

REVIEW ARTICLE

FRONTotemporal dementia Incidence European Research Study—FRONTIERS: Rationale and design

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the list of FRONTIERS members is provided in the Appendix at the end of the manuscript.

[Correction added on May 12, 2022, after first online publication: CRUI-CARE funding statement has been added.]

Abstract

Introduction: The incidence of Frontotemporal Lobar Degeneration (FTLD)-related disorders and their characteristics are not well known. The "FRONTotemporal dementia Incidence European Research Study" (FRONTIERS) is designed to fill this gap.

Methods: FRONTIERS is a European prospective, observational population study based on multinational registries. FRONTIERS comprises 11 tertiary referral centers across Europe with long-lasting experience in FTLD-related disorders and comprehensive regional referral networks, enabling incidence estimation over well-defined geographical areas.

Endpoints: The primary endpoints are (1) the incidence of FTLD-related disorders across Europe; (2) geographic trends of FTLD-related disorders; (3) the distribution of

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FTLD phenotypes in different populations and ethnicities in Europe; (4) inheritance of FTLD-related disorders, including the frequencies of monogenic FTLD as compared to overall disease burden; and (5) implementation of data banking for clinical and biological material.

Expected impacts: FRONTIERS will improve the understanding of FTLD-related disorders and their epidemiology, promoting appropriate public health service policies and treatment strategies.

KEYWORDS

epidemiology, frontotemporal dementia, frontotemporal lobar degeneration, incidence, rare diseases, registry

1 | INTRODUCTION

Frontotemporal lobar degeneration (FTLD) encompasses a spectrum of focal neurodegenerative diseases with progressive atrophy of the frontal and temporal lobes.¹⁻³ FTLD-related disorders are heterogeneous clinical conditions, characterized by social dysfunctions and personality change along with impairment in language, executive, and motor functions.⁴ Current clinical diagnostic criteria characterize specific presentations of FTLD, including the behavioral variant frontotemporal dementia (bvFTD)⁵ and the primary progressive aphasia, with the agrammatic variant (avPPA) and semantic variant (svPPA) subtypes.⁶ Progressive supranuclear palsy (PSP)⁷ corticobasal syndrome (CBS),⁸ and FTD with amyotrophic lateral sclerosis (FTD-ALS) are also usually caused by subtypes of FTLD. There is limited correlation between these clinical syndromes and neuropathological features.⁹ The neuropathological signature is associated mainly with either tau or transactive response (TAR)-DNA-binding protein-43 (TDP-43) protein inclusions.¹⁰ Despite limited clinicopathological correlations, some types of FTLD have a strong genetic background. Up to ≈30% of FTD patients have positive family history, with mutations in the *chromosome 9 open reading frame 72 (C9orf72)*, *progranulin (GRN)*, or *microtubule-associated protein tau (MAPT)* genes each accounting for 5% to 10% of patients.¹¹

In the last 10 years, in depth clinical characterization of FTLD-associated features improved and operationalized clinical diagnostic criteria, and the use of biomarkers aimed at excluding Alzheimer's disease (AD),¹² have prompted a wider recognition of the diseases in clinical settings. This in turn increases the estimated incidence. However, epidemiological studies assessing the FTLD-related disorders overall incidence and the relative frequency of the different phenotypes in the general population are scarce, with marked variation in results.¹³⁻²¹ This variation can be attributed in part to narrow disease-specific and phenotype based focus of individual studies; restriction to different age-delimited sections of the population; and use of historical diagnostic criteria (before current consensus guidelines for each FTLD-related disorder). Data on genetic correlates in different population-representative cohorts remain sparse.

The FTLD-related disorders are individually relatively rare, and so accurate epidemiological studies require surveillance of large popula-

tions with a registry-based approach. This has been effective in the ALS field.²²⁻²⁵ A recent Italian retrospective research registry (the Salento-Brescia registry) aimed to assess the incidence of different FTLD phenotypes in the general population, demonstrating that FTLD-related disorders are more common than previously recognized. There was a progressive increase in FTLD incidence across age groups, reaching its peak in individuals older than 70 years of age.²⁶ Comparable results have been provided in a survey study conducted with similar methodology in the UK.¹⁵

Improved knowledge of FTLD-related disorders and their epidemiology will help to promote appropriate public health service policies and treatment approaches. We have established the FRONTotemporal dementia Incidence European Research Study (FRONTIERS) as a collaborative European research initiative to assess FTLD epidemiology across Europe, aligning prospective multinational disease population-based disease registries.

