PwD on caregiver burden and problems
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment,	n=104 caregivers to a person with dementia, n=42 wait-list control group (CG), n=62 intervention group (IG), recruited in the community between 11/2014 and 12/2016 Exclusion criteria: non-fluency in English, currently participating in another caregiver intervention, history of severe psychiatric disorder, other severe disease or disorder impairing caregiving ability Informed consent and ethical approval obtained

caregiver relationship to patient, initial scores)	Patients overall: 62% AD, other diagnoses: FTD, LBD, mixed dementia Patients CG (mean/SD): age 78.6 (9.5) years, FAST stage 5.7 (1.3) Patients IG (mean/SD): age 78.2 (10.8) years, FAST stage 5.7 (1.2) Caregivers overall: 52% children, 45% spouses, 3% siblings Caregivers CG (mean/SD): age 63.4 (10.9) years, 79% female, education 15.7 (2.8) years, time spent caring 3.0 (2.6) years, 59% living with patient, baseline BDI 11.7 (7.1), baseline BAI 7.7 (7.2), baseline PSS 16.3 (5.6), baseline CBI 34.3 (12.2) Caregivers IG (mean/SD): age 62.5 (9.9) years, 69% female, education 15.6 (2.9) years, time spent caring 4.3 (4.5) years, 53% living with patient, baseline BDI 11.8 (7.7), baseline BAI 8.1 (8.0), baseline PSS 16.0 (6.5), baseline CBI 34.9 (15.3)
Methods/measures	Patients. Functional Assessment Tool (FAST) for dementia stage Caregivers: Perceived Stress Scale (PSS) for stress (two subscales: perceived helplessness, perceived self-efficacy, score range 0-48, higher scores indicate higher stress); Caregiver Burden Inventory (CBI) for caregiver burden (score range 0-96, higher scores indicate higher burden), Beck Depression Inventory-II (BDI-II) for depression (score range 0-63, higher score indicate greater levels of depression), Beck Anxiety Inventory (BAI) for anxiety (0-63, higher scores indicate greater levels of anxiety) Caregiver questionnaire about living situation, time spent caring and open-ended comments about their experiences Statistical data analyses
Interventions (where applicable)	Random assignment to CG and IG after screening for eligibility, different instructions for CG and IG about dates and procedures of the intervention CG: 1.5h-session to obtain consent, complete FAST, BDI-II, BAI, PSS, CBI, and questionnaire; follow-up completion of these measures at 1, 3, and 6 months → intervention at 6 months IG: completion of measures at 2-day intervention, follow-up completion at 1, 3, and 6 months Intervention: manualized intervention facilitated by one of the authors (not involved in recruitment, assignment, data collection, or analysis), facilitator arrived after completion of measures to reduce possibility of knowing group assignment Group workshop with topics 1) psychoeducation about dementia, 2) self-care for caregivers, 3) using verbal and non-verbal language to communicate effectively with individuals with dementia, 4) identifying and validation emotions in individuals with dementia, 5) using mindfulness skills to notice the current needs of the individuals with dementia, 6) managing difficult behaviors Mindfulness exercises to 1) learn how to identify and understand own emotions as well as those of the individual with dementia, 2) meet the individual cared for in the present moment Active role plays and exercises, practice newly-learned skills with the individual with dementia, discuss success of skills and generate alternative approaches

Outcomes (variables, main findings)	Attrition: out of 104 caregivers, 94 completed measures at all 4 points of the study, 4 had to discontinue because of the patient's death, 5 discontinued with no disclosure of reason, 1 did not return measures at 3 months Perceived stress: on average, perceived stress decreased significantly after 1 month, overall rate of decrease of stress increased over time; IG participants showed a faster rate of improvement between baseline and 1 month compared to CG, marginally significant difference in IG reduction of perceived stress to accelerate faster than in CG Perceived self-efficacy: faster rate of increased self-efficacy in IG when compared to CG, faster acceleration of perceived self-efficacy change in IG over time (baseline to 1 month) Perceived helplessness: no significant effect of the intervention on perceived helplessness Caregiver burden: no group difference at baseline, significant decrease of burden each month, rate of decrease increased over time; higher baseline burden when caring for a patient with higher dementia severity, no significant differences in caregiver burden change in group comparisons, no significant effect of intervention on caregiver burden Depression: no group difference at baseline, significant decrease of depression from baseline to 1 month, rate of decrease increased over time, no significant differences in depression rate change in group comparisons, no significant effect of intervention on depression Anxiety: no group difference at baseline, significant decrease of anxiety levels from baseline to 1 month, rate of decrease increased over time, no significant differences in anxiety level change rate in group comparisons, no significant effect of intervention on anxiety Adherence and perception of the intervention:98% used skills 1 month later, 94% used skills 6 months later, 52% used skills often or very often at 6 months post intervention, 71% found the skills not at all or slightly difficult to apply at 6 months post intervention, 75% found the skills helpful, skills better for reconnecting with the person cared for, better management of distressing behaviors Open-ended caregiver comments: need for a specific FTD caregiver support group in the area, more information on how to deal with FTD patients Discussion: lack of effect on burden, depression, and anxiety might be explained with general distress caused by progression of the incurable disease
Limitations	Self-reported: relatively small sample size making investigation of different background situations difficult; three patients were admitted into a nursing home, effects could not be investigated; possible lack of outcome measures, recruitment bias (caregivers might only respond if they are currently experiencing stress), need for an ethnically and racially more diverse population

