Frontotemporal dementia in late life

Prevalence, risk factors and mortality

Thorsteinn B. Gislason

Department of Psychiatry and Neurochemistry

Institute of Neuroscience and Physiology
Sahlgrenska Academy at University of Gothenburg

UNIVERSITY OF GOTHENBURG

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thorsteinn.gislason@neuro.gu.se

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Tileinkað Unni minni
To my wife, Unnur

It's the same with every career and life decision. You just have to keep driving down the road.

It's going to bend and curve and you'll speed up and slow down, but the road keeps going …

Ellen DeGeneres

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ABSTRACT

Aims: The overall aim of this thesis was to increase knowledge about late-life behavior variant frontotemporal dementia (bvFTD). One aim was to estimate the prevalence of bvFTD among older adults and to determine the agreement between different bvFTD criteria. Further aims were to study the correlation between bvFTD and frontal lobe atrophy (on CT) and to explore non-genetic risk factors and mortality in bvFTD among older adults.

Methods: Population-based samples of 70 to 95-year-olds (N=2404) from Gothenburg, Sweden, underwent neuropsychiatric examinations and key informant interviews performed by neuropsychiatrists or psychiatric research nurses in 1986-2001. A subset (n=1074) underwent CT of the brain. BvFTD was diagnosed according to the International bvFTD Criteria Consortium (FTDC) and according to two other bvFTD criteria sets (FTLD-CC and LMRC). An exploratory nested case-control study examined potential risk factors among bvFTD cases, one control group without dementia and one with non-FTD dementia according to DSM-III-R. Mortality associated with bvFTD was compared to mortality among comparison groups with non-FTD dementia (DSM-III-R) and no dementia.

Results: The prevalence of bvFTD varied between 0.2-0.5% at age 70-79, between 2.5-3.6% at age 80-89, and between 1.7-2.2% at age 90-95. To a large extent, different FTD criteria captured different individuals. Among those with bvFTD, 80% had frontal lobe atrophy on CT, compared to 9% of those without bvFTD. Alcohol abuse, stroke/TIA, head trauma, hypothyroidism, and being divorced were associated with increased odds of bvFTD. A diagnosis of bvFTD was associated with higher risk of death than a diagnosis of non-FTD dementias, especially among the oldest old.

Conclusions: The findings suggest that bvFTD is more prevalent among older adults than previously supposed. The findings on risk factors have implications for future studies into the etiology of bvFTD, and ultimately, for prevention. Finally, it is important that clinicians are aware of this diagnosis among older adults, as it associated with a more aggressive course than other late-life dementias.

Keywords: Frontotemporal dementia, older adults, prevalence, risk factor, mortality

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SAMMANFATTNING PÅ SVENSKA

Frontallobsdemens (FLD) är en plågsam, obotlig och dödlig demenssjukdom som anses drabba främst individer i åldrarna 40-65, men eventuell förekomst av denna sjukdom hos äldre individer (>70 år) har hittills inte undersökts på ett utförligt sätt. FLD orsakar en långsam försämring av högre intellektuella funktioner, speciellt de som är viktiga för omdöme och förmågan att upprätthålla sociala relationer. Det är för närvarande en vanlig uppfattning att frontallobsdemens är ytterst sällsynt hos äldre. Det finns dock indikationer om att FLD kan vara betydligt vanligare bland äldre än man hittills trott. Patienter som drabbas av FLD kan gå oupptäckta under en lång tid, då anhöriga och andra i patientens omgivning inte förknippar symptomen med en demenssjukdom, utan man försöker förgäves hitta någon annan förklaring till patientens ändrade beteende. Det är även svårt för läkare att ställa diagnosen, speciellt om man inte förväntar sig att träffa på denna sjukdom hos en äldre individ. Behandling av FLD skiljer sig även från behandling av andra demenssjukdomar, vilket är ett ytterligare skäl till att skärpa diagnostiken i denna utsatta grupp.

Denna studie undersökte förekomsten och dödligheten av FLD i ett representativt befolkningsurval av 70–95-åringar från Göteborg. Alla deltagare genomgick identiska neuropsykiatriska undersökningar. Intervjuer gjordes med nära anhöriga eller vårdgivare till den undersökte. Dessa gav information om symtom som förekommer vid FLD och andra demenssjukdomar (såsom Alzheimers sjukdom). Intervjuerna gav också information om personens ålder vid insjuknandet och förloppet av dessa symtom. Detta gjorde oss möjligt att särskilja FLD från andra demenssjukdomar.

I denna studie var frontallobsdemens vanligare bland äldre än tidigare trott (nästan 4% av alla 80-89-åringar var drabbade). Alkoholmissbruk, slaganfall, skallskador, hypotyreos (låg ämnesomsättning), och att vara frånskild var förknippade med ökad risk för FLD. FLD visade sig förkorta livet avsevärt, även mer än andra demenssjukdomar, särskilt bland de allra äldsta.

Dessa resultat har också betydelse för framtida studier angående uppkomsten av FLD, och för att kunna etablera effektiva förebyggande åtgärder. Dessutom är det viktigt att öka medvetenheten om denna sjukdom, eftersom FLD är förknippad med stort lidande och utgör en svår börda för anhöriga och vårdpersonal, samt att den förkortar livet hos den drabbade även mer än andra demenssjukdomar hos äldre.

ÚTDRÁTTUR

Framheilabilun (frontotemporal dementia) er ólæknandi sjúkdómur sem veldur heilabilun og leiðir óhjákvæmilega til dauða. Framheilabilun veldur hægri hrörnun á dómgreind, samkennd og félagslegri færni. Á fyrstu stigum sjúkdómsins getur því verið vandasamt að átta sig á því að um heilabilun sé að ræða. Sjúklingurinn hagar sér oft mjög afbrigðilega, en minnið og önnur vitræn geta er nánast óskert. Nánustu ættingjar og aðrir í umhverfi sjúklingsins tengja því ekki einkennin við heilabilun, og reyna árangurslaust að finna einhverja skýringu á breyttri hegðun sjúklingsins. Það er einnig erfitt fyrir lækna að greina þennan sjúkdóm á fyrstu stigum. Meðhöndlun á framheilabilun er frábrugðin meðferð á öðrum heilasjúkdómum og er því enn frekar ástæða til að bæta greiningu á þessum sjúkdómi. Fram til þessa hefur verið talið, að framheilabilun komi fyrst og fremst fram hjá einstaklingum á aldrinum 40-65 ára, og að framheilabilun sé mjög sjaldgæf eftir sjötugt. Þessi rannsókn kannaði tíðni, áhættuþætti og dánartíðni framheilabilunar meðal aldraða einstaklinga.

Rannsóknirnar, sem kynntar eru í þessari ritgerð, voru gerðar á úrtaki meðal einstaklinga 70-95 ára í Gautaborg, Svíþjóð. Allir þátttakendur fóru í ýtarlega læknisskoðun og tekin voru greiningarviðtöl við nána aðstandendur. Með þessum athugunum var hægt að greina einkenni og framvindu heilabilunar, bæði framheilabilunar og annarra sjúkdóma, sem valda heilabilun (t.d. Alzheimers-sjúkdómur).

Í þessari rannsókn kom í ljós, að framheilabilun meðal aldaðra var algengari en áður var talið (næstum 4% af öllum 80-89 ára voru greindir með framheilabilun). Framheilabilun reyndist einnig leiða hraðar til dauða en aðrir sjúkdómar, sem valda heilabilun. Skv. þessari rannsókn komu einnig fram eftirfarandi áhættuþættir fyrir framheilabilun: misnotkun áfengis, heilablóðföll, höfuðáverkar, vanstarfsemi skjaldkirtils og að vera fráskilin(n). Rannóknir á áhættuþáttum eru mikilvægar til að greina orsakir framheilabilunar, og til að finna viðeigandi fyrirbyggjandi ráðstafanir.

Að lokum, þá er mikilvægt að vekja athygli á þessum sjúkdómi, því hann leggur alvarlegar byrðar á herðar aðstandenda og styttir líf sjúklinga umtalsvert, jafnvel meira en aðrar tegundir heilabilunar.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Gislason TB, Sjögren M, Larsson L, Skoog I. The prevalence of frontal variant frontotemporal dementia and the frontal lobe syndrome in a population based sample of 85 year olds. J Neurol Neurosurg Psychiatry. 2003 Jul;74(7):867-871.

II. Gislason TB, Ostling S, Börjesson-Hanson A, Sjögren M, Simoni M, Pantoni L, Skoog I. Effect of diagnostic criteria on prevalence of frontotemporal dementia in the elderly. Alzheimers Dement. 2015 Apr;11(4):425-433.

III. Gislason TB, Östling S, Guo X, Börjesson-Hanson A, Kern S, Skoog I. Potential risk factors for late-life frontotemporal dementia: A nested case-control study. *In manuscript.*

IV. Gislason TB, Ostling S, Guo X, Sigström R, Kern S, Skoog I. A population study on mortality in late-life frontotemporal dementia. *In manuscript.*

CONTENT

Abbreviations

AD	Alzheimer's disease
BPSD	Behavioral and psychological symptoms of dementia
bvFTD	Behavioral variant frontotemporal dementia
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CT	Computerized tomography
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
FLS	Frontal lobe syndrome
FTD	Frontotemporal dementia
FTDC	International Behavioral Variant FTD Criteria Consortium
FTLD	Frontotemporal lobar degeneration
FTLD-CC	Consensus criteria on frontotemporal lobar degeneration
LMRC	Lund-Manchester Research Criteria
MADRS	Montgomery-Åsberg Depression Rating Scale
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination
OR	Odds ratio

NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders (criteria for Alzheimer's disease)
NINDS-AIREN	National Institute of Neurological Disorders and Stroke and l'Association Internationale pour la Recherce et l'Enseignement en Neurosciences (criteria for vascular dementia)
PI	Principal investigator
SD	Standard deviation
VAD	Vascular dementia
WML	White matter lesion

INTRODUCTION

Personality, emotions, language, the capability for complex social interactions and to anticipate future consequences of present actions; all are dependent on the continuous and proper function of the frontal lobes and associated circuits. It is therefore not surprising that selective degeneration of the frontal lobes can have devastating consequences, not only for those affected, but also for their families. Frontotemporal dementia (FTD) is a neurodegenerative disorder with circumscribed degeneration of the frontal lobes and anterior temporal lobes[1]. The Czech neuropsychiatrist Arnold Pick first described this type of degeneration in 1892[2], but it still remained relatively obscure for almost a century. In the last three decades, interest for frontotemporal dementia (FTD) has increased substantially, as it has become recognized that FTD is the second most common neurodegenerative dementia among individuals under the age of 65[3]. However, FTD is still believed to be rare among older adults, and epidemiological aspects have not been extensively explored, and there is a paucity of population-based studies on FTD. Few prevalence estimates exist among the older adults and the influence of different criteria on the prevalence of FTD is unclear. About 50% of individuals diagnosed with FTD have no family history and are considered to be sporadic cases[4], but risk factors for non-genetic FTD have not been extensively studied, especially among older adults. Furthermore, as life expectancy in the Western world is increasing, an increasing number of older adults may be diagnosed with FTD. Accurate mortality estimates of FTD are therefore crucial, not only for those afflicted with FTD, but also for relatives, caregivers and health care providers.

Historical background

During the first eighty years of the twentieth century, the only known form of frontotemporal dementia (FTD) was Pick's disease. Arnold Pick (1851-1924) was a neuropsychiatrist working in Prague, who in 1892 wrote a case report describing a 71-year-old man with progressive dementia with unusually prominent aphasia. Autopsy revealed cortical atrophy, primarily of the left temporal lobe, with no focal lesions [2]. Previously, dementia had been thought to be caused by diffuse degradation of mental abilities [5], and Pick's major contribution to neuroscience was to associate dementia with macroscopic *focal* cortical atrophy[6]. However, it was Alois Alzheimer (1864-1915), who first described what subsequently became known as Pick cells and Pick bodies[7]. Pick's bodies are argyrophilic inclusions within neurons and Pick

cells are neurons swollen with argyrophilic material. The correlation between the clinical syndrome and the pathology was determined in the 1920's, with Onari and Spatz introducing the eponym Pick's disease for this disorder [8]. Patients with autopsy findings of Pick bodies and Pick cells were diagnosed as having had typical Pick's disease [9]. Patients with frontal and/or temporal atrophy but without the typical microscopic findings were diagnosed as "atypical Pick's disease". During the twentieth century Pick's disease was considered quite rare and sometimes Pick's disease was lumped together with Alzheimer's disease (AD) as Pick-Alzheimer spectrum[10, 11].

Although many researchers contributed to an increased understanding of Pick's disease during the first part of the twentieth century[11-17], a major breakthrough came in the 1970's when the Lund dementia research group noted a number of dementia cases that presented with frontal symptoms, but had neuropathological findings that were not consistent with either Pick's disease type or Alzheimer disease [18]. These patients had substantial clinical symptoms, but on a macroscopic level the brains showed little frontal atrophy in most cases. The microscopic findings were mild to vague, almost similar to artifacts[18]. The first study published with these findings was in 1977 [19], and the first international conference on FTD was held as a satellite symposium of the tenth International Congress of Neuropathology[18, 20, 21]. Neary et al. described independently in 1988 a "dementia of the frontal lobe type" from a centre in Manchester, England[22], and Knopman et al. in 1990 published a paper describing "dementia lacking distinctive histology" [23].

The first clinical and neuropathological criteria for FTD came in 1994, when the research groups in Lund and Manchester published clinical and pathological criteria for FTD[1], and substantially revised FTD criteria were then published in 1998[24] and in 2011[25].

During the past 15 years the research on FTD has expanded rapidly[18] with progress in many fields, but particularly with regards to neuropathology[26, 27] and genetics[28], some aspects of which will be covered in the following sections.

Clinical features of FTD

The major presenting feature of FTD is a profound change in personal and social conduct coupled with a deterioration of frontal lobe functioning (e.g. executive function) [29]. This change in frontal lobe functioning may initially

not be apparent except on neuropsychological testing. However, the change in personality is almost invariably jarring to close relatives and friends, and is not related to pre-morbid personality[30]. The onset of symptoms is typically insidious, and therefore often interpreted as being caused by psychiatric illness, such as an affective disorder [29, 31]Also, psychiatric manifestations often occur early, with dysthymia being present in one third of patients with FTD at initial presentation[32], and anxiety being more common in FTD than in AD[33].

FTD patients are strikingly unaware of the change in their personality and behavior, but may admit that they are feeling ill[34], often without being able to specify that more exactly. As individuals with FTD have limited insight into their illness, it becomes crucial to have a close informant, e.g. a close family member, in order to make the correct diagnosis[3].

The frontal lobe deficits are often revealed in a social context as inappropriate behavior becomes troubling to the environment. The FTD patient's behavior becomes marked by mental inflexibility and failure to adapt to new social situations, and there may be incidents of inappropriate joking or touching, and not respecting interpersonal space. Some patients are restless and overactive[31], but some are most often inactive and seem to lack motivation for previously important activities[34]. Some patients have alternating periods of hyperactivity and inactivity[34].

FTD patients are more likely than patients with Alzheimer's disease to come into contact with the judicial system[35]. Some patients experience a particularly malignant combination of losing moral sense and empathy, as well as developing disinhibited and compulsive behavior[36, 37]. This acquired sociopathy can lead to unacceptable behavior such as traffic violations, physical assaults and unsolicited sexual acts[38].

FTD patients also often exhibit altered eating patterns and changes in appetite or food preference; in early stages this usually takes the form of increased appetite and table manners, e.g. taking food first, and overeating where that is socially inappropriate. This may also be accompanied by excessive alcohol consumption[39].

Emotional blunting is also a characteristic feature of FTD[40], often accompanied by loss of empathy and emotional unconcern[41], a common early feature being loss of interest in one's family[42].

Repetitive and stereotyped behaviors may be seen in patients with FTD, e.g. simple mannerisms, repetitive motor acts or hand-clapping. There may also be more complex acts, such as repeating phrases or parts of sentences (palilalia), repeating another person's words (echolalia) or repeatedly singing the same song[34]. Furthermore, a patient with FTD may exhibit utilization behavior[43], i.e. if the patient sees an object, he may start to use that object,

even if that action is inappropriate. For example, if presented with a pen, the patient may start writing on any nearby surface, e.g. a table.
Although memory dysfunction may not be apparent in the early stages of FTD, neuropsychological testing may reveal impairments in episodic memory, even early in the course of the disease[44]. However, visuospatial functions are often spared in the initial stages [3].
The above description of symptoms refers to the variant of FTD that is known as behavioral FTD (bvFTD), which is the most common presentation of FTD (nearly 60% of cases)[4]. However, FTD may also present with decline in language skills, which is known as primary progressive aphasia[45]. This language variant is further subdivided into semantic dementia, progressive non-fluent aphasia and logopenic progressive aphasia[24, 45, 46], according to the predominant pattern of language disturbance[40].

Ultimately, all individuals develop a global dementia, regardless of initial phenotype[47].

Genetics of FTD

A family history of FTD is present in 25–50% of cases, indicating a considerable genetic component[28]. The first reports of genetic mutations associated with FTD came in 1998[48-50], when mutations in the microtubule-associated protein tau (MAPT) gene on chromosome 17 were identified in a number of families with FTD and Parkinsonism. It has subsequently become clear that FTD can be caused by several other mutations, the most common being progranulin (PGRN) [51, 52] and chromosome 9 open reading frame 72 (C9orf72) expansions [53, 54]. Much rarer causes of FTD are mutations in the valosin-containing protein (VCP) gene [55] and a mutation in the gene for charged multivesicular body protein 2B (CHMP2B) [56].

A recent genome-wide association study among 3526 patients with FTD suggested that loci encompassing the major histocompatibility complex (on chromosome 6) and possibly lysosomal and autophagy pathways (on chromosome 11) are potentially involved in FTD [57]. Furthermore, a genome-wide exome array study that included 168 patients with FTD suggests that low-frequency coding variants with intermediate effect size may account for a significant fraction of the genetic susceptibility to FTD, but did not otherwise uncover any new associations [58, 59].

Neuropathology

Unlike AD, the neuropathology associated with the clinical syndrome of FTD is heterogeneous, the common feature being a selective degeneration of the frontal and anterior temporal lobes [60]. The current nomenclature uses the term "frontotemporal dementia" (FTD) to denote the clinical entity and "frontotemporal lobar degeneration" (FTLD) for the neuropathological condition. The classical histopathology of FTLD shows cortical neuronal loss, astrocytic gliosis and microvacuolation, most prominent in cortical layers II and III in the frontal and anterior temporal lobes[20, 61].

White matter changes are usually those of astocytic gliosis and myelin loss[21]. The white matter changes generally follow the affected cortical regions, but there may also be some white matter involvement in regions where the cortex is not affected [62]. It still remains to be resolved if the white matter changes are a result of Wallerian degeneration per se, or if the changes are caused by a combination of direct pathology of the white matter and Wallerian degeneration[63, 64].

Immunohistochemistry has revealed several types of abnormal intracellular protein deposits in FTLD, and these inclusions have linkage with genetics and to some degree with clinical symptoms [3]. The main neuropathological types of FTLD according to current classification are FTLD-tau, FTLD-TDP (types A-D), FTLD-UPS and FTLD-FUS (fused in sarcoma).

There is a clear correspondence between genetic mutations and pathology, MAPT mutations leading to tau pathology, PGRN mutations leading mainly to FTLD-TDP pathology Type A, C9orf72 mutations to FTLD-TDP pathology Type B and CHMP2B to FTLD-UPS [28]. The main histopathological subtypes associated with bvFTD are FTLD-tau, FTLD-TDP and FTLD-FUS[28].

FTD Criteria

The need for consensus on clinical and neuropathological criteria became evident as more studies were published from different centers during the late 1980's and early 1990's. In 1994, the research groups in Lund and Manchester published clinical and pathological criteria for FTD [1], the Lund-Manchester research criteria (LMRC). These criteria include three frontotemporal dementia symptom constellations: (1) behavioral symptoms, (2) affective symptoms and (3) symptoms of a speech disorder (table). The

onset has to be insidious and the course invariably progressive. However, the criteria do not describe how many symptoms or symptom constellations have to be present for a diagnosis. A re-working of the Lund-Manchester Research Criteria (LMRC) was published in 1998 with the Consensus criteria on frontotemporal lobar degeneration (FTLD) [24]. These criteria included even the categories of semantic dementia and progressive aphasia. However, the 1998 criteria came to be considered to be too rigid for clinical and research purposes[65]. In 2011, the International Behavioral Variant FTD Criteria Consortium (FTDC) proposed revised criteria[25]. These three sets of diagnostic criteria include different combinations of impairments in social and emotional abilities. According to earlier terminology, FTD with behavioural symptoms was called frontal variant FTD (fvFTD) [66]. For the sake of clarity, only the term "bvFTD" will be used in this dissertation.

Table 1. The Lund-Manchester Research Criteria for clinical diagnosis of frontotemporal dementia [1].

