ORIGINAL ARTICLE

The Prevalence and Incidence of Frontotemporal Dementia: a Systematic Review

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ABSTRACT: ***Background:*** Population-based prevalence and incidence studies are essential for understanding the burden of frontotemporal dementia (FTD). ***Methods:*** The MEDLINE and EMBASE databases were searched to identify population-based publications from 1985 to 2012, addressing the incidence and/or prevalence of FTD. References of included articles and prior systematic reviews were searched for additional studies. Two reviewers screened all abstracts and full-text reviews, abstracted data and performed quality assessments. ***Results:*** Twenty-six studies were included. Methodological limitations led to wide ranges in the estimates for prevalence (point prevalence 0.01-4.6 per 1000 persons; period prevalence 0.16-31.04 per 1000 persons) and incidence (0.0-0.3 per 1000 person-years). FTD accounted for an average of 2.7% (range 0-9.1%) of all dementia cases among prevalence studies that included subjects 65 and older compared to 10.2% (range 2.8-15.7%) in studies restricted to those aged less than 65. The cumulative numbers of male (373 [52.5%]) and female (338 [47.5%]) cases from studies reporting this information were nearly equal ($p = 0.18$). The behavioural variant FTD (bvFTD) was almost four times as common as the primary progressive aphasias. ***Conclusions:*** Population-based estimates for the epidemiology of FTD varied widely in the included studies. Refinements in the diagnostic process, possibly by the use of validated biomarkers or limiting case ascertainment to specialty services, are needed to obtain more precise estimates of the prevalence and incidence of FTD.

RÉSUMÉ: Prévalence et incidence de la démence fronto-temporale : une revue systématique du sujet. ***Contexte :*** Les études de population sur la prévalence et l'incidence sont essentielles à la compréhension du fardeau associé à la démence fronto-temporale (DFT). ***Méthodologie :*** Nous avons cherché dans les bases de données MEDLINE et EMBASE les articles publiés entre 2000 et 2012 portant sur l'incidence et/ou la prévalence de la DFT dans la population. Nous avons également examiné les références des articles inclus dans notre étude ainsi que celles des revues systématiques antérieures. Deux évaluateurs ont examiné tous les résumés et le texte intégral des publications et l'extraction des données, et ils en ont évalué la qualité. ***Résultats :*** Vingt-six études ont été retenues. Des limites méthodologiques expliquent les écarts dans les estimations de prévalence (prévalence ponctuelle de 0,01 à 4,6 par 1 000 ; prévalence d'une période donnée de 0,16 à 31,04 par 1 000) et incidence (0,0 à 0,3 par 1 000 personnes-années). La DFT constituait en moyenne 2,7% (écart de 0 à 9,1%) de tous les cas de démence dans les études de prévalence qui incluaient des sujets de 65 ans et plus par rapport à 10,2% (2,8 à 15,7%) dans les études portant sur des sujets âgés de moins de 65 ans. Les nombres cumulatifs d'hommes (373 [52,5%]) et de femmes (338 [47,5%]) tirés des études dans lesquelles cette information était mentionnée étaient pratiquement égaux ($p = 0,18$). La variante comportementale DFT était presque quatre fois plus fréquente que les aphasies progressives primaires. ***Conclusions*** : Les estimations basées sur la population en ce qui concerne l'épidémiologie de la DFT étaient très variables dans les études que nous avons retenues. Il faudra raffiner le processus diagnostique, possiblement par l'utilisation de biomarqueurs validés ou limitant la constatation des cas à ceux confirmés par des services spécialisés, pour obtenir des estimations plus précises de la prévalence et de l'incidence de la DFT.

Keyword: Dementia, Alzheimer's Disease, Lewy Body Dementia, Frontotemporal Dementia, systematic review, meta-analysis

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Introduction

Frontotemporal dementia (FTD) is a clinically and pathologically heterogeneous group of non-Alzheimer neurodegenerative dementias characterized by progressive decline in behaviour (behavioural variant FTD [bvFTD]) and/or language (primary progressive aphasias, such as semantic dementia and progressive non-fluent aphasia [PNFA]) associated with degeneration of the frontal and anterior temporal lobes.[1,2] These presentations can overlap with atypical parkinsonian disorders (i.e., corticobasal syndrome [CBS], progressive supranuclear palsy [PSP]) and amyotrophic lateral sclerosis [ALS]). Though a variety of terms have been employed to describe these conditions (e.g., frontotemporal degeneration, frontotemporal lobar degeneration [which some restrict to pathologically confirmed cases], dementia of the frontal type, Pick complex disorder), in this paper we will use FTD. First described in the late 19th century,[2] FTD is generally held to be a relatively common cause of early-onset (<65 years) dementia.[3] Dementia clinic-based studies suggest that FTD may account for approximately 5% of all dementia cases,[4] but this may represent an inaccurate estimate of the proportion of dementia cases arising from this condition because of selection or referral bias.[5]

In the absence of autopsy confirmation, the diagnosis of FTD is dependent on searching for clinical diagnostic features. In research and practice, the most commonly used criteria for detection of FTD over the last 20 years were those developed by the Lund and Manchester Groups,[6] Gregory and Hodges,[7] Neary et al.[8] and the Work Group of Frontotemporal Dementia and Pick's Disease (also referred to as the McKhann criteria).[9] Revised diagnostic criteria have been recently developed.[10,11]

Population-based prevalence and incidence studies are essential for understanding the societal burden of FTD and planning for the range of healthcare services needed for those with this condition. In this paper, we report on a systematic review of population-based prevalence and incidence studies of FTD.

