Distinguishing frontotemporal dementia from Alzheimer's disease through everyday function profiles: Trajectories of change

Clarissa M Giebel, PhD[a,b], David Knopman, MD, PhD[c], Eneida Mioshi, PhD[d], Mizanur Khondoker, PhD[e]*

[a] Institute of Population Health Sciences, University of Liverpool, Liverpool, UK
[b] NIHR CLAHRC NWC, Liverpool, UK
[c] Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA
[d] School of Health Sciences, University of East Anglia, Norwich, UK
[e] Norwich Medical School, University of East Anglia, Norwich, UK.

**Correspondence should be addressed to:* Mizanur Khondoker, Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, England; Tel.: +44(0)1603 591501; Email: m.khondoker@uea.ac.uk

ABSTRACT

Background: Different dementia syndromes display different patterns of everyday functioning. This paper explored different patterns of functioning at baseline and trajectories of change in behavioural-variant fronto-temporal dementia (bvFTD) and Alzheimer's disease (AD).

Methods: Data from the Uniform Data Set of the National Alzheimer's Coordinating Centre were employed. The Functional Assessment Questionnaire assessed functioning at up to seven follow-up visits. Independent t-tests assessed variations in functioning between syndromes at baseline. Linear mixed effect modelling explored longitudinal functional trajectories between syndromes.

Results: Data from 3,351 patients (306 bvFTD; 3,045 AD) were analysed. At baseline, bvFTD patients performed all daily activities poorer than AD-dementia. Linear mixed models showed a significant effect of syndrome and time on functioning, and evidence of interaction between syndrome and time, with bvFTD showing a steeper decline for using the stove and travel.

Conclusions: Findings can help in the effective care planning of everyday functioning for bvFTD and AD-dementia.

Keywords: Activities of daily living, Alzheimer's disease, frontotemporal dementia.

Introduction

Increased dependency in everyday life is a hallmark of dementia[1]. Whilst deteriorations in basic and instrumental activities of daily living (bADLs/ IADLs) are common in all dementia syndromes, some research indicates that everyday activities deteriorate differently across syndromes[2,3].

Frontotemporal dementia is characterised by heightened behavioral or semantic difficulties, language (semantic processing for svPPA and motor speech for nfvPPA), as well as motor functioning[4-6], and comprises a variety of syndromes, including behavioral-variant fronto-temporal dementia (bvFTD)[7]. Some research suggests that bvFTD patients experience greater levels of IADL impairments than Alzheimer's disease (AD) dementia patients[8], with a recent study showing that directly observed performance of IADLs did not vary amongst syndromes, but initiative and planning were more impaired in bvFTD than in AD-dementia based on indirect assessments[9]. However, there is some ambiguity in that Wicklund and colleagues[10] reported no significant variations amongst AD-dementia and bvFTD patients in activities of self-care, household, employment and recreation, shopping and money, and travel, but instead only in communication. In light of the limited evidence comparing different dementia syndromes, there is a need to investigate these variations to help differentiate individual syndromes better from one another at the assessment stage.

ADLs decline hierarchically, with specific activities such as dressing to deteriorate early on in the disease, whilst activities such as feeding deteriorate to a greater extent in the later stages[10-12]. However, IADL research has been more limited to date. Peres and colleagues[13] showed how finance management, telephoning, using transport, and managing medication were significantly impaired in a mixed sample of people with dementia and declined longitudinally over 10 years, as opposed to healthy older adults. In a recent study by Giebel et al.[14], a larger number of IADLs was compared across mild, moderate, and severe dementia, although the study was not based on longitudinal data. As expected, individual activities such as preparing a hot meal and finance management were more impaired the more advanced the dementia stage. This hierarchical decline of everyday activity performance is found to be associated with a decline in cognition[15], with literature suggesting that deficits in general[16] and specific areas of cognition, such as executive functioning[17], are linked with increased dependency levels. Considering different dependency levels across fronto-temporal dementias and AD-dementia at baseline, it is important to investigate whether these variations are reflected in the longitudinal decline of everyday functioning abilities across syndromes.

Everyday activities probably deteriorate differently across dementia syndromes. Mioshi and Hodges[18] reported different levels of ADL decline between bvFTD, semantic dementia,

and progressive non-fluent aphasia (PNFA) variants over 12 months. In particular, only PNFA patients were reported to have a significant deterioration in total ADL and total IADL functioning over 12 months. In two recent studies similarly focusing on FTD syndromes, O'Connor et al.[2] reported similar levels of everyday functioning decline between semantic and non-fluent variant of primary progressive aphasia patients over five years, whilst in a separate analysis bvFTD patients were found to show faster levels of IADL decline[19]. These studies provide some important first insights, however, to existing knowledge, no study to date has compared individual IADL functioning across bvFTD and AD over a prolonged period of time. It is important to highlight the significant burden that problems with everyday activities can place both on the person living with dementia[20,21], and on the caregiver[22,23]. In particular, the increased decline in symptomatology in bvFTD[24] can have a more severe impact on caregiver well-being than in other syndromes. Therefore, investigating these trajectories can help preparing both people with dementia and caregivers better in advance.

