Title: A systematic review of the prevalence of depression, anxiety and apathy in frontotemporal dementia, atypical and young-onset Alzheimer's disease and inherited dementia

Authors: Jessica D. Collins, Susie M.D. Henley & Aida Suarez-Gonzalez*

Affiliations: Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, University College London, London, United Kingdom.

***Author for correspondence:**

Aida Suarez-Gonzalez

Dementia Research Centre, UCL Institute of Neurology

Box 16, National Hospital

Queen Square

London WC1N 3BG

United Kingdom

Tel: +44 (0)20 3448 3113

Email: aida.gonzalez@ucl.ac.uk

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Abstract

Depression, anxiety and apathy are the most commonly reported neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD). Understanding their prevalence in rarer dementias such as frontotemporal dementia (FTD), primary progressive aphasia (PPA), posterior cortical atrophy (PCA), young-onset AD (YOAD) and inherited dementias has implications for both clinical practice and research. In this study we aimed to examine the current state of knowledge of the prevalence of these three NPS in less prevalent dementias. We conducted a systematic review based on searches of EMBASE, PsycINFO and PubMed up to September 2019. 47 papers meeting inclusion criteria were identified. Depression, anxiety and apathy were commonly reported across the phenotypes studied but their prevalence showed large variation between studies. Apathy showed the highest reported frequency in FTD (50-100% across studies), behavioral variant frontotemporal dementia (bvFTD) (73-100%) and YOAD (44-100%). Anxiety was frequently reported in FTD (0-100%) and bvFTD (19-63%). Depression showed the highest prevalence in FTD (7-69%) and YOAD (11-55%). Among the three variants of PPA, sv-PPA is the one most investigated (seven papers). Three or fewer papers were identified examining NPS in the remaining PPA variants, PCA, familial AD and familial FTD. Inconsistency in the tools used to measure symptoms and small sample sizes were common methodological limitations. Future studies should consider the inclusion of larger sample sizes (e.g. through multicenter collaborations) and the use of harmonized protocols that include the combination of caregiver and patient-derived measures and symptom-specific questionnaires. More research is needed on the phenotype-specific barriers and facilitators for people living with dementia to successfully engage in self-reports of NPS.

Keywords: depression; anxiety; apathy; early onset dementia, frontotemporal dementia

1. Introduction

Alzheimer's disease (AD) is the most frequent cause of neurodegenerative dementia, where the hallmark clinical phenotype is characterized by progressive loss of episodic memory (McKhann et al., 2011). Depending on the age at onset AD is classified into late-onset (LOAD) and young-onset (YOAD), with YOAD being defined by onset of symptoms before the age of 65 (Rossor, Fox, Mummery, Schott, & Warren, 2010). YOAD is a less common form of AD, representing less than 10% of all cases of AD. It is estimated that up to 64% of all YOAD cases develop an atypical presentation, where memory loss is not the main symptom (Alladi et al., 2007; Koedam et al., 2010; Mendez, Lee, Joshi, & Shapira, 2012). Instead, people may show progressive language impairment, as in the logopenic variant of primary progressive aphasia (lv-PPA) (Gorno-Tempini et al., 2011) which is characterized by word-finding difficulties with impaired sentence comprehension due to phonological working memory deficits (Snowden et al., 2007). In other cases, the main clinical symptom may be difficulties with vision, as in posterior cortical atrophy (PCA) (Tang-Wai et al., 2004), a clinical syndrome that involves progressive decline in visual processing skills and other posterior symptoms (Snowden et al., 2007). Additionally, for those individuals under 65, dementia phenotypes arising from frontotemporal degeneration (FTD) are as frequent as AD (Seltman & Matthews, 2012; Waldö, 2015). FTD comprises a group of disorders affecting primarily the frontal and temporal lobes of the brain giving rise to a clinical picture of changes in personality, behavior and language. Three main syndromes have been recognized under the FTD umbrella: 1) a behavioral variant frontotemporal dementia (bv-FTD) (Rascovsky et al., 2011) characterized by progressive changes in personality and social behavior, 2) a semantic variant primary progressive aphasia (sv-PPA) (Gorno-Tempini et al., 2011) characterized by impaired

word and object comprehension and 3) a non-fluent variant primary progressive aphasia (nfv-PPA) (Gorno-Tempini et al., 2011), which progresses with agrammatism and effortful, non-fluent speech (Neary et al., 1998). Lastly, a small proportion of AD cases are inheritable, referred to as familial AD (FAD), caused by autosomal dominantly-inherited mutations in one of the genes presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*) or amyloid precursor protein (*APP*) (Bateman et al., 2012; Wu et al., 2012). Similarly, approximately 20-30% of FTD cases are inheritable, referred to as familial FTD (fFTD), the most common causes of which are autosomal dominant inheritance of a mutation in one of the genes progranulin (*GRN*), microtubule-associated protein tau (*MAPT*) or chromosome 9 open reading frame (*C9ORF72*) (Rohrer, Warren, Fox, & Rossor, 2013). A commonality between all the above phenotypes is that they are less prevalent or rarer forms of dementia.

Depression, apathy and anxiety are the most frequently reported NPS in dementia (Brodaty, Connors, Xu, Woodward, & Ames, 2015; Zhao et al., 2016) and are strongly associated with increased caregiver burden and lower quality of life in people living with dementia (Gibbons et al., 2002; Gómez-Gallego, Gómez-Amor, & Gómez-García, 2012; González-Salvador et al., 2000; Greene, Smith, Gardiner, & Timbury, 1982; Hoe, Hancock, Livingston, & Orrell, 2006; Kaufer et al., 1998; Seignourel, Kunik, Snow, Wilson, & Stanley, 2008; Springate & Tremont, 2014). Apathy, in particular, is reported to be highly prevalent and persistent throughout the course of the disease (Van Der Linde et al., 2016). Although these three symptoms have also been reported in rarer dementias such as YOAD (Van Vliet et al., 2013) and PCA (Suárez-González et al. 2016), there is less research and less understanding of the neuropsychiatry of these types of dementia in comparison with the prominent body of research looking at their phenotype-specific symptoms, such as language difficulties in PPA (Gorno-

Tempini et al., 2004; Grossman & Ash, 2004) or visual impairment in PCA (Lee & Martin, 2004; Maia da Silva, Millington, Bridge, James-Galton, & Plant, 2017). It is however now widely accepted that people living with these young-onset and rare dementias have needs that are specific and different from those with more typical forms, and that remain poorly understood (Ducharme et al., 2014; Millenaar et al., 2016). Better understanding of the particular psychological needs of this population is crucial to deliver age-appropriate support and care, and for the development of phenotype-tailored interventions.

In this piece of work, we aim to produce the first systematic review on the prevalence of depression, anxiety and apathy in FTD, atypical and young-onset AD and inherited dementia. By doing that, we expect to gather, summarize and share the evidence produced to date in the field, so researchers and clinicians working with people affected by rare dementias can have a comprehensive, updated and descriptive piece of information that can be used to inform their research and clinical practice.