Methods

This is one in a series of systematic reviews on the prevalence and incidence of priority neurological conditions identified by the Public Health Agency of Canada and the Neurological Health Charities Canada as part of the National Population Health Study of Neurological Conditions.[12]

Search Strategy

The systematic review was conducted according to a predetermined protocol based on the PRISMA Statement for systematic reviews and meta-analyses.[13] The search strategy (see Appendix A) was developed by the study authors, who possess extensive expertise in dementia and/or epidemiology, in consultation with a research librarian experienced in the performance of systematic reviews. The initial MEDLINE and EMBASE search was conducted in February of 2011 and then updated in May of 2012. The review was restricted to studies written in English or French and published from the year 2000 or later for international studies and 1985 or later for Canadian studies. References were exported and managed using EndNote X5.

Study Selection

Two reviewers independently screened all abstracts in order to identify original research that appeared to be reporting on the prevalence or incidence of dementia. These papers were selected for full-text review. Studies were excluded at this stage if the abstract clearly indicated that the study was not population-based.

Two reviewers independently performed the full-text reviews. Articles were included in this systematic review if they met the following criteria: (1) represented original research; (2) were population-based (i.e., involved a defined "general population" as opposed to a specific hospital- or clinic-based population); and (3) reported an incidence and/or prevalence estimate of FTD. English and French articles were screened and reviewed in a similar fashion by reviewers fluent in English and French, respectively. The references of included articles were hand searched for additional articles. All additional articles were evaluated in a manner identical to what has been previously outlined. The references of systematic reviews and literature reviews on the epidemiology of dementia were also hand searched. Disagreements were resolved by consensus, with involvement of a third party if necessary (this step was never required).

Data Extraction and Study Quality

Two reviewers extracted data from included articles using a standard data collection form. Agreement was reached on all items. If multiple articles reported data on the same study population, the most comprehensive data were utilized. In cases where the studies reported on different time frames or subgroups (e.g., by sex and/or age), all data were included. Demographic data retrieved included age, sex and study location. Source/type of clinical data and the definition/diagnostic criteria used for the diagnosis of FTD were noted. Incidence and prevalence estimates of dementia from each study were recorded, along with any stratification by age, sex or year of data collection. The quality of the included studies was evaluated using an assessment instrument[14,15] (see Appendix B). This instrument included an evaluation of sample representativeness, condition assessment and statistical methods. Each study was given a quality score that ranged from 0 to 8 (higher being better).

Data Analysis

Pooled meta-analyses were not done due to significant between-study heterogeneity and small sample size. Forest plots presenting the distribution of study estimates were produced. As it is held that FTD disproportionately affects middle-aged individuals,[2] we compared studies that included older participants (65 +) with those that restricted themselves to younger (<65) individuals. All statistical analyses were carried out in *R* version 2.14. The *meta* package was employed to produce the forest plots. Depending on the methodology of the study, incidence proportion, incidence rate, period prevalence and point prevalence are provided.

Results

Identification and Description of Studies

The search strategy yielded 16,066 citations (8743 from MEDLINE, 7323 from EMBASE, with 7923 remaining after the removal of duplicates) (Figure 1). A total of 707 articles were selected for full-text review. Of the 176 studies (total of the original and updated searches plus the hand search of included articles) that presented data on the prevalence and/or incidence of dementia and its subtypes, 26 reported on FTD and were included in our systematic review.