1.1 | Rationale of FRONTIERS

The rationale of FRONTIERS is to assess the epidemiology of FTLD-related disorders across Europe, resolving some of the current issues in the field.

First, FTLD has often been considered a presenile dementia.¹¹ However, it is clear that FTLD should not be confined exclusively within the early onset dementias, as peak incidence may well be above 65 years, and may continue to rise if case ascertainment were complete. Second, the distribution of clinical phenotypes in the general population is not yet known. Estimates are based on clinical series from tertiary referral centers, which are liable to be biased and nonrepresentative. Third, the distribution of monogenic FTLD-related disorders in Europe has been deduced by ad hoc observational studies, with *C9orf72* expansion being more prevalent in Northern Europe, whereas *GRN* is in Southern Europe, in areas like Northern Italy and Basque Country.²⁷ However, unbiased estimates of the incidence of monogenic FTLD causes disorders have not yet been established.

To address these issues, a population-based approach through multinational registries has several advantages: (1) in each registry there is a prospective ascertainment of cases, seeking to minimize

missing cases; (2) registries are generated from multiple sources of case ascertainment; (3) there is a continuous surveillance of the disease; and (4) matching diagnostic work-up and diagnostic criteria are adopted.²⁵

1.2 | End points of FRONTIERS

The primary aims of FRONTIERS are (1) to assess the incidence of FTLD-related disorders across Europe, considering presenile and more advanced age groups; (2) to assess the geographic distribution of the disease; (3) to describe the distribution of FTLD phenotypes and their heterogeneity in different populations and different ancestral origins in Europe; (4) to define FTLD-related disorders inheritance, and the frequencies of monogenic FTLD-related disorders across Europe, including but not limited to the most frequent causes (ie., mutations within *GRN*, *MAPT*, and *C9orf72* genes); (5) to implement data banking for clinical and biological material.

2 | METHODS

2.1 | Setting

FRONTIERS was established in February 6-7, 2020 at a consensus meeting in Tricase, Italy. It was established with 11 centers across Europe, each with long-lasting experience in the FTLD field and with the ability to cover a well-defined geographical area. The pre-requisite of a population-based registry is the correct definition of the population at risk and the identification of proper sources of cases (see Figure 1 and Table 1 for centers and Principal Investigators).

2.2 | Participants and protocols

Patients with a new FTLD-related diagnosis in the defined ascertainment time window and in the defined geographical boundaries will be considered in FRONTIERS. The diagnosis will be made according to current clinical criteria and supportive features for bvFTD, PPA (semantic and agrammatic variants), PSP, CBS, and FTD-ALS diagnoses.⁵⁻⁸ FRONTIERS will consider mixed or indeterminate PPA with negative AD markers, but will not consider the logopenic variant of PPA, as the majority of logopenic PPA cases have AD pathology. Moreover, FRONTIERS will not include patients in their prodromal stage and asymptomatic subjects carrying pathogenetic mutations, and FRONTIERS will not consider prevalent cases.

FRONTIERS participants will be assessed with a set of clinical, neuropsychological, imaging and biomarkers protocols, according to standard diagnostics in each participating center, following which diagnostic criteria of one of the FTLD phenotypes will be fulfilled as reported above.⁵⁻⁸ A standardized set of data will be considered and recorded by each center, including demographic characteristics and clinical features, lifestyle and family history data, genetic screening results, and biomarkers testing.

RESEARCH IN CONTEXT

- 1. Systematic Review:** Frontotemporal lobar degeneration (FTLD) is the second most common cause of early onset dementias. However, studies assessing the incidence of clinically manifest FTLD-related disorders and the related clinical and genetic features are still limited. The "FRONTotemporal dementia Incidence European Research Study" (FRONTIERS) is designed to fill this gap.
- 2. Interpretation:** FRONTIERS will allow us to determine the epidemiology of FTLD-related disorders across Europe as well as the distribution of clinical phenotypes and genotypes. Furthermore, FRONTIERS will represent a source of cases for pragmatic trials and analytic population-based studies, as well as a population-based biobanking.
- 3. Future Directions:** FRONTIERS will improve the understanding of FTLD-related disorders and their epidemiology, promoting appropriate public health service policies and treatment strategies.