Core diagnostic features
Behavioral disorder
* Insidious onset and slow progression
* Early loss of personal awareness (neglect of personal hygiene)
* Early loss of social awareness (lack of social tact)
* Early signs of disinhibition
* Mental rigidity and inflexibility
* Hyperorality
* Stereotyped and perservative behavior
* Utilization behavior
* Choreo-athetosis
* Distractibility, impulsivity, and impersistence
* Early loss of insight
Affective symptoms
* Depression, anxiety, excessive sentimentality
* Hypochondriasis, bizarre somatic preoccupation
* Emotional unconcern
* Amimia (inertia, aspontaneity)
Speech disorder
* Progressive reduction of speech
* Stereotypy of speech
* Echolalia and perseveration
* Late mutism

Table 2. Diagnostic exclusion features in the Lund-Manchester Research Criteria for clinical diagnosis of frontotemporal dementia [1].

Diagnostic exclusion features
* Abrupt onset with ictal events
* Head trauma related to onset
* Early severe amnesia
* Early spatial disorientation
* Early severe apraxia
* Logoclonic speech with rapid loss of train of thought
* Myoclonus
* Cortical bulbar and spinal deficits
* Cerebellar ataxia
* Choreo-athetosis

Table 3. The clinical diagnostic features of FTD: Clinical profile from the Consensus criteria on frontotemporal lobar degeneration (FTLD-CC) [24]

Core diagnostic features
A. Insidious onset and gradual progression
B. Early decline in social interpersonal conduct
C. Early impairment in regulation of personal conduct
D. Early emotional blunting
E. Early loss of insight

Historical and clinical exclusion features
1. Abrupt onset with ictal events
2. Head trauma related to onset
3. Early, severe amnesia
4. Spatial disorientation
5. Logoclonic, festinant speech with loss of train of thought
6. Myoclonus
7. Corticospinal weakness
8. Cerebellar ataxia
9. Choreoathetosis

Table 4. International consensus criteria for behavioural variant FTD (FTDC)[25].

I. The following symptom must be present to meet criteria for bvFTD

A. Shows progressive deterioration of behavior and/or cognition by observation or history (as provided by a knowledgeable informant).

II. Possible bvFTD

Three of the following behavioral/cognitive symptoms (A–F) must be present to meet criteria.
Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. Early behavioral disinhibition (one of the following symptoms):
- A.1. Socially inappropriate behavior
- A.2. Loss of manners or decorum
- A.3. Impulsive, rash or careless actions

B. Early apathy or inertia (one of the following symptoms):
- B.1. Apathy
- B.2. Inertia

C. Early loss of sympathy or empathy (one of the following symptoms):
- C.1. Diminished response to other people's needs and feelings
- C.2. Diminished social interest, interrelatedness or personal warmth

D. Early perseverative, stereotyped or compulsive/ritualistic behavior (one of the following symptoms):
- D.1. Simple repetitive movements
- D.2. Complex, compulsive or ritualistic behaviors
- D.3. Stereotypy of speech

E. Hyperorality and dietary changes (one of the following symptoms):
- E.1. Altered food preferences
- E.2. Binge eating, increased consumption of alcohol or cigarettes
- E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions (all of the following symptoms must be present):
- F.1. Deficits in executive tasks
- F.2. Relative sparing of episodic memory
- F.3. Relative sparing of visuospatial skills

III. Probable bvFTD

All of the following symptoms (A–C) must be present to meet criteria.

A. Meets criteria for possible bvFTD

B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)

C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]:
- C.1. Frontal and/or anterior temporal atrophy on MRI or CT
- C.2. Frontal and/or anterior temporal hypoperfusion on PET or SPECT

IV. Behavioural variant FTD with definite FTLD Pathology

Criterion A and either criterion B or C must be present to meet criteria.
- A. Meets criteria for possible or probable bvFTD
- B. Histopathological evidence of FTLD on biopsy or at post-mortem
- C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD

Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD.
- A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders
- B. Behavioral disturbance is better accounted for by a psychiatric diagnosis
- C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

Prevalence of FTD

Population studies on FTD have usually been performed within a regional catchment area, using medical records or disease registers [4]. Only a few have recruited individuals directly from the population[67, 68]. Prevalence estimates vary from 2/100 000 to 31/100 000[67-73]. Most studies have focused on the age group under age 65 and few population studies have examined epidemiological aspects of FTD in older adults. The prevalence is reported to be lower than one percent using LMRC or FTLD-CC in individuals above age 65 years[74-77]. However, these studies only included cases of FTD who also fulfilled criteria for global dementia, in which memory problems are mandatory. Thus, individuals with FTD who do not fulfill criteria for global dementia may remain undetected[42, 78]. Furthermore, key informant interviews (with close relatives and caregivers) were used in only two of these studies[74, 77]. Key informant interviews are crucial to obtain retrospective information about early symptoms and course of symptoms, as these are necessary to differentiate bvFTD from other dementia disorders.
While it has been suggested that FTD may be more common than previously supposed[40, 79, 80], few previous studies have examined the prevalence of FTD in a wider range of ages among the elderly. Neither has the utility of different criteria been examined in elderly populations.

Neuroimaging

Most previous studies on neuroradiological findings in bvFTD have used MRI and consistently report cortical atrophy in the frontal and anterior temporal lobes[81, 82]. The frontal atrophy involves medial, dorsolateral and orbiotofrontal regions [81] and longitudinal studies have shown that the atrophy is progressive, especially in the medial frontal cortex[83-85]. Other cortical areas (i.e. parietal cortex) may also be involved, but usually to a lesser degree. Deep cortical gray matter structures (caudate nucleus, globus pallidus and nucleus accumbens) may also be affected in FTD[86].

Risk factors in FTD

About 50% of individuals diagnosed with FTD have no family history and are considered to be sporadic cases [87]. Only three previous case-control studies have examined non-genetic risk factors for FTD (table 1)[88-90]. These

studies recruited cases from patient samples. Two of the studies used controls without dementia and memory complaints. One of these studies recruited controls from nursing homes and the other recruited controls from a general medical practice list[88, 90]. The third study used controls with non-FTD dementias recruited from the same Veterans Affairs medical center as the cases[89]. One study focused on the association of FTD and potential cardiovascular risk factors [90].

The main finding in two of these studies was that head trauma was associated with increased risk of FTD [88, 89], while one study found an association with diabetes mellitus [90]. Furthermore, two studies found trends for associations with thyroid disease[88, 90], and one reported that cardiovascular disease was less common among bvFTD cases [89].

Table 5. Previous case-control studies on non-genetic risk factors in frontotemporal dementia.

	Controls	Major findings	Trends
Rosso et al. 2003 [88]	No dementia	Head trauma ↑	Hypothyroidism ↑
Kalkonde et al. 2012 [89]	Non-FTD dementia	Head trauma ↑	Cardiovascular diseases ↓
Golimstok et al. 2014 [90]	No dementia	Diabetes mellitus ↑	Hypothyroidism ↑

Furthermore, a study specifically exploring the relationship of head trauma and FTD, found that head trauma with extended loss of consciousness was more common among individuals with bvFTD than among normal controls[91]. Moreover, individuals with a language variant of FTD (semantic dementia) and a history of head trauma, had more behavioral problems than affected individuals without history of head trauma[91].

Mortality in FTD

Although previously thought to be rare, FTD is increasingly being recognized among the older adults[80]. Furthermore, life expectancy in the Western world is increasing [92]. Thus, it is to be expected that more elderly individuals will be

diagnosed with FTD. Accurate mortality estimates of FTD are therefore crucial, not only for those afflicted with FTD, but also for relatives, caregivers and health care providers. However, mortality in FTD has so far not been studied in elderly populations.
Moreover, population studies of mortality of FTD are difficult to conduct, because FTD is relatively rare and the clinical presentation is heterogeneous [4]. Thus, most previous studies on mortality are derived from specialist clinics or are based on retrospective information from neuropathological series[4]. Three-year mortality from *clinical diagnosis* of FTD ranges from 20 to 40% in studies from specialist clinics [93-95] and from 30 to 45% in neuropathology series[96-98]. Three-year mortality from *symptom onset* ranges from 5-10 % in clinical studies[93, 95] and 10-15% in neuropathology series[97, 98]. Furthermore, ten-year mortality ranges from 75-95% in clinical studies [93-95] and 80-95% in neuropathology series [96-98], and from *symptom onset* from 45-75% in studies from specialist clinics [93, 95] and 50-75% in neuropathology series[97, 98].

The mean or median survival time from *clinical diagnosis* of FTD has been estimated to range from 3.0 to 6.2 years in clinical samples [93-95] and from 3.0 to 4.2 years in neuropathological series [97, 98], and from *symptom onset* to death from 6.6 to 10.4 years in studies from specialist clinics [93-95, 99-103], and from 6.0 to 8.0 years in neuropathology series [97, 104, 105]. Some studies suggest that individuals with FTD progress to death faster than individuals with Alzheimer's disease (AD) [40], but other studies have found similar survival times in FTD and AD [100]. The main causes of death in FTD according to previous studies are pneumonia, cardiovascular disorders and cachexia [4, 100, 106]. However, causes of death in FTD have not been extensively examined in population-based studies.

Gender distribution

Previous studies vary with regards to reports of the sex distribution in FTD; a study from Cambridgeshire [69] reported a five-fold higher prevalence among men and a study from Zuid-Holland reported an equal sex distribution [71]. Other studies have reported a slight female preponderance[68, 73, 107].

THE CURRENT STUDY OF FTD

Aims

The overall aim of this thesis was to increase knowledge about late-life behavior variant frontotemporal dementia (bvFTD) using a population-based setting in Gothenburg, Sweden. The specific aims were:

1. To study the prevalence of frontal lobe syndrome and bvFTD using the Lund-Manchester research criteria (LMRC) in a representative sample of 85-year-olds. (Paper I).

2. To examine the prevalence of bvFTD in population samples of 70-95-year-olds using three sets of criteria (the FTDC, the FTLD-CC and the LMRC; Paper II).

3. To determine the agreement between these three FTD criteria sets (Paper II).

4. To study the correlation between bvFTD and the occurrence of frontal and/or temporal lobe atrophy on computerized tomography of the brain (Paper II).

5. To perform an exploratory nested case-control study of possible risk factors among 70-95-year-olds diagnosed with bvFTD and two age- and sex-matched control groups derived from the same population, one with non-FTD dementia and one without (Paper III).

6. To examine mortality associated with bvFTD in a population-based study among 70-95-year-olds and to compare mortality in bvFTD with mortality in non-FTD dementias and no dementia (Paper IV).

7. To examine cause of death in bvFTD according to death certificates, and to determine if cause of death differed between bvFTD, non-FTD dementias and no dementia (Paper IV).

SUBJECTS AND METHODS

Between 1986 and 2001, studies on representative elderly populations in Gothenburg, Sweden were conducted using identical examinations (including neuropsychiatric examinations and key informant interviews) at each occasion[108]. The samples included the H85-study [109], the 95+study [110], the Prospective Population Study of Women (PPSW) [111] and the H70-study [112]. All samples were systematically obtained from the Swedish population register based on birth dates, and included people living in private households and in residential care. An overview of the samples included in this study is shown in figure 1.

Subjects

H-85 participants

In 1986-7, an effective sample of 783 85-year-olds was selected and a total of 494 individuals (351 women and 143 men) agreed to participate (response rate 63%) [109]. There were no differences between participants and non-participants regarding sex, marital status, registration as psychiatric outpatients or inpatients, three-year mortality rate and institutionalization. Identical studies in this sample were conducted at ages 88 (n=260), 90 (n=200) and 92 years (n=190)[113].

95+study participants

In 1996-98, an effective sample of 529 95-year-olds was selected and a total of 338 individuals (263 women and 75 men) agreed to participate (response rate 64%). There were no significant differences between participants and non-participants regarding marital status and three-year mortality rate [110].

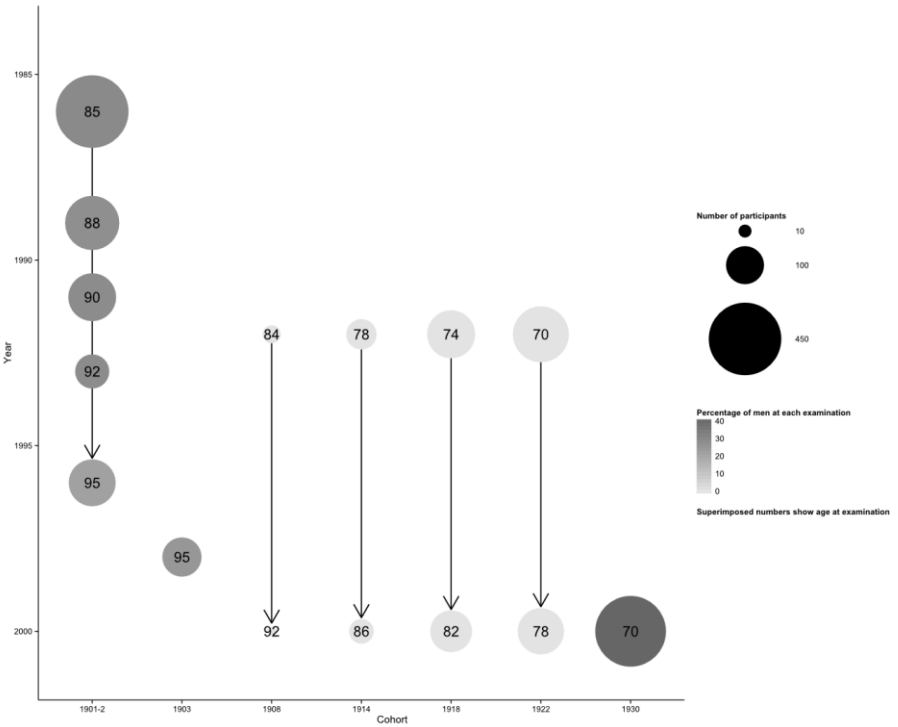
PPSW participants

In 1992-93, an effective sample of 837 women (aged 70, 74, 78 and 84) was selected and a total of 559 women (response rate 67%) agreed to take part (255 aged 70, 215 aged 74, 70 aged 78 and 19 aged 84) [111, 114-116]. In 2000-2001, 629 of the women were alive, and 439 (response rate 70%) agreed to participate in neuropsychiatric examinations (216 aged 78, 171 aged 82, 44 aged 86 and 8 aged 92).

H-70 participants

In 2000-01, an effective sample of 827 70-year-olds was selected and a total of 579 individuals (350 women and 229 men) agreed to participate (response rate 70%)[117]. There were no differences between participants and non-participants regarding sex, marital status or previous outpatient or inpatient psychiatric care. Non-participants had higher five-year mortality rate than participants both among women (9.0% vs. 2.3% p<0.001) and among men (23.7% vs. 7.5%, p<0.001), as described previously[117].

Figure 1. Overview of samples included in this study (H-85, H-95+, PPSW, H-70).



Graph by Erik Joas

Sample in paper I

In paper I, the sample of 494 85-year-olds (143 men, 351 women) described on page 13 (2nd paragraph) was used and individuals without key informant interview were excluded, leaving an effective sample of 451 individuals (131 men and 320 women). As key informant interviews were necessary to confirm or exclude the diagnosis of bvFTD, the final step in selecting study samples was to exclude those individuals that did not have a key informant interview.

Merged sample in paper II

In paper II, the data from the four studies described on pages 13-14 were merged, and 630 individuals without key informant interviews were excluded. This merged sample was stratified by ages 70-79, 80-89 and 90-95 years (table 9). The proportion of women in this sample was high (80%), partly because the study included samples from the PPSW (exclusively women), and partly because of an oversampling of individuals above age 85 years (who were predominantly women).

Merged sample in paper III-IV

In papers III-IV, the data from the four studies described on pages 13-14 were also merged, resulting in a sample of 2404 individuals. Furthermore, 630 individuals without key informant interview were excluded, resulting in a sample of 1774 individuals (388 men, 1386 women; 940 aged 70-79 years, 470 aged 80-89 years and 364 aged 90-95 years). Response rates for the different studies in the merged sample varied from 63-70% [118]. As discussed in the previous section, the proportion of women in this sample was high (80%).

Methods

Neuropsychiatric examination

Identical neuropsychiatric examinations and key informant interviews were used for all participants included in this study. The neuropsychiatric examinations were semi-structured and performed by trained neuropsychiatrists, except in 2000-2001 when they were performed by experienced psychiatric research nurses. The examinations included ratings of symptoms and signs common in dementia and a cognitive test battery[109]. Psychiatric symptoms and signs were rated with the Comprehensive Psychopathological Rating Scale[119]. Frontal lobe symptoms assessed included disinhibition, aggressiveness, hyperorality, hyperphagia, hypersexuality, perseverative or stereotypic behavior, utilization behavior, apathy, emotional bluntness and loss of empathy. Tests of cognitive function included assessments of recent and remote memory, orientation for time, place, person and situation, apraxia, constructional apraxia, ideational apraxia, ability to understand proverbs, ability to follow commands, finger agnosia, judgment, and language. The Mini Mental State Examination [120] Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-Cog)[121], the Montgomery–Åsberg Depression Rating Scale (MADRS)[122] and a global rating of mental health were also performed in all studies.

Self-report

As a part of the neuropsychiatric examination, a modified medical history was completed, including questions about previous and current medical disorders (e.g. cardiovascular disorders, stroke, diabetes mellitus, cancer, surgery and fractures), previous and current mental disorders, current use of medication, occurrence of dementia in first-degree relatives, alcohol consumption and sleep.

Key informant interviews

The semi-structured telephone-interviews with key informants included questions about cognitive, emotional and behavioral symptoms, e.g. global changes in personality, memory, orientation, difficulties in finding way in familiar surroundings, intellectual ability, language, speech, motivation, disinhibition, emotional bluntness, suspiciousness and paranoid ideas,

depression, lachrymosity, anxiety and worries, irritability, aggressive behavior, performances in activities of daily living, and insight. Questions were asked about age at onset and course of symptoms[109]. The retrospective information from key informants was needed to elucidate early symptoms and course of symptom development. The data were collected blindly to any diagnostic aspects.

Other sources of information

Medical and psychiatric diagnoses were derived from self-reports, neuropsychiatric examinations, key informant interviews and data from the Swedish hospital discharge register. Since 1978, everybody admitted to a Swedish hospital are registered in a hospital-discharge system with diagnoses registered according to the International Statistical Classification of Diseases and Related Health Problems (ICD-8, ICD-9 or ICD-10) [123-125].

Date and causes of death were obtained from the Swedish population register. This is a national register (The Swedish Health and Welfare Statistical Database for Cause of Death) that includes all individuals living in Sweden and Swedish citizens living abroad [126]. The register is known to be complete regarding data on mortality and cause of death.

Diagnostic procedures

Diagnosis in paper I

The Lund-Manchester research criteria (LMRC)[1] include three frontotemporal dementia symptom constellations: (1) behavioral symptoms, (2) affective symptoms and (3) symptoms of a speech disorder. The onset has to be insidious and the course invariably progressive. The criteria do not describe in detail the required severity of the symptoms, or how many symptoms or symptom constellations have to be present for a diagnosis. Therefore, an algorithm was constructed for the identification of FLS based on the core symptoms of FTD noted during the psychiatric examination and the close informant interview. The symptoms were selected to avoid misclassification with other disorders. Therefore, symptoms of language disturbance were not included, as language disturbance does not separate AD from FTD[127]. For a symptom to be classified as present it had to lead to significant disturbance. The symptoms were grouped into four clusters: (1) behavioral signs typical for FTD from the neuropsychiatric examination, (2)

behavioral symptoms typical for FTD from the informant interview, (3) affective symptoms typical for FTD from the neuropsychiatric examination and (4) affective symptoms typical for FTD from the informant interview. The individual symptoms selected in the different symptom constellations were based on the description in the LMRC, and are shown in table 6.

Table 6. Symptoms and signs of frontal lobe dysfunction as defined by the Lund-Manchester Research Criteria.

