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RISK FACTORS TO MORTALITY AND CAUSES OF DEATH IN FRONTOTEMPORAL DEMENTIA: AN AUSTRALIAN PERSPECTIVE

RUNNING TITLE: Mortality in FTD: an Australian perspective

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Abstract

Objectives: Frontotemporal dementia (FTD) is a common cause of dementia in younger people. There is less information known about risk factors to mortality such as the type of symptom onset and cause of death in this group.

Method: This was a retrospective file review of inpatients with FTD admitted to a tertiary neuropsychiatry unit located in Australia from 1992 – 2014. Mortality information including linkage of names and causes of death were obtained from the Australian Institute Health and Welfare National Death Index.

Results: One hundred inpatients were diagnosed with FTD, including behavioural-variant, language-variant FTDs and FTD-motor neuron disease (FTD-MND). Mean age was 52.8 years (SD=10, range 31-76 years). Sixty-seven of them had died at linkage. Median survival of the sample was 10.5 years and FTD-MND had the shortest survival, 3.5 years. Increasing age of onset and FTD-MND were found to be significant predictors of association for mortality. Compared to the general population, having a FTD had an 8x increased risk of death. Females had double the standardised mortality ratio compared to males.

Discussion: This study provides important prognostic information for people diagnosed with FTD living in Australia. It highlights the importance of obtaining a definitive diagnosis as early as possible for future planning. More investigation into the relationship of symptom onset type and sex differences in FTD is required.

Keywords: mortality, survival, frontotemporal dementia, risk, death

Introduction

Frontotemporal dementia (FTD) is a frequent cause of dementia in people under 65 years old [1,2] and while symptom onset typically occurs in mid-life, there is considerable variability with individuals being affected from their 20s through to their 80s [3]. There are three major phenotypes in FTD, the most common being behavioural-variant FTD (bv-FTD) characterised by changes in personality, lack of empathy, disinhibition, hyperorality and apathy [4]. The language-variant FTDs comprises of semantic dementia, SD (fluent) and progressive non-fluent aphasia, PNFA (non—fluent) [5] and the least common form is FTD associated with motor neuron disease (FTD-MND). Corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) can also be considered within the FTD-spectrum but have symptoms seen in other neurodegenerative conditions such as Parkinson's plus and Alzheimer's diseases [6].

Predicting mortality and its risk factors in FTD has been investigated in the last 20 years [7]. A clear understanding of the prognostic role of these factors is essential for people and families affected by this disorder, for appropriate life planning and service provision.

FTD-MND is consistently associated with the shortest survival, approximately 2.5 - 3 years from onset [8,9]. The language-variants are reported to have the longest survival, with some inconsistency regarding whether SD has a longer survival than PNFA [8,10] or vice versa [9,10]. Factors associated with increased mortality have included tau-negative pathology [9,10] or the involvement of certain brain region such as frontal-subcortical circuits [10]. Sex, education or severity of dementia do not appear to predict survival [8,10,11]. Younger age of onset has been cited as a risk factor for mortality by some [12,13] but others have reported the opposite effect [14-16]. In bv-FTD, greater atrophy in anterior cingulate and motor cortex and language deficits may predict decreased survival in bv-FTD [14,17].

With regard to symptom presentation and progression in bv-FTD, Agarwal et al. [14] reported behavioural symptoms at onset was associated with faster progression in bv-FTD, whereas Garcin et al. [17] reported that progression was associated with language impairment. In all variants of FTD,

Grasbeck et al. [18] concluded that psychiatric/behavioural symptoms at onset were associated with faster progression while neurological symptoms at onset were associated with shorter survival. Our previous work in over 400 people with both a younger-onset dementia (including FTD) and older-onset dementia, found that those with symptom onset of a cognitive nature had 1.5 times risk of death compared to those presenting with a psychiatric presentation[19].

The causes of death in people with FTD usually relate to respiratory or cardiovascular disorders [11,12,18], although one study reported many unknown and accidental causes of death in FTD [20]. There have not been any more recent studies investigating this issue.

In this study, we aimed to investigate mortality in a group of people with the three main clinical subtypes of FTD, investigating survival duration, risk factors to mortality including symptom presentation, causes of death and comparisons of mortality rates to the Australian population.

Materials and methods

Sample: This was a retrospective file review of inpatients who were admitted to Neuropsychiatry, a tertiary specialist unit located at the Royal Melbourne Hospital, from 1992 - 2014 inclusive. For more details of this methodology, please see our previous paper[19]. In brief, inpatients receive comprehensive assessment comprising of neuropsychiatry, neurology, neuropsychology, neuroimaging and biological assessments. Consensus criteria for FTD at the time was used, such as the Manchester/Lund or Rascovsky criteria [4] for bv-FTD and Gorno-Tempini et al. [5] for the language-variant FTD. Up to 50% had a diagnostic re-evaluation for assessing atypical presentation and excluding phenocopy syndrome [21].