Inclusion criteria will be the followings: (1) ≥ 18 -years-old; (2) participants must fulfill current clinical criteria of FTD, PSP, or CBS⁵⁻⁸; (3) diagnosis of the FTLD-related disorder must be made in the referral period of time of the current prospective study; (4) participants must be living in the referral geographical area selected in each country for the purpose of the present study; and (5) participants must have an identified informant if necessary.

Exclusion criteria will be the followings: other medical or psychiatric illness that would interfere in completing assessments/diagnosis.

To minimize missing cases, the facilities of the referral geographical area, lay local associations, and charities involved in dementia care will be contacted by each center.

2.3 | Demographic, clinical, and biomarkers data collection

Place of birth and residence as well as date of FTLD-related disorders diagnosis will be recorded. We will consider age, age at disease onset, sex, clinical phenotype, the onset of symptoms, and disease duration (in the recall of the patient or family). Age at onset will be defined as the age at which first symptoms consistent with FTLD were observed by patients or caregivers. Years of full-time education and occupation attainment will be also recorded. Family history for neurodegenerative dementias, ALS, or parkinsonism will be assessed by using a standardized family history questionnaire.²⁸

A standardized recording of extrapyramidal signs or motor neuron disease will be carried out. Disease severity at diagnosis will be

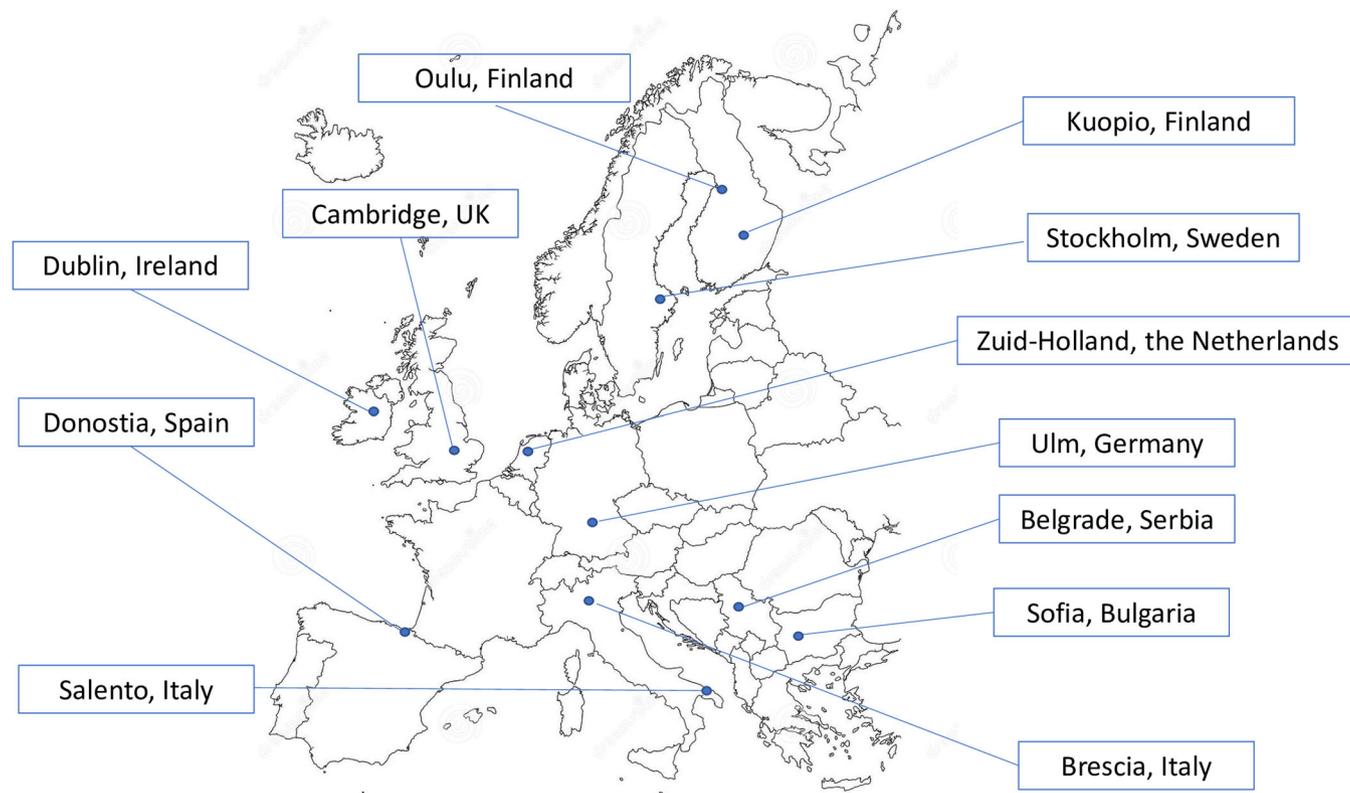


FIGURE 1 List of participating geographical areas

assessed by the Clinical Dementia Rating plus NACC,FTLD,²⁹ and with the PSP-Rating Scale (PSPRS)³⁰ or the Cortico Basal ganglia Functional Scale,(CBFS),³¹ when appropriate.