The objective of this study was to explore the trajectories of everyday functioning between bvFTD and AD-dementia over time, by specifically focusing on individual daily activities and overall daily functioning. With only limited previous research on IADL functioning across differential diagnoses, and more specifically on trajectories of functioning decline over time, we aimed to investigate the levels of dependence at baseline and the performance trajectories over time. We hypothesised that people with bvFTD and ADD would experience different levels of decline over time, without specific hypotheses on which type would deteriorate faster. This knowledge can have important applications for clinical practice by potentially helping in planning effective care management for differential diagnoses, as the Alzheimer's Disease International Report (2011)[25] also outlines the value of early diagnosis for intervention planning.

Method

Participants

Data were used from the United States National Alzheimer's Coordinating Center (NACC) data set which collects longitudinal data from 34 Alzheimer's Disease Centers (ADCs) on demographic characteristics, dementia progression, and clinical diagnosis by clinicians from people with any cognitive status living in the community and long-term care institutions[26,27]. Written informed consents were obtained from participants at each ADC and approved by the ADC's Institutional Review Board (IRB). Research using the NACC database was approved by the University of Washington IRB. Dementia diagnoses are provided by clinicians at each study centre, and a diagnosis of AD-dementia was based on recommendations from the

National Institute on Aging – Alzheimer's Association workgroups[28]. The International Consensus Criteria for bvFTD[4] was used for a diagnosis of bvFTD.

The NACC data set was requested on 2nd November 2012 and contained patient data from September 2005 to August 2012. For this study, 5000 patient cases were used, which had 36,456 individual visits in the extracted database. Each patient had several entries due to the follow-up data, so that each patient needs to be allocated an ID at first by the researchers. Of the 5,000 coded cases, data from people with a diagnosis of bvFTD (N=306) and AD-dementia (N=3,043), all living in the community, were included in this analysis. The total eligible sample size was 3,351, and the flow diagram for selection of the baseline sample is shown in Figure 1. With AD-dementia being the most common dementia syndrome, more NACC cases had this diagnosis as opposed to bvFTD, so that the sample size of the bvFTD group was smaller. The NACC dataset is representative of the dementia population at large, and therefore contains a larger proportion of people with AD-dementia. In order to increase the power of our analysis, we have chosen to analyse the two groups in observational (natural) setting without artificially downsizing the AD group, but with adequate statistical adjustment of potential confounding factors to make the two groups as balanced as possible.

Measures

The Functional Activities Questionnaire (FAQ)[29] measured performance on 10 IADLs (bills; taxes; shopping; hobbies; using kitchen appliances; meal preparation; remembering events; paying attention; remembering appointments; travelling), which were scored from 0 to 3 (no problems to dependent). The total FAQ score is generated by adding up the individual activity scores, resulting in a maximum score of 30 (indicating full dependence).

General cognition was measured using the Mini-Mental State Examination (MMSE)[30]. A total of 30 can be obtained on the MMSE, with higher scores indicating improved cognition. MMSE is used as a tool to measure severity of cognitive impairment. Cut-off points vary by study[31,32], but typically scores of 26 or above are considered normal, 21 to 25 are suggested to indicate mild cognitive impairment, from 11 to 20 moderate, and scores from 0 to 10 are considered as severe cognitive impairment[32].

Dementia severity was assessed using the Clinical Dementia Rating scale (CDR)[33]. CDR scores range from 0 to 3 with higher scores indicating increased severity. A score of '0' suggests no change in everyday living abilities, patients with very mild to mild dementia usually score '0.5' or '1', respectively. A score of '2' or '3' is indicative of moderate and severe dementia, respectively.

Information on socio-demographics was collected at the first study visit, and included data on age, gender, education, ethnicity, marital status, and living situation. The NACC data set does not collect data on age at diagnosis, but only at NACC visit.

Data analysis

Data were analysed using IBM SPSS Version 25. Descriptive analysis of demographic characteristics were performed using summary statistics such as mean, standard deviation and frequency distributions. Continuous measures at baseline were compared between bvFTD and AD using Independent samples t-tests, and categorical measures were compared using Chi-square tests. Performance measure on each IADL at baseline was analysed individually for each dementia syndrome and compared using independent-samples t-tests.

The longitudinal (repeated) performance measures of each IADL across dementia syndromes were analysed using linear mixed effect models. The linear mixed effects models enabled comparing the differences in overall mean of performance scores across time points as well as the differences in trajectories over time between the dementia syndromes. Fixed effects in the models included diagnosis (bvFTD, AD-dementia), time (the visit number with a maximum of seven visits), and the interaction between diagnosis and time. We have used visit number as a proxy for the time variable. As can be expected in an observational study, successive visits were not equally spaced, but visits were on average one year apart. The models included random intercepts for subject IDs to account for any correlation between the repeated measures within subjects. One model was built for each individual IADL and for the total of all IALDs (FAQ_{Total}) comparing performance measure for bvFTD and AD-dementia. First, a linear mixed model as described above was built for the FAQ_{Total} as the outcome measure. The same approach was used to analyse each of the individual 10 IADLs subsequently. The independent variables were diagnosis (categorical), time (continuous) and a set of potential confounders (patient age, patient gender, patient ethnicity, and years of education). In all models, AD-dementia syndrome was used as the reference category for the diagnosis variable. As is the case for most longitudinal studies, there were fewer people in later visits (Table 2) due to dropouts. To minimise any potential bias due to differential dropout rates between the groups, we identified baseline variables that were associated with the dropout (e.g., ethnicity) and included within the list of covariates in linear mixed model analyses.