2. Methods

2.1 Search methods

2.1.1 Electronic searches

Searches were run in Embase, PsycINFO and PubMed, from the first paper found published to September 2019 and limited to peer-reviewed published articles written in English only. The search strategy and syntax were developed with the support of an expert librarian and piloted. The search keywords were translated into the different syntaxes used by the different databases and can be found in Appendix A. Results

were manually de-duplicated. Title, abstract and full-text screening was carried out by JDC and SMDH.

2.2 Inclusion criteria for considering studies for this review

2.2.1 Types of participants

Studies were included if they measured prevalence of depression and/or anxiety and/or apathy symptoms in YOAD, PCA, bv-FTD, PPA and its variants (sv-PPA, nfv-PPA and lv-PPA), FAD or fFTD. In studies examining familial dementias, only NPS reported in symptomatic mutation carriers were eligible to be included in the review.

2.2.2 Types of studies

Studies were required to provide either a percentage of people exhibiting at least one of the NPS of interest (depression, anxiety or apathy), or a raw figure from which a percentage could be calculated. Both cross-sectional and longitudinal studies were eligible. Intervention studies were accepted, as long as the prevalence of symptoms was presented at baseline (in which case this would be the figure included in the review).

2.2.3 Measures

Studies were included providing they reported results based on a measure from which the prevalence of the symptom(s) in the sample could be obtained. A range of measures were eligible, such as validated and non-validated tools, and prospective and retrospective measures including observations from clinical records.

2.2.4 Data extraction and management

JDC extracted the data using a standard extraction form which covered the following: sample size(s), demographic information (age and disease severity), neuropsychiatric

measure(s) used, prevalence of NPS, recruitment setting, the diagnostic assessment of dementia, and whether the study excluded individuals with a psychiatric history.

2.2.5 Quality assessment

Quality assessment was used to describe the characteristics of the body of knowledge of the frequency of depression, anxiety and apathy in the phenotypes examined. and not to make decisions regarding the weight of different papers towards the final results.

A tailored set of criteria (Table 1) were designed for assessing the methodological quality of individual studies, given the heterogeneity of the studies retrieved and the risk of information loss by using standard measures of quality. There was a maximum possible score of 24, with higher scores indicating smaller risk of bias and therefore better-quality evidence.

2.2.6 Data synthesis

Individual prevalence values were extracted by JDC from each paper and collated as percentages.

3. Results

The initial search identified 3129 records, which was reduced to 1651 after first level screening and de-duplication. 47 were selected for full-text assessment (details shown in Figure 1).

Characteristics of included studies can be found in Table 2. 39 studies reported depressive symptoms, 29 reported symptoms of anxiety, and 29 reported symptoms of apathy. A descriptive overview of the data follows below, grouped into the three NPS of interest, apathy, anxiety and depression. A final section is devoted to considering methodological issues examined in the quality appraisal.

3.1. Outcomes

3.1.1 Apathy

Symptoms of apathy appeared most frequently in studies of FTD (ranging 50-100%). All ten FTD studies measuring apathy in FTD reported symptoms in at least 50% of their population, five of which indicated presence of apathy in at least 95% of their sample (Amoo et al., 2011; Diehl & Kurz, 2002; Kazui et al., 2016; Levy et al., 1998; Martínez et al., 2008; Mourik et al., 2004; Riedijk et al., 2009; Srikanth, Nagaraja, & Ratnavalli, 2005). Three studies of apathy in PPA reported symptoms in 48.1-62% of patients (Chow et al., 2009; Chow, Miller, Boone, Mishkin, & Cummings, 2002; Fatemi et al., 2011). Five studies reported apathy in YOAD, ranging from 44.7% to 100% (Ballarini et al., 2016; Ferreira et al., 2017; Park et al., 2015; Tanaka et al., 2015; Toyota et al., 2007). Two of these studies stratified their sample by disease severity; Park et al. (2015) reported prevalence of apathy in patients with a CDR score of 0.5 as 45%, and 71% in those with a score of 1. Tanaka et al. (2015) reported apathy in 76.4% of mild, 82.4% of moderate, and 100% of severe dementia patients.

Studies of bv-FTD reported a high prevalence of apathy symptoms (Lopez et al., 1996), with a range of 73-100% across seven studies (Chow et al., 2009; Chow, Miller, Boone, Mishkin, & Cummings, 2002; Diehl-Schmid, Pohl, Perneczky, Förstl, & Kurz, 2006; Liu et al., 2004; Perri, Monaco, Fadda, Caltagirone, & Carlesimo, 2014; Rosen et al., 2002; Tartaglia et al., 2014). Diehl-Schmid et al. (2006) stratified by CDR score, with 91% of mild patients (CDR score of 1) and 100% of moderate/severe patients (CDR score of 2 or 3) reporting symptoms of apathy. Three further studies indicated apathy in at least 90% of patients (Chow et al., 2002; Liu et al., 2004; Perri et al., 2014). Five studies reported apathy in sv-PPA patients with a range of 23-80%

(Kashibayashi et al., 2010; Liu et al., 2004; Rohrer & Warren, 2010; Rosen et al., 2002; Singh et al., 2015). Two studies of lv-PPA reported symptoms in 32% and 57% of patients (Rohrer & Warren, 2010; Singh et al., 2015), and three studies reported symptoms in 9-64% of patients with nfv-PPA (Rohrer & Warren, 2010; Singh et al., 2015; Xiong et al., 2011). Xiong et al. (2011) reported symptoms in nfv-PPA patients stratified by pathology, finding that 55% of those with AD pathology presented with apathy, compared with 40% of those with FTD pathology. There were fewer studies reporting apathy in other phenotypes. Two studies of PCA reported apathy in 42% and 60% of patients (Isella et al., 2015; Suárez-González, Crutch, Franco-Macías, & Gil-Néciga, 2016). Only one study reported apathy in FAD, with 40% of mildly symptomatic and 69.7% of overtly affected individuals exhibiting symptoms (Ringman et al., 2015). One study reported apathy in fFTD, with symptoms reported in 67% of patients (Rohrer & Warren, 2010).

3.1.2 Anxiety

Thirteen studies measured anxiety symptoms in FTD, with prevalence figures ranging from 0 to 100%. However, it is worth noting that the two studies which reported symptoms in 0% (Amoo et al., 2011) and 100% (Martínez et al., 2008) of people with FTD recruited very small samples (N = 4, N = 3, respectively). Among studies with more substantial sample sizes (N = 13 and above), prevalence of anxiety in FTD was reported at a much smaller range of 10.3-53.8%, similar to that reported by the six studies of YOAD, whose findings were between 10-55.7% (Ballarini et al., 2016; Panegyres & Chen, 2014; Park et al., 2015; Tanaka et al., 2015; Toyota et al., 2007; van Vliet et al., 2013). One study reported anxiety in PPA, with a prevalence figure of 14.8% (Fatemi et al., 2011).