Behavioral signs from the neuropsychiatric interview
• Loss of insight
• Loss of social tact
• Disinhibition
• Hypersexuality
• Hyperorality (2 items)
• Perseverative or stereotypic behavior (2 items)
• Utilization behavior
Behavioral symptoms from the informant interview
• Change in personality
• Loss of insight
• Impaired judgment
• Lack of social tact
• Disinhibition
• Inappropriate jocularity
Affective signs from the neuropsychiatric examination
• Apathy (2 items)
• Emotional blunting
Affective symptoms from the informant interview
• Aspontaneity (2 items)
• Emotional blunting (3 items)
• Emotional unconcern and indifference (3 items)
• Neglect of grooming
• Neglect of hygiene

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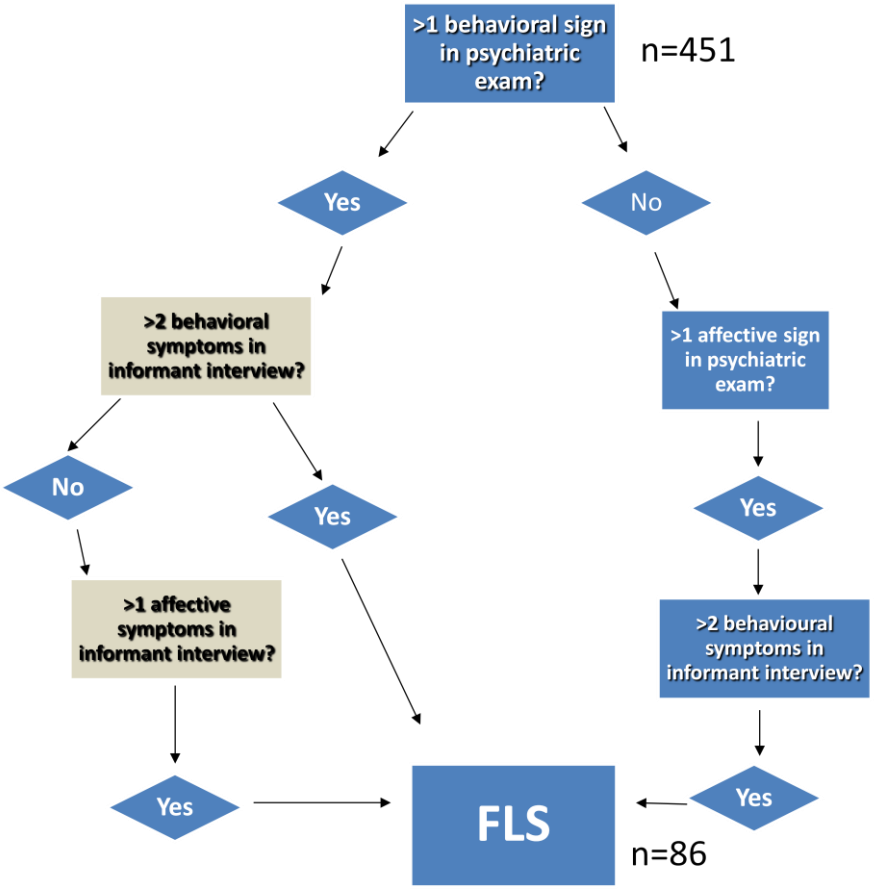
Diagnosis of FLS in Paper I

The algorithm for the identification of FLS is described in figure 2. An individual had to have a minimum number of symptoms in **both** the neuropsychiatric examination and the informant interview, and always a minimum number of behavioral symptoms. Thus if an individual had two or more behavioral symptoms in the neuropsychiatric examination, he had to have at least three behavioral symptoms in the informant interview in order to be classified as having FLS. If there were less than two behavioral symptoms in the neuropsychiatric examination, it was required that at least two affective symptoms in the neuropsychiatric examination should be present and at least

three behavioral symptoms in the informant interview. If an individual had two (or more) behavioral symptoms in the neuropsychiatric examination, but fewer than three behavioral symptoms in the informant interview, at least three affective symptoms had to be present in the informant interview for a classification of FLS (fig. 2).

Figure 2. Diagnostic algorithm for frontal lobe syndrome (FLS) based on the Lund-Manchester Research Criteria (LMRC).

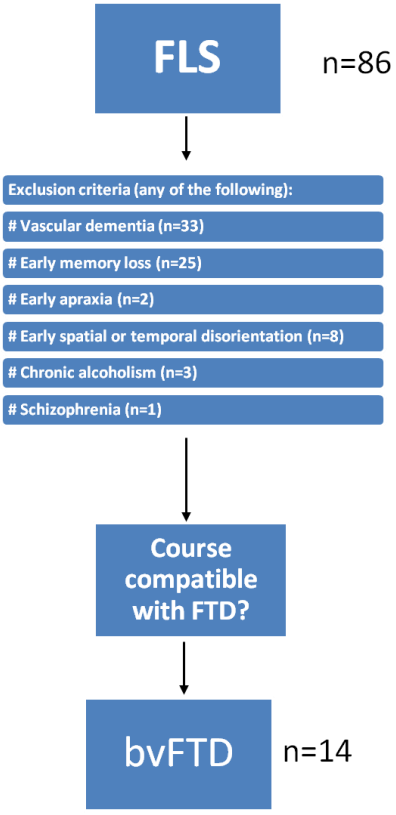


Gislason et al. J Neurol Neurosurg Psych 2003;74:867-71

Diagnosis of bvFTD in Paper I

Behavioral variant frontotemporal dementia (bvFTD) was diagnosed in subjects with FLS who presented with only frontal lobe symptoms or with behavioural symptoms that clearly preceded (by two years or more) memory loss or other cognitive signs, such as agnosia or apraxia. The diagnosis of bvFTD could not be applied in the presence of early onset of memory problems, early spatial disorientation, early apraxia, vascular dementia, chronic alcoholism and schizophrenia (exclusion criteria shown in figure 3).

Figure 3. Diagnostic algorithm for behavioral variant frontotemporal dementia (bvFTD) according to the Lund-Manchester Reseach Criteria (LMRC).



Gislason et al. J Neurol Neurosurg Psych 2003;74:867-71

Diagnosis of bvFTD in Papers II-IV

The FTDC criteria of bvFTD define five symptom clusters for the diagnosis of possible bvFTD: disinhibition, perseveration, apathy, lack of empathy and hyperorality. Furthermore the FTDC criteria define a sixth cluster, executive dysfunction. Symptoms from at least three clusters need to be present for a diagnosis[25]. The algorithm based on the FTDC is described in figure 4, describing the use of the clinical symptom constellations from the FTDC.

Figure 4. Algorithm for diagnosis of bvFTD from International consensus criteria for behavioral variant FTD (FTDC).

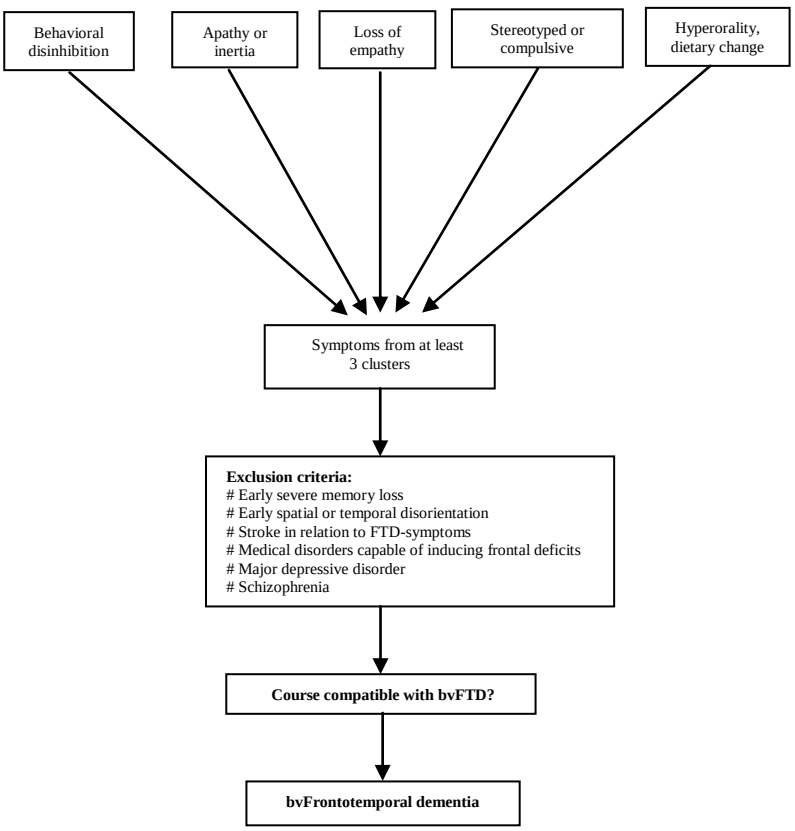


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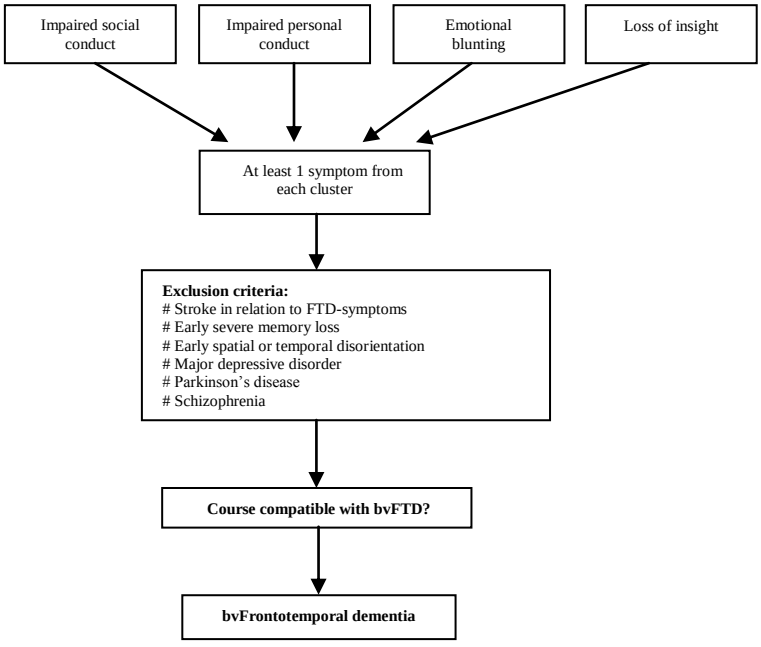
Figure 5. Algorithm for diagnosis of bvFTD from FTLD consensus criteria (FTLD-CC).



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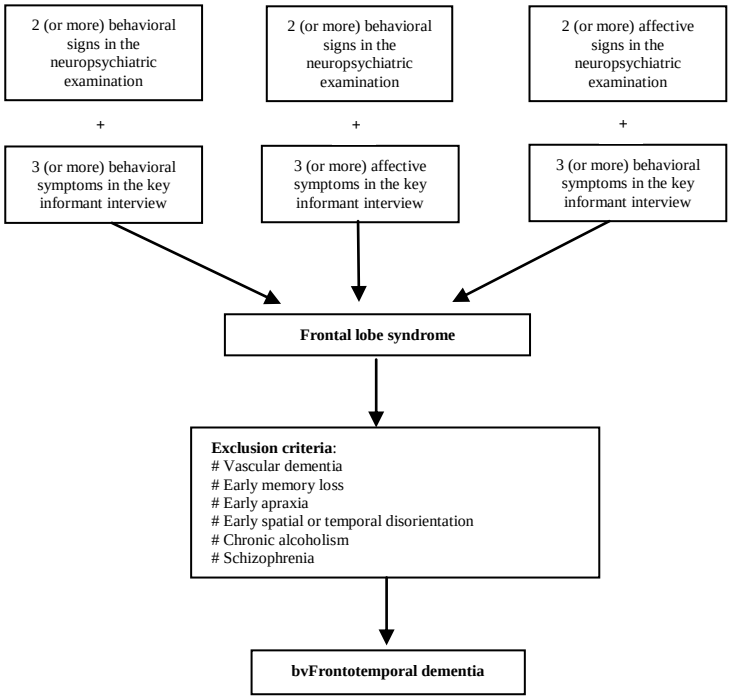
The FTDC do not include early spatial or temporal disorientation as an exclusion feature, but it was added here as an exclusion feature in order to better separate bvFTD from non-FTD dementia in this population with high prevalence of non-FTD dementia.

The 1998 consensus criteria (FTLD-CC) of bvFTD define four frontal lobe symptom clusters: impaired social conduct, impaired personal conduct, emotional blunting and loss of insight [24]. For a diagnosis of bvFTD, it is mandatory to have symptoms from all symptom clusters. The algorithm based on the FTLD-CC is described in figure 5.

Figure 6. Algorithm for diagnosis of bvFTD from Lund-Manchester Research Criteria (LMRC).



Gislason et al. Alzheimers Dement. 2015;11:425-33

As previously described (p. 20), the LMRC define three clusters of frontal lobe symptoms (behavioral, affective and language)[1]. Language disturbance is not included as a symptom in FTDC and FTLD-CC criteria for bvFTD. To make criteria comparable with FTDC and FTLD-CC criteria, we therefore only used the first two clusters from LMRC to define a 'LMRC bvFTD'. The algorithm based on the LMRC is described in figure 6.

The first step in the diagnostic process was to select individuals fulfilling symptom criteria, as described above[1, 24, 25]. Second, these individuals were evaluated regarding initial symptoms, course, and additional information needed to diagnose or exclude bvFTD (figures 3, 4 and 5). Frontal lobe symptoms had to precede severe amnesia or loss of spatial skills for a

diagnosis of bvFTD. Likewise, the course of the symptom clusters had to be compatible with bvFTD with insidious onset and a progressive, non-episodic course. The final diagnosis was reached by consensus between two of the authors of paper II (TBG, MSj.).
The data were collected blindly to any diagnostic aspects, and bvFTD diagnoses were set blindly to other dementia diagnoses.

Diagnosis of non-FTD dementia

Non-FTD dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Third edition, revised (DSM-III-R) [123]. The data were collected blindly to any diagnostic aspects, and bvFTD diagnoses were set blindly to other dementia diagnoses.

Dementia etiology

In papers I and IV, individuals with dementia as defined by DSM-III-R were classified further into etiological subgroups: Alzheimer's disease (AD) according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [128], and vascular dementia (VAD) as proposed by Erkinjuntti [129] (paper I) and the National Institute of Neurological Disorders and Stroke and l'Association Internationale pour la Recherce et l'Enseignement en Neurosciences (NINDS-AIREN) criteria [130] (paper IV).

Methods in paper III

Definitions of potential risk factors

Medical and psychiatric diagnoses were derived from self-reports, neuropsychiatric examinations, key informant interviews and data from the Swedish Hospital Discharge Register. Since 1978, everybody admitted to a Swedish hospital are registered in a hospital-discharge system with diagnoses registered according to the International Statistical Classification of Diseases and Related Health Problems (ICD-8, ICD-9 or ICD-10) [123-125].
Blood pressure was measured in the right arm in the seated position after 5 minutes' rest with a mercury manometer. Systolic and diastolic blood pressures were registered to the nearest 5 mm Hg. Further tests included

electrocardiography and an extensive biochemical evaluation. Apolipoprotein E isoforms were determined in a subgroup (n=191), using isoelectric focusing and Western blotting[131].

Stroke and/or TIA was only diagnosed among individuals with a definite history of acute focal symptoms (e.g. paresis or aphasia) according to self-reports or key informants, or who received a diagnosis of stroke or TIA in the hospital discharge register. All records were examined by neuropsychiatrists, who made the final diagnoses[132].
Ischemic heart disease: Angina pectoris was diagnosed according to the Rose criteria [133], and myocardial infarction by history and ECG-evidence of ischemia, i.e. complete left bundle branch block or major Q-waves; pronounced ST-depression and/or negative T-waves according to the Minnesota code [134]. Angina pectoris and myocardial infarction were also diagnosed if a diagnosis was found in the hospital discharge register.
Concurrent hypertension was defined as a systolic blood pressure $\geq$ 140 mm Hg and/or a diastolic blood pressure $\geq$ 90 mm Hg at examination, or use of antihypertensive treatment at examination.
Previous hypertension was defined as having been given the diagnosis by a doctor or having had previous, but not current, antihypertensive treatment, or if a diagnosis was found in the hospital discharge register.
Diabetes mellitus was diagnosed if the participant had been given the diagnosis by a doctor (self-report), if on anti-diabetic treatment (diet and/or medication), or if the diagnosis was found in the hospital discharge register.
Head trauma: Information was obtained from key informants and from the hospital discharge register on any type of head trauma.
Alcohol abuse was defined as alcohol misuse coupled with any type of adverse consequences (social, medical and/or psychiatric) as reported from key informants, or if a diagnosis of alcohol dependence and/or alcohol-related medical complications (e.g. alcohol related hepatitis or neuropathy) were found in the hospital discharge register.
Epilepsy and/or seizures: Information regarding any form of seizures was obtained from key informants or the hospital discharge register.
Smoking: Information was obtained from both self-reports and key informants and participants were categorized as non-smokers, current smokers or former smokers (who ceased smoking >1 year before examination).
Thyroid disease and chronic obstructive pulmonary disease (COPD) were defined if the participant had been given the diagnoses by a doctor according to self-report (*chronic bronchitis*), or if the diagnoses were found in the hospital discharge register.

Family history of dementia: Information on first-degree relatives was obtained from both self-reports and key informants. First-degree relatives were defined as parents, siblings and offspring of participants.
Level of education was defined as compulsory education (i.e. 6-7 years) versus at least one year of post-compulsory education.
Neuroinfectious diseases and *herpes zoster:* Information was obtained from the Swedish hospital discharge register.
Previous depression: Information was obtained from self-reports and key informants.
Concurrent major depression and anxiety disorders (generalized anxiety disorder, obsessive-compulsive disorder and phobias) were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Third edition, revised (DSM-III-R) [123]. *Minor depression* was diagnosed according to DSM-IV research criteria [135]. *Any depression* incorporated both minor and major depression.

Statistical methods

Differences in proportions were determined with Pearson's chi-square (χ^2) or, if appropriate, Fisher's Exact Test. Differences in means were assessed with a t-test. All p-values were two-tailed and p-values <0.05 were considered statistically significant. Cohen's un-weighted kappa was used to assess agreement between different criteria.

Statistical methods specific to paper III

For each individual with bvFTD, we identified at random 10-14 controls without any dementia, matched by age and sex, from the same population-based sample. We also identified at random 3-4 controls, matched by age and sex, among the individuals with global dementia as defined by DSM-III-R. Controls had to be free from frontal lobe symptoms as defined by the FTDC[25].

Possible risk factors included major medical and psychiatric disorders, family history of dementia, head trauma and exposure to smoking and alcohol, social factors and the presence of white matter lesions on CT (table 13). Conditional logistic regression was used to calculate odds ratios and 95% confidence intervals (CI).

Statistical methods specific to paper IV

Two comparison groups were selected from the same population as the bvFTD cases; one comprised individuals with dementia as defined by DSM-III-R (but without FTD) and the other comprised individuals without any dementia. These comparison groups were larger than the control groups in paper III in order to increase power to detect differences in mortality between bvFTD and non-FTD dementias.

Individuals with dementia as defined by DSM-III-R were classified further into etiological subgroups: Alzheimer's disease (AD) according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [128], and vascular dementia (VAD) according to the NINDS-AIREN criteria [130].

Individuals who had three or more frontal lobe symptoms but did not fulfill all bvFTD criteria as defined by the FTDC (e.g. having an atypical onset or course) were excluded from all comparison groups in order to prevent inclusion of bvFTD cases that only partially fulfilled FTDC criteria.[25]

The associations between the different diagnoses and survival (time to death) were calculated with the Kaplan-Meier method. The analyses were also stratified by age (70-79, 80-89 and 90-95 years) in order to examine age-related effects on the survival times. Risk times were calculated from date of examination to date of death, or until end of March 2013. A log rank test was performed to test differences in survival times between the group with bvFTD and the groups with other (non-FTD) dementias, AD, VAD and no dementia. Risk times were also calculated from date of symptom onset to date of death, or until end of March 2013. Key informant interviews were used to determine age of symptom onset. For bvFTD, age of onset was defined as the age at which the first FTD symptom appeared. For other (non-FTD) dementias, age of onset was defined as the age at which memory impairment or other dementia symptoms first appeared.

Cox regression analyses were performed to estimate hazard ratios (HR) for death associated with a diagnosis of bvFTD compared to a diagnosis of other (non-FTD) dementias, AD, VAD and no dementia. Cox regression analyses were performed using time from examination to death (or the end of March 2013), and also using time from symptom onset to death (or the end of March 2013). First, the HRs were adjusted for gender and baseline age, and second for gender, baseline age and MMSE (as a measure of cognitive function when comparing bvFTD and non-FTD dementia). Third, in addition to baseline age, the risk of death among the oldest old may also be expected to increase during follow-up. Therefore, in order to control for this increasing risk of death during follow-up, we adjusted for the age updated in risk time in a third

Cox regression analysis (also adjusting for baseline age and gender). Fourth, we performed a Cox regression analysis adjusting for gender, baseline age and birth cohort, as survival increased in later-born birth cohorts. Fifth, a Cox regression analysis was adjusted for stroke/TIA, comparing bvFTD with non-FTD dementia and no dementia.

Computerized tomography

A systematic subsample of 1900 individuals was invited to undergo CT-scanning of the head, and 1074 accepted (244 men, 830 women). Of these, 161 had global dementia as diagnosed by DSM-III-R (41 men, 120 women), and 913 were without dementia (203 men, 710 women).

All CT-scans were performed without contrast enhancement and with 10 mm continuous slices. The CT-scans were evaluated either by radiologists or a neurologist experienced in rating CT-scans. The evaluations were done blindly to the results of the neuropsychiatric examination. Location of cortical atrophy was categorized as frontal, temporal, parietal or occipital, according to the anatomical subdivision[136]. A scale with three grades (absent vs. mild vs. moderate or severe) was used to estimate cortical atrophy according to the extent of sulcal widening[137]. Inter-rater agreement for the assessment of atrophy was "fair" for frontal lobe atrophy (kappa = 0.34) and "moderate" for temporal lobe atrophy (kappa =0.43)[137]. The intra-rater kappa values for the assessment of atrophy were "moderate" for frontal lobe atrophy (kappa = 0.53) and "good" for temporal lobe atrophy (kappa =0.61) [138, 139].

White matter lesions (WMLs) were defined as periventricular or subcortical areas of decreased attenuation when compared to normal white matter. The changes were always diffusely distributed within the white matter. Decreased attenuation was subjectively rated on a scale with three grades (no, mild, moderate or severe) in relation to the attenuation of normal white matter.[140] Inter-rater agreement for the CT assessment regarding the occurrence and severity of WMLs was 84% (kappa = 0.75)[140].

Ethical considerations

The Ethics Committee for Medical Research at Gothenburg University approved all studies. Informed consent was obtained from the participants, their nearest relatives, or both.