Results

Demographics

Table 1 shows the demographic characteristics across dementia syndromes at baseline. People with bvFTD were younger (bvFTD mean age = 63 years, AD mean age = 75 years, independent sample t-test p-value <0.001) and slightly more educated (bvFTD mean years of education = 15, AD mean years of education = 14, p<0.05). The bvFTD group had on average higher severity levels (mean = 6.5) based on the CDR ratings than people with AD-dementia (mean =4.2, p<0.001). Chi-square tests showed significant differences across ethnicity ($\chi^2_{(1)}$=30.5, p<0.001), gender ($\chi^2_{(1)}$ =40.5, p<.001), and marital status ($\chi^2_{(1)}$=48.39, p<0.001), with a larger proportion of people with bvFTD being male (64.7%; AD-dementia=45.6%), white (bvFTD=93.7%; AD-dementia=80.8%), and married (bvFTD=86.3%; AD-dementia=68.7%).

Table 1 also shows the outcome measures on tests of cognition. Dementia severity as measured with the MMSE was not found to vary between people with AD-dementia and bvFTD.

Table 2 shows the number of people with assessment data at different visits for each patient group. Participants had a maximum of seven visits, with bvFTD patients having assessment data up to the 6th visit. As is the case for most longitudinal studies, there are less people with assessment data at higher visits.

[insert here Table 1 and 2]

Baseline everyday functioning profiles by syndrome

Table 3 shows the performance measures on the 10 IADLs across AD-dementia and bvFTD at baseline. Managing bills (AD-dementia= 1.4 (1.3); bvFTD= 2.2 (1.1)) and assembling tax records (AD-dementia= 2.3 (1.0); bvFTD= 1.5 (1.3)) were the most impaired IADLs across both syndromes. Using kitchen appliances (AD-dementia= 1.1 (1.2); bvFTD= 0.6 (1.0)) was the least impaired across AD-dementia and bvFTD. Independent samples t-tests showed that people with bvFTD experienced greater impairments in all 10 IADLs compared to AD-dementia patients.

Figure 2 shows the proportion of people with bvFTD and AD-dementia who were impaired on each IADL at baseline. A larger proportion of bvFTD patients were impaired on all activities compared to those with AD-dementia. Comparing the proportion of people who were impaired (Figure 2) with the average severity rating (Table 3) highlights that remembering appointments was impaired in a larger number of people with AD-dementia than deficits with bills and taxes.

[insert here Table 3 and Figure 2]

Trajectories of everyday function over time

Longitudinal FAQ_{Total} scores as well as scores on each individual IADL were analysed using linear mixed effect models across the four syndromes. Table 4 shows the results of the mixed models considering FAQ_{Total} and the individual 10 IADLs. All mixed models controlled for the effects of age, gender, ethnicity, and education, to account for the differences at baseline.

Across all activities and FAQ_{Total}, bvFTD patients showed significantly worse performance than AD-dementia patients (*Bills* coeff=0.82, $p<0.001$; *Taxes*=0.86, $p<0.001$; *Shopping* = 0.78, $p<0.001$; *Hobbies*=0.69, $p<0.001$; *Kitchen appliances*=0.58, $p<0.001$; *Meal preparation*=0.80, $p<0.001$; *Events*=0.58, $p<.0.001$; *Paying attention*=0.60, $p<0.001$; *Remembering dates* = 0.43, $p<0.001$; *Travel*=0.66, $p<0.001$, FAQ_{Total}=5.57, $p<0.001$).

The regression coefficients of time (visits), which represent the gradients or slopes of the IADL trajectories for the reference (AD) group, were positive for the total as well as each individual IADL indicating that overall performance deteriorated over time. The rates of increase in impairment (slopes) were statistically significant for the total as well as for each individual IADL (*Bills* =0.17, $p<0.001$; *Taxes* =0.16, $p<0.001$; *Shopping* = 0.19, $p<0.001$; *Hobbies* =0.17, $p<0.001$; *Kitchen appliances*=0.18, $p<0.001$; *Meal preparation*=0.19, $p<0.001$; *Events*=0.17, $p<0.001$; *Paying attention*=0.16, $p<0.001$; *Remembering appointments*=0.17, $p<0.001$; *Travel*= 0.19, $p<0.001$; FAQ_{Total} =1.47, $p<0.001$).

We compared the IADL trajectory slopes between the dementia syndromes by including the interaction (cross product) term between diagnosis and time (visits). The coefficients of the interaction terms (displayed in Table 4) represent the difference in slopes of the IADL trajectories between bvFTD and AD-dementia (the reference group). These results showed that performance on IADLs for bvFTD patients declined at significantly faster rates than that of AD-dementia patients for *Using the stove* (0.08, $p<0.01$) and *Travel* (0.06, $p<0.05$). All other IADLs including the overall measure (FAQ total) declined similarly across AD-dementia and bvFTD.