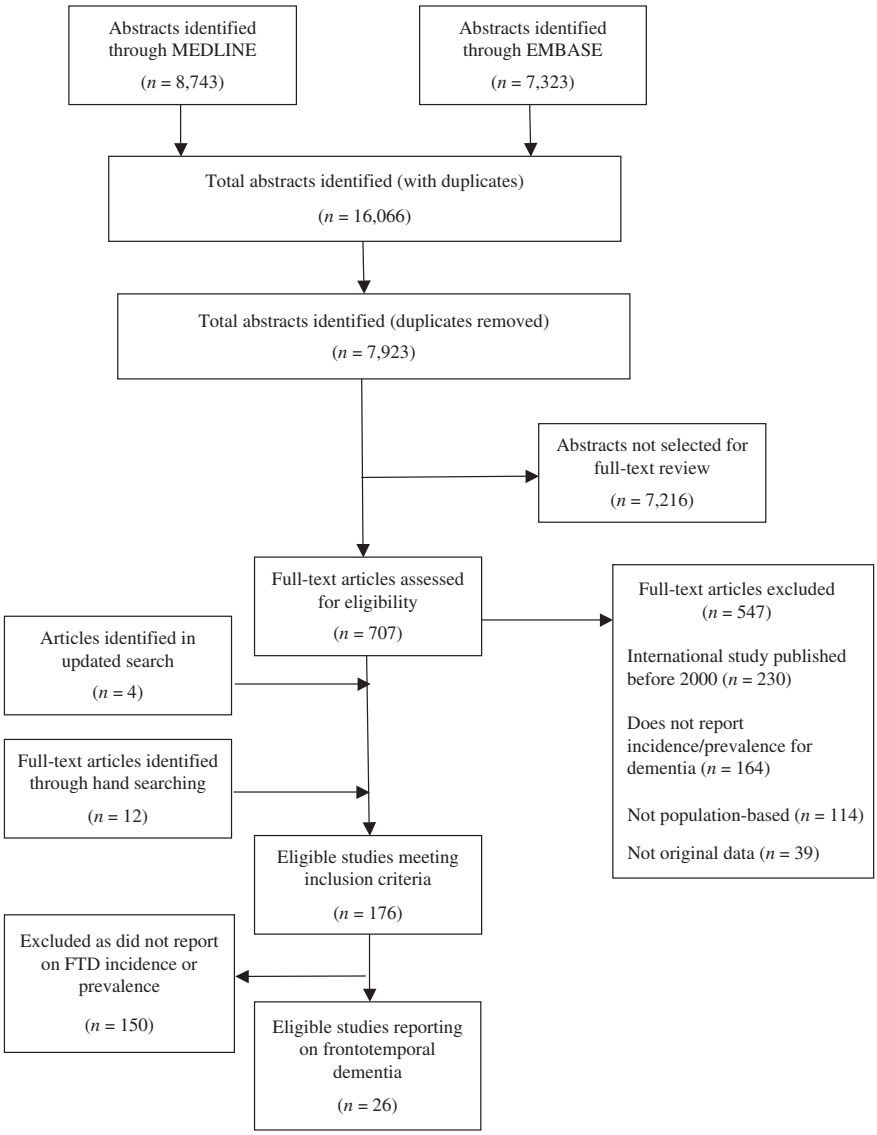

Figure 1: *Study flow diagram.*

The characteristics of the 26 included studies are summarized in Tables 1-3. Nineteen[16-34] reported on prevalence, six[35-40] on incidence and one study provided data on both the incidence and prevalence of FTD.[41] Sixteen studies presented data from Europe, seven from Asia, two from South America, and one from North America. While a variety of approaches was employed, most studies were either surveys of residents of a specific location ($n = 12$) or based on cases identified by specialty services serving a defined catchment area ($n = 8$). The Neary[8] ($n = 16$) and/or Lund and Manchester[6] ($n = 9$) criteria were the diagnostic criteria most commonly used, with diagnosis typically based on an assessment by a healthcare professional ($n = 22$), often coupled with imaging studies ($n = 18$) and/or laboratory investigations ($n = 15$), and/or health record review ($n = 10$).

Prevalence of Frontotemporal Dementia

Fourteen articles reported on point prevalence[17,18,20,22-24,26-28,30-34] (Figure 2). Estimates ranged widely from 0.01 to 4.61 per 1000. Among studies restricted to individuals less than 65 years of age,[17,23,27,30] point prevalence was in a narrower range (0.07-0.30 per 1000). Studies that surveyed a defined population[22,24,26,32-34] generally reported higher estimates than those based on enumerating cases identified by specialty services[17,18,20,30] (range of estimates in surveys 0.13-4.61 per 1000 compared to 0.15-0.40 per 1000 for specialty services), but the latter were in a narrower range.

Six studies[16,19,21,25,29,41] reported on period prevalence (Figure 3). Period prevalence estimates ranged from 0.16 to 31.04 per 1000. The Gislason study[21] reported a strikingly high prevalence. A number of features of this study are unique: a single-phase survey approach was used; only a relatively small number of participants were examined ($n = 494$); the age range studied (85-86) was both narrow and quite advanced; and the focus of the study was detecting what was termed a frontal lobe syndrome, with these individuals diagnosed as having bvFTD if they did not meet exclusionary criteria, irrespective of whether they met DSM–III–R criteria for a dementia (9/14 cases did not). Estimates derived from surveys[16,19,21,29] tended to be higher

Table 1: Studies Reporting on the Prevalence of Frontotemporal Dementia

Author, date	Country	Age range studied	Data source	Diagnosis based on	Diagnostic criteria	Years of data collection	Subgroups reported/ comments
Community-only							
Andreasen (1999)	SWEDEN *Piteå River Valley*	42-92	All persons in the Piteå River Valley with suspected dementia in need of community-provided housing who underwent mandatory assessment at neurogeriatric section of the local hospital	Standardized health professional assessment Neuropsy-chology Imaging EEG Laboratory	Lund and Manchester[6]	1990-1995	40-64 65-69 70-74 75-79 80-84 85-89 90+ Overall, FTD accounted for 27/703 (3.8%) cases of dementia; no significant differences by sex or age
Banerjee (2008)	INDIA *Kolkata*	>50	Two-phase door-to-door survey of four adjacent municipal wards in southern part of Kolkata	Health professional assessment Neuro-psychology	Neary[8]	2002-2003	Overall, FTD accounted for 1/42 (2.4%) dementia cases
Gurvit (2008)	TURKEY *Istanbul* Kad-koy	70+ (mean age 74.9 [±5.0])	Two-phase door-to-door survey in district of Istanbul	Health professional assessment Consensus diagnosis	Neary[8]	1998	Overall, FTD accounted for 1/93 (1.1%) cases of dementia
Ikeda (2001)	JAPAN *Nakayama*	65+	Two-phase door-to-door survey of all residents 65 + in Nakayama	Health professional assessment Informant interview Medical chart review Imaging and laboratory	Neary[8]	1997	Overall, FTD accounted for 3.3% (2/60) of all dementia cases
Kivipelto (2002)	FINLAND *Kupio and Joensuu*	65-79	Two-phase survey of a random sample of participants of four population-based studies who met inclusion criteria	(Note: specific approach used described in referenced paper) Health professional assessment Neuro-psychology Imaging and laboratory tests in suspected dementia Consensus diagnosis	None stated	1998	Overall, FTD accounted for 1.8% (1/57) of dementia cases
Lee (2002)	KOREA *Seoul* Kwanak District	65+	Two-phase survey of age-stratified random sample of Kwanak district residents 65+	Health professional assessment Collateral interviews Medical chart review Imaging (subset) and laboratory (all) Consensus diagnosis	None stated	1999-2000	Overall, FTD accounted for 1/40 (2.5%) cases of dementia
Wada-Isoe (2009)	JAPAN *Ama-cho*	65+	Two-phase door-to-door survey of all Ama-cho residents 65+	Health professional assessment Imaging Laboratory	Neary[8]	2008	65-69 70-74 75-79 80-84 85-89 90+ Overall Male 65-69 Male 70-74 Male 75-79 Male 80-84 Male 85-89 Male 90+ Male overall Female 65-69 Female 70-74 Female 75-79 Female 80-84 Female 85-89