Data collection: SL and PT performed the file review. Age at symptom onset was used to determine illness duration. Symptom onset were categorised as psychiatric/behavioural, cognitive or neurological depending on what was reported by the caregiver and person with dementia. The

Neuropsychiatry Cognitive Assessment, NUCOG [22] was used for bedside cognitive testing. It assesses five domains of cognition with a total score of 100. Lower scores are indicative of worse cognition. The Global Assessment GAF [23] was used to assess function, with lower scores indicating worse functional impairment. Comorbidities included alcohol use (past heavy/current heavy or nil); presence of cardiovascular risk factors (CVRFs), such as hypertension, obesity and hypercholesterolaemia; and family history of dementia or psychiatric conditions were also measured.

Statistical analyses: Tests included ANOVA, t-tests and $\chi 2$ were used depending on whether comparisons were made using continuous or categorical data. The duration of survival was taken from age of onset, if known, and the Kaplan Meier survival curves were used to determine time to death from onset for the FTD-subtypes. Cox proportional hazard regression analysis was used to assess predictors of association of mortality using clinically-relevant factors. We used tertiles for age of onset (< 45 years, 46-60 years and > 60 years in order to delineate the "very" young-onset[24], to the most frequently occurring age of onset and older-onset[25]. Tests of proportional hazard assumption were performed using Schoenfeld residuals and no covariate violated the assumption. Significance was set at $p<0.05$ and Bonferroni correction was used for multiple comparisons. Statistical Package for Social Sciences was used (version 26, IBM Corporation, Armonk, New York, USA) and Stata (Statacorp version 6).

Identification and causes of death, according to the International Classification of Disease version 10 (ICD-10) were obtained from the Australian Institute of Health and Welfare National Death Index. Linkage date for censoring was dated at 30/9/2019 and 100% of all names submitted were identified. We used standardised mortality ratios (SMRs) to compare mortality with published Australian Bureau of Statistics (ABS) data of age-sex-specific population norms.

Ethics approval was provided by the local hospital human research ethics committee (2016.038) and from the AIHW (E02017/5/398) for linkage to the National Death Index.

Results

Demographics

As per our previous study, there were 468 inpatients admitted who had a "dementia" diagnosis[19]. Of these, we identified 100 patients who had a diagnosis of FTD. There were 53 females (53%) and 90 (90%) were of Caucasian background. The majority had at least secondary education (71%) and 65% lived in metropolitan areas. Mean (*M*) age of onset was 52.8 years old (SD=10.1, range 31.0-76.0) and mean admission age was 55.6 years old (SD=10, range 32.0-78.0). In terms of function using the GAF, the most frequent categories were 31-40 (29.6%) and 41-50 (24.1%), indicating moderate functional impairment. Cognition, measured by the NUCOG, showed moderate impairment with a mean score of 64.5/100 (SD=20.5, range 16-98.5). The cognitive domain of executive function had the lowest mean score, 8.9/20 (SD=5.2, range 0.5-19.5), compared to the other domains, but was not significantly (p=0.414). The majority of the sample (78%) endorsed being non-drinkers. In terms of symptom onset type, 60 (60%) had a psychiatric/behavioural presentation.

The sample featured all three main subtypes of FTD. These were bv-FTD (n=76, 76%), language-variant FTD (n=8 had PNFA and n=6 with SD, 14%) and FTD-MND (n=10, 10%). Table 1 shows the clinicodemographic features of the sample.

----------INSERT TABLE 1 ABOUT HERE ----------

Mortality in the three FTD groups

Overall median survival of the sample was 10.5 years (95% CI 7.9, 12.2). Table 2 shows the details for the FTD-subtypes. Median survival was 10.6, 14.2 and 3.5 years for bv-FTD, language-variant FTD and FTD-MND, respectively. Survival in FTD-MND was the shortest, ($f(2)=11.0$, $p=0.004$) overall and compared to bv-FTD, FTD-MND had a hazard ratio (HR) of 3.46 ($p=0.001$) and compared to language-variant FTD, FTD-MND had a HR of 7.78 ($p<0.001$). Median follow-up duration was 3.6 years, 8.9 years and 11.6 years for FTD-MND, bv-FTD and language-variant FTD, respectively. 67% of the total

group had died and the mean age of death was 61.6 years (SD=12.2, range 37-90). There were proportionally more people who died who had FTD-MND (χ2(2)=16.2, p=0.0003). There were no differences between the three FTD-subtypes in alcohol use, CVRF, family history or presenting symptoms (p=0.649, 0.743 and 0.112, respectively). There was no difference between the subtypes for NUCOG total score (p=0.228) but those with language-variant FTD demonstrated significantly lower NUCOG-language scores (*M* 12.6, f(2)=3.321, p=0.047). For females and males with FTD, median survival was 10.6 years (95% CI 6.5, 14.2) and 10.0 years (95% CI 7.8, 14.9), respectively, with no difference in survival (χ2(1)=0.44, p=0.5055).