Six studies measured anxiety in bv-FTD, reporting a prevalence range of 19-63% (Diehl-Schmid et al., 2006; Liu et al., 2004; Mendez et al., 2006; Perri et al., 2014; Rosen et al., 2002; Tartaglia et al., 2014). Diehl-Schmid et al. (2006) stratified by CDR, though similar levels were found among those with CDR 1 (19%) and those with CDR 2 or 3 (21.1%). Of the more specific phenotypes, anxiety reached the highest frequency in lv-PPA patients; Rohrer and Warren (2010) reported 71%, while Singh et al. (2015) reported 37.8%. This was followed by studies of PCA, reporting symptoms in 64% (Suárez-González et al., 2016) and 45% (Isella et al., 2015) of patients. Four studies measured anxiety in sv-PPA patients, all of which found symptoms in approximately half of patients, ranging from 41% to 56% (Liu et al., 2004; Rohrer & Warren, 2010; Rosen et al., 2002; Singh et al., 2015). Lower frequency of symptoms of anxiety was most consistently reported in nfv-PPA patients, with figures of 26.7% (Rohrer & Warren, 2010) and 36% (Singh et al., 2015) reported.

Only one study reported anxiety in FAD, reporting symptoms in 54.6% of overtly affected individuals (Ringman et al., 2015). The prevalence of anxiety in mildly symptomatic people was not reported. One study reported the prevalence of anxiety in people with fFTD as 33% (Rohrer & Warren, 2010).

3.1.3 Depression

Depression symptoms were found in 7.7-69.6% of FTD patients across 15 studies (Amoo et al., 2011; Chiu, Chen, Yip, Hua, & Tang, 2006; de Vugt et al., 2006; Diehl & Kurz, 2002; Engelborghs et al., 2005; Gregory, 1999; Levy et al., 1998; Lopez et al., 1996; Martínez et al., 2008; Mourik et al., 2004; Riedijk et al., 2009; Srikanth et al., 2005; Williams, Nestor, & Hodges, 2005). Ten studies reported depressive symptoms in YOAD, with figures of 11-55.6% reported. Yoon et al. (2016) stratified by disease severity; symptoms were found in 37.2% of people with CDR 0.5, 44.4% of those with

CDR 1, and 23.1% of those with CDR 2. Tanaka et al. (2015) also stratified by disease severity, reporting depressive symptoms in 41.8% of mild, 47.1% of moderate, and 25% of severe dementia. Of the remaining eight studies, two reported symptoms in less than a quarter of people (Atkins, Bulsara, & Panegyres, 2012; Sabodash, Mendez, Fong, & Hsiao, 2013), five found symptoms in between one quarter and one half of people (Ballarini et al., 2016; Clark et al., 1998; Panegyres & Chen, 2014; Toyota et al., 2007), and one study reported symptoms in just over half of cases (van Vliet et al., 2013). Reported prevalence of depressive symptoms appeared fairly consistent across three PPA studies, with a range of 38.2-43.4% (Chow et al., 2002; Fatemi et al., 2011; Medina & Weintraub, 2007).

Nine studies were found to measure symptoms of depression in bv-FTD. One study reported prevalence as low as 7% (Bozeat, Gregory, Ralph, & Hodges, 2000). However, the majority of findings fell between 22-52% (Atkins et al., 2012; Chow et al., 2002; Diehl-Schmid et al., 2006; Liu et al., 2004; Mendez et al., 2006; Perri et al., 2014; Rosen et al., 2002; Tartaglia et al., 2014). Diehl-Schmid et al. (2006) stratified by disease severity, reporting symptoms in 28.6% of those scoring CDR 1, and 47.4% of those scoring CDR 2 or 3. Of the more specific phenotypes, frequency of depressive symptoms reached the highest among sv-PPA patients, with six studies included in the review reporting a range of 44-78% (Bozeat et al., 2000; Liu et al., 2004; Rohrer & Warren, 2010; Rosen et al., 2002; Sabodash et al., 2013; Singh et al., 2015). Four of these studies reported prevalence at 44-48%. Two studies of people with lv-PPA identified depressive symptoms in 29-45.9% of patients (Rohrer & Warren, 2010; Singh et al., 2015). The same two studies, along with one other, reported on depressive symptoms in nfv-PPA, finding a prevalence of 33-57% (Rohrer & Warren, 2010; Singh et al., 2015; Xiong et al., 2011). Xiong et al. (2011) divided their sample

by pathology, reporting depression in 38.5% of those with AD pathology and in 45% of those with FTD pathology. Two studies reported frequency of depressive symptoms in PCA as 42% (Suárez-González et al., 2016) and 55% (Isella et al., 2015).

There were two studies of depressive symptoms in FAD patients. Edwards, Larson, Hughes, and Kukull (1991) divided their sample by those with only one relative affected by AD and those with two or more affected relatives, and found that frequency of depressive symptoms was similar among the two groups, at 42% and 47% respectively. Ringman et al. (2015) stratified by disease severity, reporting prevalence of depressive symptoms as 56% in mildly symptomatic and 60.6% in overtly affected individuals with FAD. Only one study reported depressive symptoms in fFTD, and reported prevalence as 33% (Rohrer & Warren, 2010).

3.2 Quality of studies

Table 3 summarizes the scoring of each paper on all quality criteria. Scores ranged from 7 to 20 points (out of a maximum of 24 points).The majority of studies recruited a small sample (N <41), with only seven studies recruiting a sample of more than 100 participants. Recruitment setting was also a common source of bias across studies. The majority of studies recruited from specialist research, or secondary/tertiary care settings. There was only one population-based study identified. Furthermore, there was some inconsistency in how NPS were measured across the papers included in the review, though the majority of studies (38/47 studies) used the Neuropsychiatric Inventory to measure NPS.

3.3 Summary

Table 4 summarizes the range of quality scores and prevalence figures of anxiety, depression and apathy found across each dementia phenotype. Apathy was reported to be of high prevalence across all phenotypes, reported frequently in studies of bv-FTD, FTD, sv-PPA and YOAD. Although lower than apathy, there was also evidence of symptoms of anxiety and depression across all phenotypes, with highest levels of anxiety in lv-PPA and PCA, and highest levels of depression in sv-PPA and FTD.

With regards to quality assessment, the majority of studies scored between 10 and 14 out of 24 points. The highest scoring study scored 20 points, and the two lowest scoring studies scored 7. Studies investigating YOAD populations were among those obtaining the highest quality scores, followed by bv-FTD and FTD in general. Nevertheless, a wide variability of quality was exhibited in studies involving the three patient groups. Regarding more rare phenotypes, namely PCA, PPA and the specific PPA phenotypes (sv-PPA, nfv-PPA and lv-PPA), along with familial dementias, the variability in the quality of studies was less, but quality assessment in these studies was generally in the middle range.

4. Discussion

Depression, anxiety and apathy have been particularly frequently investigated in FTD, particularly bv-FTD, followed by YOAD, and PPA. Seven papers examined these symptoms in sv-PPA, but only two or three studies looked at lv-PPA, nfv-PPA, PCA and FAD, and only one investigated fFTD. The differences in the number of publications across phenotypes may partly be due to the fact that behavioral symptoms are a feature of the FTD diagnostic criteria. Additionally, FTD (particularly bv-FTD) and YOAD are more prevalent than the other phenotypes included in this review, thus samples are more accessible.