Table 1. *Continued*

Author, date	Country	Age range studied	Data source	Diagnosis based on	Diagnostic criteria	Years of data collection	Subgroups reported/ comments
							Female 90+ Female Overall Overall, FTD accounted for 1/104 (1%) dementia cases or 3/104 (2.9%) if two PSP cases were included as FTD
Yamada (2001)	JAPAN *Amino-cho*	>65	Two-phase door-to-door survey of all Amino-cho residents >65	Health professional assessment Imaging Laboratory Note: an unspecified number were not examined; diagnosis for them based on information from family, public health nurses and local physicians	Neary[9]	1998	Overall, FTD accounted for 0/46 cases or 1/46 (2.1%) if a PSP included as a FTD
Community and institution							
Borroni (2010)	ITALY *Brescia County*	45+	Dementia registries of local neurology and geriatric units	Health professional assessment Imaging Laboratory LP in subgroup Consensus diagnosis	Neary,[8] McKhann[0]	2008	Male Female 45-65 66-75 >75 Overall, mean age of onset 65.6; prevalence highest 66-75; no difference in prevalence between men and women overall
Borroni (2011)	ITALY *Brescia County*	45-65	Dementia registries of local neurology and geriatric units	Health professional assessment Imaging Laboratory LP in subgroup Consensus diagnosis	Neary,[8] McKhann[9]	2009	Overall Male overall Female overall 94 cases of FTD compared to 81 cases of Alzheimer's disease among those with early-onset dementia (FTD/AD ratio 1/0.86)
Gascón-Bayarri (2007)	SPAIN *Catalonia* El Prat del Llobregat	70+	Two-phase survey of random age and sex stratified sample of El Prat residents 70+	Health professional assessment Neuro-psychology CT scan and lab tests if diagnosed with a dementia Joint diagnosis	Neary[8]	2002-2003	70-74 75-79 80-84 85-89 90+ Male 70-74 Male 75-79 Male 80-84 Male 85-89 Male 90+ Male overall Female 70-74 Female 75-79 Female 80-84 Female 85-89 Female 90+ Female overall Overall, FTD was diagnosed in 5/165 (3%) cases of dementia
Gilberti (2012)	ITALY *Brescia*	All ages (mean age at onset of FTD cases 66.1, *SD* 7.9)	Registry	Standardized assessment by health professionals based in the local neurology unit Imaging and laboratory tests	Neary,[8] McKhann[9]	2010	45-65 66-75 >75 Overall Male 45-65

							Male 66-75 Male >75 Male overall Female 45-65 Female 66-75 Female >75 Female overall
Gislason (2003)	SWEDEN *Gothenburg*	85-86 (mean age 85 years and 5 months)	One-phase survey (half of all individuals 85-86 in Gothenburg at the time systematically selected to participate; response rate 63%)	Semi-structured neuropsy-chiatric assessment (performed by psychiatrist) and collateral interview Imaging (subset) Algorithm used to diagnose frontal lobe syndrome with bvFTD diagnosed in those who did not have exclusion criteria (note: DSM-III-R defined dementia not a requirement for diagnosis of bvFTD)	Lund and Manchester[6]	1986-1987	Male overall Female overall Overall, among the population studied, 86/451 (19.1%) had frontal behavioural/ affective symptoms and 3.1% were diagnosed with a bvFTD, accounting for 14/154 (145 DSM-II-R dementia cases +9 additional bvFTD cases who did not meet DSM-III-R criteria) or 9.1% of all dementia cases
Harvey (2003)	ENGLAND	<65 (mean age 58.7, $CI_{95\%}$ 57.4-60.1)	Multiple practitioners and services asked to report early onset dementia cases Administra-tive databases searched for early onset cases Chart review of suspected cases identified from above two sources	Medical chart review Diagnosis based on use of algorithm (consensus used to deal with uncertain cases) Health professional assessment in 47% of cases identified above done to confirm diagnosis	Lund and Manchester[6]		40-44 45-49 50-54 55-59 60-64 30-64 Overall, FTD accounted for 23/187 (12%) early-onset dementia cases; 2 cases of CBD also noted
Herrera (2002)	BRAZIL *Sao Paulo* Catanduva	65+	Two-phase survey of every fourth house where persons 65 + resided in the urban area of Catanduva	Health professional assessment Imaging, EEG, and laboratory studies in patients with dementia	Lund and Manchester[6]		Overall, FTD accounted for 3/118 (2.5%) dementia cases
Ikejima (2009)	JAPAN *Ibaraki Prefecture*	< 65	Two-phase mailed survey to relevant institutions and agencies in the prefecture asking for information on early-onset dementia cases	Mail survey results Medical chart review done in nine institutions with the most reported cases as quality control exercise	Lund and Manchester[6]	2006	20-24 25-39 30-34 35-39 40-44 45-49 50-54 55-59 60-64 Overall, among those 45-64, FTD accounted for 2.8% of early-onset cases of dementia (among those who underwent a detailed evaluation, the proportion was 5.3%)
Ratnavalli (2002)	UNITED KINGDOM *Cambridgeshire*	45-64 (mean age at onset for FTD cases 52.8, *SD* 8.7/ diagnosis 56.1, *SD* 8.6	Primary source: three specialist clinics Secondary sources: local community resource teams, clinical psychology services, hospital records, nursing homes, support groups, GPs, and geriatric psychiatrists	Health professional assessment based on review of case records	Neary[8]	2000	Overall Male overall Female overall Overall, FTD accounted for 11/59 (18.6%) cases of dementia; all cases of FTD known to specialty clinics
Rosso (2003)		30+				1998	