---------- INSERT TABLE 2 ABOUT HERE ----------

The mortality risk was very high in people with FTD (SMR=8.1, 95%CI 6.3, 10.6) compared to the population (table 3). Females with FTD had double the SMR compared to males with FTD (SMR=12.2, 95% CI 8.6, 17.3 cf SMR=5.8, 95% CI 3.9, 8.5, respectively). Compared to the general population, the SMR in people with FTD was increased 11-fold (95% CI 6.8, 18.8) in those aged 50-59 and 7-fold (95% CI 4.7, 11.4) in those aged 60-69, and remained significantly elevated in people aged over 80 (SMR 6.8, 95% CI 2.2, 21.1).

---------- INSERT TABLE 3 ABOUT HERE ----------*Risk factors*

Variables entered into the Cox regression included tertiles of age of onset (<45 years old, 46-60 years old; > 60 years old), FTD-subtype and type of presenting symptom onset (table 4). This model was significant, χ(6)=24.36, p=0.0004. The predictors of association were older age of onset (>60 years old) and FTD-subtype (both bv-FTD and language-variant FTD compared to FTD-MND, p<0.0001 for both). The hazards ratio for these predictors were: if the age of symptom onset was more than 60 years old, there was a 3 x risk of death compared to onset at < 45 years; and having a bv-FTD has 72% less risk of mortality compared to FTD-MND and having a language-variant FTD has 87% less risk of mortality.

---------- INSERT TABLE 4 ABOUT HERE ----------

Figure 1a and 1b show the Kaplan Meier curves for the FTD subtypes (p=0.001) and for the age categories $\chi(2)=10.83$, p=0.0045.

----------INSERT FIGURES 1a and 1b ABOUT HERE ----------

Causes of death

The majority of underlying causes of death according to the ICD-10 of the 67 deceased people, were in the "Diseases of the nervous system" and "Mental and behavioural disorders" categories (n=23, 34.3% and n= 17, 25.4%, respectively). There were 10 (14.9%) people where the underlying cause of death was unknown. With regards to associated causes of death (figure 2), for FTD-MND, all associated causes were related to dementia (including n=5, 62.5%, who had spinal muscular atrophy – i.e motor neuron disease). For bv-FTD, n=20 (39.2%) had associated causes related to dementia; n=10 (19.5%) had cardiovascular-related causes such as diabetes, stroke, acute myocardial infarction or ischaemic heart disease; 4 (7.8%) had associated malignancies; n=3 (5.9%) had alcohol-related causes; n=4 (7.8%) had psychiatric-related associated causes and n=1 (2%) had respiratory associated causes. For language-variant FTD, associated causes of death included n=3 (60%) were dementia-related, n=1 (20%) was alcohol-related and n=1 (20%) had pneumonia.

----------INSERT FIGURE 2 ABOUT HERE ----------

Discussion and conclusions

This study examined mortality in people with bv-FTD, language-variant FTDs and FTD-MND, focusing on survival, risk factors, cause of death and comparisons to the Australian population. It provides important data relevant to people living in Australia which can be used to support service provision and future planning. Risk factors to mortality included being of older age and having FTD-MND. We

found that FTD-MND had the shortest survival (3.5 years), followed by bv-FTD (10.6 years) and the longest found in language-variant FTD (14.2 years) [9,13,26].

With regard to risk factors for mortality, a significant predictor of association was an FTD-subtype, FTD-MND, rather than symptom onset type. This suggests that regardless of how one initially presents, whether it is with behavioural or psychiatric, cognitive or neurological symptoms, the FTD-subtype is a factor that predicts survival duration. This is in contrast to Gräsbeck et al. [18] who reported that anxiety and suicidal ideation were associated with longer survival. They also found that significant language reduction ("semi-mutism") and neurological deficits (such as incontinence and primitive reflexes) were associated with shorter survival, possibly symptoms related to FTD-MND. Similar to our findings, Roberson et al. [10] did not find that neuropsychiatric symptoms nor neurological findings were associated with survival. They hypothesised that frontal-subcortical disease seen in bv-FTD may increase mortality more than diseases that affect the temporal lobe such as Alzheimer's disease and SD.