We have also conducted a sub-group analysis using linear mixed model for the overall functional measure (FAQ total) by splitting the sample into two groups by disease severity (CDR ≤ 1 vs. CDR>1). **The results (additional Table A1) show that among the less severe patients (CDR ≤ 1), bvFTD group demonstrates poorer functional outcomes at baseline (coef = 4.22, p-value <0.001) compared to the AD patients. Among the more severe patients (CDR > 1), bvFTD group demonstrates slightly better (coef= - 0.14, but not statistically significant) functional outcomes than the AD patients. However, in terms of the rate of change of longitudinal trajectory of overall everyday functioning profile, the bvFTD group did not differ significantly from the AD patients within either of the**

severity categories which is in agreement with the main analysis (CDR ≤ 1: interaction coefficient = 0.05, p-value = 0.91, 95% CI -0.84 to 0.94; CDR > 1: interaction coefficient = -0.35, p-value = 0.36, 95% CI -1.09 to 0.40, see Additional Table A1). In summary, it appears that bvFTD patients demonstrate poorer functional outcomes, particularly in earlier stages of the disease with similar rates of change over time to AD. This is an interesting and important finding that provides support against the speculation that effects may have been driven by bvFTD patients simply being further along in their disease stage.

Figure 3 shows the overall (FAQ total) IADL trajectories over time (visit) for each dementia syndrome based on the linear mixed model analysis. Compared to AD-dementia, people with bvFTD showed a similar rate of increase in impairment across the seven visits, where data available, but starting at a higher initial level of impairment at the baseline visit.

[insert here Figure 3]

Discussion

This study adds novel findings based on in-depth everyday functioning profiles and their longitudinal trajectories between bvFTD and AD-dementia. Previous research primarily focused on global performances[8,16,34], or only on some activities[13], whilst some research did not compare syndromes all together[13]. With everyday functioning deficits linked to higher care costs and increased levels of carer burden[35], this study may help identify more targeted care management for everyday functioning for AD-dementia and bvFTD.

Corroborating previous evidence[9], bvFTD patients were found to be significantly more impaired than AD-dementia patients at baseline. This corroborates previous findings by Mioshi and colleagues[8] stating that global IADL functioning is impaired to a greater extent in bvFTD than in AD-dementia, whilst adding further insights by showcasing the detailed levels of impairments for individual activities in the present study. Findings showed how bvFTD patients were significantly more impaired on individual tasks such as finance management and engaging in hobbies compared to people with AD-dementia. One potential reason for these variations in functional profiles both at baseline and in their rates of decline could be different rates and areas of cognition affected in each syndrome. Cognition has been shown to be one of the primary contributors to functional dependence in dementia[9,36] and declines alongside IADL functioning[15]. Whilst there are other factors that can contribute to dependence, such as physical limitations, depression, and environmental factors[37,38], cognitive profiles and behavioural symptomatology differ between AD-dementia and bvFTD[39-41]. Therefore, it is likely

that these variations in cognitive profiles and behavioural changes throughout the dementia course are primary underlying factors as to the different functional profiles in those dementia syndromes. **Executive functioning has been particularly linked with IADL performance[42], specifically with finance management tasks[43], and is shown to deteriorate early on in the course of dementia. Comparing the longitudinal trajectory of executive dysfunction across bvFTD and AD-dementia, only disinhibition is shown to distinguish both syndromes, whilst most other executive functions deteriorate relatively similarly[41]. Therefore, executive function may only partially explain differences in deterioration for *using the stove* and *travel* in this study. However, it may be worthwhile to note that the behavioural dysregulation, stereotyped behaviours (e.g., rigidity), and apathy which are core distinguishing features of bvFTD are arguably the most functionally impairing (to families) but not captured on neuropsychological testing. These features are likely to be contributing to their early functional impairment.** Future research ought to explore the precise relationship of individual types of cognition, including executive function, prospective memory, and attention, as well as the contributions of behavioural symptoms, such as apathy, to the successful performance of everyday activities. Considering the paucity of literature on these relationships[44,45], this study further showcases the relevance and value of improving this evidence base.

bvFTD patients showed a faster decline in functioning only for using the stove and travel. Variations in these two selected activities may be the result of different cognitive or neural correlates compared to other daily activities, which may be subject to greater or faster decline in bvFTD than in AD-dementia. Literature on the cognitive and neural correlates of individual IADLs is still in its infancy[17,46-48], and more research needs to be conducted to obtain a clearer picture of these potential underlying causes of faster decline in specific IADLs in bvFTD, as opposed to AD-dementia. Previous research has shown that bvFTD patients showed a faster decline than PPA-sv patients in total ADL function over a period of three years[19], whereas no research to date had emerged comparing the speed of decline between bvFTD and AD-dementia. When breaking the activities down, it was basic ADL function that particularly showed the greater rate of decline, as opposed to IADL function[19]. It is important to consider that the longitudinal decline in this study was based on visit number as a proxy for the time variable. The successive visits were not equally spaced, which could have had an effect on the level of deterioration between visits. These variations in time space between visits were however present for both subgroups, so this should not have affected the comparison of decline rates between the subgroups.