Table 1. *Continued*

Author, date	Country	Age range studied	Data source	Diagnosis based on	Diagnostic criteria	Years of data collection	Subgroups reported/ comments
	NETHERLANDS *South Holland*		All hospital-based neurologists and psychiatrists solicited to refer suspected cases Administrative databases of four university medical centres with health record review of suspected cases	Health professional assessment with collateral history Medical chart review Imaging Consensus diagnosis Genetic testing and/or autopsies on subgroup	Lund and Manchester,[6] Neary[8]		30-39 40-49 50-59 60-69 70-79 Overall Mean age at onset was 58, with 22% over 65; estimated overall prevalence in the Netherlands 0.01 per 1,000, while in South Holland it was 0.03 (possibly from under-ascertainment in regions further from study centre in south)
Stevens (2002)	UK *London* Islington	65+ (mean age 75)	Two-phase door-to-door survey of all Islington residents 65+	Health professional assessment Medical chart review Laboratory Joint diagnosis	Clinical, Gregory[7] and Neary[8] criteria		Overall. FTD accounted for 2/64 (3.1%) to 5/64 (7.8%) dementia cases depending on the criteria used
Institution-only							
Ibach (2003)	GERMANY *Population covered by participating state hospitals*	45-79 (63.9 mean age of FTD cases)	Admissions to 36 psychiatric state hospitals (mandated admission of referred cases in 35/36 hospitals)	Health professional assessment (psychiatrist and assistant psychiatrist) Neuro-psychology Structural and functional neuroimaging EEG Laboratory	Neary[8]	2001	45-50 50-60 60-70 70-79 45-64 45-79 Overall, estimated to account for 1.9% of all dementia cases

AD = Alzheimer's disease; bvFTD = behavioural variant FTD; CBD = corticobasal degeneration; $CI_{95\%}$ = 95% confidence interval; CT = computed tomography; DSM–III–R = *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed., revised; EEG = electroencephalography; FTD = frontotemporal dementia; LP = lumbar puncture; SD = standard deviation.

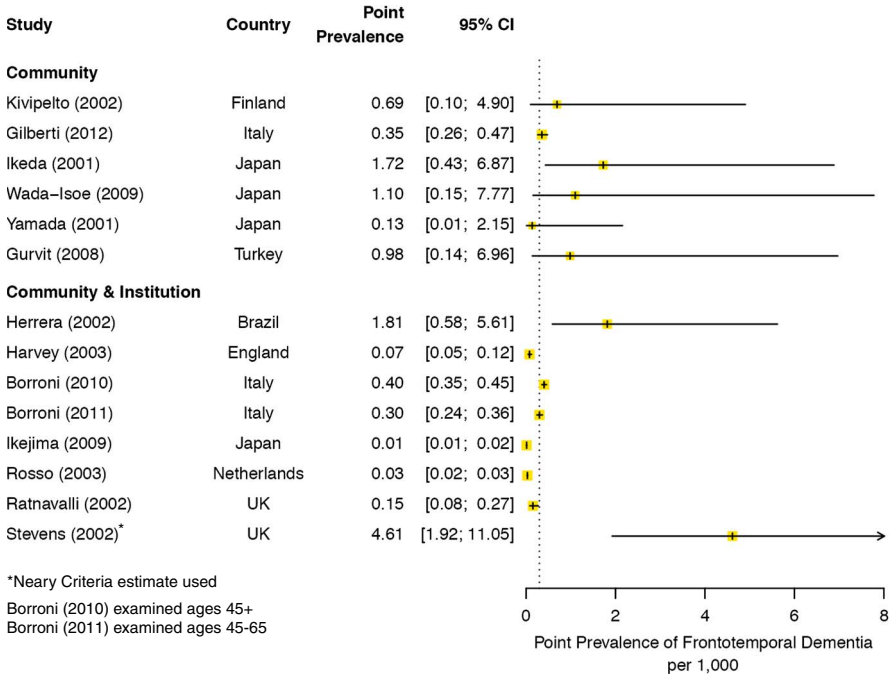

Figure 2: *Point prevalence of frontotemporal dementia.*

than those based on cases identified by specialty services[25,41] (range 0.15-31.04 per 1000 vs. 0.27-0.48 per 1000), but the latter were in a narrower range.

FTD accounted for 2.7% (range 0-9.1%) of all dementia cases in the prevalence studies that included individuals older than 65 years of age[16,19,21,22,24-26,28,29,32-34,41] compared to 10.2% (2.8-15.7%) among studies restricted to those younger than 65.[23,27,30]

Incidence of Frontotemporal Dementia

Only one study reported on incidence proportion.[41] This community-based study of subjects between 42 to 92 years of age consisted of 29,357 persons followed for 6 years. Incidence proportion was estimated to be 0.11 per 1000.

Six studies[35-40] reported on incidence rate (Figure 4). Participants were followed for between 3 and 25 years. Incidence rate estimates ranged from 0.00 to 0.33 per 1000 person-years. Among studies restricted to individuals less than 65[35,37] or 70[36] years of age, incidence rate was in a narrower range (0.00-0.06 per 1000 person-years) compared to studies that included older subjects (0.17-0.33 per 1000 person-years). Estimates derived from surveys[38,40] were higher than specialty service-based ones[35,37] (range 0.28-0.55 per 1000 person-years vs. 0.03-0.05 per 1000 person-years), but the latter were in a narrower range.