4.1. Prevalence of depression, anxiety and apathy in young-onset and rare dementias

Apathy was frequently reported across all diagnostic groups. It was reported particularly frequently in bv-FTD, which is unsurprising considering that apathy is a feature of the diagnostic criteria for bv-FTD, but not a diagnostic criterion of any of the language-led dementias (Bang, Spina, & Miller, 2015). This may lead to certain circularity in studies addressing apathy in bv-FTD, inflating real prevalence rates. Although slightly less frequently reported, apathy was also found in sv-PPA. Sv-PPA can develop significant behavioral symptoms across the course of the disease, which may include apathy among others. Although very few studies addressing apathy in PCA, lv-PPA and nfv-PPA were identified, upper limits of prevalence ranges were all above 50%, with a lower limit of 32% (in the case of lv-PPA) and 42% (PCA) of individuals affected. Exceptionally, a much lower minimum value of 9.3% was identified in nfv-PPA.

Anxiety and depression were present in a lower number of individuals than apathy, but reached high upper boundaries in the ranges of prevalence in FTD and YOAD and slightly lower in PPA. When looking at the specific phenotypes, lv-PPA is the phenotype showing the highest upper limit of anxiety (71%), with lower rates of depression reported. However, sv-PPA displayed the opposite pattern, with depression present in up to 78% of the cases and anxiety in half the cases, and nfv-PPA also showing greater presence of depression than anxiety. PCA and bv-FTD both showed more frequent presence of anxiety than depression but up to half of patients in each group showed depressive symptoms. These results suggest that depression and anxiety are overlapping processes, likely sharing related underlying mechanisms.

Studies applying stratification by disease severity suggest that prevalence of apathy increases with disease progression in YOAD, FAD and bv-FTD. Studies of people with YOAD that stratified by disease severity revealed a slight reduction in symptoms of anxiety and depression across disease span. One study stratifying people with FAD by disease severity revealed a relatively steady level of depression over disease development. A study of bv-FTD indicated an increase in depressive symptoms over the disease while anxiety remained stable. Differences in the course of these three NPS across phenotypes may indicate different underlying biological mechanisms and/or different emotional reactions to the challenges arising from the specific clinical pictures. Altogether, studies involving stratification are scarce and methodologies applied are varied, even though they could provide essential input about the evolution of NPS over cognitive and functional decline. In addition, it remains unclear whether stability of symptoms in moderate and severe stages may reflect in some cases the inability of the patient to accurately convey this information due to progressive cognitive impairment, instead of actually reflecting a plateau in NPS.

4.2. Quality of studies and sources of bias

There was substantial variability in the quality of studies identified by this review. Studies examining YOAD, bv-FTD and FTD were rated as better quality, while those of PPA (and its subvariants), PCA and familial dementia tended to be of lower quality, with a key source of bias being the recruitment of small sample sizes.

Most of the studies reported used a validated measure, instead of the gold-standard of clinical assessment, to determine the presence of NPS. Although the majority of studies used the Neuropsychiatric inventory (NPI), there was substantial variability among the remaining studies regarding the use of measurement tools. This may have added further bias to estimates of prevalence. A key limitation of standardized

neuropsychiatric measures is their reliance on caregivers' reflection. Proxy reports are frequently relied on for measuring NPS in dementia due to risk of symptoms such as cognitive impairment, poor insight and communication difficulties confounding self-report, particularly as disease progresses (Millenaar et al., 2017). However, there is often discrepancy in self- and proxy-reports (Gomez-Gallego, Gomez-Garcia, & Ato-Lozano, 2015), with a trend for caregivers to over-report symptoms (Reisberg, Auer, & Monteiro, 1997). In addition, studies identified in this review used both self- and proxy-ratings, which are difficult to directly compare. Furthermore, there is a lack of purposely designed questionnaires for people with communication difficulties, which occur in PPA and other dementia phenotypes (Alsawy, Mansell, McEvoy, & Tai, 2017).

Ten papers excluded individuals with a previous psychiatric history, leading to a slightly lower quality score since figures reported by these papers might underestimate the true prevalence of NPS in the population. The majority of studies recruited from a research or tertiary care setting, with only one community-based study identified, which limits the generalizability of these results. As age and disease severity are likely closely connected with the dementia diagnosis and the occurrence of NPS respectively, absence of relevant demographic data also reduces generalizability of findings and therefore points were deducted in the appraisal of quality of the nine studies with missing demographics. Lastly, the majority of studies included in this review relied on clinical diagnostic criteria, in which pathological confirmation was not available. Although this is considered a bias, its weight in the current study is however limited. This study is focused on phenotypes, not pathological types, and since the symptoms studied are dictated by the clinical picture and not by the neuropathological process driving them, the clinical diagnosis should be the standard to rely on.

4.3. Limitations

The quality categories and criteria used in this study were data-driven, that is, produced by the researcher in response to the data. These categories were not exhaustive, which means there were a number of relevant variables that may have not been considered by this review, such as the cut-off at which studies considered NPS to be present, location from which people were recruited, and the sampling procedure used (e.g. random vs. opportunity sampling). Studies that investigated only one or two of the target NPS were eligible for inclusion, meaning there is a risk of information bias depending on which NPS were being studied by each identified paper; overall, depression was more frequently measured than anxiety and apathy. Furthermore, both longitudinal and cross-sectional studies were included in the review, where the former reports cumulative prevalence and the latter reports point prevalence. This may elicit bias as cumulative prevalence would likely lead to overestimation of frequencies.

Attempting to reduce a wide range of study variables into categorical scoring criteria may result in subtle differences being overlooked. It was agreed by the authors of this review that, in cases where a study used multiple corroborating methods and did not adhere to one method for all participants, the lowest score should be assigned. This, however, means that the potential additional value of corroborating multiple methods was lost.

The quality assessment conducted as part of this review was intended to be descriptive This means that papers were given equal weighting during analysis, regardless of quality score.

The search strategy included the terms "familial", "inherited" and "autosomal" to elicit studies of familial dementia. However, it is possible that studies of familial dementia

that did not include these terms in the title/abstract may have not been identified in the search and therefore not included in the review. Furthermore, reference lists of the identified papers were not scrutinized to identify any papers not found in the search, which may be a source of bias in terms of paper selection.

4.4. Conclusion

This review has identified very few studies that measured NPS in young-onset and atypical dementias, especially in some specific phenotypes such as nfv-PPA, lv-PPA, PCA, FAD and fFTD. In addition, the average quality of studies is moderate, and studies examining NPS over the course of disease progression are almost non-existent. Nevertheless, depression, anxiety and apathy seem to be very frequently reported in rare dementias.