Additional instrumental evaluations aimed at accomplishing a diagnosis will be recorded. In particular, we will consider cerebrospinal fluid (CSF) markers (tau, phospho-tau and amyloid beta [A β]42 and A β 40 dosage levels) or positron emission tomography (PET) amyloid scan, to exclude AD, and PET-tau tracer or brain PET- fluorodeoxyglucose (FDG) scan. For each of these markers, the result will be recorded as “supporting FTL D diagnosis,” “uninformative,” or “not supporting FTL D diagnosis.” We will also record FTL D mimickers, namely, those subjects fulfilling FTL D criteria but with positive AD biomarkers and likely with mixed pathologies, especially in the older group, to determine their incidence in population-based setting.

Finally, we will additionally measure neurofilament light in plasma and CSF in FTL D patients.³²

2.4 | Genetic testing and sample biobanking

Each patient will undergo blood sampling for genetic screening and biobanking. The most frequent monogenic causes are *C9orf72*, *MAPT*, and *GRN* pathogenetic mutations. These will be assessed locally, according to standard procedures.²⁷ Where the genetic testing is locally unavailable, genetic analyses will be provided by other centers in the network. Biological samples, namely DNA,

plasma, and serum, will be stored locally for additional future analyses, such as genome-wide association studies or exome sequencing analyses. CSF storage for future analyses will be considered optional.

2.5 | Data handling and record keeping

Data will be pseudo-anonymized, and each participant will be assigned a unique investigation number (progressive number—country code), and the patient identity will be accessible only to the referral center where the data is acquired. Web-based data acquisition will be carried out.

2.6 | Ethical and regulatory considerations

The study will be performed on the basis of International Conference on Harmonisation/WHO (World Health Organization) Good Clinical Practice (ICH-GCP) standards (www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice). Ethical approval for the study will be obtained from the coordinating center and from each local ethical review committees. Informed consent will cover participation in all the aspects of the study, except where a participant has lost the mental capacity to consent, in which case site-specific national laws will be followed regarding the procedures to include legal incapacity participants in