	- No comparison of CG and IG after intervention

3.4 Wagner and Taylor, 2018

Reference	Wagner, Eveleigh B.; Taylor, Warren D. (2018): Poster Number. EI 38 - Community Awareness Model for Frontotemporal Dementia: Improving Recognition of Illness and Amplifying Support for Caregivers. In *The American Journal of Geriatric Psychiatry* 26 (3, Supplement), S105 - S106. DOI: 10.1016/j.jagp.2018.01.129.
Type	Intervention (poster abstract) 2018 AAGP Annual Meeting
Location/Country	USA
Aim/subject	To present feedback from a support group for FTD caregivers
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	Children, spouses, and friends of persons with FTD
Methods/measures	Feedback comments from participants
Interventions (where applicable)	Monthly support group; 5-10 participants, alternating between open forum sessions and structured educational talks, Support group sponsored a multi-part community event to raise awareness about FTD: open Q&A forum, grand rounds, connections for patients and families, education for families and care providers
Outcomes (variables, main findings)	Participant feedback: importance of a space to share experiences, learning about the disease, share resources, help other caregivers; Caregivers want more awareness (i.e. AD is very well-known and represented, FTD is not), healthcare professionals who can diagnose the disease and understand it
Limitations	Poster abstract without detailed data

4. Educational articles and reviews
   4.1 FTLD

4.1.1 Bartochowski et al. 2018

Reference	Bartochowski, Zachary; Gatla, Shravan; Khoury, Rita; Al-Dahhak, Roula; Grossberg, George T. (2018): Empathy changes in neurocognitive disorders. A review. In *Annals of clinical psychiatry : official journal of the American Academy of Clinical Psychiatrists* 30 (3), pp. 220–232.
Type	Review

Location/Country	
Aim/subject	To summarize knowledge on empathy in major neurocognitive disorders (MNCDs)
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	n/a
Methods/measures	Literature search using PubMed and google scholar, “similar articles” and “cited by” tools as well as cross-referencing used to identify other eligible articles Inclusion criteria: Study examined empathy in at least one MNCD, exclusion of articles measuring only Theory of Mind (ToM)
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Synthesis of pathophysiology of empathy impairment Measures to quantify empathy Patients with FTD had lower empathy; lower cognitive empathy in FTD, both lower cognitive and emotional empathy in SD in one study, other showed both emotional and cognitive empathy to be impaired in bvFTD (in one study only for negative stimuli); neuroimaging correlates Impact on family and caregivers: empathy loss may erode caregiver-patient connection, thus high burden in bvFTD caregivers, some studies show significant correlation, bvFTD caregivers reported less caring relationships compared to svPPA,; other studies showed no correlation between patient empathy loss and caregiver depression or anxiety (empathy was however measured by a qualitative yes/no caregiver report and not an objective tool) Treatment approaches: oxytocin administration in FTD might increase empathy; empathy training, caregiver education
Limitations	Lack of reported search and inclusion methodology

4.1.2 Lewis et al. 2018

Reference	Lewis, Courtney; Walterfang, Mark; Velakoulis, Dennis; Vogel, Adam P. (2018): A Review. Mealtime Difficulties following Frontotemporal Lobar Degeneration. In *Dementia and geriatric cognitive disorders* 46 (5-6), pp. 285–297. DOI: 10.1159/000494210.
Type	Narrative review
Location/Country	Australia