Findings from this study can have several implications both for clinical practice and for everyday care management of dementia. This study adds novel insights into the variations in everyday functioning profiles between AD-dementia and bvFTD, which may be helpful in

contributing to effective care management planning by tailoring care to the individual functional needs of different syndromes. For example, the knowledge that the ability to use kitchen appliances deteriorates faster in bvFTD patients compared to AD-dementia patients might suggest that care management needs to accommodate for these deficits and plan ahead. This is particularly important for those people with dementia who are being supported by a family carer. Family carers are vital in supporting their relative with dementia with daily activities, and provide a large proportion of care in the home environment[49]. Particularly, caregiver stress is related to increased symptomatology of the person they are caring for[50], suggesting that care planning should not only focus in the person with dementia, but also on their family. Therefore, it is important to distinguish between different syndromes, but also to investigate and understand the decline for individual IADLs.

There are several limitations and strengths to this study. An important unknown is how the diagnoses of bvFTD and AD-dementia are differentially delayed. It is quite possible that bvFTD diagnoses are more difficult and thus patients are more impaired when they are seen in a research center compared to AD-dementia. We were unable to directly control for possible effects of length of disease on the comparability of the trajectories between the two groups due to lack of such information in the dataset. We have however adjusted all our linear mixed model analyses for participants' age, which we believe, would have mitigated the potential effects of the length of disease to some extent. To justify this further, it may be noted that the average age of diagnosis of FTD is about 60, which is a full 10 years before the average Alzheimer patient is diagnosed (Fast Facts About Frontotemporal Degeneeration, 2011)[51]. This difference in average age at diagnosis is similar to the difference in average age of the participants between the bvFTD and AD groups in our study sample (bvFTD patients are on average 12 years younger, see Table 1). The adjustment for participants' age should therefore make the two groups more balanced (comparable) in terms of the age at diagnosis as well. Whilst this study benefits from a very large national sample, by data having been collected from 34 Alzheimer's disease research centres, the AD-dementia group was substantially larger than the bvFTD group. Considering the higher incidence rate of AD-dementia compared to bvFTD however[52], it is expected to have smaller numbers in the bvFTD subgroup. With the aim of maximising the power of this study, all AD-dementia patients were included in the analysis. The pre-selection of the first 5,000 cases only of the existing Uniform dataset could represent a limitation, in that it may be considered as a selection bias of the data. However, as elaborated above, the first 5,000 cases were selected as they were deemed sufficiently large to ensure the statistical comparison of the dementia subgroups. A total of 27,772 individual entries of patient visits remained (both baseline and follow-up visits), which were not coded and allocated an individual patient ID. One further limitation could be the informant-reported nature of the everyday functioning abilities. These may provide potential bias in that

carers have been shown to differ from directly observed measures of everyday functioning[53]. Indirect reports, as opposed to directly observed performances of ADL functioning, are however frequently employed in ADL research[23,54,55], and without directly observed ADL data collected as part of the NACC Uniform data set, the fact that indirect reports of functioning may only represent a minor limitation.

Conclusions

Findings from this study have implications for the effective care management of everyday functioning across different dementia syndromes. People with bvFTD show faster rates of decline for *using the stove* and *travel* compared to people with AD-dementia. Care management can take these variations into account at the point of diagnosis, and address those activities that are found to be more or earlier impaired in certain syndromes compared to others. With IADL and ADL dependence constituting one of the major cost factors in dementia[56], and being one of the primary reasons for admission into a long-term care institution, effectively managing increased dependence for each syndrome can potentially have an effect on long-term care admissions. Future research should explore how these variations in everyday functioning can indeed be integrated in interventions and clinical practice.

Author contributions

EM conceived the idea and both EM and CG co-designed the study. MK designed the statistical analysis plan, CG and MK conducted the analyses. CG drafted the manuscript. DK, EM and MK provided critical comments on important intellectual contents. CG and MK revised the manuscript. All authors contributed in the interpretation of data for the work.

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Disclosures

Dr. Knopman serves on a Data Safety Monitoring Board for the DIAN study, and previously had served on a Data Safety Monitoring Board for Lundbeck Pharmaceuticals; is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals and the Alzheimer's Disease Cooperative Study; and receives research support from the NIH.

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Table 1. Demographic characteristics across dementia subtypes

	bvFTD (N=306)	**AD (N=3,045)**
PwD Age, mean (sd)	63.29 (10.05)	75.46 (9.17)
Education, mean (sd)	14.82 (3.25)	14.36 (3.79)
PwD Gender, N(Column %)		
Female	108 (35.3)	1,655 (54.4)
Male	198 (64.7)	1,390 (45.6)
Ethnicity, N (Column %)		
White	281 (93.7)	2,455 (80.8)
Non-White	19 (6.3)	583 (19.2)
Marital Status, N (Column %)		
Married/living as married	264 (86.3)	2038 (68.7)
Widowed/divorced/separated/other	42 (13.7)	1007 (31.3)
CDR Global, N (Column %)		
0	8 (2.6)	280 (9.2)
0.5	84 (27.5)	1487(48.8)
1	133 (43.5)	921 (30.2)
2	59 (19.3)	273 (9.0)
3	22 (7.2)	84 (2.8)
CDR sum	6.49 (4.28)	4.18 (3.92)
MMSE (Min=0, Max=30)	22.72 (6.30)	23.07 (6.09)

AD= Alzheimer's disease; bvFTD= behavioral variant fronto-temporal dementia;
CDR= Cognitive Deterioration Rating; MMSE= Mini-Mental State Examination

Table 2. Number of people with data at different assessment visits across dementia subtypes.