RESULTS

Prevalence of bvFTD among 85-year-olds

The selection of cases for bvFTD in paper I is shown in figure 3. The prevalence of bvFTD was 3.1% (n=14; table 7). Of those with bvFTD, 64% (n=9) did not fulfill criteria for dementia according to DSM-III-R, and five were classified as AD.

Prevalence of FLS among 85-year-olds

The selection procedure for FLS is shown in figure 2. The prevalence of FLS was 19% (n=86), with no difference between men and women (table 7). Of those with FLS, 75 (87%) were diagnosed with other types of dementia according to the DSM-III-R criteria, see table 8. Dementia according to the DSM-III-R was diagnosed in 145 (32.2%) individuals, thus 52% (n=75) of the demented fulfilled criteria for FLS, compared to 3.6% (n=11) among the non-demented.
Among the eleven individuals who fulfilled criteria for FLS, but not for dementia according to DSM-III-R, nine were classified as bvFTD, one had early onset of apraxia, and one had a stroke at age 81 with a change in personal conduct and aphasia. These two latter cases were therefore not diagnosed as bvFTD.

Table 7. The prevalence of frontal lobe syndrome (FLS) and behavioral variant frontotemporal dementia (bvFTD) in 85-year-olds.

	Men (N=131)	**Women** (N=320)	**Total** (N=451)
	% (n)	% (n)	% (n)
FLS	18.9 (25)	19.0 (61)	19.1 (86)
bvFTD	4.5 (6)	2.5 (8)	3.1 (14)

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Frontal atrophy among 85-year-olds

CT-scan was performed in 238 individuals, including 53 cases of FLS and 6 cases of bvFTD.

Among those with FLS 92.5% (N=49) had moderate-severe frontal atrophy, as compared to 48.6% (n=90) of those without FLS. All 6 cases with bvFTD had moderate-severe frontal atrophy.

Among those with moderate-severe frontal atrophy (N=139), 49 (35.3%) had FLS. Only four (2.9%) among those without moderate-severe frontal atrophy had FLS.

Table 8. Individuals with frontal lobe syndrome (FLS) among 85-year-olds with and without dementia according to DSM-III-R.

		FLS cases	
		N	%
Dementia	(N=145)	75	51.7
Types of dementia:			
AD	(N=63)	32	50.7
VAD	(N=69)	34	49.3
Other	(N=13)	9	69.2
No dementia	(N=306)	11	3.6

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Prevalence of bvFTD among 70-95-year-olds

Characteristics of merged sample in paper II are given in table 8. The prevalence of bvFTD varied between 0.2-0.5% at age 70-79, between 2.5-3.6% at age 80-89, and between 1.7-2.2% at age 90-95 using the different criteria (table 10 and figure 7).
Agreement between criteria was low to moderate with kappa values ranging from 0.20-0.42 (table 11 and figure 8).

Table 9. Demographic characteristics of merged sample in paper II.

	Men % (n)	Women % (n)	All % (n)	p-value for difference between men and women
Age (years)				
70-79	16.4 (175)	83.6 (893)	100 (1068)	<0.001
80-89	22.6 (195)	77.4 (666)	100 (861)	<0.001
90-95	25.0 (133)	75.0 (400)	100 (533)	<0.001
Marital status				
Never married	4.4 (22)	9.7 (190)	8.6 (212)	<0.001
Married	55.7 (280)	16.4 (322)	24.5 (602)	<0.001
Divorced	6.4 (32)	15.1 (296)	13.3 (328)	<0.001
Widowed	23.8 (120)	48.4 (947)	43.3 (1067)	<0.001
N/A	9.7 (49)	10.4 (204)	10.3 (253)	0.658
Dementia at ages*				
70-79	2.3 (5)	5.0 (45)	4.7 (50)	0.211
80-89	27.7 (54)	34.8 (232)	33.2 (286)	0.063
90-95	37.6 (50)	54.0 (216)	49.9 (266)	0.001
Level of education**	23.6 (119)	13.2 (258)	15.3 (377)	<0.001

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Pearson's chi-square ($\chi 2$) or, if appropriate, Fisher's Exact Test, were used to test differences in proportions.

* Dementia as diagnosed by DSM-III-R.

** Proportion of individuals with at least one year of post-compulsory education.

Only 7 out of 88 bvFTD cases diagnosed with at least one set of criteria were captured by every set of criteria, and 65 were diagnosed according to only one criteria set. Among bvFTD cases, 79% of those diagnosed by FTDC, 92% of those diagnosed by FTLD-CC, and 53% of those diagnosed by LMRC had dementia according to DSM-III-R ($p<0.05$ FTDC vs. LMRC; $p>0.05$ FTDC vs. FTLD-CC; $p<0.05$, FTLD-CC vs. LMRC).

Table 10. The prevalence of the behavioral variant of frontotemporal dementia (bvFTD) between age 70 and 95 years using three sets of criteria.

Age	**FTDC** %(n)	**FTLD-CC** % (n)	**LMRC** % (n)
70-79 (n=1068)	0.5 (5)	0.3 (3)	0.2 (2)
95% CI	(0.2-1.9)	(0.1-0.8)	(0.1-0.7)
80-89 (n=861)	3.6 (31)	2.5 (22)	2.7 (23)
95% CI	(2.5-5.1)	(1.7-3.8)	(1.8-4.0)
90-95 (n=533)	2.2 (12)	1.7 (9)	2.1 (11)
95% CI	(1.3-3.9)	(0.9-3.2)	(1.1-3.6)

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FTDC: Criteria of the International Behavioral Variant FTD Criteria Consortium.

FTLD-CC: Frontotemporal Lobar Degeneration Consensus Criteria.

LMRC: Lund-Manchester Research Criteria.

Dementia severity as measured by MMSE was not significantly associated with bvFTD as diagnosed by any diagnostic criteria (FTDC: p=0.791; FTLD-CC: p=0.066; LMRC: p=0.353). Furthermore, dementia severity as measured by MMSE was not significantly associated with frontal and/or temporal lobe atrophy (FTDC: p=0.301; FTLD-CC: p=0.101; LMRC: p=0.333).

Figure 7. The prevalence of the behavioral variant of frontotemporal dementia (bvFTD) between age 70 and 95 years using three sets of criteria.

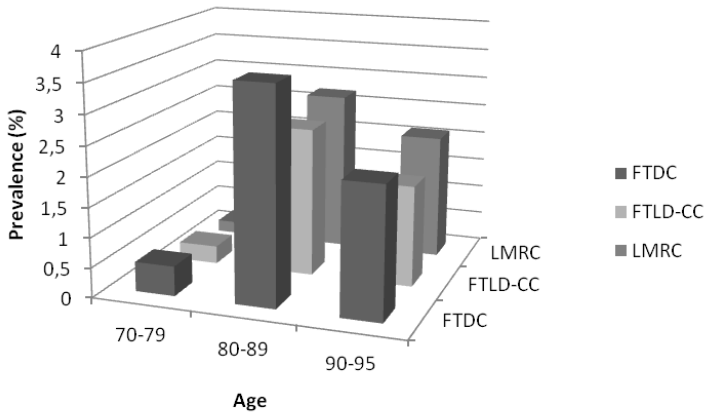

Table 11. Agreement between LMRC, FTLD-CC and FTDC criteria for behavioral variant frontotemporal dementia (bvFTD).

	FTDC n (%)	FTLD-CC n (%)	LMRC n (%)
FTDC (n=48)	X	13 (27.1)	17 (35.4)
Kappa		0.30	0.42
FTLD-CC (n=34)	13 (38.2)	X	7 (20.6)
Kappa	0.30		0.20
LMRC (n=36)	17 (47.2)	7 (19.4)	X
Kappa	0.42	0.20	

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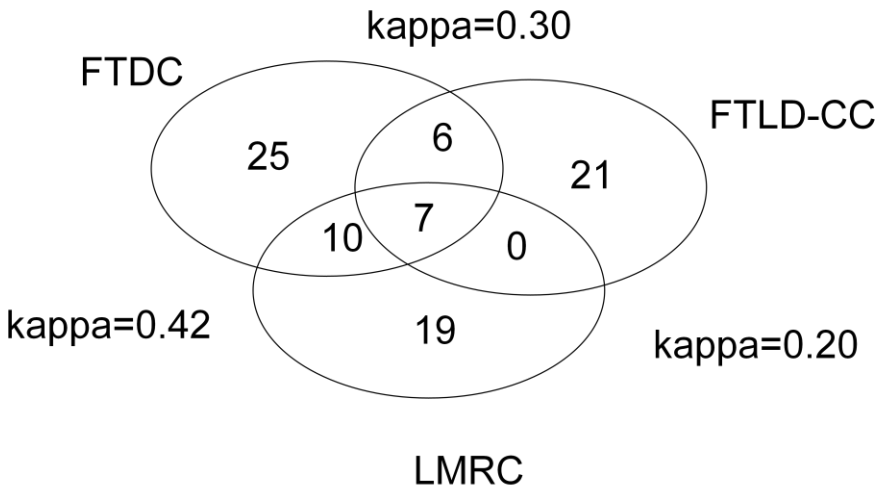
Cohen's un-weighted kappa was used to assess agreement between different criteria.

FTDC: Criteria of the International Behavioral Variant FTD Criteria Consortium.

FTLD-CC: Frontotemporal Lobar Degeneration Consensus Criteria.

LMRC: Lund-Manchester Research Criteria.

Figure 8. The agreement between criteria for behavior variant frontotemporal dementia.



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Cohen's un-weighted kappa was used to assess agreement between different criteria.

FTDC: Criteria of the International Behavioral Variant FTD Criteria Consortium.

FTLD-CC: Frontotemporal Lobar Degeneration Consensus Criteria.

LMRC: Lund-Manchester Research Criteria.

Frontal/temporal atrophy

CT-scan was performed in 1074 individuals. Among these, 1.4% (n=15) had bvFTD according to FTDC, 1.0% (n=11) according to FTLD-CC and 0.7% (n=8) according to LMRC.

Furthermore, 89.4 % (n=960) of the participants in the CT examination did not have frontal lobe symptoms as defined by any of the three criteria sets (no frontal lobe symptoms; non-FLS). In this group the prevalence of moderate-severe frontal atrophy was 8.9% (n=85) and out of these 11.8% (n=10) had global dementia as diagnosed by DSM-III-R. Furthermore, in the non-FLS group, the prevalence of moderate-severe temporal atrophy was 8.1% (n=78) and 19.2% (n=15) of these had global dementia. In the non-FLS group the prevalence of moderate-severe frontal and/or temporal atrophy was 4.4% (n=42) with 42.8% (n=18) having global dementia.

The association between frontal and/or temporal lobe atrophy and the bvFTD-diagnoses is shown in table 12. Among 15 cases with bvFTD, 14 (93.3%) had moderate-severe frontal and/or temporal atrophy compared to 12.6% in the non-FLS group (p<0.001). Among 11 persons with bvFTD according to FTLD-CC, 7 (63.6%) had moderate-severe frontal and/or temporal atrophy (p<0.001 compared to non-FLS). All 8 persons with bvFTD according to LMRC had moderate-severe frontal and/or temporal atrophy (p<0.001 compared to non-FLS).

Table 12. Frontal and/or temporal lobe atrophy on CT scan of the brain in relation to a diagnosis of behavior variant frontotemporal dementia (bvFTD) according to different FTD criteria.

	Frontal and temporal lobe atrophy† on CT scan of the brain			
	Frontal lobe atrophy	**Temporal lobe atrophy**	**Both frontal and temporal lobe atrophy**	**Frontal and/or temporal lobe atrophy**
bvFTD criteria	% (n)	% (n)	% (n)	% (n)
FTDC (n=15)	80.0 (12)*	73.3 (11)*	60.0 (9)*	93.3 (14)*
FTLD-CC (n=11)	45.4 (5)*	54.5 (6)*	36.4 (4)**	63.6 (7)*
LMRC (n=8)	75.0 (6)*	75.0 (6)*	50.0 (4)*	100 (8)*
Non-FLS (n=960)	8.9 (85)	8.1 (78)	4.4 (42)	12.6 (121)

† "Atrophy" refers to moderate or severe lobar atrophy.

FTDC: Criteria of the International Behavioral Variant FTD Criteria Consortium.
FTLD-CC: Frontotemporal Lobar Degeneration Consensus Criteria.
LMRC: Lund-Manchester Research Criteria.
Non-FLS: Participants in the CT examination who did not have frontal lobe symptoms as defined by any of the three criteria sets (FTDC, FTLD-CC or LMRC).

*p<0.001 for difference between bvFTD diagnosis and non-FLS (Fisher's exact test, two-tailed).
**p=0.001 for difference between bvFTD diagnosis and non-FLS (Fisher's exact test, two-tailed).

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Table 13. Characteristics of individuals with a diagnosis of behavior variant frontotemporal dementia (bvFTD) and controls (paper III).

	bvFTD	Controls without dementia	p-value	Controls with non-FTD dementia†	p-value
	(n=48)	(n=673)		(n=168)	
Mean age (years)	86.6	86.6	0.943	86.7	0.876
Gender [% women (n)]	81.2 (39/48)	79.6 (536/673)	0.791	81.6 (137/168)	0.962
Residence in nursing home [% (n)]	47.9 (23/48)	4.0 (27/673)	<0.001	23.2 (39/168)	<0.001
MMSE score (mean ±SD)	16.5 (±8.8)	26.9 (±2.9)	<0.001	17.7 (±6.9)	0.430
MADRS (mean±SD)	9.73 (±9.02)	6.72 (±6.38)	0.029	8.13 (±7.33)	0.343
Depressive disorders [% (n)]					
Any	33.3 (16/48)	24.5 (165/673)	0.006	29.8 (50/168)	0.639
Major	18.7 (9/48)	17.5 (118/673)	0.040	11.3 (19/168)	0.176
Minor	14.6 (7/48)	9.1 (61/673)	0.647	18.4 (31/168)	0.532
Anxiety disorders [% (n)]	25.0 (12/48)	20.4 (137/673)	0.442	13.7 (23/168)	0.061
GAD	18.7 (9/48)	11.0 (74/673)	0.104	10.7 (18/168)	0.138
OCD	2.1 (1/48)	2.5 (17/673)	0.660	0.6 (1/168)	0.396
Phobias	4.2 (2/48)	11.9 (80/673)	0.103	3.6 (6/168)	0.563
Auditory hallucinations* [% (n)]	8.3 (3/36)	0.5 (3/564)	0.003	2.5 (3/122)	0.132
Visual hallucinations* [% (n)]	2.8 (1/36)	1.1 (6/564)	0.353	2.5 (3/122)	0.648
Impaired hearing [% (n)]	32.6 (15/46)	17.0 (109/641)	0.024	32.7 (55/168)	0.767
Visual impairment [%(n)]	7.5 (3/40)	9.0 (56/622)	0.514	15.5 (26/168)	0.191
Cortical atrophy on CT [% (n)]					
Frontal lobe	80.0 (12/15)	15.1 (35/231)	<0.001	29.8 (11/37)	0.002
Temporal lobe	73.3 (11/15)	14.3 (33/231)	<0.001	43.2 (16 /37)	0.068

Pearson's chi-square ($\chi 2$) or, if appropriate, Fisher's Exact Test, were used to test differences in proportions. Differences in means were assessed with a t-test.

*****According to self-reports.
† Other (non-FTD) dementia as defined by DSM-III-R.

Risk factors (Paper III)

Characteristics of cases and controls are given in table 13, including concurrent psychiatric diagnoses, psychotic symptoms, and visual and/or hearing impairment. Delusions were rare among the FTD cases (2.8%; n=1/36), and paranoid ideation and non-visual, non-auditory hallucinations were not present among the bvFTD cases.

Table 14 shows unadjusted comparisons between bvFTD and the two control groups, with and without dementia.

Comparisons between bvFTD and controls without dementia: Stroke and/or TIA, hypothyroidism, head trauma, alcohol abuse, severe white matter lesions (WMLs) on CT of the brain and being divorced were associated with increased odds of bvFTD. Light-moderate alcohol use and being married were associated with decreased odds of bvFTD. There was a trend for history of herpes zoster ($p=0.097$) and being widowed ($p=0.051$) to be associated with bvFTD.

Comparisons between bvFTD and controls with dementia: Alcohol abuse and being divorced were associated with increased odds of bvFTD. Being married was associated with decreased odds of bvFTD. Hypothyroidism tended to be associated with increased odds of bvFTD ($p=0.070$).

Family history of dementia among first-degree relatives, ApoE ε4 status, diabetes mellitus, ischemic heart disease and history of previous depression were not related to bvFTD. No participant was diagnosed with meningitis or encephalitis.

Table 14. History of medical problems and environmental exposures among behavior variant frontotemporal dementia (bvFTD) cases and controls (paper III).

	bvFTD % (n/N)	**Controls without dementia** % (n/N)	**OR** (95% CI)	**Controls with non-FTD dementia**† % (n/N)	**OR** (95% CI)
Stroke/TIA [a]	35.4 (17/48)	18.7 (126/673)	2.11 (1.09-4.09)*	42.9 (72/168)	0.66 (0.31-1.42)
Ischemic heart disease [b]	35.4 (17/48)	42.3 (285/673)	0.69 (0.36-1.33)	30.9 (52/168)	1.13 (0.52-2.45)
Hypertension					
Concurrent	68.7 (33/48)	75.3 (510/673)	0.52 (0.21 - 1.26)	55.4 (93/168)	1.58 (0.64-3.95)
Previous	29.2 (14/48)	31.2 (210/673)	0.91 (0.48- 1.73)	20.2 (34/168)	1.62 (0.78-3.36)
Diabetes mellitus	10.4 (5/48)	9.5 (64/673)	1.04 (0.40-2.70)	8.9 (15/168)	1.19 (0.41-3.45)
Hypothyroidism	16.7 (8/48)	8.3 (56/673)	2.59 (1.10-6.11)*	5.4 (9/168)	2.72 (0.92-8.01)
Seizures or epilepsy	6.3 (3/48)	5.0 (34/673)	1.20 (0.35-4.11)	10.7 (18/168)	0.54 (0.14-2.08)
COPD [c]	2.1 (1/48)	2.2 (15/673)	0.93 (0.12-7.22)	3.0 (5/168)	0.69 (0.08-6.08)
Herpes zoster	6.2 (3/48)	1.8 (12/673)	2.94 (0.82-10.55)	2.4 (4/168)	3.14 (0.68-14.45)
Prior depression [d]	33.3 (16/48)	24.5 (165/673)	1.54 (0.83-2.87)	34.5 (58/168)	0.95 (0.48-1.87)
Head trauma	18.7 (9/48)	8.0 (54/673)	2.92 (1.28-6.65)*	19.0 (32/168)	0.98 (0.43-2.23)
Alcohol abuse	18.7 (9/48)	1.6 (11/673)	14.85 (5.64-39.07)***	4.2 (7/168)	3.52(1.12-11.09)*
Light-moderate alcohol use	58.2 (25/43)	72.5 (381/525)	0.52 (0.28-0.99)*	66.1 (111/168)	0.71 (0.36-1.41)
Smoking					
Non-smoker	65.9 (29/44)	52.7 (350/664)	1.73 (0.91-3.29)	57.0 (90/158)	1.46 (0.73-2.94)
Former smoker	29.6 (13/44)	33.4 (222/664)	0.83 (0.43-1.63)	35.4 (56/158)	0.76 (0.37-1.58)
Current smoker	4.5 (2/44)	13.9 (92/664)	0.30 (0.07-1.24)	7.6 (12/158)	0.58 (0.12-2.69)
Level of education [e]	19.0 (8/42)	32.2 (187/581)	0.51 (0.13-2.03)	28.8 (32/111)	0.58 (0.24-1.39)
Marital status					
Never married	18.7 (9/48)	11.6 (78/673)	1.76 (0.82-3.77)	14.1 (23/168)	1.40 (0.60-3.28)
Married	14.6 (7/48)	47.4 (319/673)	0.19 (0.08-0.43)***	33.7 (55/168)	0.33 (0.14-0.80)**
Divorced	18.7 (9/48)	7.0 (47/673)	3.19 (1.37-7.40)**	3.1 (5/168)	8.06 (2.35-27.59)**
Widowed	48.0 (23/48)	34.0 (229/673)	1.78 (0.99-3.21)	51.5 (84/168)	0.86 (0.45-1.65)
Family history of dementia after age 65	14.6 (7/48)	16.9 (114/673)	0.84 (80.37-1.91)	21.4 (36/168)	0.63 (0.26-1.51)
Family history of dementia before age 65	2.1 (1/48)	1.8 (12/673)	1.17 (0.15-9.21)	1.2 (2/168)	1.77 (0.16-19.90)
Any APOE ε4 allele genotype	33.3 (3/9)	34.4 (53/154)	0.95 (0.23-3.96)	53.6 (15/28)	0.43 (0.09-2.09)
Severe WMLs [f]	33.3 (5/15)	6.1 (14/231)	7.75 (2.33-25.78)**	35.1 (13/37)	0.92 (0.26-3.28)

Conditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI).

*p<0.05 for OR.
**p<0.01 for OR.
***p<0.001 for OR.

†Other (non-FTD) dementia as defined by DSM-III-R.
a) Stroke and/or transient ischemic attack (TIA).
b) Angina pectoris and/or myocardial infarction.
c) COPD: Chronic obstructive pulmonary disease or chronic bronchitis.
d) Prior depression over the life course as reported by key informant.
e) Proportion of individuals who have at least one year of education after finishing compulsory education.
f) WMLs: White matter lesions.