Aim/subject	To summarize knowledge about aberrant eating behavior and dysphagia in patients with FTLD
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	n/a
Methods/measures	Literature search using PubMed, MEDLINE and Embase No evaluation or exclusion for evidence quality
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	bvFTD: changes in eating behavior more frequent than in any other dementia, typical problematic behaviors: hyperphagia (including tachyphagia, stealing food, wandering around to find food); preference of food previously disliked described in some cases; mouthing of inedible items especially in final stages SD: milder alterations in eating behavior compared to bvFTD; greater preference for sweet food; food faddism (intake of certain food, flavors etc. only), rigid and stereotypical eating behavior (e.g. time, location); altered association between food and corresponding smell/taste; change of food preferences early in the disease, positive correlation of eating behavior disturbances and cognitive decline PNFA: overlap with motor impairment phenotypes of FTLD (CBS, MND, PSP), thus swallowing function must be assessed and monitored thoroughly Swallowing function: dysphagia as an early sign of bulbar onset, often associated with FTD-MND, high risk for aspiration and thus increased mortality; delayed swallow initiation, premature movement through the pharynx during mastication; early dysphagia often associated with rapid progression FTD-MND: combination of bvFTD eating disturbances (e.g. hyperphagia, hyperorality) with motor symptoms (oropharyngeal weakness, decreased swallowing function, expiratory weakness) → high risk of aspiration CBS: late presentation during disease course, often multiple swallows required, speech apraxia and impairment of voluntary swallowing, impaired awareness of swallowing difficulties; in FTD-CBS no frequent changes in eating behavior PSP: oral and pharyngeal swallowing deficits early during disease course, dysphagia cannot be effectively treated with Levodopa,

	awareness of difficulties in eating and drinking; aberrant behaviors, e.g. impulsive eating, are reported Treatment: Symptom amelioration, increased caregiver supervision, postural modification (sitting upright, especially effective in PSP), modification of food texture, restricted food access, monitoring the intake of sweets, cueing the patient to eat slowly → increased caregiver stress; no clinical trials, evidence relies on case reports; experimental drugs: topiramate to reduce appetite and hyperphagia, SSRIs to influence altered food preferences
Limitations	Self-reported: - findings rely on caregiver reports that may be distorted - Few studies with small population sizes - Many studies not focusing on eating behavior, but behavioral disturbances in FTLD in general - No evaluation of study quality

4.1.3 Mulkey 2019

Reference	Mulkey, Malissa (2019): Understanding Frontotemporal Disease Progression and Management Strategies. In *Nursing Clinics of North America* 54 (3), pp. 437–448. DOI: 10.1016/j.cnur.2019.04.011.
Type	Educational article
Location/Country	USA
Aim/subject	To summarize knowledge about FTD disease progression and management strategies in order to educate and raise awareness
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	n/a
Methods/measures	Literature synthesis
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Description of FTD phenotypes, disease progression (with detailed information on early, intermediate and later stages), the relief of obtaining a diagnosis FTD patients are being admitted to nursing homes more often compared to AD because of heavier caregiver burden Medications and treatment strategies Intervention and behavioral strategies: should be interdependent between patients and caregivers; reality orientation, validation therapy, progressive muscle relaxation can cause improvements;

	Communication and behavioral strategies for: communication, assessment and observation, general strategies, managing roaming behaviors, approaches to personal care, compulsive behavior Strategies for addressing challenging behaviors: aggressive behaviors, sexual behaviors, roaming behaviors
Limitations	No description of study selection – might miss conflicting data and reports

4.2 ALS/MND

4.2.1 Baumann et al. 2019

Reference	Baumann, Lisa; Klosch, Michael; Greger, Markus; Dieplinger, Anna; Lorenzl, Stefan (2019): Amyotrophic Lateral Sclerosis - Challenges of Family Caregivers. In *Fortschritte der Neurologie-Psychiatrie* 87 (9), pp. 476–482. DOI: 10.1055/a-0934-6163. (ARTICLE IN GERMAN)
Type	Review
Location/Country	Austria
Aim/subject	To describe caregiver burden in caregivers of patients with ALS with a focus on behavioral and cognition changes
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	n/a
Methods/measures	Literature search of databases CINAHL, PubMed and SpringerLink Inclusion criteria: - published between 2006 and 2018 - cognitive/behavioral changes - ALS patients - Family caregivers (spouses, parents, children) - Caregivers >18 years - EMED format - Quantitative/qualitative studies, literature studies, meta-analyses/-syntheses, case studies Synthesis of findings
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	10 relevant articles Four main themes were established: - Burden due to behavioral changes in patients – reported to make up 1/3 of perceived burden; especially impairment in memory and orientation, AdL, and motivation was