In light of current findings, we propose a number of recommendations for planning of future studies in the field. First, large sample sizes of rare dementias are difficult to gather in a single center, therefore multicentric collaborations are advised in order to strengthen the quality of evidence in future studies. Second, expert consensus should be obtained to harmonize research protocols of how to conduct studies on NPS in general, and in rare dementias in particular. For instance, agreement about what outcome measures to use, optimum sample size, level of description of the sample and requirement of stratification by disease severity will facilitate design and comparison of future studies. Third, the accuracy of information provided by proxy measures might be improved by combining caregiver and patient-derived measures using purpose-built tools. Fourth, symptom-specific tools should be systematically used if we intend to progress in the understanding of depression, apathy and anxiety (e.g. Apathy Evaluation Scale). Fifth, more research is needed about the phenotype-specific barriers to engaging in self-reports experienced by people with rare

dementia, and how they can be better supported. For instance, people living with PPA face the double challenge of having cognitive difficulties and aphasia and may benefit from the use of specific communication strategies or augmentative and alternative communication. Ensuring that participants receive adequate communication support during self-reports is a way to both facilitate their participation and increase the reliability of the data collected. Lastly, given the significant presence of depression, apathy and anxiety across dementia phenotypes, and the largely reported role of NPS on quality of life and caregiver burden in other types of dementia (such as AD and dementia with Lewy bodies), it is advisable to include quality of life as a secondary outcome measure in studies investigating depression, anxiety and apathy in rare dementias, and an evaluation of NPS within routine clinical assessment.

Conflict of interest

None.

Description of authors' roles

S. M. D. Henley designed the study, formulated the research question and supervised data collection. J. D. Collins and S. M. D. Henley developed the search strategy. S.M.D. Henley, J. D Collins and A. Suarez-Gonzalez conducted the literature search, reviewed papers, and analyzed the data. J. D. Collins, S. M. D. Henley and A. Suarez-Gonzalez wrote the manuscript.

Appendix A. Search strategy

Embase:

(("familial dementia" or "inherited dementia" or "autosomal dementia" or "young-onset dementia" or "early-onset dementia" or "semantic dementia").tw. or Pick presenile dementia/ or "pick* disease".tw. or exp frontotemporal dementia/ or "frontotemporal dementia".tw. or "primary progressive aphasia".tw. or "logopenic progressive aphasia".tw. or "posterior cortical atrophy".tw.) and ((exp *mood disorder/ or depression.tw. or neuropsychiatr*.tw. or "behavioural symptom*".tw. or "behavioral symptom*".tw. or exp *affect/ or mood.tw.) not ("behavioural variant" or "behavioral variant").tw.)

PsycInfo:

(("familial dementia" or "inherited dementia" or "autosomal dementia" or "young-onset dementia" or "early-onset dementia" or "semantic dementia").tw. or picks disease/ or "pick* disease".tw. or "frontotemporal dementia".tw. or "primary progressive aphasia".tw. or "logopenic progressive aphasia".tw. or "posterior cortical atrophy".tw.) and ((exp *affective disorders/ or "depressive disorder*".tw. or depression.tw. or neuropsychiatric.tw. or "behavioural symptom*".tw. or "behavioral symptom*".tw. or mood.tw.) not ("behavioural variant".tw. or "behavioral variant".tw.))

PubMed:

((familial[TW] OR inherited[TW] OR autosomal[TW] OR young-onset[TW] OR early-onset[TW] OR semantic[TW]) AND dementia[TW]) OR "pick disease of the brain"[MeSH Terms] OR "pick* disease of the brain"[TW] OR "frontotemporal dementia"[MeSH Terms] OR "frontotemporal dementia"[TW] OR (primary[TW] AND progressive[TW] AND aphasia[TW]) OR (logopenic[TW] AND progressive[TW] AND aphasia[TW]) OR ("posterior"[tW] AND "cortical"[TW] AND "atrophy"[TW]) AND ("depressive disorder"[MeSH Terms] OR depression[TW] OR neuropsychiatric[TW] OR ((behavioural[tW] OR behavioral[TW]) AND symptom[TW]) OR "affect"[MeSH Terms] OR affect[TW] OR mood[TW] NOT ("behavioural variant"[TW] OR "behavioral variant"[TW]))

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Figure 1. Flow diagram of study selection.

(submitted as JPEG)

Table 1
Criteria used for study quality assessment

Quality category	**Scoring criteria**
Level of diagnostic criteria	0 - No explanation/not adequately outlined 1 - Locally-developed diagnostic clinical criteria 2 - Published clinical criteria - possible, or unspecified whether probable or possible 3 - Published clinical criteria - probable 4 - Clinical criteria and neuroimaging support 5 - Clinical criteria and neuropathological confirmation OR in familial cases, DNA sequencing to ascertain genetic status
Validity of measure	0 – Not specified 1 - Retrospective observation of records 2 - Non-validated measure, such as interview or questionnaire 3 - Validated measure 4 – In-depth interview with an appropriate professional to diagnose against standardized diagnostic mental health criteria
Sample size	1 – Small (N = 1-40) 3 – Moderate (N = 41-100) 5 – Large (N = 101-200) 7 – Very large ($N \geq 201$)
Exclusion of those with psychiatric history	1 – Study excluded those with history of psychiatric diagnosis 2 - No exclusion of those with history of psychiatric diagnosis
Setting from which cases were identified	0 – Not specified 1 - Specialist research setting 2 - Secondary/tertiary care setting 3 – Primary care setting 4 - Population-based study
Reporting of relevant demographic data (age and disease severity)	0 – Age and disease severity missing 1 – Either age or disease severity missing 2 – Age and disease severity reported

Table 2
Summary of papers reporting prevalence of anxiety, depression and apathy in each dementia syndrome

Paper	*N*	Mean age in years (*SD*)*	Disease severity#	Quality score (/24)	Measure used	Prevalence		
						Anxiety	Depression	Apathy
Young-onset Alzheimer's disease								
Yoon et al. (2016)	412	CDR 0.5 = 61.5 (5.4) CDR 1 = 62.5 (5.6) CDR 2 = 61.9 (6.1)	CDR 0.5 = 21.7 (3.5) CDR 1 = 17.0 (4.4) CDR 2 = 13.6 (5.6)	20	GDS	-	CDR 0.5 = 37.2% CDR 1 = 44.4% CDR 2 = 23.1%	-
Park et al. (2015)	435	62.4 (5.4)	19.3 (5.2)	18	GDS	CDR 1 = 55.7%	NR	CDR 0.5 = 44.7% CDR 1 = 70.5%
Sabodash et al. (2013)	111	61.3 (8.3)	23.4 (3.4)	17	Self-report or caregiver report, validated through targeted questions verifying the presence of core features for these conditions	-	Depression during dementia = 24.3%	-

Table 2
Summary of papers reporting prevalence of anxiety, depression and apathy in each dementia syndrome

Paper	*N*	Mean age in years (*SD*)*	Disease severity#	Quality score (/24)	Measure used	Prevalence Anxiety	Depression	Apathy
Van Vliet et al. (2013)	142	61.6 (4.8)	Global Deterioration Scale Mild = 49.6% Moderate = 30.7% Severe = 19.7%	17	NPI	44.4%	55.6%	-
Tanaka et al. (2015)[1]	92 Mild = 55 Mod = 17 Sev = 20	Mild = 58.8 (4.1) Mod = 58.8 (3.7) Sev = 59.7 (3.1)	Mild = 19.2 (4.5) Mod = 9.4 (5.6) Sev = 0.8 (1.9)	15	NPI	Mild = 40% Mod = 41.2% Sev =20%	Mild = 41.8% Mod = 47.1% Sev = 25%	Mild = 76.4% Mod = 82.4% Sev = 100%
Ballarini et al. (2016)[2]	27[3]	57.7 (5.0)	20.8 (6.3)	14	NPI	48%	37%	67%
Ferreira et al. (2018)	35	64.5 (6.1)	16.2 (8.1)	14	NPI	48.6%	40%	60%
Toyota et al. (2007)	46	58.8 (5.0)	17.4 (7.6)	14	NPI	28.3%	43.5%	56.5%
Clark et al. (1998)	16	62.2 (5.3)	20.1 (6.6)	13	NEO-PI depression facet	-	31.3%	-