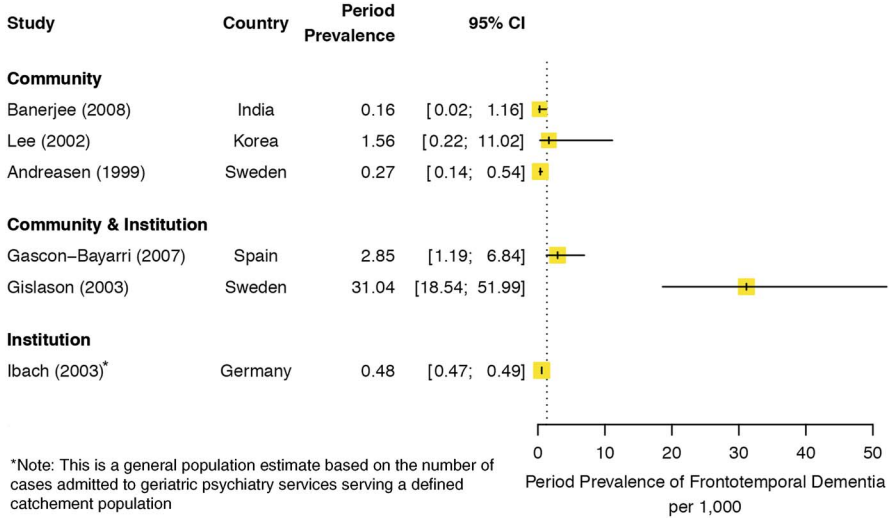

Figure 3: *Period prevalence of frontotemporal dementia.*

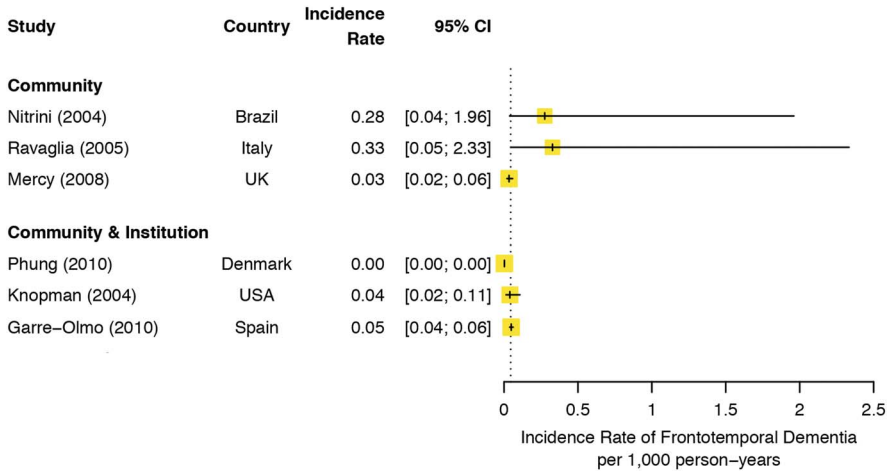

Figure 4: *Incidence rate of frontotemporal dementia.*

FTD accounted for 2.0% (range 0.2-3.9%) of all dementia cases in incidence studies including older subjects[35,38-41] and 15.3% (range 6.7-29.6%) in studies restricted to those younger than 65[35,37] or 70[36] years of age.

Sex

In the 13 studies providing information on the sex of those with FTD,[17-21,25,30,31,33,36-38,41] the cumulative numbers of female and male cases were close to equal (373 [52.5% of all FTD cases] and 338 [47.5%], respectively [$p = 0.18$]).

Type of Frontotemporal Dementia

Among studies that supplied information on the frequency of the type of FTD detected,[18,20,30,35-37] bvFTD ($n = 299$, 79.7% of the total of 375 cases, which included one classified as FTD with ALS) was approximately four times as common as the primary progressive aphasias ($n = 75$, 20%; 32 semantic dementia, 43 PNFA). A study that provided population estimates based on FTD cases admitted to state psychiatric hospitals serving defined catchment areas[25] not surprisingly reported that all had behavioural symptoms (61% had behavioural only and 39% both behavioural and language symptoms). Two studies[31,37] reporting on a total of 356 individuals with FTD noted that 12 (4.6% of the total number of FTD cases) also had a diagnosis of ALS (note that individuals with ALS were included in the FTD total). Five studies[23,33-35,37] reporting on a total of 95 individuals with FTD found an additional 5, and 17 study participants diagnosed with CBS and PSP, respectively (note that individuals with these conditions were not included in the FTD total).

Study Quality

The median study quality score was 6 (range 4-8) (Table 4).

Discussion

We found that population-based prevalence and incidence estimates for FTD were generally low and varied widely, especially among older individuals. FTD accounted for a higher proportion of dementia cases among younger (<65) individuals. In the studies reviewed, there was no apparent predisposition based on sex, and bvFTD was the most common form encountered, and relatively few individuals were felt to have CBS, PSP or ALS.

Two previous systematic reviews[42,43] based on a smaller number of studies reported similar incidence and prevalence estimates. Knopman and Roberts[42] reviewed five prevalence and three incidence studies. For those 45-64 years of age, point prevalence estimates varied tenfold, from 0.02 to 0.22 per 1000, while incidence rates were between 0.027 and 0.041 per 1000. Onyike and Diehl-Schmid[43] identified seven prevalence and three incidence studies. Their reported prevalence (0.02-0.31 per 1000) and incidence (0.013 and 0.167 per 1000) rates also ranged widely. After completion of our systematic review, three otherwise eligible studies[44-46] that reported on the incidence and/or prevalence of FTD were published. Their estimates fall within the range we report and do not change our main findings.

We suspect that the limitations of the clinical diagnostic criteria used in included studies[6-9] and concerns about how the criteria were operationalized partially explain the wide ranges in the estimates of prevalence and incidence. These criteria have been criticized for (among other things): (1) their large number of features (some of which were very rare or of debatable validity); (2) lack of guidance as to the number of features required for diagnosis and the relative importance of symptoms; (3) placing greater emphasis on behavioural manifestations compared to language (one of the studies reviewed[19] only considered behavioural symptoms, while the five studies that solely utilized the Lund and Manchester criteria[23,24,27,35,41] would be expected to preferentially detect bvFTD); (4) ambiguity in the description and time frame of behavioural manifestations; (5) need to infer some aspects of the person's state (e.g., assessment of the lack of insight); (6) uncertainty on how best to assess cognitive (traditional executive measures vs. social cognition and decision-making tasks) and behavioural (e.g., objective vs. subjective) characteristics; (7) rigidity in how criteria were applied; (8) limited role for supportive features; (9) no estimate for level of diagnostic certainty (e.g., probable or possible); (10) impact of the exclusionary criteria; (11) relative neglect of imaging and genetic characteristics; and (12) their insensitivity for early disease.[11,47-49] Patients with bvFTD are frequently misdiagnosed as suffering from a psychiatric illness early in the course of their illness[50,51] and referred to mental health services.[52] As an accurate clinical diagnosis of FTD can be