Visit number	**bvFTD**	**AD**
1	306	3045
2	168	2058
3	81	1370
4	46	893
5	26	512
6	12	225
7	0	59

AD= Alzheimer's disease; bvFTD= behavioral variant fronto-temporal dementia

Table 3. Everyday function variations between subtypes at baseline

	bvFTD (N=306)	AD (N=3045)	Independent t-tests with 95% CI
Finance management	2.2 (1.1)	1.4 (1.3)	t=10.65, p<0.001 [0.61 - 0.89]
Assembling tax records, business affairs/papers	2.3 (1.0)	1.5 (1.3)	t=12.09, p<0.001 [0.68-0.94]
Shopping	1.7 (1.1)	1.1 (1.2)	t=8.98, p<0.001 [0.50-0.78]
Hobby	1.5 (1.2)	0.8 (1.1)	t=9.63, p<0.001 [0.56 - 0.84]
Using kitchen appliances	1.1 (1.2)	0.6 (1.0)	t=7.34, p<0.001 [0.40 - 0.69]
Preparing meal	1.7 (1.2)	1.0 (1.2)	t=8.81, p<0.001 [0.52-0.82]
Keeping track of current events	1.4 (1.1)	1.0 (1.1)	t=6.97, p<0.001 [0.34 -0.60]
Paying attention	1.3 (1.0)	0.7 (1.0)	t=9.1, p<0.001 [0.44-0.68]
Remembering appointments	1.8 (1.1)	1.4 (1.1)	t=5.58, p<0.001 [0.24 - 0.50]
Travelling	1.9 (1.2)	1.3 (1.3)	t=7.64, p<0.001 [0.43-0.72]
TOTAL	20.3 (10.4)	15.5 (12.2)	t=7.53, p<0.001 [3.57 - 6.09]

NOTE: Data are in Mean (SD), ranging from 0 (independent) to 3 (dependent); AD= Alzheimer's disease; bvFTD= behavioral variant fronto-temporal dementia

Table 4: Mixed effect models for the total FAQ and individual IADLs as outcomes

IADL	Parameter of the model	Estimate (SE)	p	95% CI
Bills	Intercept	1.51 (0.21)	< 0.001	(1.11, 1.91)
	bvFTD	0.82 (0.10)	< 0.001	(0.63, 1.01)
	Visits	0.17 (0.01)	< 0.001	(0.16, 0.19)
	bvFTD*Visits	-0.001 (0.03)	0.974	(-0.06, 0.06)
Taxes	Intercept	1.73 (0.21)	< 0.001	(1.32, 2.14)
	bvFTD	0.86 (0.10)	< 0.001	(0.67,1.05)
	Visits	0.16 (0.01)	< 0.001	(0.14, 0.17)
	bvFTD*Visits	-0.01 (0.03)	0.650	(-0.07, 0.04)
Shopping	Intercept	0.51 (0.19)	0.006	(0.15, 0.88)
	bvFTD	0.78 (0.09)	< 0.001	(0.61, 0.96)
	Visits	0.19 (0.01)	< 0.001	(0.18, 0.20)
	bvFTD*Visits	0.04 (0.03)	0.129	(-0.01, 0.10)
Hobbies	Intercept	1.16 (0.18)	< 0.001	(0.81,1.51)
	bvFTD	0.69 (0.09)	< 0.001	(0.52, 0.87)
	Visits	0.17 (0.01)	< 0.001	(0.15, 0.18)
	bvFTD*Visits	0.05 (0.03)	0.100	(-0.01, 0.11)
Using the stove	Intercept	0.53 (0.17)	0.002	(0.20,0.86)
	bvFTD	0.58 (0.08)	0.001	(0.42,0.75)
	Visits	0.18 (0.01)	< 0.000	(0.17,0.19)
	bvFTD*Visits	0.08 (0.03)	0.006	(0.02, 0.13)
Preparing a meal	Intercept	0.77 (0.20)	<0.001	(0.38,1.16)
	bvFTD	0.80 (0.10)	<0.001	(0.62,0.99)
	Visits	0.19 (0.01)	<0.001	(0.17,0.20)
	bvFTD*Visits	0.04 (0.03)	0.172	(-0.02,0.10)
Current events	Intercept	0.94 (0.17)	< 0.001	(0.60,1.28)
	bvFTD	0.58 (0.08)	< 0.001	(0.41,0.74)
	Visits	0.17 (0.01)	< 0.001	(0.16,0.19)
	bvFTD*Visits	0.01 (0.03)	0.640	(-0.04,0.07)
Paying attention	Intercept	0.71 (0.15)	< 0.001	(0.40,1.01)
	bvFTD	0.60 (0.08)	< 0.001	(0.45, 0.75)
	Visits	0.16 (0.01)	< 0.001	(0.15,0.18)
	bvFTD*Visits	0.001 (0.03)	0.971	(-0.05, 0.05)
Remembering appointments	Intercept	1.35 (0.17)	< 0.001	(1.01,1.69)
	bvFTD	0.43 (0.08)	< 0.001	(0.27, 0.59)
	Visits	0.17 (0.01)	< 0.001	(0.15, 0.18)
	bvFTD*Visits	0.03 (0.03)	0.263	(-0.02, 0.08)
Travel	Intercept	0.92 (0.19)	< 0.001	(0.54,1.30)
	bvFTD	0.66 (0.09)	< 0.001	(0.48,0.84)
	Visits	0.19 (0.01)	< 0.001	(0.18, 0.21)
	bvFTD*Visits	0.06 (0.03)	0.043	(0.002,0.12)
FAQ Total	Intercept	15.63 (1.82)	< 0.001	(12.07,19.20)
	bvFTD	5.57 (0.89)	< 0.001	(3.83, 7.32)
	Visits	1.47 (0.07)	< 0.001	(1.32, 1.61)
	bvFTD*Visits	0.14 (0.30)	0.643	(-0.46, 0.74)