Table 2
Summary of papers reporting prevalence of anxiety, depression and apathy in each dementia syndrome

Paper	*N*	Mean age in years (*SD*)*	Disease severity[#]	Quality score (/24)	Measure used	Prevalence Anxiety	Depression	Apathy
Panegyres et al. (2014)	614	59.3 (3.8)	NR	13	NR	10.3%	26.1%	-
Atkins et al. (2012)	92	NR	21 (7.0)	12	Self-report, carer information, medical notes	-	11.0%	-
Frontotemporal dementia (variant not specified)								
Lai et al. (2018)	1182	*NR*[4]	*NR*[4]	18	Comparison of symptoms against ICD-9 codes. Diagnosis of same disorder had to be given on at least two occasions.	20.0%	19.0%	-
Mourik et al. (2004)	63	60.7 (9.6)	*GDS completed but not reported*	16	NPI	26.9%	15.9%	95.2%
Engelborghs et al. (2005)	29	68.1 (10.2)	15.0 (9.7)	14	BEHAVE-AD, CSDD	10.3%	34.5%	-

Table 2
Summary of papers reporting prevalence of anxiety, depression and apathy in each dementia syndrome

Paper	*N*	Mean age in years (*SD*)*	Disease severity#	Quality score (/24)	Measure used	Prevalence Anxiety	Depression	Apathy
Kazui et al. (2016)	102	69.9 (8.4)	18.2 (6.9)	14	NPI	-	-	CDR 0.5 = 68.6% CDR 2 = 92% CDR 3 = 100%
Lopez et al. (1996)	20	64.9 (11.7)	20.3 (7.5)	14	Semi-structured interview of patient and carer with geriatric psychiatrist, diagnoses made according to DSM-III-R criteria. HDRS was also completed	15.0%	40.0%	-
Porter et al. (2003)	33	65.8 (8.5)	19.3 (9.4)	13	NPI	38.9%	-	-
Riedijk et al. (2009)[5]	36 FTDH = 12 FTDN = 24	FTDH = 63.8 (8.1) FTDN = 62.1 (8.8)	*NR*	13	NPI	FTDH = 50% FTDN = 8.3%	FTDH = 25% FTDN = 0%	FTDH = 91.7% FTDN = 100%
Chiu et al. (2006)	13	*NR*	8.0 (7.7)	12	BEHAVE-AD	53.8%	7.7%	-
Levy et al. (1998)	28	63 (range 42-81)	16.5 (10.1)	12	NPI	-	11.0%	61.0%

Table 2
Summary of papers reporting prevalence of anxiety, depression and apathy in each dementia syndrome

Paper	*N*	Mean age in years (*SD*)*	Disease severity#	Quality score (/24)	Measure used	Prevalence Anxiety	Depression	Apathy
Martinez et al. (2008)	3	*NR*[6]	*NR*[6]	12	NPI	100%	33.3%	100%
Rasmussen et al. (2018)	84	74.4 (*SD* not reported)	*NR*	12	HADS	29.3%	13.0%	-
Srikanth et al. (2005)	23	55.2 (10.7)	19.5 (5.2)	12	NPI	13.0%	69.6%	95.7%
Williams et al. (2005)	18	60.8 (range 49.7-75.1)	23.6 (range 4-30)	12	NPI	16.7%	44.4%	55.6%
Amoo et al. (2011)	4	69.3 (17.1)	CDR 2.0 = 75% CDR 3.0 = 25%	11	NPI	0.0%	25.0%	50.0%
De Vugt et al. (2006)	27	59.5 (8.4)	13.2 (9.3)	11	NPI	40.7%	25.9%	88.9%
Diehl & Kurz (2002)	30	*NR*	*NR*	10	Questionnaire developed for purposes of study. Participants either questioned, or 25 had the criteria applied retrospectively to their clinical records	-	20.0%	60.0%

Table 2
Summary of papers reporting prevalence of anxiety, depression and apathy in each dementia syndrome

Paper	*N*	Mean age in years (*SD*)*	Disease severity#	Quality score (/24)	Measure used	Prevalence Anxiety	Depression	Apathy
Gregory et al. (1996)[7]	9	54.8 (range 37-72)	*NR*	7	*NR*	-	41.7%	-
Primary progressive aphasia (variant not specified)								
Chow et al. (2009)	39	65.0 (50-79)	19.2 (range = 0-30)	12	NPI	-	-	62.0%
Fatemi et al. (2011)	55	Median age = 70.5 (SD not reported)	CDR = 0.5	12	NPI	14.8%	38.2%	48.1%
Medina & Weintraub (2007)	61	67.3 (6.6)	23.0 (5.9)	12	GDS	-	34.4%	-
Chow et al. (2002)	30	*NR*	*NR*	10	NPI	-	43.4%[8]	56.7%
Behavioral variant frontotemporal dementia								
Tartaglia et al. (2014)	320	64.8 (9.8)	CDR sum = 7.9 (4.9)	19	NPI	49.0%	41.0%	73.0%
Chow et al. (2009)	53	62.0 (range 29-79)	22.6 (0-30)	14	NPI	-	-	79.0%
Mendez et al. (2006)	74	60.9 (10.9)	22.6 (5.3)	14	"FTD checklist"	29.7%	27.0%	-
Atkins et al. (2012)	63	*NR*	21.0 (7.0)	12	Self-report, carer information, medical notes		22.2%	

Table 2
Summary of papers reporting prevalence of anxiety, depression and apathy in each dementia syndrome

Paper	*N*	Mean age in years (*SD*)*	Disease severity[#]	Quality score (/24)	Measure used	Prevalence Anxiety	Depression	Apathy
Chow et al. (2002)	62	*NR*	*NR*	12	NPI	-	32.3%[7]	89.6%
Diehl-Schmid et al. (2006)	41 CDR 1 = 21 CDR 2/3 = 20	CDR 1 = 61.3 (10.0) CDR 2/3 = 64.6 (10.2)	CDR 1 = 23.2 (5.8) CDR 2/3 = 15.4 (6.9)	12	NPI	CDR 1 = 19.0% CDR 2/3 = 21.1%	CDR 1 = 28.6% CDR 2/3 = 47.4%	CDR 1 = 90.5% CDR 2/3 = 100%
Liu et al. (2004)	24	62.3 (9.0)	20.8 (8.7)	12	NPI	56.0%	26.0%	96.0%
Perri et al. (2014)	21	73.0 (4.6)	CDR = 0.7 (0.6)	12	NPI	42.9%	52.4%	90.5%
Rosen et al. (2002)	8	61.8 (range 45-73)	23.3 (4.4)	12	NPI	63.0%	50.0%	88.0%
Bozeat et al. (2000)	13	60.2 (6.0)	24.3 (range 11-30)	10	Questionnaire designed following review of literature of neuropsychiatric symptoms in FTD	-	7.0%	-
Semantic variant primary progressive aphasia								
Rohrer et al. (2010)	9	62.3 (9.0)	22.7 (5.2)	13	NPI	56.0%	78.0%	-