Table 2: Studies Reporting on the Incidence Rate of Frontotemporal Dementia

Author, date	Country and region	Age range studied	Data source	Diagnosis established by	Diagnostic criteria	Years of data collection	Groups studied
Community-only							
Mercy (2008)	UK *Cambridgeshire*	45-64	Primary source: three specialist clinics Secondary sources: clinical psychology services and community-based early-onset dementia coordinators	Health professional assessment Neuro-psychology Imaging Consensus diagnosis	Neary[8]	2000-2006	Overall, among those diagnosed <65 years of age, FTD accounted for 16/54 (29.6%); 12/16 of FTD cases were bvFTD; all cases known to specialty clinics
Nitrini (2004)	BRAZIL *São Paulo* Catanduva	65+	Two-phase survey of non-demented participants of the Herrera study (2002)	Health professional assessment Neuro-psychology Imaging and laboratory tests on those with dementia Consensus diagnosis	Neary[8]	1997-2000	Overall, FTD accounted for 1/50 (2%) cases of dementia
Ravaglia (2005)	ITALY *Conselice* Ravenna *Emilia Romagna*	65+ (mean age 74 ± 6)	Two-phase survey of non-demented (at baseline) residents of Conselice	Extensive clinical assessment Medical records Imaging Laboratory Consensus diagnosis	McKhann[9]	1999-2004	Overall, FTD accounted for 1/115 (0.9%) dementia cases, 2/115 (1.7%) if PSP case also counted as FTD
Community and institution							
Garre-Olmo (2010)	SPAIN *Catolonia*	30-64 (data given on 65+ for comparison)	Dementia registry (standardized clinical registry of new dementia cases diagnosed by geriatric, memory, and neurology OP clinics in the seven hospitals of the Health Region of Girona)	Assessment by clinical specialists Medical chart review Imaging and laboratory investigations as needed	Lund and Manchester[6]	2007-2009	Overall, FTD accounted for 14/144 (9.7%) early-onset dementia (EOD) cases; among late-onset (LOD) cases, FTD accounted for 56/1939 (2.9%) cases; among EOD cases, there was one person with PSP and two with CBD while among LOD there were 12 individuals with PSP and one with CBD
Knopman (2004)	UNITED STATES *Rochester*	Less than 70	Search of administrative databases for diagnostic codes that might indicate dementia with medical record review of suspected cases	Medical chart review with confirmation of diagnosis by study neurologist	Neary,[8] McKhann[9]	1990-1994	40-49 50-59 60-69 There were 4/60 (6.7%) cases of FTD among patients who had an onset of dementia < 70; ratio of FTD to Alzheimer's was approximately 1 to 5.25 under age 70
Phung (2010)	DENMARK	40+	Data linkage study with cases identified by ICD codes	ICD-8 and ICD-10 codes for FTD	ICD coding for FTD	1970-2004	Overall, FTD accounted for 0.2% of dementia cases, but 73.3% of cases had no specific diagnosis made (among those with a specific diagnosis, FTD accounted for 299/41052 or 0.7%)

bvFTD = behavioural variant FTD; CBD = corticobasal degeneration; EOD = early-onset dementia; FTD = frontotemporal dementia; ICD = International Classification of Diseases; LOD = late-onset dementia; PSP = progressive supranuclear palsy.

Table 3: Studies Reporting on the Incidence Proportion of Frontotemporal Dementia

Author, date	Country and region	Age range studied	Data source	Diagnosis established by	Diagnostic criteria	Years of data collection	Groups studied
Community-only							
Andreasen (1999)	Sweden *Piteå River Valley*	42-92	All persons in the Piteå River Valley with suspected dementia in need of community-provided housing are assessed at the neurogeriatric section of the local hospital	Standardized health professional assessment Neuro-psychology Imaging EEG Laboratory	Lund and Manchester[6]	1990-1995	40-64 65-69 70-74 7579 80-84 85-89 90+ Overall, FTD accounted for 19/489 (3.9%) cases of dementia

EEG = electroencephalography; FTD = frontotemporal dementia.

very difficult to make upon presentation, long-term follow-up may be needed to establish its presence.[51,53,54]

Autopsy studies indicate that the criteria used in our included studies lack sensitivity. For example, Neary criteria[8] were positive in only 79 of 152 (52%) autopsy-confirmed cases of bvFTD,[11] with particular issues among those over the age of 65. The exclusionary features (e.g., early severe amnesia, spatial disorientation) eliminated 26 confirmed cases. Another study[55] of these criteria found that they had a low sensitivity (36.5%) at the time of the person's initial presentation compared to their final clinical diagnosis. The revised diagnostic criteria[10,11] will likely have improved sensitivity,[11,56] but possibly at the cost of worse specificity and a heightened risk of misclassifying individuals as suffering from FTD when they in fact have a frontal variant of Alzheimer's disease,[57] other neurological causes or a psychiatric diagnosis.[58] Further validation of these revised criteria is qrequired. The newer criteria were not utilized in the studies we reviewed.

Experienced clinicians working in specialty clinics are able to accurately diagnose FTD.[59,60] Clinical acumen can be supplemented by appropriate use of investigations. For example, finding frontotemporal abnormalities without corresponding ones in more posterior brain areas on functional (e.g., single-photon emission computed tomography, positron emission tomography) or structural (e.g., magnetic resonance imaging) neuroimaging studies can improve on the sensitivity of clinical criteria in detecting FTD.[61] Basing estimates on patients seen by specialty services who are comprehensively investigated would partially address concerns about the validity of the diagnosis, but at the potential cost of missing cases. A proportion of affected individuals in the catchment area of the study may not be seen by the services utilized in identifying cases, as they may be referred elsewhere (though some authors minimize this possibility because of their conviction that the high regard local practitioners have for their service means that suspected cases will be referred to them[17,18,37]), are not experiencing the types of symptoms that would lead to a referral, or are unwilling to be seen.