AD diagnosis is the reference category. Coefficient of Visits represents the slope for the reference category (AD subgroup). The interaction between diagnosis and visits represents the difference in slopes between the respective group and the reference group (AD). All models have been adjusted for the baseline covariates ethnicity, gender, age, and education.

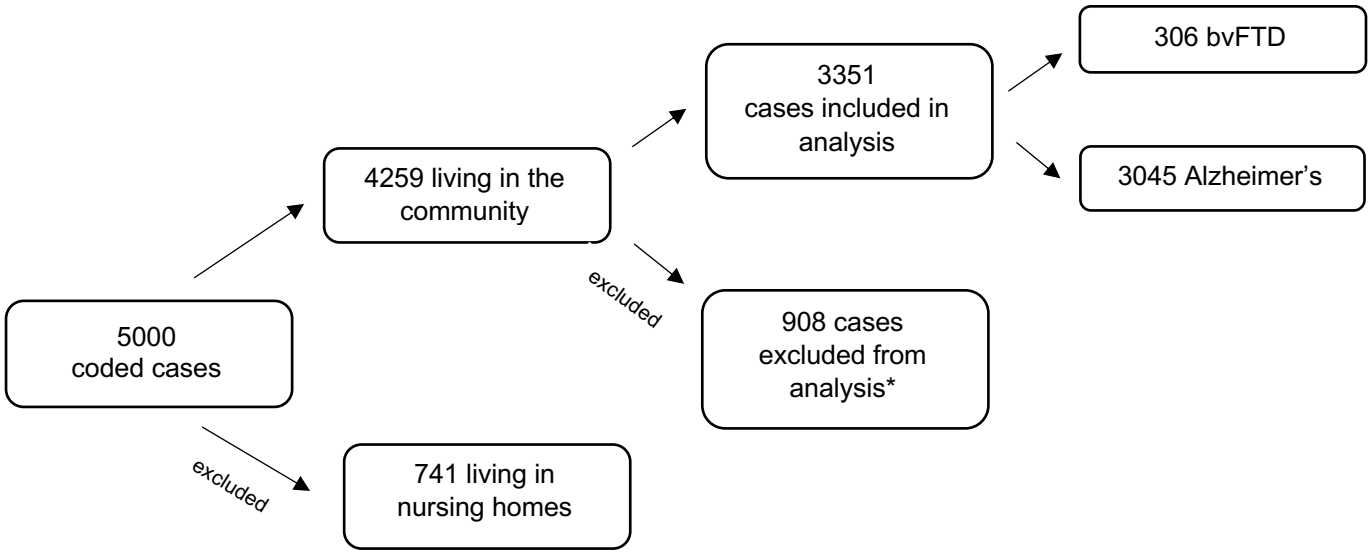

Figure 1. Schematic representation of the baseline sample selection

NOTE: *Cases were excluded because they did not have a dementia diagnosis of bvFTD or Alzheimer's disease.

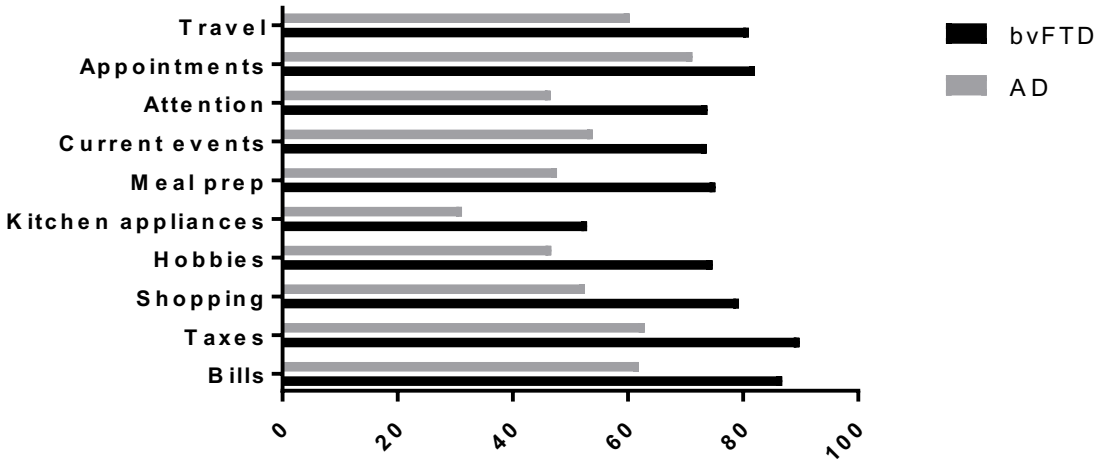

Figure 2. Everyday function profiles of different dementia subtypes at baseline

NOTE: Percentage of patients impaired on an activity within subtype diagnosis. Impairment includes a score between 1 and 3 on the FAQ item.
AD= Alzheimer's disease; bvFTD= behavioral variant fronto-temporal dementia