Table 2
Summary of papers reporting prevalence of anxiety, depression and apathy in each dementia syndrome

Paper	*N*	Mean age in years (*SD*)*	Disease severity[#]	Quality score (/24)	Measure used	Prevalence		
						Anxiety	Depression	Apathy
Sabodash et al. (2013)	25	62.4 (6.7)	24.9 (4.3)	13	Self-report or caregiver report, validated through targeted questions verifying the presence of core features for these conditions	-	48.0%	-
Liu et al. (2004)	27	65.3 (9.2)	24.1 (4.2)	12	NPI	41.0%	44.0%	-
Rosen et al. (2002)	10[9]	67.8 (range 47-80)	22.0 (7.5)	12	NPI	50.0%	60.0%	-
Singh et al. (2015)	13	65.8 (6.3)	27.8 (2.1)	12	NPI	46.2%	46.2%	-
Bozeat et al (2000)	20	63.0 (6.3)	16.4 (range 3-28)	10	Questionnaire designed by review of literature of neuropsychiatric symptoms	-	45.0%	-
Kashibayashi et al. (2010)	19	65.5 (9.1)	20.1 (7.7)	7	Mostly by interview with caregivers, some patient history, some disclosed with NPI	-	-	78.9%
Non-fluent variant primary progressive aphasia								

Table 2
Summary of papers reporting prevalence of anxiety, depression and apathy in each dementia syndrome

Paper	*N*	Mean age in years (*SD*)*	Disease severity#	Quality score (/24)	Measure used	Prevalence		
						Anxiety	Depression	Apathy
Xiong et al. (2010)	33 AD pathology: 13 FTD pathology: 20	65.8 (7.8)	NR	14	Initially obtained from case records, supplemented with CBI and NPI	-	AD pathology = 38.5% FTD pathology = 45.0%	AD pathology = 55.0% FTD pathology = 40.0%
Rohrer et al. (2010)	14	71.8 (6.8)	24.4 (5.6)	13	NPI	36.0%	57.0%	64.0%
Singh et al. (2015)	15	65.9 (8.2)	27.3 (2.8)	12	NPI	26.7%	33.0%	9.3%
Logopenic variant primary progressive aphasia								
Rohrer et al. (2010)	7	65.1 (6.4)	13.8 (5.7)	13	NPI	71.0%	29.0%	57.0%
Singh et al. (2015)	37	65.3 (7.6)	26.0 (2.3)	12	NPI	37.8%	45.9%	32.4%
Posterior cortical atrophy								
Suarez-Gonzalez et al. (2016)	28	64 (6.7)	13 (4.5)	12	NPI	64.0%	42.0%	42.0%
Isella et al. (2015)	20	69.5 (8.3)	23.5 (3.1)	11	NPI	45.0%	55.0%	60.0%

Table 2
Summary of papers reporting prevalence of anxiety, depression and apathy in each dementia syndrome

Paper	*N*	Mean age in years (*SD*)*	Disease severity#	Quality score (/24)	Measure used	Prevalence Anxiety	Depression	Apathy
Familial Alzheimer's disease								
Ringman et al. (2015)[10]	58 Mildly symptomatic = 25 Overtly affected = 33	Mildly symptomatic = 42.6 (10.7) Overtly affected = 48.6 (8.2)	Mildly symptomatic people = CDR score of 0.5 Overtly affected people = CDR score of >0.5	16	NPI	Mildly symptomatic = *NR* Overtly affected = 54.6%	Mildly symptomatic = 56% Overtly affected = 60.6%	Mildly symptomatic = 40% Overtly affected = 69.7%
Edwards et al. (1991)[11]	84	76.4 (6.4)	*NR*	10	NPI	-	FDAT = 42.0% F2DAT = 47.0%	-
Familial frontotemporal dementia								
Rohrer & Warren (2010)	3	61.6 (9.1)	17.0 (2.6)	13	NPI	33.0%	33.0%	67.0%

Table 2

Summary of papers reporting prevalence of anxiety, depression and apathy in each dementia syndrome

* Mean age is followed by standard deviation, unless otherwise stated

Disease severity is indicated by Mini Mental State Examination score, unless otherwise stated

[1] Tanaka et al. (2015) divided their sample by disease severity. Mild = CDR 0.5/1, Moderate (mod) = CDR 2, Severe (sev) = CDR 3

[2] Ballarini et al. (2016) excluded people with non-typical Alzheimer's presentation (i.e. PCA and lv-PPA), so report data on only young-onset Alzheimer's disease with typical amnestic presentation

[3] Ballarini et al. (2016) recruited 51 participants, but NPI was only conducted on 27 people

[4] Lai et al. (2018) reported demographic data for the entire sample (FTD, AD, Lewy body dementia and mixed dementia) only

[5] Riedijk et al. (2009) divided their sample by living situation, people with FTD who lived at home (FTDH) and people with FTD who lived in a nursing home (FTDN)

[6] Martinez et al. (2008) reported demographic data for the entire sample (FTD, dementia with Lewy bodies and AD) only

[7] Gregory et al. (1996)'s sample consists of FTD patients including PPA presentations but only if they have behavior change too

[8] Chow et al. (2002) measured symptoms over illness, and symptoms at onset of illness. Prevalence for symptoms over illness are reported here

[9] Rosen et al. (2002) recruited 12 SD patients, but NPI data was only available and reported for 10 people

[10] Ringman et al. (2015) divided their sample by severity of CDR score, those with CDR = 0.5 characterized as mildly symptomatic, and those with CDR >0.5 characterized as overtly affected

[11] Edwards et al. (1991) divided their sample by those diagnosed with FAD who had one affected relation (FDAT) and those diagnosed with FAD with two or more affected relations (F2DAT)

[12] Rohrer & Warren (2010) investigated familial primary progressive aphasia, a subtype of frontotemporal dementia, caused by a progranulin mutation

Measures

BEHAVE-AD = Behavioural Pathology in Alzheimer's Disease Rating Scale; CBI = Cambridge Behavioural Inventory; CDR = Clinical Dementia Rating; CSDD = Cornell Scale for Depression in Dementia; GDS = Geriatric Depression Scale; HDRS = Hamilton Depression Rating Scale; NEO-PI = Neuroticism-Extraversion-Openness Personality Inventory; NPI = Neuropsychiatric Inventory

NR = not reported

If prevalence data were stratified by severity of NPS, the figures were collated into one single prevalence figure for that sample. However, if prevalence data were stratified by severity of disease, e.g. the sample was stratified according to Clinical Dementia Rating (CDR) score, the figures were not collated. In cases where a study fulfilled two different scoring criteria in one category the lower score was allocated.