Our findings highlight that an accurate diagnosis of FTD-subtype is crucial for many reasons, for more accurate prognostication, psychoeducation for the family, ongoing management and future planning. However in many FTD-subtypes, as the illness progresses, there will be the development of neurological, cognitive and psychiatric symptoms. For example, the majority of people with SD will have behavioural issues and the majority of people with bv-FTD will develop language difficulties. Other FTD-associated syndromes such as CBS and PSP present with a range of language impairment and psychiatric features [6], but they all have a different survival duration [8,26]. Recently, Murley et al. [27] investigated a range of psychiatric/behavioural, cognitive and neurological symptoms at various stages of the disease, rather than at onset, in people with a range of FTD, including the language-variants, bv-FTD, FTD-MND, PSP and CBS. In contrast to our findings, they found that symptom onset type (rather than FTD-subtypes) were associated with outcomes - behavioural symptoms were associated with residential care admission and neurological symptoms were

associated with decreased survival. While more detailed investigation is required in this area, it is conceivable that the FTD subtype is a reasonable guide to predict survival duration once a diagnosis is known, but as the disease progresses, it may be the pattern of symptoms (i.e cognitive, psychiatric or neurological) which then provides information regarding the trajectory of the disease.

We found that older age of symptom onset (older than 60 years) was associated with 3 x risk of mortality compared to a younger age of onset (<45 years), which is in contrast to others' findings [12,13]. Others have found no association between age of onset and mortality risk [17,28]. However, older age of onset means one is "closer to death" (in our group, mean age of death was 61.1 years) and as one ages, they may be more likely to have physical comorbidities and develop the neurological symptoms of dysphagia and gait instability that can lead to increased morbidity. Recent studies have reported on increasing incidence of FTD occurring in people aged over 65 years ("older-onset FTD") [16,28]. Forty-four percent of Fieldhouse et al. [28] sample were described as older-onset FTD (compared to our study, 11%) and while they did not find that age of onset was associated with increased mortality risk, our findings suggest that people with older-onset FTD may be at particularly high risk of death due to lack of recognition, incorrect diagnosis and lack of appropriate management[28].

Regardless of age, we found that people with FTD had significantly increased risk of death compared to the population, with a 37-fold increase in the age group of 40-49 and compared to the general population, we found very high rates of mortality for people with FTD, with an 8 x increased risk, confirming that it is a particularly fatal disorder in mid-life.

A further novel finding of this study was that females with FTD had double the SMR compared to males with FTD. This adds to a growing body of knowledge investigating sex differences in various dementias. Perneczy et al. [29] reported that males with FTD may have more cognitive reserve than females, despite more severe prefrontal and anterior cingulate hypometabolism while Illán-Gala et al. [30] recently suggested that females have more cognitive reserve. There are also sex differences in FTD phenotypes, with more males diagnosed with bv-FTD [31] and more females diagnosed with PNFA

[32]. Llorca-Bofi (2019) suggested that males present with behavioural symptoms such as disinhibition and aggression so may be more likely to present earlier to services and clinicians, favouring earlier identification and treatment. A recent large FTD study found that the sex balance in genetic bv-FTD might be more balanced compared to sporadic bv-FTD[33]. Sex bias in reporting and from clinicians may also contribute [34].

Consistent with others [11,18,20], dementia, cardiovascular- and respiratory-related associated causes of death were common. In the bv-FTD group, alcohol- and psychiatric-related causes were also reported on the death certificate.

The phenocopy syndrome has been described as a dysexecutive syndrome which is pathologically and clinically distinct to bv-FTD in terms of progression and survival [35] and may bias the survival duration in bv-FTD. Our survival duration in bv-FTD was similar to Agarwal et al. [14] (median survival 10.8 years) but longer than Garcin et al. [17] (median survival 7.6 years), two studies who specifically attempted to exclude the phenocopy syndrome. It is possible that we included bv-FTD progressors and non-progressors (phenocopies) and our survival duration found is longer than what might be expected for a "true bv-FTD". However, 67% of our bv-FTD sample had died, compared to Agarwal et al. [14] and Garcin et al. [17], who reported 33.3% and 73.1% respectively, of their progressive bv-FTD cases, which suggests that the majority of our sample were not phenocopies.

Our study had several methodological limitations which affect generalisability. We did not have pathological confirmation of the dementia type unlike others [9,10,17] and the clinical criteria for bv-FTD has changed throughout the decades. The sample size over the study period only yielded 100 inpatients which is a low number, considering that the recognition for a dementia of the frontal lobe type occurred in 1988[36]. Accordingly, we only had small numbers of individuals with FTD at the very young-onset tertile (< 45 years) and older-onset FTD (> 60 years), again restricting our findings. We only had genetic findings of a small number of our patients due to limitations of our clinical service and that our study ranged from 1992 – 2014, with many patients diagnosed before testing for most

known illness-causing genes was available. Three patients from our cohort were found to have elevated C9orf72 repeat length and they were classified into the FTD-subtype depending on their phenotypical presentation. This mutation has a range of phenotypic presentations, progression and survival [37]. Genetic FTD may have shorter survival compared to sporadic FTD. Moore et al. [37] reported that for those who have the MAPT mutation, age of onset and death was partly predicted by this genetic abnormality (48%), which was the highest among the genetic mutations, with mean age at death being lowest in people with MAPT mutations.