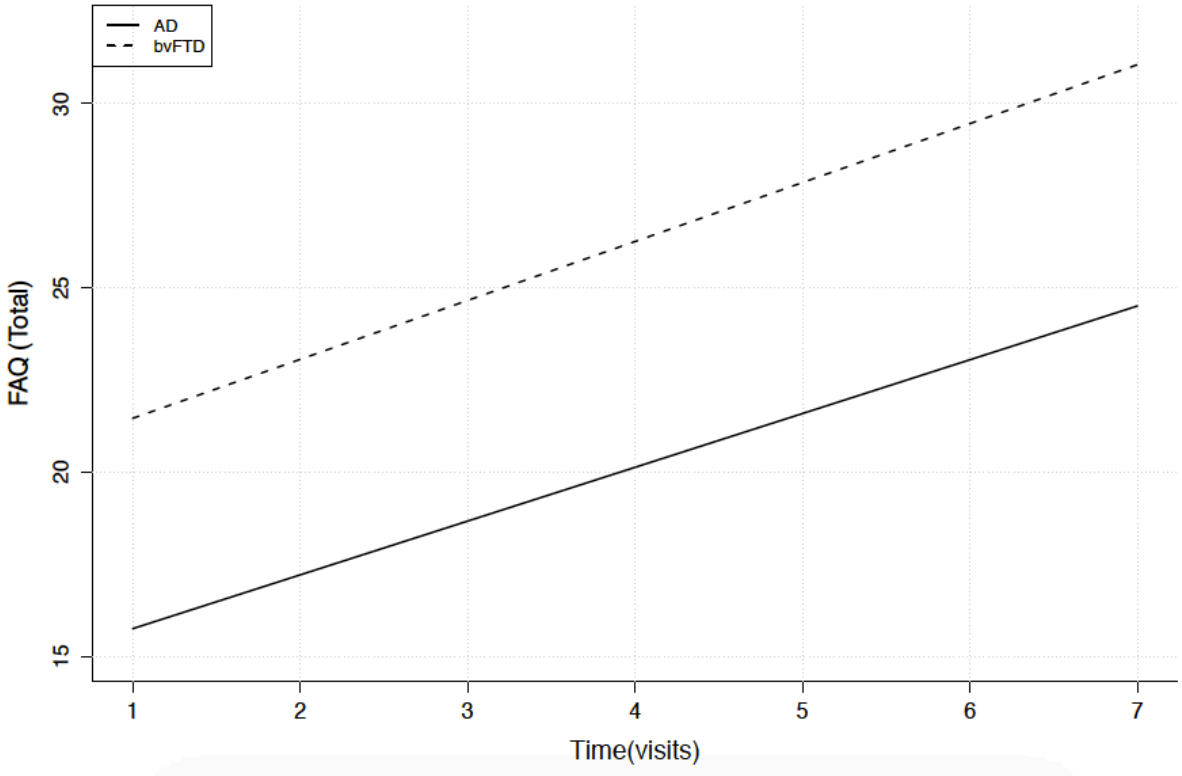

Figure 3: Predicted overall IADL (FAQtotal) trajectories for each dementia subtype based on the linear mixed model analysis. The horizontal axis (visits) refers to the time when functional performance scores (FAQ total) were measured.

Additional Table 1: Linear Mixed effect models for the overall outcome (FAQ total) by disease severity (CDR ≤ 1 vs. CDR >1).

Disease Severity	Coefficient of the model	Estimate (SE)	p-value	95% CI
CDR ≤ 1	Intercept	13.34 (1.89)	< 0.001	(9.62,17.05)
	bvFTD	4.22 (1.07)	< 0.001	(2.13, 6.31)
	Visits	1.19 (0.08)	< 0.001	(1.03, 1.35)
	bvFTD*Visits	0.05 (0.45)	0.912	(-0.84, 0.94)
CDR >1	Intercept	26.94 (2.82)	< 0.001	(23.01,30.87)
	bvFTD	-0.14 (1.08)	0.898	(-2.26, 1.99)
	Visits	0.46 (0.13)	< 0.001	(0.19, 0.72)
	bvFTD*Visits	-0.35(0.38)	0.357	(-1.09, 0.40)

AD diagnosis is the reference category. Coefficient of Visits represents the slope for the reference category (AD subgroup). The interaction between diagnosis and visits represents the difference in slopes between the respective group and the reference group (AD). All models have been adjusted for the baseline covariates ethnicity, gender, age, and education.