TABLE 1 Centers and reference geographical area

Country	Center	Principal investigator(s)	Reference geographical area	Reference population
Italy	Center for Neurodegenerative Disease and the Aging Brain, University of Bari	Giancarlo Logroscino	Salento area (Lecce province)	795,134 ^a
Italy	Centre for Neurodegenerative Disorders, University of Brescia	Barbara Borroni	Brescia province	1,265,954 ^b
Sweden	Karolinska University Hospital and Institutet, Stockholm	Caroline Graff	Stockholm area (Huddinge site)	967,160 ^c
Bulgaria	Department of Neurology, University Hospital Alexandrovska, Sofia	Latchezar Traykov	Sofia region	1,557,161 ^d
Spain	Neurology Department, Hospital Universitario Donostia	Fermin Moreno	Donostialdea area (Basque Country)	388,142 ^e
Germany	Neurology, University Hospital of Uhlm	Markus Otto, Albert C. Ludolph	Ulm/Neu-Ulm area	184,711 ^f
UK	Centre for Frontotemporal Dementia and related disorders, Cambridge University	James Rowe	East England	1,753,964 ^g
Finland	Oulu University Hospital	Anne Remes	Northern Ostrobothnia, Oulu and Northern Savonia, Kuopio	657,763 ^h
Netherlands	Alzheimer Center, Erasmus, Rotterdam	Harro Seelaar	Zuid-Holland	3,673,893 ⁱ
Serbia	Neurology, University of Belgrade	Elka Stefanova	Belgrade area	1,690,193 ^j
Ireland	Neurology, Trinity College, Dublin	Orla Hardiman	Dublin province	1,904,806 ^k
Europe (11 areas) (Total Reference Population)				14,838,881

^a<https://www.istat.it/>.

^b<https://www.istat.it/>.

^chttps://www.statistikdatabasen.scb.se/pxweb/sv/ssd/START_BE_BE0101_BE0101A/BefolkManad/.

^d<https://www.nsi.bg/bg/content/2979/%D0%BD%D0%B0%D1%81%D0%B5%D0%BB%D0%B5%D0%BD%D0%B8%D0%B5-%D0%BF%D0%BE-%D0%BE%D0%B1%D0%BB%D0%B0%D1%81%D1%82%D0%B8-%D0%B2%D1%8A%D0%B7%D1%80%D0%B0%D1%81%D1%82-%D0%BC%D0%B5%D1%81%D1%82%D0%BE%D0%B6%D0%B8%D0%B2%D0%B5%D0%B5%D0%BD%D0%B5-%D0%B8-%D0%BF%D0%BE%D0%BB>.

^e<https://www.eustat.eu/indice.html>.

^f<https://www.statistik-bw.de/BevoelkGebiet>. https://www.statistik.bayern.de/statistik/gebiet_bevoelkerung.

^g<https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland>.

^hhttp://pxnet2.stat.fi/PXWeb/pxweb/en/StatFin/StatFin_vrm_vaerak/statfin_vaerak_pxt_11re.px/.

ⁱ<https://opendata.cbs.nl/statline/#/CBS/nl/dataset/70072NED/table?fromstatweb>.

^j<https://www.stat.gov.rs/en-us/>.

^k<https://www.cso.ie/en/releasesandpublications/ep/p-cp2tc/cp2pdm/pd/>.

research. Data transfer agreements will be introduced for transfer of clinical data and biosamples.

2.7 | FRONTIERS lifespan, data access and publication policy

FRONTIERS will have a duration of 3 years from the starting date, which will be the same across the sites; a first end point will occur at 12 months and a second end point will be set at 24 months for preliminary analyses. An extension of study duration may be considered.

Each PI will have access to anonymized data, and formal requests for either data analyses or biological samples will be submitted in writing to the other PIs, along with a brief description of the project that includes specific aims, study design, and characteristics of the data requested. The data request will be reviewed by the PIs and approved.

Publication policy agreement has already been defined and articles will list as authors all PIs and all other researchers who have made a scientific and/or clinical contribution. Co-investigators will be quoted under a final corporate author reflecting the FRONTIERS collaboration.

2.8 | Statistics

The following sets of variables will be recorded: (1) demographic data; (2) family history; (3) clinical phenotype; and (4) genetic mutations. Overall, FRONTIERS will cover defined geographical areas of interest across 10 European Countries (see Table 1), with a total estimated overall population of about 15 million people. In a first step, incidence rates will be computed separately for each region. The numerator of each rate will be the number of cases from the region, collected by

each center during the study period. The denominator of each rate (person-years spent at risk during the study period) will be estimated using the information on the number of residents living in the covered geographic area at a specific time point.³³ Age-sex standardized incidence rates will be also computed using the European population as standard. Heterogeneity of incidence rate estimates across geographical regions will be assessed. In a second step, results from different geographical regions will be combined using methods to properly account for between-region variability such as mixed-effect models,³⁴ to obtain a European summary incidence estimate.