	burdensome; apathy as a main contributor to burden; disinhibition and executive dysfunction furthermore named as causing burden; pathological laughter perceived to cause stress - Burden due to cognitive changes in patients - Burden due to anxiety in caregivers - Burden due to depression in caregivers
Limitations	Self-reported: Different cultural backgrounds of included studies may make results harder to compare to caregiver situation in Germany/Austria - Child caregivers and non-family caregivers excluded - Patients with other neurological diseases/concomitant diseases excluded

4.2.2 Benbrika et al. 2019

Reference	Benbrika, Soumia; Desgranges, Beatrice; Eustache, Francis; Viader, Fausto (2019): Cognitive, Emotional and Psychological Manifestations in Amyotrophic Lateral Sclerosis at Baseline and Overtime. A Review. In *FRONTIERS IN NEUROSCIENCE* 13. DOI: 10.3389/fnins.2019.00951.
Type	Review
Location/Country	France
Aim/subject	To review knowledge about cognitive, emotional and psychological manifestations in ALS and their longitudinal development
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	n/a
Methods/measures	Bibliographical search on PubMed prior to the 1st October 2018; studies in English or French, 190 studies in total
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Cognition in ALS: presentation of risk factors (*C9orf72* among others), frequency (14% met ALS-FTD criteria in one study; frequent semantic deficits, other study suggested ALS and nfvPPA to lie on a continuum), development over time (early presentation of even mild cognitive and behavioral impairment poses high risk for later FTD syndrome, inconsistent reports about frequency of cognitive decline, tendency for cognitive deficits present at baseline to progress [lack of practice effect], cognitively normal patients remain relatively stable) Consequences: faster disease progression, poorer prognosis; cognitive dysfunction increasing caregiver burden; presentation of neuroimaging correlates Changes in Emotion Perception and Social Cognition: suggestions for frequent impairment in emotion perception, facial emotion recognition,

	recognition of own emotions (alexithymia); Theory of Mind (ToM) impairment, conflicting reports about greater impairment in cognitive or affective ToM; association of executive function and ToM abilites probable; longitudinal development assessed in only two studies, showing a decline in ToM also in patients that had no ToM impairment at baseline; presentation of neuroimaging correlates Behavioral changes: occur in 24-69% of ALS patients, 6-25% meet criteria for FTD, might even appear before motor symptoms; apathy as a main symptom, other symptoms similar to bvFTD phenotype, lack of insight in ALS-FTD (but not in ALS without dementia); behavioral disturbance has negative impact on patient's and caregiver's psychological state, QoL and patient prognosis (shorter survival time); strongest predictor of caregiver burden (stronger than physical disability), increasing caregiver depression and anxiety, lack of motivation negatively influencing CB; greater behavioral impairment when cognitive impairment is present as well, conflicting findings about association to physical impairment (apathetic behavior could also be a result of hypercapnic encephalopathy), conflicting findings about association with onset site (patients with bulbar onset might exhibit more behavioral disturbance) Longitudinal changes: most cross-sectional studies found no association between behavioral symptom severity and time since disease onset, contrasting findings show greater behavioral and cognitive impairment in advanced disease stages; behavioral symptoms either increase in severity with disease progression or new symptoms appear; presentation of neuroimaging correlates Psychological reactions and well-being: description on patient's psychological reactions such as depression, anxiety, QoL, suicidal thoughts, and distress; longitudinal development; adaptive mechanisms (greatly influenced by social support
Limitations	- Lack of information on search strategy and study selection