Mortality (Paper IV)

The characteristics of the study population are shown in table 15. During follow-up 904 individuals died (61.8% of cases and comparison groups combined). Mean follow-up time was 7.90 years (95% CI: 7.68-8.12). Stroke/TIA was more common among individuals with bvFTD than among individuals with no dementia, but did not differ compared to non-FTD dementia. There were no other differences between individuals with bvFTD and individuals with other (non-FTD) dementias or no dementia regarding history of ischemic heart disease, diabetes mellitus or COPD.

Participants had a lower risk of death than non-participants (HR=0.83; 95% CI: 0.75-0.90; $p<0.001$). There was a lower risk of death among 70-79-year-old participants compared to non-participants ($p<0.001$), but there was no significant difference in risk of death between participants and non-participants in the age groups 80-89-year-olds ($p=0.181$) and 90-95-year-olds ($p=0.314$).

Table 16 shows that HR for death was higher among those with bvFTD compared to those with other (non-FTD) dementias, AD, and no dementia, both when examining risk time from examination and risk time from symptom onset to death (or end of March 2013). In all adjusted analyses, bvFTD was associated with a higher risk of death compared to other (non-FTD) dementias, AD and no dementia. Controlling for cognitive function (MMSE) and birth cohort did not influence the results. Controlling for stroke/TIA did not influence the results when comparing bvFTD with non-FTD dementia (HR=1.58; 95% CI: 1.11-2.27; $p=0.012$), or with no dementia, although in the latter instance, the HR was lower than in other adjusted analyses (HR=2.98; 95% CI: 208-4.28; $p<0.001$). Also, when examining time from symptom onset to death, bvFTD was associated with a higher risk of death compared to VAD (controlling for age at symptom onset and gender) and tended to be associated with a higher risk of death compared to VAD when controlling for cognitive function ($p=0.062$) and birth cohort ($p=0.092$). Furthermore, when examining time from examination to death, a diagnosis of bvFTD tended to be associated with a higher risk of death compared to VAD ($p=0.089$).

Table 15. Characteristics and medical co-morbidities of individuals with a diagnosis of behavior variant frontotemporal dementia (bvFTD) compared with individuals without dementia and individuals with other (non-FTD) dementia, Alzheimer's disease and vascular dementia (paper IV).

	bvFTD (n=48)	**Non-FTD dementia** [a] (n=265)	**Alzheimer's disease** [b] (n=124)	**Vascular dementia** [c] (n=88)	**Without dementia** (n=1149)
Gender [% women (n)]	81.2 (39)	81.5 (216)	85.5 (106)	82.9 (73)	78.8 (905)
Mean age [years (95% CI)]					
All	86.6 (84.9-88.2)	88.2 (87.4-88.9)	87.6 (86.3-88.9)	87.3 (85.8-88.8)	79.1*** (78.7-79.5)
Women	86.5 (84.8-88.3)	88.1 (87.3-88.9)	87.6 (86.2-89.0)	87.2 (85.6-88.8)	78.7*** (78.3-79.2)
Men	86.8 (81.4-92.2)	88.4 (86.6-90.2)	87.7 (83.8-91.6)	87.8 (83.2-92.4)	80.4* (79.4-81.3)
Proportion living in nursing home [% (n)]	47.9 (23)	24.2 (64)***	28.2 (35)*	27.3 (24)*	4.0 (46)***
MMSE score, mean (95% CI)	16.5 (14.0-19.1)	19.1 (18.3-19.9)	18.7 (17.4-20.0)	18.5 (17.1-19.9)	27.6*** (27.5-27.7)
Ischemic heart disease [e]	35.4 (17)	27.5 (73)	23.4 (29)	37.5 (33)	30.1 (346)
Stroke/TIA [d]	31.2 (15)	40.7 (108)	17.7 (22)[†]	100 (88)	16.9 (194)*
Diabetes mellitus [f]	10.4 (5)	8.7 (23)	4.8 (6)	10.2 (9)	9.5 (109)
COPD[g]	2.1 (1)	3.0 (8)	1.6 (2)	4.5 (4)	2.3 (26)

Differences in means between bvFTD and comparison groups were tested with a t-test (two-tailed) and differences in proportions with Pearson's chi-square, two-tailed.
*p<0.05 compared to bvFTD.
**p<0.01 compared to bvFTD.
***p<0.001 compared to bvFTD.
[†]0.053 compared to bvFTD.

a) Non-FTD dementia as defined by DSM-III-R.
b) Alzheimer's disease as defined by the NINCDS-ADRDA criteria.
c) Vascular dementia as defined by the NINDS-AIREN criteria.
d) Stroke and/or transient ischemic attack (TIA). A comparison between bvFTD and VAD was not performed, as all individuals with VAD had some type of cerebrovascular episode by definition.
e) Angina pectoris and/or myocardial infarction.
f) Diabetes mellitus, any type.
g) COPD: Chronic obstructive pulmonary disease or chronic bronchitis.

Table 16. Hazard ratios (HR) for death associated with a diagnosis of behavior variant frontotemporal dementia (bvFTD) compared to a diagnosis of non-FTD dementias (DSM-III-R), Alzheimer's disease, vascular dementia and no dementia. Risk time from time of examination (A) *and from symptom onset* (B).

Risk time	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
A. From examination	Adjusted for age at onset, gender	Adjusted for age updated in risk time, gender	Adjusted for age at onset, gender, MMSE	Adjusted for age at onset, gender, birth cohort
Non-FTD dementia [a]	*ref*	*ref*	*ref*	*ref*
bvFTD	1.65 (1.19-2.31)**	1.63 (1.17-2.26)**	1.53 (1.09-2.14)**	1.64 (1.18-2.28)**
Alzheimer's disease [b]	*ref*	*ref*	*ref*	*ref*
bvFTD	1.92 (1.34-2.75)***	1.85 (1.29-2.65)**	1.59 (1.09-2.30)*	1.80 (1.25-2.57)**
Vascular dementia [c]	*ref*	*ref*	*ref*	*ref*
bvFTD	1.38 (0.95-2.00)	1.40 (0.96-2.04)	1.37 (0.94-2.00)	1.37 (0.94-1.98)
No dementia	*ref*	*ref*	-	*ref*
bFTD	3.98 (2.85-5.55)***	3.75 (2.68-5.25)***	-	3.61 (2.58-5.05)***
B. From symptom onset				
Non-FTD dementia [a]	*ref*	*ref*	*ref*	*ref*
bvFTD	1.77 (1.29-2.43)***	1.60 (1.16-2.22)**	1.84 (1.33-2.54)***	1.75 (1.27-2.40)*
Alzheimer's disease [b]	*ref*	*ref*	*ref*	*ref*
bvFTD	1.82 (1.27-2.61)**	1.75 (1.23-2.50)**	1.53 (1.07-2.19)*	1.78 (1.24-2.55)**
Vascular dementia [c]	*ref*	*ref*	*ref*	*ref*
bvFTD	1.51 (1.04-2.20)*	1.40 (0.97-2.03)	1.42 (0.98-2.06)	1.37 (0.95-2.00)

Results were obtained with Cox regression analyses, using *time from examination (**A**) or time from symptom onset (**B**)* to death or end of March 2013.

*p<0.05 compared to bvFTD.
**p<0.01 compared to bvFTD.
***p<0.001 compared to bvFTD.

a) Non-FTD dementia as defined by DSM-III-R.
b) Alzheimer's disease as defined by the NINCDS-ADRDA criteria.
c) Vascular dementia as defined by the NINDS-AIREN criteria.

Table 17 shows 3-year mortality, 10-year mortality and median survival from time of examination to death in relation to bvFTD, other (non-FTD) dementias and no dementia, stratified by age group. Between ages 80-89 years, median survival time was shorter among those diagnosed with bvFTD (2.6 years) than among those with other (non-FTD) dementias (4.3 years; log rank test: p=0.018) and those with AD (4.5 years; p=0.008). Between ages 90-95 years, median survival time was shorter among those with bvFTD (1.1 years) than among those with other (non-FTD) dementias (1.7 years; p=0.016) and those with AD (1.9 years; p=0.041). There was no difference in survival times between bvFTD and VAD. Furthermore, median survival time was shorter among those diagnosed with bvFTD than among those with no dementia regardless of age group. Among individuals with bvFTD, there was no difference in survival times among men compared to women (median survival 2.4 years vs. 2.5 years; p=0.131). Figure 9 shows the cumulative proportion surviving from time of examination to death (or end of March 2013) as determined by the Kaplan-Meier method, in relation to diagnoses of bvFTD, AD, VAD and being without dementia.

Mean age of onset was 83.1 years (95% CI: 81.3-84.8) among the bvFTD cases and 83.8 years (95% CI: 82.9-84.8) among those with other (non-FTD) dementias (p=0.431). Table 18 shows median survival times from time of symptom onset to death in relation to bvFTD and other (non-FTD) dementias stratified by age group. Between ages 80-89 years, median survival time was shorter among bvFTD cases (7.4 years) than among those with other (non-FTD) dementias (8.8 years; log rank test: p=0.016). However, between ages 70-79 years and 90-95 years there were no differences in survival times between individuals with bvFTD and other (non-FTD) dementias.

Table 19 shows that excluding individuals aged 70-79 years did not influence the results.

Causes of death according to death certificates for individuals with a diagnosis of bvFTD, other (non-FTD) dementias and no dementia are shown in table 20. The most common causes of death in bvFTD were cardiovascular disorder, dementia and infectious disease. There were no differences in causes of death between individuals with bvFTD and those with other (non-FTD) dementias, except that dementia was more often a cause of death in individuals with bvFTD compared to those with VAD. Dementia was also more common as a cause of death in individuals with bvFTD compared to individuals with no dementia. Malignant disorders tended to be a less frequent cause of death in bvFTD compared to individuals with no dementia.

Table 17. Median survival times from time of examination to death, 3-year mortality and 10-year mortality for individuals with a diagnosis of behavior variant frontotemporal dementia (bvFTD) compared to other (non-FTD) dementias, Alzheimer's disease, vascular dementia or no dementia, stratified by age.

	***Median survival times* [years (95% CI)]**				
Age	**bvFTD**	**Other (non-FTD) dementias** [a]	***Alzheimer's disease*** [b]	***Vascular dementia*** [c]	**No dementia**
All (70-95 years)	2.41 (2.04-2.78)	2.78 (2.30-3.27)	2.88 (2.05-3.71)	3.09 (2.34-3.82)	**10.44 (9.67-11.21)*****
Women	2.54 (2.08-3.00)	2.89 (2.48-3.31)	2.91 (2.11-3.71)	3.16 (2.61-3.72)	**10.91 (10.27-11.54)*****
Men	2.39 (1.77-3.00)	1.88 (1.19-2.58)	2.03 (1.60-2.47)	0.78 (0.20-2.59)	**7.09 (6.03-8.14)*****
Age (years)					
70-79	9.02 (7.82-10.23)	6.93 (4.13-9.72)	8.46 (7.54-9.37)	5.60 (3.47-7.72)	**15.91 (15.43-16.40) *****
80-89	2.60 (1.57-3.62)	**4.33 (3.21-5.45)***	**4.53 (3.65-5.41)****	3.32 (2.03-4.60)	**6.43 (6.01-6.85)*****
90-95	1.13 (0.47-1.79)	**1.69 (1.31-2.07)***	**1.88 (0.98-2.78)***	1.51 (0.55-2.46)	**3.45 (3.01-3.89)*****
	***3-year mortality* [% (n/N)]**				
All (70-95 years)	62.5 (30/48)	52.8 (140/265)	51.6 (64/124)	48.9 (43/88)	**13.8 (159/1149)*****
Age (years)					
70-79	(0/5)	14.8 (4/27)	11.8 (2/17)	15.4 (2/13)	3.1 (20/635)
80-89	58.1 (18/31)	37.1 (39/105)[d]	36.7 (22/60)[e]	40.9 (18/44)	**19.5 (68/349)*****
90-95	100.0 (12/12)	74.4 (99/133)[f]	72.3 (34/47)[g]	83.9 (26/31)	**43.0 (71/165)*****
	***10-year mortality* [% (n/N)]**				
All (70-95 years)	95.8 (46/48)	93.6 (248/265)	91.9 (114/124)	92.0 (81/88)	**49.6 (570/1149)*****
Age (years)					
70-79	60.0 (3/5)	66.7 (18/27)	64.7 (11/17)	69.2 (9/13)	**21.1 (134/635)*****
80-89	100.0 (31/31)	92.4 (97/105)	93.3 (56/60)	93.2 (41/44)	**79.1 (276/349)***
90-95	100.0 (12/12)	100.0 (133/133)	100.0 (47/47)	100.0 (31/31)	97.0 (160/165)

The Kaplan-Meier method was used to determine median survival times from time of examination to death or end of March 2013. A log-rank test was used to compare the median survival time of bvFTD with the median survival times of non-FTD dementias, AD, VAD and no dementia.

Table 17 cont.:

*p<0.05 compared to bvFTD.
**p<0.01 compared to bvFTD.
***p<0.001 compared to bvFTD.

a) Other (non-FTD) dementias as defined by DSM-III-R.
b) Alzheimer's disease as defined by the NINCDS-ADRDA criteria.
c) Vascular dementia as defined by the NINDS-AIREN criteria.
d) p=0.061 compared to bvFTD.
e) p=0.074 compared to bvFTD.
f) p=0.069 compared to bvFTD.
g) p=0.051 compared to bvFTD.

Table 18. Median survival times from time of symptom onset to death for individuals with a diagnosis of behavior variant frontotemporal dementia (bvFTD) and other (non-FTD) dementias, Alzheimer's disease and vascular dementia, stratified by age.

	***Median survival times* [years (95% CI)]**			
	bvFTD	**Other (non-FTD) dementias [a]**	***Alzheimer's disease* [b]**	***Vascular dementia* [c]**
All (70-95 years)	6.91 (5.60-8.22)	7.36 (6.67-8.05)	7.51 (6.43-8.59)	7.12 (5.77-8.47)
Age (years)				
70-79	13.19 (5.16-21.22)	11.80 (4.74-18.86)	9.10 (7.83-10.37)	13.56 (6.74-20.39)
80-89	7.39 (5.94-8.84)	**8.82 (7.87-9.76)***	**9.00 (6.90-11.08)***	8.34 (6.78-9.89)
90-95	4.63 (3.06-6.19)	5.55 (4.70-6.40)	4.84 (4.39-5.29)	3.97 (2.30-5.64)

The Kaplan-Meier method was used to determine median survival times from *time of symptom onset* to death or end of March 2013. A log-rank test was used to compare the median survival time of bvFTD with the median survival times of other (non-FTD) dementias, Alzheimer's disease and vascular dementia.

*p<0.05 compared to bvFTD.

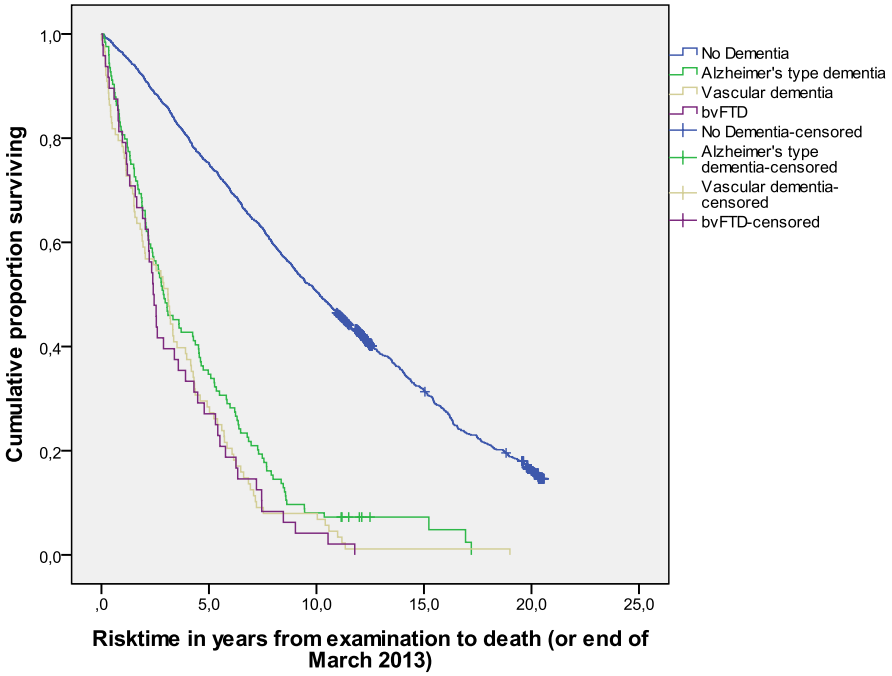
a) Other (non-FTD) dementias as defined by DSM-III-R.
b) Alzheimer's disease as defined by the NINCDS-ADRDA criteria.
c) Vascular dementia as defined by the NINDS-AIREN criteria.

Table 19. Hazard ratios (HR) for death among individuals aged 80 years and older, associated with a diagnosis of behavior variant frontotemporal dementia (bvFTD) compared to a diagnosis of other (non-FTD) dementias (DSM-III-R), Alzheimer's disease, vascular dementia and no dementia. Risk time from symptom onset.

	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
	Adjusted for age at onset, gender	Adjusted for age updated in risk time, gender	Adjusted for age at onset, gender, MMSE	Adjusted for age at onset, gender, birth cohort
Non-FTD dementia [a]	*ref*	*ref*	*ref*	*ref*
bvFTD	1.66 (1.20-2.31)**	1.51 (1.29-2.58)***	1.58 (1.13-2.21)**	1.66 (1.20-2.31)**
Alzheimer's disease [b]	*ref*	*ref*	*ref*	*ref*
bvFTD	1.96 (1.36-2.84)***	1.96 (1.34-2.88)***	1.67 (1.14-2.46)**	1.95 (1.34-2.82)***
Vascular dementia [c]	*ref*	*ref*	*ref*	*ref*
bvFTD	1.43 (0.98-2.11)	1.67 (1.11-2.50)*	1.41 (0.96-2.08)	1.43 (0.97-2.10)
No dementia	*ref*	*ref*	-	*ref*
bvFTD	3.62 (2.67-4.90)***	3.39 (2.37-4.86)***	-	3.49 (2.58-4.73)***

Results were obtained with Cox regression analyses, using *time from examination* to death or end of March 2013.
*p<0.05 compared to bvFTD.
**p<0.01 compared to bvFTD.
***p<0.001 compared to bvFTD.

Figure 9. Survival rate in relation to behavior variant frontotemporal dementia (bvFTD), Alzheimer's disease[a], vascular dementia[b] and being without dementia.



Survival rate was determined by Kaplan-Meier analysis.

a) Alzheimer's disease as defined by the NINCDS-ADRDA criteria.
b) Vascular dementia as defined by the NINDS-AIREN criteria.

Table 20. Cause of death according to death certificates for individuals with a diagnosis of behavior variant frontotemporal dementia (bvFTD), other (non-FTD) dementias and no dementia. Death certificate was obtained from The Swedish Health and Welfare Statistical Database for Cause of Death.

	bvFTD (n=48)	**Other (non-FTD) dementias [a] (n=259)**	***Alzheimer's disease* [b] (n=118)**	***Vascular dementia* [c] (n=88)**	**No dementia (n=880)**
	% (n)	% (n)	% (n)	% (n)	% (n)
Cardiovascular disorder [d]	35.5 (17)	40.1 (104)	37.4 (44)	43.1 (38)	39.2 (345)
CVD [e]	8.3 (4)	14.3 (37)	14.4 (17)	15.9 (14)	11.6 (102)
Dementia	25.0 (12)	16.6 (43)	20.3 (24)	**10.2 (9)***	**9.8 (86)*****
Infectious disease	14.6 (7)	11.6 (30)	12.7 (15)	8.0 (7)	7.9 (70)
Malignancy [f]	8.3 (4)	8.1 (21)	5.9 (7)	8.0 (7)	19.0 (167)†
Other cause	8.3 (4)	9.3 (24)	9.3 (11)	14.8 (13)	12.5 (110)

*p<0.05 compared to bvFTD (Pearson's chi-square, two-tailed).

***p<0.001 compared to bvFTD.

†p=0.083 compared to bvFTD.

a) Other (non-FTD) dementias as defined by DSM-III-R.
b) Alzheimer's disease as defined by the NINCDS-ADRDA criteria.
c) Vascular dementia as defined by the NINDS-AIREN criteria.
d) Includes any diagnosis of ischemic heart disease, heart failure, cardiomyopathy and arrhythmia as cause of death according to death certificate.
e) Includes any diagnosis of a cerebrovascular disorder (CVD) as cause of death according to death certificate.
f) Includes any diagnosis of a malignant disorder, including hematological malignancies, as cause of death according to death certificate.

DISCUSSION

Prevalence of bvFTD

We examined the prevalence of possible bvFTD in an elderly general population, using the LMRC in paper I and three different FTD criteria in paper II. Paper I can be thought of as a pilot study for the later investigation, and yielded the results that bvFTD (as detected by the LMRC) was more common among 85-year-olds than previously supposed. Paper II describes the prevalence of bvFTD among 70-95-year-olds according to three different FTD criteria, and irrespective of criteria, bvFTD was more common among older adults than expected. Furthermore, we found a higher prevalence at age 81-95 than at age 70-79 years.