Table 3
Quality scoring of all included papers

Paper	Level of diagnostic criteria	Validity of the measure	Sample size	Exclusion of those with psychiatric history	Setting from which cases were identified	Reporting of relevant demographic data	Total score (/24)
Amoo et al. (2011)	3	1	1	2	2	2	**11**
Atkins et al. (2012)	4	1	3	2	1	1	**12**
Ballarini et al. (2016)	4	1	3	2	2	2	**14**
Bozeat et al. (2000)	2	2	1	1	2	2	**10**
Chiu et al. (2006)	4	3	1	2	2	1	**13**
Chow et al. (2002)	2	3	bvFTD=3 PPA=1	2	2	0	**bvFTD=12 PPA=10**
Chow et al. (2009)	2	3	bvFTD=3 PPA=1	2	2	2	**bvFTD=14 PPA=12**
Clark et al. (1998)	4	2	1	2	2	2	**13**
De Vugt et al. (2006)	2	3	1	2	1	2	**11**
Diehl & Kurz (2002)	4	1	1	2	2	0	**10**
Diehl-Schmid et al. (2006)	4	3	1	2	0	2	**12**
Edwards et al. (1991)	2	0	3	2	2	1	**10**
Engelborghs et al. (2005)	4	3	1	2	2	2	**14**
Fatemi et al. (2011)	2	3	3	2	0	2	**12**
Ferreira et al. (2018)	4	3	1	2	2	2	**14**
Gregory et al. (1996)	1	0	1	2	2	1	**7**
Isella et al. (2015)	2	3	1	1	2	2	**11**
Kashibayashi et al. (2010)	0	1	1	1	2	2	**7**
Kazui et al. (2016)	2	3	5	1	1	2	**14**

Table 3
Quality scoring of all included papers

Paper	Level of diagnostic criteria	Validity of the measure	Sample size	Exclusion of those with psychiatric history	Setting from which cases were identified	Reporting of relevant demographic data	Total score (/24)
Lai et al. (2018)	2	4	7	2	3	0	**18**
Levy et al. (1998)	3	3	1	1	2	2	**12**
Liu et al. (2004)	2	3	1	2	2	2	**12**
Lopez et al. (1996)	4	4	1	2	1	2	**14**
Martinez et al. (2008)	2	3	1	2	4	0	**12**
Medina & Weintraub (2007)	2	3	3	2	2	2	**14**
Mendez et al. (2006)	4	2	3	1	2	2	**14**
Mourik et al. (2004)	4	3	3	2	2	2	**16**
Panegyres et al. (2014)	2	0	7	2	1	1	**13**
Park et al. (2015)	3	3	7	1	2	2	**18**
Perri et al. (2014)	2	3	1	2	2	2	**12**
Porter et al. (2003)	4	3	1	1	2	2	**13**
Rasmussen et al. (2018)	1	3	3	2	2	1	**12**
Riedijk et al. (2009)	4	3	1	2	2	1	**13**
Ringman et al. (2015)	5	3	3	2	1	2	**16**
Rohrer & Warren (2010)	2	3	1	2	1	2	**11**
Rosen et al. (2002)	2	3	1	2	2	2	**12**
Sabodash et al. (2013)	4	2	bvFTD=5 PPA=1	2	2	2	**bvFTD=17** **PPA=13**
Singh et al. (2015)	2	3	1	2	2	2	**12**
Srikanth et al. (2005)	2	3	1	2	2	2	**12**

Table 3
Quality scoring of all included papers

Paper	Level of diagnostic criteria	Validity of the measure	Sample size	Exclusion of those with psychiatric history	Setting from which cases were identified	Reporting of relevant demographic data	Total score (/24)
Suarez-Gonzalez et al. (2016)	2	3	1	2	2	2	**12**
Tanaka et al. (2015)	4	3	3	1	2	2	**15**
Tartaglia et al. (2014)	3	3	7	2	2	2	**19**
Toyota et al. (2007)	3	3	3	1	2	2	**14**
Van Vliet et al. (2013)	3	3	5	2	2	2	**17**
Xiong et al. (2010)	5	3	1	2	2	1	**14**
Williams et al. (2005)	2	3	1	2	2	2	**12**
Yoon et al. (2016)	4	3	7	2	2	2	**20**

Scoring criteria for each quality category

Level of diagnostic criteria: 0 – not adequately outlined; 1 – own criteria; 2 – published clinical criteria, possible or unspecified whether probable or possible; 3 – published clinical criteria, probable; 4 – clinical criteria and neuroimaging support; 5 – clinical criteria and neuropathological confirmation

Validity of measure: 0 – not specified; 1 – retrospective observation of records; 2 – non-validated measure, such as interview or questionnaire; 3 – validated measure; 4 – in-depth interview with an appropriate professional to diagnose against standardized diagnostic mental health criteria

Sample size: 1 – Small (N = 1-40); 3 – Moderate (N = 41-100); 5 – Large (N = 101-200); 7 – Very large ($N \geq$ 201)

Exclusion of those with psychiatric history: 1 – study excluded those with history of psychiatric diagnosis; 2 – no exclusion of those with psychiatric diagnosis

Setting from which cases were identified: 0 – not specified; 1 – specialist research setting; 2 – secondary/tertiary care setting; 3 – primary care setting; 4 – population-based study

Reporting of relevant demographic data (age and disease severity): 0 – age and disease severity missing; 1 – either age or disease severity missing; 2 – age and disease severity reported

Table 4
Summary of ranges of quality scores and prevalence of anxiety, depression and apathy in each dementia phenotype

Dementia phenotype	Number of papers	Range of quality scores	Range of prevalence of anxiety	Range of prevalence of depression	Range of prevalence of apathy
Young-onset Alzheimer's disease	11	12-20	10.3 – 55.7%	11.0 – 55.6%	56.5 – 100%
Frontotemporal dementia (variant not specified)	17†	7-18	0 – 100%	0 – 69.6%	50.0 – 100%
Primary progressive aphasia (variant not specified)	4	10-12	14.8%	34.4 – 43.4%	48.1 – 62.0%
Behavioral-variant frontotemporal dementia	10*	10-19	19.0 – 63.0%	7.0 – 52.4%	73.0 – 100%
Semantic variant primary progressive aphasia	7*	7-13	41.0 – 56.0%	44.0 – 78.0%	78.9%
Non-fluent variant primary progressive aphasia	3	12-14	26.7 – 36.0%	33.0 – 57.0%	9.3 – 64.0%
Logopenic variant primary progressive aphasia	2*	12-13	37.8 – 71.0%	29.0 – 45.9%	32.4 – 57.0%
Posterior cortical atrophy	2	11-12	45.0 – 64.0%	42.0 – 55.0%	42.0 – 60.0%
Familial Alzheimer's disease	2	10-16	54.6%	42.0 – 60.6%	40.0 – 69.7%
Familial frontotemporal dementia	1*	13	33.0%	33.0%	67.0%

† 3 papers with a sample size <10
* 1 paper with a sample size <10