4.2.3 Caga et al. 2019

Reference	Caga, Jashelle; Hsieh, Sharpley; Lillo, Patricia; Dudley, Kaitlin; Mioshi, Eneida (2019): The Impact of Cognitive and Behavioral Symptoms on ALS Patients and Their Caregivers. In *Frontiers in neurology* 10, p. 192. DOI: 10.3389/fneur.2019.00192.
Type	Review
Location/Country	Australia
Aim/subject	To summarize findings on behavioral and cognitive symptoms in ALS patients and their impact on caregivers
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver	n/a

relationship to patient, initial scores)	
Methods/measures	Literature search primarily using PubMed; non-pharmacological interventions in ALS searched using MEDLINE, EMBASE, PsycINFO, AMED and CINAHL English papers published between 05/2013 and 07/2018 Articles relevant to ALS and FTD included
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	Psychological symptoms in ALS: variable rates of anxiety and depression, but higher risk of diagnosis; QoL may be underestimated by caregivers and healthy controls, greater patient QoL when assistive aids are provided in an early disease stage Cognitive and behavioral symptoms' impact on patient's psychological well-being: depression tends to be associated with worse cognitive performance, associations between anxiety and cognition are inconsistent; behaviorally impaired patients experience higher levels of depression Cognitive and behavioral symptoms' impact on treatment adherence: non-adherence to non-invasive ventilation (NIV) and percutaneous endoscopic gastrostomy (PEG) recommendations reduced by half if ALS-FTD was present; patients with MCI and behavioral impairment adhered to less recommendations; motor predictors of adherence are reported more often than non-motor predictors Caregiver burden in ALS: ALS affects caregivers' distress and QoL with psychological symptoms having a significant impact on CB; anxiety and distress predict burden Impact of cognitive and behavioral symptoms on CB: caregiver burden associated with psychological symptoms, e.g. apathy and disinhibition; inconsistent findings on the impact of cognitive deficits on CB; few studies on motor symptoms' impact on CB Lack of interventions to manage cognitive and behavioral symptoms; findings on management of FTD symptoms might be useful to explore in behaviorally impaired ALS individuals
Limitations	- No reported number of inclusion strategy or included articles - Selection bias of publications in English only

4.2.4 Linse et al. 2018

Reference	Linse, Katharina; Aust, Elisa; Joos, Markus; Hermann, Andreas (2018): Communication Matters-Pitfalls and Promise of Hightech Communication Devices in Palliative Care of Severely Physically Disabled Patients With Amyotrophic Lateral Sclerosis. In *Frontiers in neurology* 9, p. 603. DOI: 10.3389/fneur.2018.00603.

Type	Review
Location/Country	Germany
Aim/subject	To summarize knowledge about high-tech communication devices for ALS patients and factors to consider
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial treatment, caregiver relationship to patient, initial scores)	n/a
Methods/measures	
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	- Description of HT-AAC: function, usefulness - Decrease caregiver burden, help in decision-making - ALS with behavioral (ALSbi) or cognitive (ALSci) impairment or ALS-FTD can impair the use of communication devices - Especially language impairments can make the use of such devices difficult or impossible - Individuals with minor cognitive impairment still profit from HT-AAC
Limitations	

4.2.5 de Wit et al. 2018

Reference	Wit, Jessica de; Bakker, Leonhard A.; van Groenestijn, Annerieke C.; van den Berg, Leonard H.; Schroder, Carin D.; Visser-Meily, Johanna M. A.; Beelen, Anita (2018): Caregiver burden in amyotrophic lateral sclerosis. A systematic review. In *PALLIATIVE MEDICINE* 32 (1), pp. 231–245. DOI: 10.1177/0269216317709965.
Type	Review
Location/Country	Netherlands
Aim/subject	To review factors contributing to caregiver burden in ALS and evaluate their evidence
Participants (number, patient diagnosis, gender, age range, race, ethnicity, type of residency [home, care facility], initial	n/a

treatment, caregiver relationship to patient, initial scores)	
Methods/measures	Literature search according to PRISMA guidelines, using PsycINFO, Medline (PubMed), CINAHL, and EMBASE, searches conducted up to 2017, cross-referencing Inclusion criteria: papers that investigated the relationship between caregiver or patient factors to caregiver burden in informal ALS caregivers; explicitly defined and measured factors, burden assessed with a total caregiver burden construct; English, Dutch, or German language Exclusion criteria: mixed sample studies (unless subsample analysis for ALS was performed), subscales of burden measures, caregiver burden as part of an overall outcome construct Study selection: by two researchers, disagreements solved by consensus Risk of bias assessment: by two researchers, using the Methodological Quality Assessment List (score range 0-8, higher scores indicating higher study quality) Data synthesis: by two researchers, applying statistical analyses Quality of evidence: by two researchers, using the Grading of Recommendations Assessment, Development and Education (GRADE) (modified), overall quality of evidence rated as high, moderate, low or very low
Interventions (where applicable)	n/a
Outcomes (variables, main findings)	- 25 studies included - methodological quality scores ranging from 2 to 7, one study excluded of quality of evidence assessment because of low total score - published between 1998 and 2016, eight countries, 20 cross-sectional studies, 5 longitudinal studies, 22 studies investigating univariate associations, 10 used multivariate analyses; sample size from 19 to 415 caregivers, 22 reported relationship with the patient, majority partners; majority of female caregivers, mean age 48 to 61 years, mean time since disease onset ranged from 15 to 40 months - burden measures most frequently used: ZBI (n=11), CBI (n=6), CSI (n=2), Burden Scale for Family Caregivers (n=1), CBS (n=1), selected items of ZBI (n=2), single-item measure (n=2) Caregiver factors: moderate quality of evidence for relationship between higher CB and “feelings of depression”, low quality of evidence for relationship between higher CB and “anxiety”, “distress”, “age”; very low quality of evidence for relationship between higher CB and “social support”, “family functioning”