It is believed that FTD occurs mainly among individuals aged 45–65 years[79, 80], and most prevalence studies have been performed in this age group[4]. Most studies in populations above age 65 years have reported lower rates (0-0.6%)[74-77] than this study. Prevalence estimates for the elderly based on register data are lower (only 4-54 per 100 000), probably reflecting that many cases of FTD are not detected by the health care system, or that they receive other diagnoses than FTD[42, 78]. One explanation for this relatively high prevalence in the present study may be that bvFTD criteria were applied directly to the population without prior screening for global dementia. Another reason may be the use of comprehensive key informant interviews to gather information on frontal lobe symptoms and the early course of the disease. The diagnosis of bvFTD is probably even more underestimated in the oldest old, as this diagnosis is seldom considered in this age group [40, 79].

Agreement between FTD criteria

Despite a similar prevalence using different criteria, the agreement between criteria was only low to moderate. Among those with bvFTD according to the FTDC, only 27% had a diagnosis according to FTLD-CC, and 35% according to LMRC (with kappa values 0.30-0.42). The LMRC and FTLD-CC had an overlap of only 19-21%, with a kappa of 0.20. Thus, these criteria captured to a large extent different individuals. The FTLD-CC diagnosed somewhat fewer cases than FTDC, in line with suggestions that these criteria are more rigid[65]. Furthermore, almost all cases diagnosed with FTLD-CC, a large majority of those with FTDC, but only less than half of those diagnosed with LMRC fulfilled criteria for global dementia. One explanation may be

that the LMRC is more weighted towards externalized symptoms, such as loss of inhibition and aggressive behaviors, while the FTLD-CC is more weighted towards negative symptoms, such as apathy and loss of initiative, and the FTLD-CC may thus miss a large proportion of cases with mainly loss of inhibition[65]. The FTDC seems to be somewhere in-between the other criteria in this regard. This finding is remarkably similar to reports describing low concordance between different criteria for global dementia[141].

Neuroimaging

A large proportion of those diagnosed according to the FTDC and LMRC (93-100%) had moderate-severe frontal and/or temporal lobe atrophy on CT, which could be compared to 13% in those without frontal lobe symptoms. Few studies have compared the clinical criteria of bvFTD with neuroimaging or neuropathology. One study reported that among 137 cases with frontal lobe degeneration at neuropathological examination, 85% fulfilled FTDC criteria for possible bvFTD and 53% fulfilled FTLD-CC criteria[25]. No previous studies have directly compared FTD criteria with MRI or CT in the setting of a population study. However, reports from memory clinics show that the proportion of patients with clinically diagnosed bvFTD who have frontal and/or temporal atrophy on neuroimaging ranges from 50 to 95% [25, 142-145].

Among those with moderate-severe frontal lobe atrophy on CT, 85 individuals did not have frontal lobe symptoms as defined by any of the three criteria sets. Only 12% of those had other dementias. One explanation for this result may be that cortical thinning of the frontal lobes is also found in normal aging[146], and in these cases may not lead to detectable frontal lobe symptoms. In addition, we cannot exclude the possibility that prior head trauma may partially explain the presence of frontal and/or temporal lobe atrophy in non-demented individuals[147]. Furthermore, it has to be emphasized that neuroimaging is a supportive, but not mandatory diagnostic feature of all FTD criteria. Thus, these criteria allow a diagnosis of possible bvFTD in the absence of neuroimaging. However, the high correlation between frontal and/or temporal lobe atrophy and bvFTD according to FTDC and LMRC in our population study is similar to that reported from clinical studies and lends support for the validity of our diagnoses.

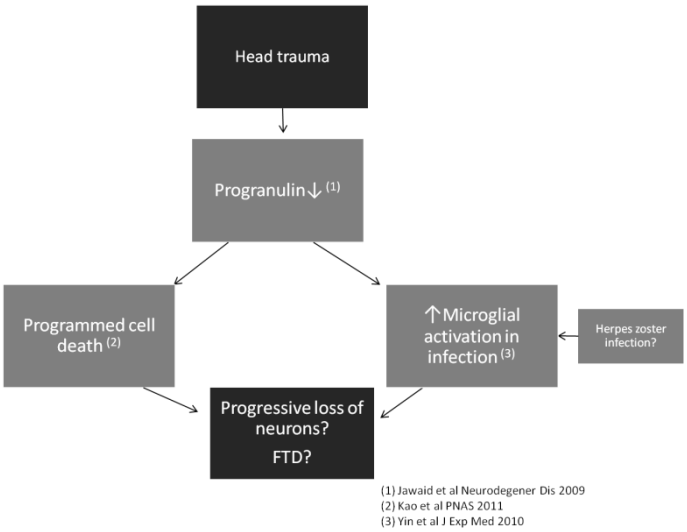
Risk factors

History of alcohol abuse, head trauma, stroke and/or TIA, hypothyroidism, severe white matter lesions on CT of the brain and being divorced were associated with bvFTD in this population-based nested case-control study. Alcohol abuse and being divorced were associated with bvFTD in comparison to both control groups. Hypothyroidism was associated with bvFTD compared to the control group with dementia, and there was trend for an association (p=0.055) in comparison to the control group without dementia. Both head trauma[88, 89], and hypothyroidism [88, 90] have previously been related to bvFTD in clinic-based case-control studies.
It needs to be emphasized that this was an exploratory study, which examined a large number of potential risk factors. It is thus possible that some associations were found by chance. However, most of the findings could be considered as biologically plausible, and we believe that the exploratory approach is reasonable considering present knowledge regarding non-genetic risk factors in bvFTD.

It is difficult to compare our study with previous case-control studies as both cases and controls in our study were recruited from the same general population, whereas previous case-control studies recruited cases from patient samples, and controls from other samples. Two of the previous studies used cognitively intact controls[88, 90], while the third had controls with dementias other than FTD [89]. The mean age of participants was also lower than in our study (64, 70 and 71 years versus 87 years) [88-90].

Despite these differences, two of the previous case-controls studies and our study found that head trauma increased odds for bvFTD[88, 89]. Head trauma has also been identified as a risk factor for Alzheimer's disease [148]. The frontal lobes are particularly vulnerable to trauma, although the pathogenic mechanisms leading to bvFTD remain to be elucidated[149, 150]. Mutations leading to loss of function in the progranulin gene are among the known genetic causes of FTD [151], and it has been suggested that head trauma may reduce CNS levels of progranulin, thus increasing the risk for FTD [152].
A potential pathway is shown in figure 9; based on research with PGRN-deficient mice, it has been suggested that low progranulin levels may lead to neurodegeneration by disrupting the kinetics of programmed cell death[153]. Also, a study has shown that the brains of PGRN-deficient mice exhibit an exaggerated inflammatory response after infection, compared to wild-type mice[154].
Furthermore, studies have also suggested that head trauma may be linked with abnormal aggregation of tau and β-amyloid [155, 156].

Figure 10. Potential relationship between head trauma, progranulin and behavior variant frontotemporal dementia (bvFTD).



This study found that alcohol abuse was related to increased risk of bvFTD compared to both controls with and without dementia, while light-moderate consumption was related to a decreased risk. A similar U-shaped association has been reported for dementia and Alzheimer's disease[157, 158]. However, two of the previous studies on FTD that examined measures of alcohol consumption found no association with alcohol abuse[88, 89], but one of these studies included individuals with alcohol-related dementia in the control group[89].

Severe alcohol abuse is known to lead to neurodegeneration, and up to 75% of chronic alcoholics have significant degenerative changes according to postmortem studies[159]. This degeneration primarily affects the frontal lobes and cerebellum[160-162], and alcohol-related dementia frequently presents with frontal lobe symptoms [163]. Moreover, older individuals with alcoholism have been shown to have to greater gray matter deficits (on MRI) in the prefrontal and frontal regions compared younger individuals with alcoholism[164]. Alcohol abuse is also associated with cognitive impairment, especially executive dysfunction[162]. In summary, alcohol abuse often leads to frontal dysfunction and it can cause structural damage in the frontal lobes and associated circuits, both in grey and white matter[165].

Furthermore, alcohol abuse is known to influence the exposure to other potential risk factors, such as head trauma[161], and exacerbate hypertension and diabetes mellitus[159]. Thus, there exist numerous pathways through which alcohol abuse could influence the development of bvFTD.

This study found an association with hypothyroidism when comparing cases to controls without dementia, and a trend compared to controls with dementia. It has long been recognized that overt hypo- and hyperthyroidism can be accompanied by dementia symptoms that are reversible with treatment[166]. The association of hypothyroidism with non-FTD dementias has been studied in population studies; in the Framingham study, low and high thyrotropin levels were associated with an increased risk of AD in women[166]. However, another population study found no association with mild cognitive impairment (MCI)[167]. A previous study among elderly patients with neuropsychiatric disorders found that thyroid hormone abnormalities were common in FTD[168] and two of the previous case-control studies on FTD found trends for associations with thyroid disease[88, 90]. Potential pathogenic mechanisms leading to bvFTD remain to be elucidated, but it has been suggested that thyroid hormone abnormalities may influence tau pathology and thus contribute to the risk for bvFTD[88, 90, 169]. Furthermore, hypothyroidism may influence vascular risk factors. Overt hypothyroidism frequently lead to hypercholesterolemia[170] and subclinical hypothyroidism increases LDL and lowers HDL[170], although the clinical significance of this remains disputed[171]. Hypothyroidism can also lead to or aggravate hypertension and heart failure[172], which in turn may have deleterious effects on cognitive function.

We also found a trend for an association with a history of shingles (rash caused by the varicella-zoster virus [VZV]), a finding that has not previously been reported for FTD. It is known that patients with previous VZV *encephalitis* may develop long-term cognitive impairment[173, 174], but no participant had a history of neuroinfectious disorder (including encephalitis) according to the Hospital Discharge Register. Potentially, activation of the varicella-zoster virus could influence FTD development through increased microglial activation (figure 10). However, the implications of this finding remain unclear, waiting further study and possible confirmation.

Stroke and/or TIA and severe white matter lesions on CT of the brain were associated with bvFTD when cases were compared to normal controls, despite that frontal lobe symptoms evolving in connection with a stroke was an exclusion criteria according to FTDC. One previous case-control study found a trend for a negative association with stroke/TIA[89] and one found no

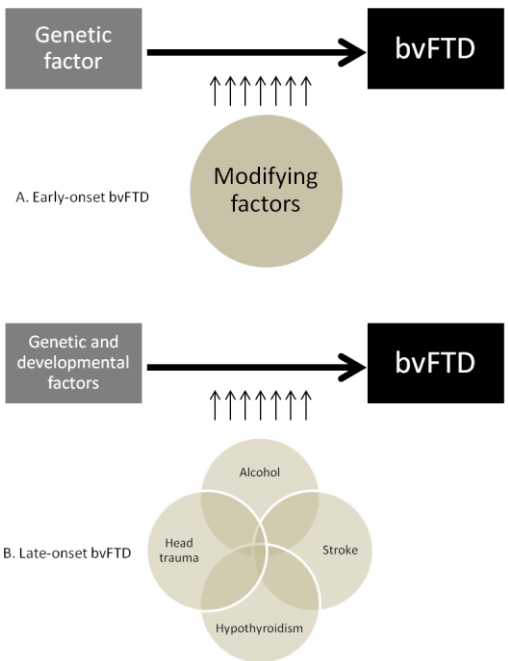
association with stroke/TIA[88]. Studies on FTD neuropathology in younger samples have found associations with white matter damage [175], but not with other cerebrovascular pathology [176]. It has been suggested that white matter damage in bvFTD represents secondary effects of neuronal degeneration, and not a primary vascular lesion[177]. However, these neuropathological studies included mainly patients with early-onset FTD [175, 176], and other factors, such as vascular pathology, might influence the development of late-onset FTD. It is known that mixed pathologies (i.e. Alzheimer's disease and vascular pathology) become more prevalent as a cause of dementia with increasing age [178, 179], and this may also be true for bvFTD.
One previous study found a negative association between bvFTD and cardiovascular disorders[89], which we could not confirm. This previous study that found a negative association between FTD and cardiovascular disease included patients with vascular dementia in the control group, and these patients had a high prevalence of cardiovascular disease[89]. One previous study found an association with diabetes mellitus[90], which we could not confirm. Family history of dementia was not associated with bvFTD, whereas a high proportion of early-onset FTD has a positive family history[180]. This suggests that genetic factors may be less important in late-onset than in early-onset bvFTD. Furthermore, the Apolipoprotein E ε4 allele was not associated with bvFTD, in line with most previous studies [181].

Cross-sectionally, major depression (compared to controls without dementia) was associated with bvFTD. There was also a trend for anxiety disorders to be associated with bvFTD (compared to controls with dementia). It is likely that these findings are secondary to the disorder itself, which is further supported by the finding that depression earlier in life was not associated with bvFTD. Psychiatric manifestations often occur early, with dysthymia being present in one third of patients with FTD at initial presentation[32], and anxiety being more common in FTD than in AD[33, 100]. Psychotic symptoms were rare among bvFTD cases in our study, in line with most previous studies[182].
The finding that bvFTD cases were more likely than both control groups to be divorced may reflect the great caregiver burden associated with bvFTD[183, 184].

In summary, these findings suggest that the development of late-life bvFTD may be influenced by factors with such as alcohol abuse, head trauma, stroke and hypothyroidism. Late-life bvFTD might to a lesser degree be due to genetic factors than early-onset bvFTD. This might also explain the higher prevalence of bvFTD after age 80, as different risk factors might have time

emerge during a long life and have an additive effect on the development of bvFTD (figure 10). However, it must be emphasized that the methods employed in this study do not allow for any determination of causality with regards to these factors, and can only give suggestions for further research into the pathogenic mechanisms behind FTD.

Figure 11. Hypothetical pathways for the development of (A) early-onset behavioral variant frontotemporal dementia (bvFTD) and (B) late-onset bvFTD.



Furthermore, the impact of preventive interventions on FTD, such as life-style interventions, is not known. Higher education has been associated with higher levels of late-life cognition, and might delay the development of cognitive impairment[185]. However, this might not be true for FTD, as a study from Brescia, Italy has found that individuals with FTD generally had higher

levels of education than individuals with AD[186]. Still, the findings in the present study suggest that some potential risk factors might be amenable to preventive interventions, i.e. stroke, hypothyroidism and alcohol abuse.

Mortality

In a population-based sample of 70-95-year-olds, bvFTD was associated with a higher risk of death than non-FTD dementias, AD and no dementia, and a trend towards a higher risk of death compared to VAD. These findings hold true both when investigating time from examination and time from symptom onset to death, and when controlling for potential confounders. The difference in survival times between bvFTD and the other dementias was apparent after the age of 80 years. Depending on age at examination, individuals with bvFTD had from 2 to 7 years less life expectancy than individuals without dementia.

Dementia disorders are suggested to be one of the major killers among the oldest old[187]. The findings in this study suggest that bvFTD is associated with even higher mortality than other dementias. Some previous studies suggested that individuals with bvFTD progress faster to death than patients with AD [93], but other studies have found similar survival times for these disorders[97]. These findings are in line with a recent study from the Swedish Dementia Registry which reported that FTD had the highest risk of death among all dementia diagnoses[188]. The higher risk of death in bvFTD compared to other dementias may reflect a more aggressive neurodegenerative process than in other dementias leading to early dysregulation of blood pressure, respiration and swallowing[100]. In line with this, it was reported that FTD is associated with higher CSF levels of neurofilament light (NFL) [189], known to correlate with damage to subcortical structures[190], than both AD and VAD. However, bvFTD encompasses a wide range of behavioral and psychological symptoms (BPSD) that are also common in other dementia disorders[191]. Studies of BPSD in AD have reported that individuals with severe behavioral or affective/apathetic symptoms have shorter survival times than individuals with minimal behavioral symptoms[192]. Thus, the presence of behavioral symptoms might in itself be a marker of increased mortality.

In conclusion, a diagnosis of bvFTD in this population-based sample of older adults was associated with a higher risk of death than a diagnosis of other dementias. This suggests that late-life bvFTD has a more aggressive course than other late-life dementias.

Considerations common to Papers I-IV

Among the strengths of this study is the large population-based study, the comprehensive examinations including interviews with key informants, and that cases and controls were taken from the same population. Furthermore, all individuals were examined with a wide range of psychiatric and neurological variables, including those described in the new FTDC criteria, the FTLD-CC and the LMRC. Therefore, it was possible to design symptom algorithms, even though some data were collected before the criteria were published. A further advantage is that it was possible to examine the different criteria in relation to frontal and/or temporal lobe atrophy on CT. However, there are also some limitations.

First, the validity of a clinical diagnosis of bvFTD without neuropathological confirmation could be questioned. However, the correlation between our diagnosis of bvFTD and frontal atrophy on CT was high (80%) and the correlation between bvFTD according to FTDC criteria and neuropathology has also been found to be high[25]. Furthermore, it is important to emphasize, that the bvFTD diagnosis presented in this dissertation refers to a possible bvFTD, as it is outlined in the FTDC criteria[25]. Even with a high correlation with neuroimaging, it is impossible to exclude that some of the persons with bvFTD might have had atypical Alzheimer's disease (AD), argyrophilic grain disease or some other neurodegenerative or vascular disease. This distinction may be especially difficult to make at very high ages, where AD is common. Moreover, the prevalence of frontal-predominant AD has been difficult to establish[193]. Previous studies report that frontal-predominant AD pathology is found in up to 10% of clinical FTD cases[194, 195].

Second, FTD among older adults may occasionally present as an amnesic state and neuroimaging in these cases often shows focal hippocampal sclerosis[80]. The LMRC and FTLD-CC do not permit a diagnosis of FTD in these cases. The FTDC permits a diagnosis of bvFTD in individuals who present with an amnesic state if psychometric testing is compatible is with FTD, i.e. if the psychometric tests show executive deficits with relative sparing of episodic memory and visuospatial functions[25]. This criterion could thus not be applied in our cross-sectional study which uses retrospective information to elucidate the early course of the disorder. Some FTD cases according to FTDC may thus have been missed, leading to underestimation of the prevalence of bvFTD. Furthermore, if this criterion had been applied, the correlation between FTDC and the other criteria would have been even lower. Unfortunately, the neuroimaging technique (CT) employed in this study did not allow us to detect hippocampal sclerosis.

Third, some results are based on retrospective information from key informants, which may lead to recall bias. Key informants of affected

individuals may remember more previous events than relatives of controls, leading to false positive results. On the other hand, key informants of such old individuals as in our study may not know about or remember events occurring decades ago, leading to false negative results.

Fourth, due to the study design, we were not able to study other types of FTD such as semantic dementia and primary progressive aphasia. Fifth, the proportion of women in our study was high (80%), partly because our study included samples from the Prospective Population Study of Women. However, the proportion of women in the Swedish general population over age 70 was always higher than the proportion of men during the period when the data was collected (1986-2001), especially for those older than 85 years [196]. Sixth, we had a larger refusal rate for CT in those with bvFTD than in the rest of the population, resulting in few individuals in that substudy. The results of neuroimaging should therefore be taken with caution.

Finally, the study was conducted over a long time span with pooling of several different population studies. However, all studies included the same protocol and were performed by the same research group, and the last author was PI of all studies. Furthermore, evaluation of data and diagnosis of bvFTD were done by the same neuropsychiatrists irrespective of year of examination. Still, we cannot exclude the possibility that examination procedure changed during this period.

Considerations specific to Paper III (Risk Factors)

First, due to the cross-sectional design, we cannot make any inferences regarding direction of associations. For example, the neurotoxic action of alcohol may lead to degenerative changes in the frontal lobes, but frontal lobe dysfunction may also lead to increased alcohol intake[160]. Furthermore, alcohol abuse increases the risk of being exposed to other detrimental factors (e.g. smoking, head trauma and socioeconomic problems). However, the low incidence of bvFTD makes it difficult to study risk factors for bvFTD in longitudinal studies. Second, there is a possibility of false positive findings due to multiple comparisons. We did not control for multiple comparisons as this may give rise to false negative results. One way to treat this problem is to make no adjustments for the number of comparisons but to give information on how many comparisons have been made and to emphasize that any new findings should be biologically plausible and considered only suggestive until further confirmed [197]. Third, it needs to be re-emphasized that some results

are based on retrospective information from key informants, which may lead to recall bias. Key informants of cases may remember more previous events than relatives of controls, leading to false positive results. On the other hand, key informants may not know about or remember events occurring decades ago, leading to false negative results. Fourth, the quality of diagnosis from hospital discharge registers could vary. Low validity of these sources might lead to false negative results. Fifth, the age of our sample is considerably higher than in previous case-controls studies of bvFTD, and other risk factors might be involved in this older population than in younger age groups. Sixth, the study was conducted over a long time span with pooling of several different population studies. Thus, we can however not exclude that the effect of different risk factors might have been influenced by time-trends. Finally, the number of individuals in some of the groups was rather small. Negative findings should therefore be taken cautiously due to lack of statistical power.

Considerations specific to Paper IV (Mortality)

Among the strength of this paper is the use of the Swedish Health and Welfare Statistical Database for Cause of Death, which is known to be almost complete regarding mortality data [126].