3 | EXPECTED RESULTS AND IMPACT

Registries are powerful tools to develop clinical research, to improve patients care by appropriate planning of public policies for health care and to facilitate the correct design for clinical trials.²⁵ This is particularly true in case of relatively rare neurodegenerative disorders, characterized by clinical complexity and heterogeneity as well as low incidence and prevalence. In this setting, population-based registries represent the only cost-effective way to estimate the incidence of a disease.^{25,26} Assessing disease incidence and studying how the frequency changes over time in a given geographical area and among subgroups are crucial in epidemiology to understand disease causation and to investigate possible risk factors.³⁵

FRONTIERS, a multinational prospective population-based registry, will provide multi-source case ascertainment and will allow the description of FTLD-related phenotypes across Europe as well as the distribution of causative genetic traits. We will work with other cohort studies of related disorders, including the Genetic Frontotemporal Dementia Initiative (GENFI; seven FRONTIERS sites are members of GENFI consortium), and UK, German and Italian research cohorts for PSP and CBS (ie., PROgressive Supranuclear Palsy Cortico-Basal Syndrome, PROSPECT study), FTLD consortium (www.ftld.de), Treatment Research Initiative to Cure ALS, TRICALS Consortium for ALS.

FRONTIERS will represent a source of cases for pragmatic trials and analytic population-based studies, as well as a population-based biobanking. A major impact of FRONTIERS will be an accurate understanding of epidemiology of FTLD-related disorders, to answer a broad range of questions: (1) Are FTLD-related disorders common? (2) Is incidence of FTLD-related disorders comparable across European ancestral populations and countries? (3) Should FTLD-related disorders be considered a disorder of midlife? (4) Is bvFTD more common than PPAs, or vice versa? (5) Are FTLD-related disorders associated with specific risk factors? (6) Is distribution of FTLD-related disorders comparable across Europe? (7) Which is the impact of monogenic FTLD to the overall burden of disease? (8) Is distribution of monogenic FTLD-related disorders comparable across ethnicities/countries? (9) What are the characteristics of the diagnostic journey for FTLD-related disorders? (10) Can we confirm suggestions for the staging of FTLD, both neuropathologically and clinically?^{36,37}

FRONTIERS will be equipped to address these questions, as the study is population based, and all the new cases in a defined period of

time and in a defined geographical area will be collected for comprehensive analysis of demographics, phenotypes, and outcomes across different geographic regions.²⁵

FRONTIERS will allow us to determine the distribution of clinical phenotypes and genotypes, as well as the relative weight of each in each country in Europe. Moreover, we seek new insights into the spreading of FTLD-related mutations throughout Europe.³⁸

High quality data of registries and near-completeness of case ascertainment is one of key elements to obtain reliable data. FRONTIERS will attempt to minimize misclassification biases with the inclusion of tertiary referral centers with long-lasting experiences in FTLD diagnosis, with the rigorous definition of geographic boundaries of areas of interest, with the standardization of diagnostic and inclusion/exclusion criteria, and with the implementation of effective case identification strategies by referrals through networks of clinical professionals and charities. Furthermore, if suitable sources like administrative data are available, we are going to implement capture-recapture analyses to estimate the rate of missing cases,³⁹ as previously has been successfully done in ALS.⁴⁰ An important effort will be devoted to the harmonization of data among centers with periodic meetings with special focus on diagnosis of different phenotypes.

We recognize that this project does not involve systematic collection and storage of CSF and brain tissue, thus representing a limitation to the study. Moreover, assessment of biological markers that have recently aroused interest in the FTLD field have not been included in the FRONTIERS primary outcomes; however, additional studies may be carried out in the next future on stored biosamples.

Finally, we acknowledge that population-based registers require a number of years of activity to ensure that early biases are resolved; this is generally a bias toward enrollment of prevalent cases, wrongly classified as incident within the first year of the study.²⁵

In conclusion, FRONTIERS will be a unique contribution to the field, primarily in the area of epidemiology, and will allow improving our understanding of clinical and biological FTLD heterogeneity within and across different populations, which may help to guide future regulatory policies and clinical decision-making. FRONTIERS will be an exceptional platform to develop new pharmacological and non-pharmacological trials.

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