We did not find a lower FTD prevalence or incidence among older (65+) compared to younger (<65) individuals. Five studies[18,20,30,31,36] reporting estimates by age subgroups found the highest prevalence and incidence rates between 60 and the mid-70s. The study[21] with the oldest subjects included in our systematic review reported the highest prevalence of FTD, but this investigation had other unique features that may have contributed to the high estimate. Studies published subsequent to our review have reported high prevalence[44] and incidence[45] rates in older populations. While we found that FTD made up a larger proportion of dementia cases among those less than 65 compared to older patients, this appeared to be driven more by the exponential increase in prevalence and incidence with advancing age of other neurodegenerative causes of dementia, in particular Alzheimer's disease (AD), than a higher incidence of FTD among those less than 65 compared to older individuals. Differentiating FTD from AD can be particularly challenging at more advanced ages. Compared to younger individuals with FTD, older (65+) persons with this condition tend to have more memory and visuospatial deficits suggestive of AD while showing less pronounced frontal and temporal lobar atrophy on imaging studies.[62,63] The perception that FTD becomes less common as we age may be due to the increasing difficulty in differentiating it from other forms of dementia.

Our systematic review was not restricted to population-based studies with autopsy confirmation of the clinical diagnosis. There are but few of these studies—a systematic review published in 2006[64] could only identify six. Their restriction to high-income countries, questions about the generalizability of their results and the relative rarity of FTD coupled with the limited number of brains being collected mean that these extremely valuable studies cannot fully address questions about the population-based prevalence and incidence of FTD. As well, in an era without specific disease-modifying therapies, the patient's clinical profile rather than their underlying pathology will be driving service provision.

Notwithstanding the limitations noted above, our systematic review of the incidence and prevalence of FTD updates and expands on prior work. Because of the nature of their symptoms, it has been argued that individuals with FTD, especially early-onset cases,[17,35] will be referred to assessment and management services. While relying on figures from these sources will underestimate the overall prevalence and incidence of this condition, collating data from specialty services might still be an efficient way of capturing data on patients requiring assistance

Table 4: Quality Assessment Scores of Frontotemporal Dementia Incidence and Prevalence Studies

Study (year)	Q1: Target population described?	Q2: Cases from entire population or probability sampling?	Q3: Response rate >70%?	Q4: Non-responders clearly described?	Q5: Sample representa-tive of population?	Q6: Data collection methods standardized?	Q7: Validated criteria to assess disease?	Q8: Were estimates given with confidence intervals or subgroups?	Total quality score (/8)
Andreasen (1999)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Banerjee (2008)	Yes	Yes	NR	NR	NC	Yes	Yes	Yes	5
Borroni (2010)	Yes	No	No	No	No	Yes	Yes	Yes	4
Borroni (2011)	Yes	Yes	NR	NR	NR	Yes	Yes	Yes	5
Garre-Olmo (2010)	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes	6
Gascon-Bayarri (2007)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Gilberti (2012)	Yes	Yes	NA	NR	NR	Yes	Yes	Yes	5
Gislason (2003)	Yes	Yes	No	No	NC	Yes	Yes	Yes	5
Gurvit (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Harvey (2003)	Yes	Yes	NA	No	NC	Yes	Yes	Yes	5
Herrera (2002)	Yes	Yes	Yes	No	NC	Yes	Yes	Yes	6
Ibach (2003)	Yes	Yes	NA	NA	NR	Yes	Yes	Yes	5
Ikeda (2001)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Ikejima (2009)	Yes	Yes	NR	NR	NC	Yes	Yes	Yes	5
Kivipelto (2002)	Yes	Yes	Yes	No	NR	Yes	Yes	No	5
Knopman (2004)	No	NC	Yes	Yes	Yes	Yes	Yes	Yes	6
Lee (2002)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	7
Mercy (2008)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Nitrini (2004)	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	7
Phung (2010)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Ratnavalli (2002)	Yes	Yes	NC	NR	NA	Yes	Yes	Yes	5
Ravaglia (2005)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7
Rosso (2003)	Yes	Yes	NR	No	Yes	Yes	Yes	Yes	6
Stevens (2002)	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	7
Wada-Isoe (2009)	Yes	Yes	NR	No	Yes	Yes	Yes	Yes	6
Yamada (2001)	No	Yes	NR	No	NR	Yes	Yes	Yes	5

NR = not reported; NC = not clear; NA = not applicable.

from the healthcare system. The Cambridgeshire studies of early-onset dementia found that all those with FTD in contact with the healthcare system were known to local specialist services,[30,37] while in Sweden[45] diagnoses of FTD were almost exclusively made by specialist clinics. Standardization of methods and refinements in the diagnostic process, possibly by the use of validated biomarkers, will hopefully improve the precision of prevalence and incidence estimates of this challenging condition.

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Statement of Authorship

DBH, NJ, KMF, JIR, TP and CJM contributed to study conception and design. DBH, NJ, KMF, JIR, DP, EES, PR, AK and CJM contributed to the acquisition of data. KMF and DBH conducted the data analysis. DBH, NJ, KMF, JIR, EES and CJM participated in the interpretation of study data. All authors participated in critically revising the manuscript for important intellectual content and gave final approval for the submission of this manuscript and any further submissions of this work.

Supplementary Material

To view the supplementary material that exist for this study (Appendix e-1 and e-2), please visit http://dx.doi.org/10.1017/cjn.2016.25.

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