There are also some limitations. First, the data were collected over a long period of time using several different population studies. During this time, survival increased in the general population. Controlling for birth cohort did however not change the results. We cannot, however, exclude the possibility that secular trends in the frequency of FTD and survival might have influenced the results.
Second, only few participants among those aged 70-79 years had bvFTD. We could therefore not make any conclusion about mortality and survival in bvFTD in this age group. Third, response rates were around 65-70%. Responders and non-responders differed with regards to mortality, mainly explained by higher mortality among 70-79-year-old non-responders. Thus, it is possible that responders and non-responders also differed regarding frontal lobe symptoms.
Fourth, individuals with bvFTD were more likely to have a history of stroke/TIA than individuals with no dementia. However, adjusting for stroke did not influence the results. Fifth, the validity of death certificates could be questioned. It has been suggested that up to one third of death certificates are likely to be incorrect [198], maybe explained in part by declining autopsy rates.

Finally, part of the diagnostic criteria and estimation of age at onset in this study required retrospective information from key informants. This was necessary to elucidate early symptoms and course of symptom development, and age of onset. Although information from key informants may be uncertain, it is also used in clinical studies to determine age of onset.

CONCLUSIONS

The prevalence of bvFTD in this elderly population was higher than expected, especially among the oldest old. The correlation between the different criteria for bvFTD was low, suggesting that further development of research criteria is required. Both the FTDC and the LMRC had a high correlation with frontal and/or temporal lobe atrophy, but only a moderate agreement with each other, suggesting that both FTDC and LMRC could be underestimating the prevalence of bvFTD. This suggests that any modified bvFTD criteria should allow for a more flexible combination of frontal lobe symptoms than is possible in the current FTD criteria, as it is important to capture all presentations of FTD. Furthermore, as potential treatments for FTD (aimed at increasing progranulin levels) may become available in the foreseeable future[199], it becomes crucial to accurately diagnose FTD, and to do so as early in the course of the disorder as possible.

It is important to identify possible non-genetic risk factors for FTD, as up to 50% of FTD cases may be sporadic. History of alcohol abuse, stroke/TIA, head trauma and hypothyroidism were associated with increased odds of bvFTD in this study. These findings have implications for future studies into the etiology of sporadic bvFTD, and ultimately, for prevention among older adults.

In conclusion, a diagnosis of bvFTD in this population-based sample of older adults was associated with a higher risk of death than a diagnosis of other dementias. This suggests that late-life bvFTD has a more aggressive course than other late-life dementias, a finding that can be used to inform relatives, care givers and health care providers. These findings have also implications for future studies into the clinical course of sporadic bvFTD.

In 1926, Onari and Spatz wrote: “We are convinced that Pick’s disease is not extremely rare, but often both the clinician and the anatomist do not recognize it, because not enough focus is directed towards it” [8]. In some way, these words hold true, even today. The findings presented in this dissertation point to the need for increased awareness of bvFTD among older adults, and for further research in this field.

FUTURE PERSPECTIVES

The longitudinal design of the studies among older adults in Gothenburg allows for further investigations regarding different facets of FTD. This design makes it possible to study secular trends in the prevalence of bvFTD and to prospectively study the impact of factors such as alcohol consumption, thyroid function tests (TSH, free T4), medications affecting thyroid function, head trauma, cerebrovascular disease and changes in socio-economic status.

Also, other potential risk factors could be examined, such as physical inactivity, dietary aspects, sleep, breastfeeding, female reproductive health, oral health and the impact of early and/or mid-life stress. Furthermore, future studies will also give an opportunity to examine secular trends in the mortality of FTD.

Future studies could give important insights into the etiology and course of bvFTD, and could ultimately inform diagnostic guidelines and preventive strategies.

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REFERENCES

1. Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. J Neurol Neurosurg Psychiatry. 1994; **57**(4): 416-8.
2. Pick. Über die Beziehungen der senilen Hirnatrophie zur Aphasie. Prager Medizinische Wochenschrift 1892; **17**: 165-7.
3. Pressman PS, Miller BL. Diagnosis and management of behavioral variant frontotemporal dementia. Biol Psychiatry. 2014; **75**(7): 574-81.
4. Onyike CU, Diehl-Schmid J. The epidemiology of frontotemporal dementia. Int Rev Psychiatry. 2013; **25**(2): 130-7.
5. Spatt J. Arnold Pick's concept of dementia. Cortex. 2003; **39**(3): 525-31.
6. Spatt J. The role of Arnold Pick for modern concepts of degenerative dementias: remembrance and appreciation. Nervenarzt. 2000; **71**(12): 1016-9.
7. Alzheimer A. über eigenartige Krankheitsfälle des späteren Alters. Z f d g Neur u Psych. 1911; **4**(1): 356-85.
8. Onari K, Spatz H. Anatomische beiträge zur lehre von der pickschen umschriebenen grosshirnrinden-atrophie („picksche krankheit“). Z f d g Neur u Psych. 1926; **101**(1): 470-511.
9. Love S, Spillantini MG. Unpicking frontotemporal lobar degeneration. Brain. 2011; **134**(Pt 9): 2453-5.
10. Morris JC, Cole M, Banker BQ, Wright D. Hereditary dysphasic dementia and the Pick-Alzheimer spectrum. Ann Neurol. 1984; **16**(4): 455-66.
11. Derouesne C. [From Arnold Pick's original descriptions to frontotemporal dementia: the present enlightened by the past an historical approach]. Geriatr Psychol Neuropsychiatr Vieil. 2014; **12**(1): 74-84.
12. Sjogren T, Sjogren H, Lindgren AG. Morbus Alzheimer and morbus Pick; a genetic, clinical and patho-anatomical study. Acta Psychiatr Neurol Scand Suppl. 1952; **82**: 1-152.
13. van Mansvelt J. Pick's disease: A syndrome of lobar, cerebral atrophy; its clinico-anatomical and histopathological types. Enschede: Utrecht; 1954.
14. Schenk C. Re-examination of a family with Pick's disease. Ann Hum Genet. 1959; **23**: 325-33.

15. Escourolle R. La maladie de Pick. Étude critique d'ensemble et synthèse anatomo-clinique. Paris: R Foulon; 1958.
16. Delay JB, S. Les Démences Tardives. Paris: Masson; 1962.
17. Constantinidis J, Richard J, Tissot R. Pick's disease. Histological and clinical correlations. Eur Neurol. 1974; **11**(4): 208-17.
18. Brun A, Gustafson L. The Birth and Early Evolution of the Frontotemporal Dementia (FTD) Concept. Journal of Molecular Neuroscience. 2011; **45**(3): 324-9.
19. Gustafson LBAID. Presenile dementa:clinical symptoms, pathoanatomical findings and cerebral blood flow. In: Meyer JL, H. Reivich, M., editor. Cerebral vascular disease. Amsterdam: Excerpta Medica; 1977. p. 5-9.
20. Brun A. Frontal lobe degeneration of non-Alzheimer type. I. Neuropathology. Arch Gerontol Geriatr. 1987; **6**(3): 193-208.
21. Englund E, Brun A. Frontal lobe degeneration of non-Alzheimer type. IV. White matter changes. Arch Gerontol Geriatr. 1987; **6**(3): 235-43.
22. Neary D, Snowden JS, Northen B, Goulding P. Dementia of frontal lobe type. J Neurol Neurosurg Psychiatry. 1988; **51**(3): 353-61.
23. Knopman DS, Mastri AR, Frey WH, 2nd, Sung JH, Rustan T. Dementia lacking distinctive histologic features: a common non-Alzheimer degenerative dementia. Neurology. 1990; **40**(2): 251-6.
24. Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology. 1998; **51**(6): 1546-54.
25. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011; **134**(Pt 9): 2456-77.
26. Cairns NJ, Bigio EH, Mackenzie IR, Neumann M, Lee VM, Hatanpaa KJ, et al. Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. Acta Neuropathol. 2007; **114**(1): 5-22.
27. Santillo AF, Nilsson C, Englund E. von Economo neurones are selectively targeted in frontotemporal dementia. Neuropathol Appl Neurobiol. 2013; **39**(5): 572-9.

28. Rademakers R, Neumann M, Mackenzie IR. Advances in understanding the molecular basis of frontotemporal dementia. Nat Rev Neurol. 2012; **8**(8): 423-34.
29. Neary D, Snowden J. Fronto-temporal dementia: Nosology, neuropsychology, and neuropathology. Brain Cogn. 1996; **31**(2): 176-87.
30. Lebert F, Pasquier F, Petit H. Personality traits and frontal lobe dementia. Int J Geriatr Psychiatry. 1995; **10**(12): 1047-9.
31. Brun A. The emergence of the frontal lobe and its morbidity, as opposed to the central lobe. Dement Geriatr Cogn Disord. 1999; **10**: 3-5.
32. Mendez MF, McMurtray A, Chen AK, Shapira JS, Mishkin F, Miller BL. Functional neuroimaging and presenting psychiatric features in frontotemporal dementia. J Neurol Neurosurg Psychiatry. 2006; **77**(1): 4-7.
33. Porter VR, Buxton WG, Fairbanks LA, Strickland T, O'Connor SM, Rosenberg-Thompson S, et al. Frequency and characteristics of anxiety among patients with Alzheimer's disease and related dementias. J Neuropsychiatry Clin Neurosci. 2003; **15**(2): 180-6.
34. Sjögren M. Frontotemporal Dementia-Clinical and Pathophysiological Aspects. Gothenburg, Sweden: Gothenburg University; 1999.
35. Liljegren M, Naasan G, Temlett J, Perry DC, Rankin KP, Merrilees J, et al. Criminal behavior in frontotemporal dementia and Alzheimer disease. JAMA Neurol. 2015; **72**(3): 295-300.
36. Mendez MF. The unique predisposition to criminal violations in frontotemporal dementia. J Am Acad Psychiatry Law. 2010; **38**(3): 318-23.
37. Chow TW. Personality in frontal lobe disorders. Curr Psychiatry Rep. 2000; **2**(5): 446-51.
38. Mendez MF, Chen AK, Shapira JS, Miller BL. Acquired sociopathy and frontotemporal dementia. Dement Geriatr Cogn Disord. 2005; **20**(2-3): 99-104.
39. Miller BL, Darby AL, Swartz JR, Yener GG, Mena I. Dietary-Changes, Compulsions and Sexual-Behavior in Frontotemporal Degeneration. Dementia. 1995; **6**(4): 195-9.
40. Piguet O, Hornberger M, Mioshi E, Hodges JR. Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management. The Lancet Neurology. 2011; **10**(2): 162-72.

41. Miller BL, Darby A, Benson DF, Cummings JL, Miller MH. Aggressive, socially disruptive and antisocial behaviour associated with fronto-temporal dementia. Br J Psychiatry. 1997; **170**: 150-4.
42. Pasquier F, Lebert F, Lavenu I, Guillaume B. The clinical picture of frontotemporal dementia: diagnosis and follow-up. Dement Geriatr Cogn Disord. 1999; **10 Suppl 1**: 10-4.
43. Lhermitte F. Human autonomy and the frontal lobes. Part II: Patient behavior in complex and social situations: the "environmental dependency syndrome". Ann Neurol. 1986; **19**(4): 335-43.
44. Hodges JR, Davies RR, Xuereb JH, Casey B, Broe M, Bak TH, et al. Clinicopathological correlates in frontotemporal dementia. Ann Neurol. 2004; **56**(3): 399-406.
45. Grossman M. Primary progressive aphasia: clinicopathological correlations. Nat Rev Neurol. 2010; **6**(2): 88-97.
46. Hodges JR, Patterson K. Semantic dementia: a unique clinicopathological syndrome. Lancet Neurol. 2007; **6**(11): 1004-14.
47. Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. Brain. 2005; **128**(Pt 9): 1996-2005.
48. Spillantini MG, Murrell JR, Goedert M, Farlow MR, Klug A, Ghetti B. Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. Proc Natl Acad Sci U S A. 1998; **95**(13): 7737-41.
49. Poorkaj P, Bird TD, Wijsman E, Nemens E, Garruto RM, Anderson L, et al. Tau is a candidate gene for chromosome 17 frontotemporal dementia. Ann Neurol. 1998; **43**(6): 815-25.
50. Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. Nature. 1998; **393**(6686): 702-5.
51. Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature. 2006; **442**(7105): 916-9.
52. Cruts M, Gijselinck I, van der Zee J, Engelborghs S, Wils H, Pirici D, et al. Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. Nature. 2006; **442**(7105): 920-4.

53. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron. 2011; **72**(2): 245-56.
54. Renton AE, Majounie E, Waite A, Simon-Sanchez J, Rollinson S, Gibbs JR, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron. 2011; **72**(2): 257-68.
55. Watts GD, Wymer J, Kovach MJ, Mehta SG, Mumm S, Darvish D, et al. Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. Nat Genet. 2004; **36**(4): 377-81.
56. Skibinski G, Parkinson NJ, Brown JM, Chakrabarti L, Lloyd SL, Hummerich H, et al. Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. Nat Genet. 2005; **37**(8): 806-8.
57. Ferrari R, Hernandez DG, Nalls MA, Rohrer JD, Ramasamy A, Kwok JB, et al. Frontotemporal dementia and its subtypes: a genome-wide association study. Lancet Neurol. 2014; **13**(7): 686-99.
58. Chen JA, Wang Q, Davis-Turak J, Li Y, Karydas AM, Hsu SC, et al. A multiancestral genome-wide exome array study of Alzheimer disease, frontotemporal dementia, and progressive supranuclear palsy. JAMA Neurol. 2015; **72**(4): 414-22.
59. Bertram L, Klein C. Probing the exome in alzheimer disease and other neurodegenerative disorders. JAMA Neurol. 2015; **72**(4): 389-91.
60. Mackenzie IR, Neumann M, Bigio EH, Cairns NJ, Alafuzoff I, Kril J, et al. Nomenclature for neuropathologic subtypes of frontotemporal lobar degeneration: consensus recommendations. Acta Neuropathol. 2009; **117**(1): 15-8.
61. McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol. 2001; **58**(11): 1803-9.
62. Santillo A. Morphological Alterations in Frontotemporal Dementia. Malmö: Lund University; 2014.
63. Neumann M, Kwong LK, Truax AC, Vanmassenhove B, Kretzschmar HA, Van Deerlin VM, et al. TDP-43-positive white matter pathology in frontotemporal lobar

degeneration with ubiquitin-positive inclusions. J Neuropathol Exp Neurol. 2007; **66**(3): 177-83.
64. Agosta F, Scola E, Canu E, Marcone A, Magnani G, Sarro L, et al. White matter damage in frontotemporal lobar degeneration spectrum. Cereb Cortex. 2012; **22**(12): 2705-14.
65. Piguet O, Hornberger M, Shelley BP, Kipps CM, Hodges JR. Sensitivity of current criteria for the diagnosis of behavioral variant frontotemporal dementia. Neurology. 2009; **72**(8): 732-7.
66. Hodges JR, Miller B. The classification, genetics and neuropathology of frontotemporal dementia. Introduction to the special topic papers: Part I. Neurocase. 2001; **7**(1): 31-5.
67. Feldman H, Levy AR, Hsiung GY, Peters KR, Donald A, Black SE, et al. A Canadian cohort study of cognitive impairment and related dementias (ACCORD): study methods and baseline results. Neuroepidemiology. 2003; **22**(5): 265-74.
68. Bernardi L, Frangipane F, Smirne N, Colao R, Puccio G, Curcio SA, et al. Epidemiology and genetics of frontotemporal dementia: a door-to-door survey in southern Italy. Neurobiol Aging. 2012; **33**(12): 2948 e1- e10.
69. Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. Neurology. 2002; **58**(11): 1615-21.
70. Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. Journal of Neurology Neurosurgery and Psychiatry. 2003; **74**(9): 1206-9.
71. Rosso SM, Donker Kaat L, Baks T, Joosse M, de Koning I, Pijnenburg Y, et al. Frontotemporal dementia in The Netherlands: patient characteristics and prevalence estimates from a population-based study. Brain. 2003; **126**(Pt 9): 2016-22.
72. Ikejima C, Yasuno F, Mizukami K, Sasaki M, Tanimukai S, Asada T. Prevalence and causes of early-onset dementia in Japan: a population-based study. Stroke. 2009; **40**(8): 2709-14.
73. Gilberti N, Turla M, Alberici A, Bertasi V, Civelli P, Archetti S, et al. Prevalence of frontotemporal lobar degeneration in an isolated population: the Vallecamonica study. Neurol Sci. 2012; **33**(4): 899-904.
74. Yamada T, Hattori H, Miura A, Tanabe M, Yamori Y. Prevalence of Alzheimer's disease, vascular dementia and

dementia with Lewy bodies in a Japanese population. Psychiatry Clin Neurosci. 2001; **55**(1): 21-5.
75. Stevens T, Livingston G, Kitchen G, Manela M, Walker Z, Katona C. Islington study of dementia subtypes in the community. British Journal of Psychiatry. 2002; **180**: 270-6.
76. Gascon-Bayarri J, Rene R, Del Barrio JL, De Pedro-Cuesta J, Ramon JM, Manubens JM, et al. Prevalence of dementia subtypes in El Prat de Llobregat, Catalonia, Spain: the PRATICON study. Neuroepidemiology. 2007; **28**(4): 224-34.
77. Wada-Isoe K, Uemura Y, Suto Y, Doi K, Imamura K, Hayashi A, et al. Prevalence of dementia in the rural island town of Ama-cho, Japan. Neuroepidemiology. 2009; **32**(2): 101-6.
78. Varma AR, Snowden JS, Lloyd JJ, Talbot PR, Mann DM, Neary D. Evaluation of the NINCDS-ADRDA criteria in the differentiation of Alzheimer's disease and frontotemporal dementia. J Neurol Neurosurg Psychiatry. 1999; **66**(2): 184-8.
79. Rabinovici GD, Miller BL. Frontotemporal lobar degeneration: epidemiology, pathophysiology, diagnosis and management. CNS Drugs. 2010; **24**(5): 375-98.
80. Baborie A, Griffiths TD, Jaros E, Momeni P, McKeith IG, Burn DJ, et al. Frontotemporal dementia in elderly individuals. Arch Neurol. 2012; **69**(8): 1052-60.
81. Rosen HJ, Gorno-Tempini ML, Goldman WP, Perry RJ, Schuff N, Weiner M, et al. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. Neurology. 2002; **58**(2): 198-208.
82. Whitwell JL, Josephs KA. Recent advances in the imaging of frontotemporal dementia. Curr Neurol Neurosci Rep. 2012; **12**(6): 715-23.
83. Frings L, Mader I, Landwehrmeyer BG, Weiller C, Hull M, Huppertz HJ. Quantifying change in individual subjects affected by frontotemporal lobar degeneration using automated longitudinal MRI volumetry. Hum Brain Mapp. 2012; **33**(7): 1526-35.
84. Krueger CE, Dean DL, Rosen HJ, Halabi C, Weiner M, Miller BL, et al. Longitudinal rates of lobar atrophy in frontotemporal dementia, semantic dementia, and Alzheimer's disease. Alzheimer Dis Assoc Disord. 2010; **24**(1): 43-8.
85. Brambati SM, Renda NC, Rankin KP, Rosen HJ, Seeley WW, Ashburner J, et al. A tensor based

morphometry study of longitudinal gray matter contraction in FTD. Neuroimage. 2007; **35**(3): 998-1003.
86. Moller C, Dieleman N, van der Flier WM, Versteeg A, Pijnenburg Y, Scheltens P, et al. More atrophy of deep gray matter structures in frontotemporal dementia compared to Alzheimer's disease. J Alzheimers Dis. 2015; **44**(2): 635-47.
87. Riedl L, Mackenzie IR, Forstl H, Kurz A, Diehl-Schmid J. Frontotemporal lobar degeneration: current perspectives. Neuropsychiatr Dis Treat. 2014; **10**: 297-310.
88. Rosso SM, Landweer EJ, Houterman M, Donker Kaat L, van Duijn CM, van Swieten JC. Medical and environmental risk factors for sporadic frontotemporal dementia: a retrospective case-control study. J Neurol Neurosurg Psychiatry. 2003; **74**(11): 1574-6.
89. Kalkonde YV, Jawaid A, Qureshi SU, Shirani P, Wheaton M, Pinto-Patarroyo GP, et al. Medical and environmental risk factors associated with frontotemporal dementia: a case-control study in a veteran population. Alzheimers Dement. 2012; **8**(3): 204-10.
90. Golimstok A, Campora N, Rojas JI, Fernandez MC, Elizondo C, Soriano E, et al. Cardiovascular risk factors and frontotemporal dementia: a case-control study. Transl Neurodegener. 2014; **3**: 13.
91. Deutsch MB, Mendez MF, Teng E. Interactions between traumatic brain injury and frontotemporal degeneration. Dement Geriatr Cogn Disord. 2015; **39**(3-4): 143-53.
92. UN: World population prospects. 2014 [cited 2014 23 October 2014]; Available from: http://esa.un.org/wpp/
93. Roberson ED, Hesse JH, Rose KD, Slama H, Johnson JK, Yaffe K, et al. Frontotemporal dementia progresses to death faster than Alzheimer disease. Neurology. 2005; **65**(5): 719-25.
94. Steenland K, MacNeil J, Seals R, Levey A. Factors Affecting Survival of Patients with Neurodegenerative Disease. Neuroepidemiology. 2010; **35**(1): 28-35.
95. Lillo P, Garcin B, Hornberger M, Bak TH, Hodges JR. Neurobehavioral features in frontotemporal dementia with amyotrophic lateral sclerosis. Arch Neurol. 2010; **67**(7): 826-30.
96. Garcin B, Lillo P, Hornberger M, Piguet O, Dawson K, Nestor PJ, et al. Determinants of survival in behavioral variant frontotemporal dementia. Neurology. 2009; **73**(20): 1656-61.