An important limitation refers to our service being the only one included in this study, and the type of patients who are referred to us. Firstly, eue to our service being a psychiatry clinic, our sample is potentially biased towards bv-FTD and we only included a small number of language-variant FTD patients, precluding separation of these into the fluent and non-fluent types. This restricted our ability to determine survival in these subtypes. Additionally, we excluded CBS and PSP from our analysis. We also did not include neuroimaging in our analyses due to the heterogeneity in structural imaging over the 20 years of the study duration, limiting our ability to examine imaging correlates of survival. Focal atrophy and regional hypoperfusion may be correlated with reduced survival in various FTD-subtypes [7]. Secondly, this study spanned over two decades with our Neuropsychiatry service having made changes to our referral process and the types of patients we see. During the 1990s to 2010, the service assessed individuals with treatment-resistant psychiatric conditions and dementias of all ages, however, in the last 5-10 years, the service has focused more on the younger-onset neurocognitive and neurodegenerative disorders[38]. This affected representation and generalisation of the people assessed and included in retrospective studies such as this. Finally, there are limitations on the retrospective collation of information from comprehensive summaries. The type of initial symptom presentation and age of onset can be difficult to determine. However using age at diagnosis can similarly be problematic due to delays in diagnosis which is common in these dementias [39]. More generalizable findings may be resulted from studies with larger sample sizes, the inclusion of genetic FTD and other FTD-subtypes, obtained

through collaborations with other centres, such as the recent study done by de Boer and colleagues[33].

The current study provides important information relevant to people with FTD living in Australia. We described survival duration in the three broad FTD-subtypes and investigated risk factors of mortality, with FTD-MND and increasing age of onset being predictors of association. We confirm that FTD has a high risk of death overall, this risk being highest in women. A better understanding of mortality predictors and prognosis in FTD facilitates lifestyle, medical and service provision for these patients as part of optimal post-diagnostic care. By being able to inform our patients and families an approximate duration of survival, this assists with planning legal issues such as power of attorney and financial needs such as accessing superannuation as well as providing information about potentially modifiable risk and resilient factors and access to clinical trials might yield some hope for individuals with FTD.

Acknowledgements: We would like to acknowledge the patients and families who attend the service as well as all previous members of the clinical team.

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Conflict of interest: Nil

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Tables

Table 1. Demographic information of the n=100 patients with frontotemporal dementia

	N (%)	*N=67* died (%)	Mean (SD)	Range
Females	54 (54)	36		
Location				
Metropolitan	65 (65.7)			
Rural/regional	31 (31.3)			
Interstate	3 (3.0)			
Education				
Primary	4 (4)	3		
Secondary	54 (54)	36		
Tertiary	27 (27)	15		
M age of onset, years	97 (97)		52.8 (10.1)	31.0, 76.0
M age at admission, years	100 (100)		55.6 (10.0)	32.0, 78.0
M age at death, years			62.5 (12.2)	37.7, 76.0
NUCOG total score			64.5 (20.5)	16.0, 98.5
Attention			13.1 (5.4)	8.0, 20.0
Visuospatial			15.0 (4.2)	5.0, 20.0
Memory			11.8 (4.7)	2.0, 20.0
Executive			8.9 (5.2)	0.5, 19.5
Language			15.6 (4.0)	4.0, 20.0
Alcohol				
No	78 (78)	49		
Yes – current or previous heavy	22 (22)	18		

Presence of CVRF				
No (%)	49 (49.5)	30		
Yes (%)	50 (50.5)	37		
Family history of psychiatric conditions or dementia				
No (%)	46 (46.5)	32		
Yes (%)	45 (45.5)	38		
Symptom onset type				
Psychiatric/behavioural (%)	60 (60)	40		
Neurological (%)	6 (6)	3		
Cognitive (%)	34 (34)	24		
FTD-subtype				
Bv-FTD (%)	76 (76)	51		
Language-variant FTD (%)	14 (14)	7		
FTD-MND (%)	10 (10)	9		

Bv-FTD behavioural variant frontotemporal dementia; CVRF cardiovascular risk factors; FTD frontotemporal dementia; FTD-MND frontotemporal dementia motor neuron disease; lang-variant FTD language-variant frontotemporal dementia; NUCOG Neuropsychiatry Unit Cognitive assessment; SD standard deviation

Table 2. Subtypes of frontotemporal dementia (FTD)