	Patient factors: high quality of evidence for relationship between higher CB and “behavioral impairments”, moderate quality of evidence for relationship between higher CB and “patients’ physical functioning”, very low quality of evidence for relationship between higher CB and “limb function”, “respiratory function”, “executive functioning”, “cognitive functioning”, “age”; Low quality of evidence for factors not associated with CB for “bulbar function”, “feelings of depression”, very low quality of evidence for factors not associated with CB for “disease durations” Behavioral impairments: important to differentiate ALS, ALS with cognitive impairment, ALS with behavioral impairment, and ALS-FTD, highest quality of evidence for relationship between high CB and behavioral disturbances
Limitations	Self-reported: no meta-analysis, different caregiver burden measures, selection bias to full-text, peer-reviewed publications; lack of longitudinal studies - Selection bias with regard to language

12. Appendix II - PRISMA-Scoping Review Checklist

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE # (2017/2019)
TITLE			
Title	1	Identify the report as a scoping review.	1/I
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	1/37
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	2/6
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	2/6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	-
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	2,3/7,8
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	2,3/7,8
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	3/8
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	3/8
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	3/8,9
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	3/8
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	-

Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	3/9

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE # (2017/2019)
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	3/8
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Appendix/ Appendix
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	-
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Appendix/ Appendix
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	3-17/10-29
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	17/30
Limitations	20	Discuss the limitations of the scoping review process.	18/35-36
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	18/36
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	18/-

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

13. Appendix III - Publication

Karnatz, T., Monsees, J., Wucherer, D., Michalowsky, B., Zwingmann, I., Halek, M., . . . René Thyrian, J. (2021). Burden of caregivers of patients with frontotemporal lobar degeneration – a scoping review. *International Psychogeriatrics, 33*(9), 891-911. doi:10.1017/S1041610219000176

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Eidesstattliche Erklärung

Hiermit erkläre ich, dass ich die vorliegende Dissertation selbständig verfasst und keine anderen als die angegebenen Hilfsmittel benutzt habe.

Die Dissertation ist bisher keiner anderen Fakultät, keiner anderen wissenschaftlichen Einrichtung vorgelegt worden.

Ich erkläre, dass ich bisher kein Promotionsverfahren erfolglos beendet habe und dass eine Aberkennung eines bereits erworbenen Doktorgrades nicht vorliegt.

Datum Unterschrift

Hamburg, den 08.12.2021

Lebenslauf

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Danksagung

Ich danke meinem Betreuer Prof. Dr. rer. med. René Thyrian für die Überlassung des Themas und die vielen kompetenten Ratschläge und Hilfestellungen beim Verfassen der Publikation und der Dissertationsarbeit. Ich danke Frau Prof. Dr. rer. medic. Margareta Halek sowie Frau Prof. Dr. Ina Zwingmann für ihre hilfreiche Begleitung bei der Abfassung meiner Publikation.

Mein größter Dank gilt meinen Eltern sowie meinem Bruder, welche mich in jeder noch so arbeitsreichen Zeit unterstützt haben und ohne die die Abfassung dieser Arbeit nicht möglich gewesen wäre. Ebenso danke ich Emily Louise Islip für die hilfreiche Unterstützung in sprachlichen Fragen und ihr geduldiges Korrekturlesen. Darüber hinaus danke meinen Freund*innen und Kommiliton*innen, insbesondere Maren Klare und Melanie Kalinowski, sowie Familie Ente für ihre moralische wie auch praktische Unterstützung während des gesamten Studiums.