97. Hodges JR, Davies R, Xuereb J, Kril J, Halliday G. Survival in frontotemporal dementia. Neurology. 2003; **61**(3): 349-54.
98. Rascovsky K, Salmon DP, Lipton AM, Leverenz JB, DeCarli C, Jagust WJ, et al. Rate of progression differs in frontotemporal dementia and Alzheimer disease. Neurology. 2005; **65**(3): 397-403.
99. Chiu WZ, Kaat LD, Seelaar H, Rosso SM, Boon AJ, Kamphorst W, et al. Survival in progressive supranuclear palsy and frontotemporal dementia. J Neurol Neurosurg Psychiatry. 2010; **81**(4): 441-5.
100. Pasquier F, Richard F, Lebert F. Natural history of frontotemporal dementia: comparison with Alzheimer's disease. Dement Geriatr Cogn Disord. 2004; **17**(4): 253-7.
101. Le Rhun E, Richard F, Pasquier F. Natural history of primary progressive aphasia. Neurology. 2005; **65**(6): 887-91.
102. Borroni B, Grassi M, Agosti C, Premi E, Alberici A, Paghera B, et al. Survival in frontotemporal lobar degeneration and related disorders: latent class predictors and brain functional correlates. Rejuvenation Res. 2009; **12**(1): 33-44.
103. Kang SJ, Cha KR, Seo SW, Kim EA, Cheong HK, Kim EJ, et al. Survival in Frontotemporal Lobar Degeneration in a Korean Population. Alzheimer Dis Assoc Disord. 2010.
104. Xie SX, Forman MS, Farmer J, Moore P, Wang Y, Wang X, et al. Factors associated with survival probability in autopsy-proven frontotemporal lobar degeneration. J Neurol Neurosurg Psychiatry. 2008; **79**(2): 126-9.
105. Josephs KA, Knopman DS, Whitwell JL, Boeve BF, Parisi JE, Petersen RC, et al. Survival in two variants of tau-negative frontotemporal lobar degeneration: FTLD-U vs FTLD-MND. Neurology. 2005; **65**(4): 645-7.
106. Onyike CU. What is the life expectancy in frontotemporal lobar degeneration? Neuroepidemiology. 2011; **37**(3-4): 166-7.
107. Borroni B, Alberici A, Grassi M, Turla M, Zanetti O, Bianchetti A, et al. Is frontotemporal lobar degeneration a rare disorder? Evidence from a preliminary study in Brescia county, Italy. J Alzheimers Dis. 2010; **19**(1): 111-6.
108. Skoog I. Psychiatric epidemiology of old age: the H70 study--the NAPE lecture 2003. Acta Psychiatr Scand. 2004; **109**(1): 4-18.

109. Skoog I, Nilsson L, Palmertz B, Andreasson LA, Svanborg A. A population-based study of dementia in 85-year-olds. The New England journal of medicine. 1993; **328**(3): 153-8.
110. Borjesson-Hanson A, Edin E, Gislason T, Skoog I. The prevalence of dementia in 95 year olds. Neurology. 2004; **63**(12): 2436-8.
111. Bengtsson C, Blohme G, Hallberg L, Hallstrom T, Isaksson B, Korsan-Bengtsen K, et al. The study of women in Gothenburg 1968-1969--a population study. General design, purpose and sampling results. Acta medica Scandinavica. 1973; **193**(4): 311-8.
112. Sacuiu S, Sjogren M, Johansson B, Gustafson D, Skoog I. Prodromal cognitive signs of dementia in 85-year-olds using four sources of information. Neurology. 2005; **65**(12): 1894-900.
113. Aevarsson O, Skoog I. A population-based study on the incidence of dementia disorders between 85 and 88 years of age. Journal of the American Geriatrics Society. 1996; **44**(12): 1455-60.
114. Bengtsson C, Gredmark T, Hallberg L, Hallstrom T, Isaksson B, Lapidus L, et al. The population study of women in Gothenburg 1980-81--the third phase of a longitudinal study. Comparison between participants and non-participants. Scandinavian journal of social medicine. 1989; **17**(2): 141-5.
115. Bengtsson C, Ahlqwist M, Andersson K, Bjorkelund C, Lissner L, Soderstrom M. The Prospective Population Study of Women in Gothenburg, Sweden, 1968-69 to 1992-93. A 24-year follow-up study with special reference to participation, representativeness, and mortality. Scandinavian journal of primary health care. 1997; **15**(4): 214-9.
116. Palsson S, Larsson L, Tengelin E, Waern M, Samuelsson S, Hallstro T, et al. The prevalence of depression in relation to cerebral atrophy and cognitive performance in 70- and 74-year-old women in Gothenburg. The Women's Health Study. Psychological medicine. 2001; **31**(1): 39-49.
117. Sacuiu S, Gustafson D, Sjogren M, Guo X, Ostling S, Johansson B, et al. Secular changes in cognitive predictors of dementia and mortality in 70-year-olds. Neurology. 2010; **75**(9): 779-85.
118. Gislason TB, Ostling S, Borjesson-Hanson A, Sjogren M, Simoni M, Pantoni L, et al. Effect of diagnostic criteria

on prevalence of frontotemporal dementia in the elderly. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2014.
119. Asberg M, Schalling D. Construction of a new psychiatric rating instrument, the Comprehensive Psychopathological Rating Scale (CPRS). Progress in neuro-psychopharmacology. 1979; **3**(4): 405-12.
120. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research. 1975; **12**(3): 189-98.
121. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry. 1984; **141**(11): 1356-64.
122. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979; **134**: 382-9.
123. Manual of the international statistical classification of diseases, injuries and causes of death, 8th edn. . Geneva: World Health Organization; 1967.
124. World Health Organization. International Classification of Diseases. Manual of the international statistical classification of diseases, injuries and causes of death, Ninth Revision. . Geneva: World Health Organization; 1977.
125. World Health Organization. The ICD-10 Classification of mental and behavioral disorders– clinical descriptions and diagnostic guidelines. . Geneva: World Health Organization; 1992.
126. Socialstyrelsen. The Swedish Health and Welfare Statistical Database for Cause of Death. 2015 [cited; Available from: http://www.socialstyrelsen.se/statistics/statisticaldatabase/help/causeofdeath.
127. Rosen HJ, Hartikainen KM, Jagust W, Kramer JH, Reed BR, Cummings JL, et al. Utility of clinical criteria in differentiating frontotemporal lobar degeneration (FTLD) from AD. Neurology. 2002; **58**(11): 1608-15.
128. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984; **34**(7): 939-44.

129. Erkinjuntti T, Haltia M, Palo J, Sulkava R, Paetau A. Accuracy of the clinical diagnosis of vascular dementia: a prospective clinical and post-mortem neuropathological study. Journal of neurology, neurosurgery, and psychiatry. 1988; **51**(8): 1037-44.
130. Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993; **43**(2): 250-60.
131. Skoog I, Wallin A, Fredman P, Hesse C, AevarssonO, Karlsson I, et al. A population study on blood-brain barrier function in 85-year-olds: relation to Alzheimer's disease and vascular dementia. Neurology. 1998; **50**(4): 966-71.
132. Liebetrau M, Steen B, Skoog I. Stroke in 85-year-olds: prevalence, incidence, risk factors, and relation to mortality and dementia. Stroke; a journal of cerebral circulation. 2003; **34**(11): 2617-22.
133. Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. Bulletin of the World Health Organization. 1962; **27**: 645-58.
134. Lernfelt B, Landahl S, Svanborg A. Coronary heart disease at 70, 75 and 79 years of age: a longitudinal study with special reference to sex differences and mortality. Age and ageing. 1990; **19**(5): 297-303.
135. American Psychiatric Association. Diagnostic and statistical manual of mental disorders-revised (DSM-III-R), 3rd edn. . Washington, DC: APA; 1987.
136. De Leon MJ, Ferris SH, George AE, Reisberg B, Kricheff, II, Gershon S. Computed tomography evaluations of brain-behavior relationships in senile dementia of the Alzheimer's type. Neurobiology of aging. 1980; **1**(1): 69-79.
137. Gustafson D, Lissner L, Bengtsson C, Bjorkelund C, Skoog I. A 24-year follow-up of body mass index and cerebral atrophy. Neurology. 2004; **63**(10): 1876-81.
138. Simoni M, Pantoni L, Pracucci G, Palmertz B, Guo X, Gustafson D, et al. Prevalence of CT-detected cerebral abnormalities in an elderly Swedish population sample. Acta neurologica Scandinavica. 2008; **118**(4): 260-7.
139. Guo X, Pantoni L, Simoni M, Bengtsson C, Bjorkelund C, Lissner L, et al. Blood pressure components and changes in relation to white matter lesions: a 32-year prospective population study. Hypertension. 2009; **54**(1): 57-62.

140. Skoog I, Palmertz B, Andreasson LA. The prevalence of white-matter lesions on computed tomography of the brain in demented and nondemented 85-year-olds. Journal of geriatric psychiatry and neurology. 1994; **7**(3): 169-75.
141. Erkinjuntti T, Ostbye T, Steenhuis R, Hachinski V. The effect of different diagnostic criteria on the prevalence of dementia. N Engl J Med. 1997; **337**(23): 1667-74.
142. Kipps CM, Davies RR, Mitchell J, Kril JJ, Halliday GM, Hodges JR. Clinical significance of lobar atrophy in frontotemporal dementia: application of an MRI visual rating scale. Dement Geriatr Cogn Disord. 2007; **23**(5): 334-42.
143. Miller BL, Gearhart R. Neuroimaging in the diagnosis of frontotemporal dementia. Dement Geriatr Cogn Disord. 1999; **10 Suppl 1**: 71-4.
144. Sjogren M, Wallin A, Edman A. Symptomatological characteristics distinguish between frontotemporal dementia and vascular dementia with a dominant frontal lobe syndrome. Int J Geriatr Psychiatry. 1997; **12**(6): 656-61.
145. Knopman DS, Boeve BF, Parisi JE, Dickson DW, Smith GE, Ivnik RJ, et al. Antemortem diagnosis of frontotemporal lobar degeneration. Ann Neurol. 2005; **57**(4): 480-8.
146. McGinnis SM, Brickhouse M, Pascual B, Dickerson BC. Age-related changes in the thickness of cortical zones in humans. Brain Topogr. 2011; **24**(3-4): 279-91.
147. Bigler ED, Maxwell WL. Neuroimaging and neuropathology of TBI. NeuroRehabilitation. 2011; **28**(2): 63-74.
148. Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A. Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. J Neurol Neurosurg Psychiatry. 2003; **74**(7): 857-62.
149. Stuss DT. Traumatic brain injury: relation to executive dysfunction and the frontal lobes. Curr Opin Neurol. 2011; **24**(6): 584-9.
150. Hoffmann M. The human frontal lobes and frontal network systems: an evolutionary, clinical, and treatment perspective. ISRN Neurol. 2013; **2013**: 892459.
151. Petkau TL, Leavitt BR. Progranulin in neurodegenerative disease. Trends Neurosci. 2014; **37**(7): 388-98.
152. Jawaid A, Rademakers R, Kass JS, Kalkonde Y, Schulz PE. Traumatic brain injury may increase the risk for

frontotemporal dementia through reduced progranulin. Neurodegener Dis. 2009; **6**(5-6): 219-20.
153. Kao AW, Eisenhut RJ, Martens LH, Nakamura A, Huang A, Bagley JA, et al. A neurodegenerative disease mutation that accelerates the clearance of apoptotic cells. Proc Natl Acad Sci U S A. 2011; **108**(11): 4441-6.
154. Yin FF, Banerjee R, Thomas B, Zhou P, Qian LP, Jia T, et al. Exaggerated inflammation, impaired host defense, and neuropathology in progranulin-deficient mice. Journal of Experimental Medicine. 2010; **207**(1): 117-28.
155. Blennow K, Hardy J, Zetterberg H. The neuropathology and neurobiology of traumatic brain injury. Neuron. 2012; **76**(5): 886-99.
156. Smith DH, Johnson VE, Stewart W. Chronic neuropathologies of single and repetitive TBI: substrates of dementia? Nat Rev Neurol. 2013; **9**(4): 211-21.
157. Mehlig K, Skoog I, Guo X, Schutze M, Gustafson D, Waern M, et al. Alcoholic beverages and incidence of dementia: 34-year follow-up of the prospective population study of women in Goteborg. Am J Epidemiol. 2008; **167**(6): 684-91.
158. Anttila T, Helkala EL, Viitanen M, Kareholt I, Fratiglioni L, Winblad B, et al. Alcohol drinking in middle age and subsequent risk of mild cognitive impairment and dementia in old age: a prospective population based study. Bmj. 2004; **329**(7465): 539.
159. de la Monte SM, Kril JJ. Human alcohol-related neuropathology. Acta Neuropathol. 2014; **127**(1): 71-90.
160. Peters R, Peters J, Warner J, Beckett N, Bulpitt C. Alcohol, dementia and cognitive decline in the elderly: a systematic review. Age Ageing. 2008; **37**(5): 505-12.
161. Sinforiani E, Zucchella C, Pasotti C, Casoni F, Bini P, Costa A. The effects of alcohol on cognition in the elderly: from protection to neurodegeneration. Funct Neurol. 2011; **26**(2): 103-6.
162. Moselhy HF, Georgiou G, Kahn A. Frontal lobe changes in alcoholism: a review of the literature. Alcohol Alcohol. 2001; **36**(5): 357-68.
163. Brun A, Andersson J. Frontal dysfunction and frontal cortical synapse loss in alcoholism - The main cause of alcohol dementia? Dement Geriatr Cogn Disord. 2001; **12**(4): 289-94.
164. Pfefferbaum A, Sullivan EV, Mathalon DH, Lim KO. Frontal lobe volume loss observed with magnetic resonance

imaging in older chronic alcoholics. Alcohol Clin Exp Res. 1997; **21**(3): 521-9.
165. Buhler M, Mann K. Alcohol and the human brain: a systematic review of different neuroimaging methods. Alcohol Clin Exp Res. 2011; **35**(10): 1771-93.
166. Tan ZS, Beiser A, Vasan RS, Au R, Auerbach S, Kiel DP, et al. Thyroid function and the risk of Alzheimer disease: the Framingham Study. Arch Intern Med. 2008; **168**(14): 1514-20.
167. Parsaik AK, Singh B, Roberts RO, Pankratz S, Edwards KK, Geda YE, et al. Hypothyroidism and risk of mild cognitive impairment in elderly persons: a population-based study. JAMA Neurol. 2014; **71**(2): 201-7.
168. Faldt R, Passant U, Nilsson K, Wattmo C, Gustafson L. Prevalence of thyroid hormone abnormalities in elderly patients with symptoms of organic brain disease. Aging (Milano). 1996; **8**(5): 347-53.
169. Aniello F, Couchie D, Bridoux AM, Gripois D, Nunez J. Splicing of juvenile and adult tau mRNA variants is regulated by thyroid hormone. Proc Natl Acad Sci U S A. 1991; **88**(9): 4035-9.
170. Duntas LH. Thyroid disease and lipids. Thyroid. 2002; **12**(4): 287-93.
171. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev. 2008; **29**(1): 76-131.
172. Jabbar A, Razvi S. Thyroid disease and vascular risk. Clin Med. 2014; **14 Suppl 6**: s29-32.
173. Grahn A, Nilsson S, Nordlund A, Linden T, Studahl M. Cognitive impairment 3 years after neurological Varicella-zoster virus infection: a long-term case control study. J Neurol. 2013; **260**(11): 2761-9.
174. Bangen KJ, Delano-Wood L, Wierenga CE, Stricker NH, Hesselink JR, Bondi MW. Dementia following herpes zoster encephalitis. Clin Neuropsychol. 2010; **24**(7): 1193-203.
175. De Reuck JL, Deramecourt V, Cordonnier C, Leys D, Pasquier F, Maurage CA. Cerebrovascular lesions in patients with frontotemporal lobar degeneration: a neuropathological study. Neurodegener Dis. 2012; **9**(4): 170-5.
176. De Reuck J, Deramecourt V, Cordonnier C, Auger F, Durieux N, Bordet R, et al. Detection of microbleeds in post-mortem brains of patients with frontotemporal lobar degeneration: a 7.0-Tesla magnetic resonance imaging study

with neuropathological correlates. Eur J Neurol. 2012; **19**(10): 1355-60.
177. Baborie A, Griffiths TD, Jaros E, McKeith IG, Burn DJ, Richardson A, et al. Pathological correlates of frontotemporal lobar degeneration in the elderly. Acta Neuropathol. 2011; **121**(3): 365-71.
178. Jellinger KA, Attems J. Prevalence of dementia disorders in the oldest-old: an autopsy study. Acta Neuropathol. 2010; **119**(4): 421-33.
179. Jellinger KA, Attems J. Challenges of multimorbidity of the aging brain: a critical update. J Neural Transm. 2015; **122**(4): 505-21.
180. Warren JD, Rohrer JD, Rossor MN. Clinical review. Frontotemporal dementia. Bmj. 2013; **347**: f4827.
181. Kirshner HS. Frontotemporal dementia and primary progressive aphasia: an update. Curr Neurol Neurosci Rep. 2010; **10**(6): 504-11.
182. Mendez MF, Shapira JS, Woods RJ, Licht EA, Saul RE. Psychotic symptoms in frontotemporal dementia: prevalence and review. Dement Geriatr Cogn Disord. 2008; **25**(3): 206-11.
183. Diehl-Schmid J, Schmidt EM, Nunnemann S, Riedl L, Kurz A, Forstl H, et al. Caregiver burden and needs in frontotemporal dementia. J Geriatr Psychiatry Neurol. 2013; **26**(4): 221-9.
184. Oyebode JR, Bradley P, Allen JL. Relatives' experiences of frontal-variant frontotemporal dementia. Qual Health Res. 2013; **23**(2): 156-66.
185. Vemuri P, Lesnick TG, Przybelski SA, Machulda M, Knopman DS, Mielke MM, et al. Association of lifetime intellectual enrichment with cognitive decline in the older population. JAMA Neurol. 2014; **71**(8): 1017-24.
186. Borroni B, Alberici A, Agosti C, Premi E, Padovani A. Education plays a different role in Frontotemporal Dementia and Alzheimer's disease. Int J Geriatr Psychiatry. 2008; **23**(8): 796-800.
187. Katzman R. Editorial: The prevalence and malignancy of Alzheimer disease. A major killer. Arch Neurol. 1976; **33**(4): 217-8.
188. Garcia-Ptacek S, Farahmand B, Kareholt I, Religa D, Cuadrado ML, Eriksdotter M. Mortality risk after dementia diagnosis by dementia type and underlying factors: a cohort of 15,209 patients based on the Swedish Dementia Registry. J Alzheimers Dis. 2014; **41**(2): 467-77.

189. Skillback T, Farahmand B, Bartlett JW, Rosen C, Mattsson N, Nagga K, et al. CSF neurofilament light differs in neurodegenerative diseases and predicts severity and survival. Neurology. 2014; **83**(21): 1945-53.
190. Sjogren M, Blomberg M, Jonsson M, Wahlund LO, Edman A, Lind K, et al. Neurofilament protein in cerebrospinal fluid: A marker of white matter changes. J Neurosci Res. 2001; **66**(3): 510-6.
191. van der Linde RM, Dening T, Matthews FE, Brayne C. Grouping of behavioural and psychological symptoms of dementia. Int J Geriatr Psychiatry. 2014; **29**(6): 562-8.
192. Tun SM, Murman DL, Long HL, Colenda CC, von Eye A. Predictive validity of neuropsychiatric subgroups on nursing home placement and survival in patients with Alzheimer disease. Am J Geriatr Psychiatry. 2007; **15**(4): 314-27.
193. Warren JD, Fletcher PD, Golden HL. The paradox of syndromic diversity in Alzheimer disease. Nat Rev Neurol. 2012; **8**(8): 451-64.
194. Alladi S, Xuereb J, Bak T, Nestor P, Knibb J, Patterson K, et al. Focal cortical presentations of Alzheimer's disease. Brain. 2007; **130**(Pt 10): 2636-45.
195. Snowden JS, Thompson JC, Stopford CL, Richardson AM, Gerhard A, Neary D, et al. The clinical diagnosis of early-onset dementias: diagnostic accuracy and clinicopathological relationships. Brain. 2011; **134**(Pt 9): 2478-92.
196. Statistics Sweden. 2015 [cited; Available from: http://www.scb.se/en_/.
197. Rothman K. Modern epidemiology. Boston: Little, Brown; 1986.
198. Roulson J, Benbow EW, Hasleton PS. Discrepancies between clinical and autopsy diagnosis and the value of post mortem histology; a meta-analysis and review. Histopathology. 2005; **47**(6): 551-9.
199. Alquezar C, Esteras N, Encarnacion Ade L, Moreno F, de Munain AL, Martin-Requero A. Increasing progranulin levels and blockade of the ERK1/2 pathway: Upstream and downstream strategies for the treatment of progranulin deficient frontotemporal dementia. Eur Neuropsychopharmacol. 2015; **25**(3): 386-403.