	Bv-FTD n=76	Lang-variant FTD n=14	FTD-MND, n=10	
N females (% of subtype)	43 (56.6)	8 (57.1)	3 (30)	$\chi 2(2) = 2.58$, p=0.276
N dead (% of subtype)	51 (67.1)	7 (50)	9 (90)	$\chi 2(2)=16.24$, p=0.0003*
M age of onset (SD)	51.9 (10.5)	55.7 (7.9)	55.7 (9.5)	F(2) 1.259, =p=0.289
M age of admission (SD)	54.6 (10.4)	59.4 (7.5)	57.7 (8.8)	F(2) 1.608, p=0.206
M age of death (SD)	62.0 (13.0)	67.8 (11.2)	61.3 (6.7)	F(2)=0.755, p=0.479
M survival duration (95% CI)	10.6 (7.9, 13.1)	14.2 (7.2, ^)	3.5 (0.11, 7.3)	F(2), 11.033, p=0.004*
NUCOG total	64.5 (19.4)	57.7 (26.1)	79.0 (5.9)	F(2) 1.531, p=0.228
NUCOG attention (SD)	13 (5.5)	12.1 (5.9)	16 (2.0)	F(2)= 0.540, p=0.587
NUCOG visuospatial (SD)	14.9 (4.3)	14.8 (4.8)	16.5 (1.3)	F(2)=0.204, p=0.816
NUCOG memory (SD)	11.4 (4.8)	12.1 (5.0)	14.5 (1.8)	F(2)=0.601, p=0.554
NUCOG executive (SD)	8.4 (5.4)	9.5 (4.6)	11.8 (5.0)	F(2)=0.628, p=0.539
NUCOG language (SD)	16.1 (3.1)	12.6 (6.1)	18 (1.0)	F(2)=3.321, p=0.047*
Alcohol				$\chi 2(2) = 0.864$, p=0.649
No (%)	59 (77.6)	12	7 (70)	
Yes or previous heavy (%)	17 (22.4)	2	3 (30)	
Presence of CVRF				$\chi(2) = 0.00323$, p=0.998
No	37	7 (50)	5 (50)	
Yes	38	7 (50)	5 (50)	

Family history of psychiatric condition or dementia				$\chi(2) = 1.96$, p=0.743
No	34	7 (50)	5 (62.5)	
Yes	35	7 (50)	3 (37.5)	
Symptom-onset type				$\chi(4)=7.49$, p=0.112
Psychiatric/behavioural (%)	50 (65.8)	4 (28.6)	6 (60.0)	
Neurological (%)	4 (5.3)	1 (7.1)1	1 (10.0)	
Cognitive (%)	22 (28.9)	9 (64.3)	3 (30.0)	

Bv-FTD behavioural variant frontotemporal dementia; CVRF cardiovascular risk factors; FTD frontotemporal dementia; FTD-MND frontotemporal dementia motor neuron disease; lang-variant FTD language-variant frontotemporal dementia; NUCOG Neuropsychiatry Unit Cognitive assessment; SD standard deviation

^ insufficient cases for confidence interval

Table 3. Standardised mortality ratios (SMRs) for people with frontotemporal dementia compared to population norms

	Observed death	Expected death	SMR	95% CI
Sex - All	56	6.89	8.12	6.25, 10.56
Females	31	2.55	12.18	8.57, 17.32
Males	25	4.35	5.75	3.89, 8.51
Age category				
30-39	3	0.06	54.47	17.56, 168.89
40-49	10	0.27	36.73	19.76, 68.26
50-59	15	1.34	11.23	6.78, 18.63
60-69	21	2.83	7.43	4.84, 11.40
70-79	12	3.16	3.79	2.15, 6.68
80-89	3	1.59	1.88	0.61, 5.84

Table 4. Cox regression analysis for predictors of association for mortality in frontotemporal dementia (FTD)

	Hazard ratio	Standard error	Z score	P value	95% CI
Age of onset [#] 45-60 years old	1.07	0.36	0.20	0.84	0.55, 2.07
>60 years old	3.14	1.22	2.95	0.003*	1.47, 6.75
FTD-subtype^					
Behavioural-variant FTD	0.29	0.11	-3.32	0.001*	0.13, 0.60
Language-variant FTD	0.13	0.07	-3.78	0.0001*	0.04, 0.37
Symptom onset type [@]					
Neurological	0.58	0.37	-0.85	0.393	0.17, 2.0
Psychiatric/behaviour	0.61	0.17	-1.73	0.083	0.35, 1.1

reference <45 years old

^ reference frontotemporal dementia-motor neuron disease (FTD-MND)

[@] reference: cognitive presentation

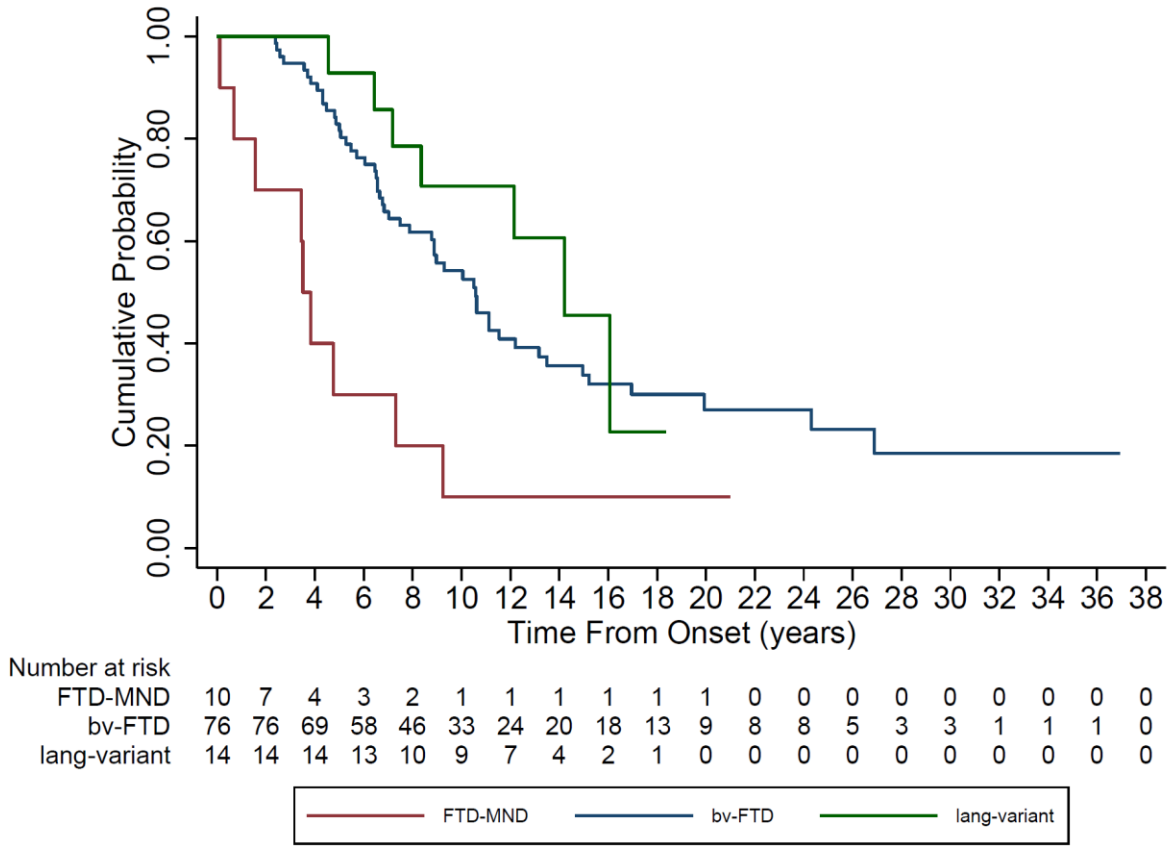
List of figure captions

Figure 1a. Kaplan Meier curve for FTD-subtypes

Figure 1b. Kaplan Meier curve for age categories

Figure 2. Associated causes of death by frontotemporal dementia subtypes

Figure 1a. Kaplan Meier curve for FTD subtypes



bvFTD behavioural-variant FTD; FTD frontotemporal dementia; FTD-MND frontotemporal dementia related to motor neuron disease; lang-variant language-variant FTD;

Figure 1b. Kaplan Meier curve for age categories

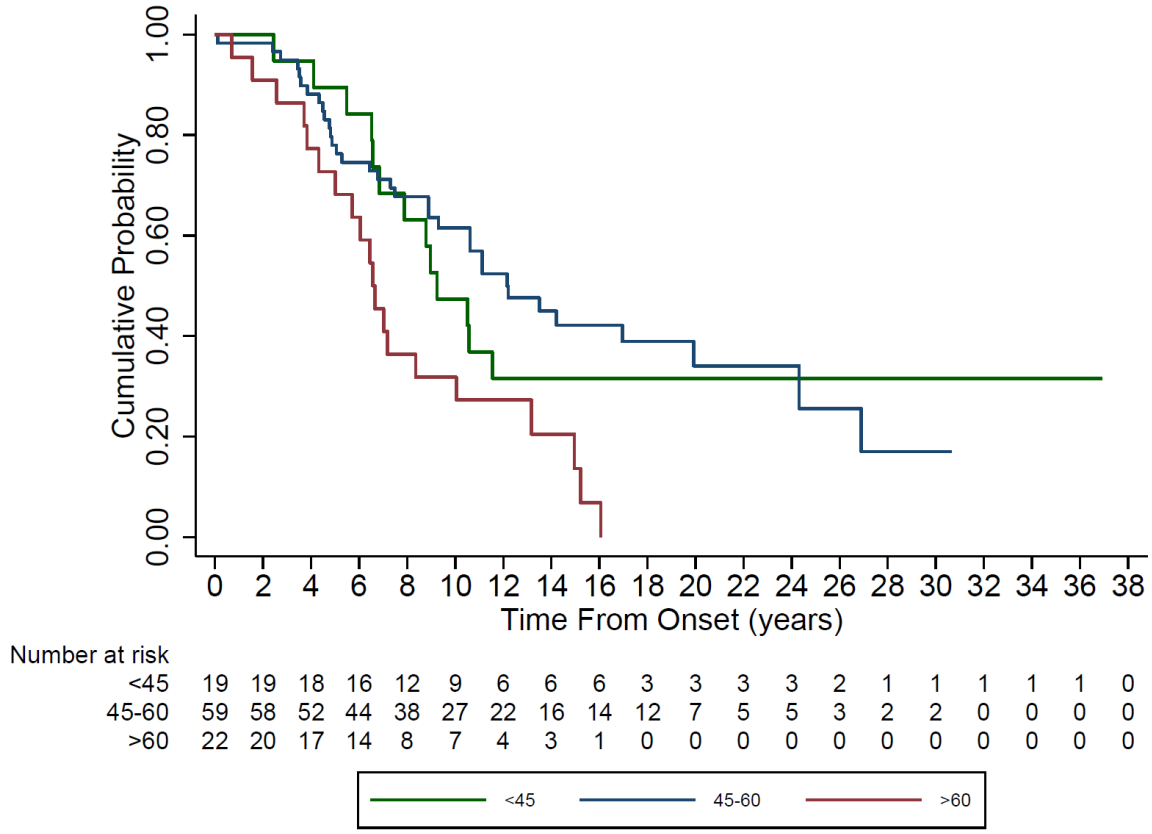
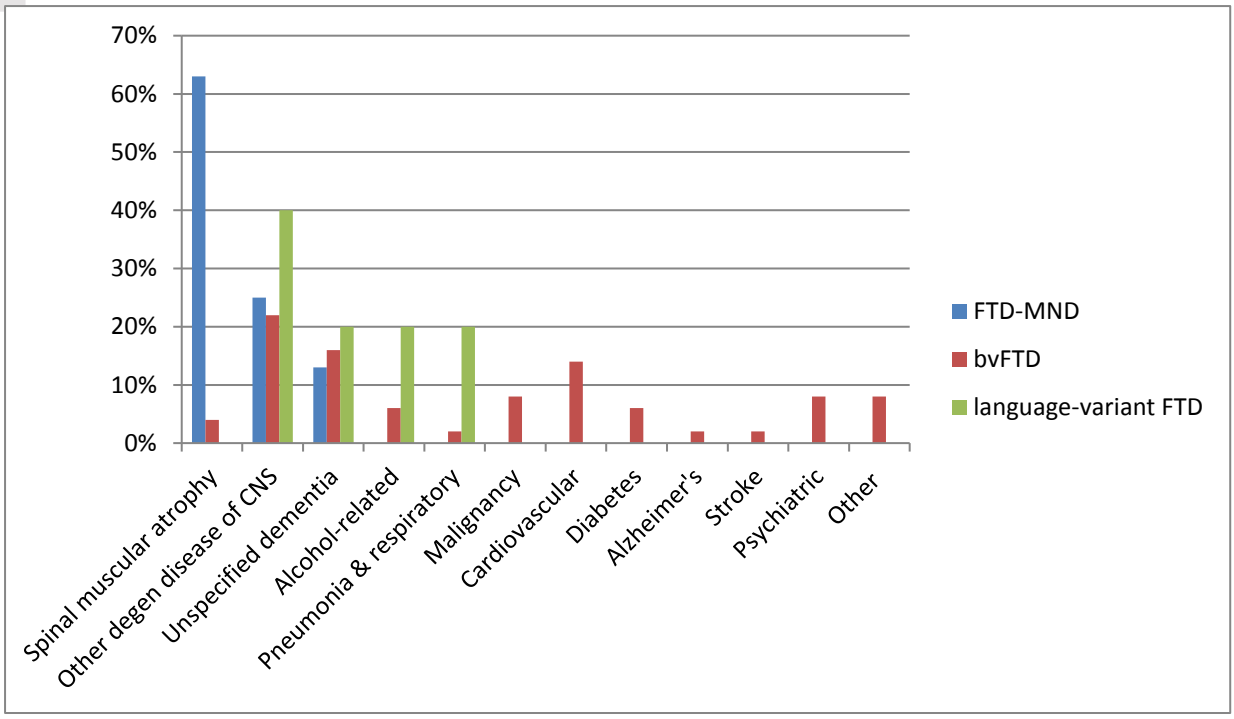


Figure 2. Associated causes of death by frontotemporal dementia subtype



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