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RESEARCH ARTICLE

Epidemiology of early onset dementia and its clinical presentations in the province of Modena, Italy

Annalisa Chiari[1] | **Giulia Vinceti**[1,2,3] | **Giorgia Adani**[2,3] | **Manuela Tondelli**[4] | **Chiara Galli**[4,6] | **Luigi Fiondella**[1,2] | **Manuela Costa**[5] | **Maria A. Molinari**[4] | **Tommaso Filippini**[2,3] | **Giovanna Zamboni**[1,2,3,8] | **Marco Vinceti**[2,7]

[1] U.O. di Neurologia, Azienda Ospedaliero Universitaria di Modena, Modena, Italy

[2] Dipartimento di Scienze Biomediche, Metaboliche e Neuroscienze, Università di Modena e Reggio Emilia, Modena, Italy

[3] Centro Interdipartimentale di Neuroscienze e Neurotecnologie, Università di Modena e Reggio Emilia, Modena, Italy

[4] Dipartimento di cure primarie, AUSL Modena, Modena, Italy

[5] Neurologia Ospedale di Carpi, AUSL Modena, Modena, Italy

[6] NeuroFARBA, Dipartimento di Neuroscienze, Psicologia, Area del Farmaco e Salute del Bambino, Università degli Studi di Firenze, Italy

[7] Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts, USA

[8] Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

Correspondence
Giovanna Zamboni, Via Giardini 1355, 41126 Modena, Italy.
Email: giovanna.zamboni@unimore.it

Giovanna Zamboni and Marco Vinceti are joint senior authors.

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Abstract

Introduction: Patients with early onset dementia (EOD), defined as dementia with symptom onset at age <65, frequently present with atypical syndromes. However, the epidemiology of different EOD presentations, including variants of Alzheimer's disease (AD) and frontotemporal dementia (FTD), has never been investigated all together in a population-based study. Epidemiologic data of all-cause EOD are also scarce.

Methods: We investigated EOD epidemiology by identifying patients with EOD seen in the extended network of dementia services of the Modena province, Northern Italy (≈700,000 inhabitants) from 2006 to 2019.

Results: In the population age 30 to 64, incidence was 13.2 per 100,000/year, based on 160 new cases from January 2016 to June 2019, and prevalence 74.3 per 100,000 on June 30, 2019. The most frequent phenotypes were the amnestic variant of AD and behavioral variant of FTD.

Discussion: EOD affects a significant number of people. Amnestic AD is the most frequent clinical presentation in this understudied segment of the dementia population.

KEYWORDS
Alzheimer's disease, clinical variants of dementia, early onset dementia, epidemiology, frontotemporal dementia, incidence, posterior cortical atrophy, prevalence, primary progressive aphasia

1 | INTRODUCTION

The term "early onset dementia" (EOD) indicates dementia with symptom onset before the age of 65, regardless of the underlying dementia syndrome. EOD has a significant impact on patients and families, which may include young children,[1] as well as on employment and income.[2] General dementia care networks are frequently unable to respond to the specific needs of patients with EOD, since they are

tailored to older patients with different social and family situations.[3] In addition, patients with EOD wait longer than patients with late-onset dementia before receiving a correct diagnosis after symptom onset, probably because they are not referred to dementia centers soon enough and because reaching a correct diagnosis in these patients is more challenging,[4] since they frequently present with atypical manifestations of dementia syndromes.[5] As an example, in young patients, Alzheimer's disease frequently presents with a number of non-amnestic variants, including posterior cortical atrophy (PCA) and the logopenic variant of primary progressive aphasia (lvPPA), compared to the more common amnestic presentation of dementia due to Alzheimer's disease (AD) in older patients.[6]

EOD prevalence has been variably reported ranging between 38 and 420 EOD cases per 100,000 in the age group 30 to 64,[7] whereas EOD incidence has been reported to vary between 2.4 and 22.6 new cases per 100,000 per year.[8,9] However, no previous population-based studies on EOD have reported the epidemiology of different presentations or phenotypes of AD and frontotemporal dementia (FTD) spectrum.

Providing the epidemiology of all the different clinical presentations of EOD would not only benefit medical professionals in their diagnostic reasoning when faced with young patients with cognitive symptoms. More importantly, it would also allow a better understanding of the impact of different presentations on society and an improved planning of dementia services and resource allocation.

We aimed to establish the prevalence and incidence of all-cause EOD as well as of EOD presentations in a Northern Italy community by studying demographic and clinical features of patients with dementia symptom onset before the age of 65.

RESEARCH IN CONTEXT

- Systematic review: The authors reviewed the literature using traditional (eg, PubMed) sources and meeting abstracts and presentations. There have been several reports on the prevalence of all-cause early onset dementia (EOD), fewer on its incidence. There are no population-based studies on incidence and prevalence of different presentations of EOD including clinical variants of dementia due to Alzheimer's disease (AD) or frontotemporal dementia. A large multisite longitudinal clinical and biomarker study (not population-based) on a convenience cohort of young adults with AD is currently ongoing (Longitudinal Early-Onset AD Study, LEADS).
- Interpretation: The present population-based study established the incidence and prevalence of all the presentations of EOD, including different variants of AD.
- Future directions: Up-to-date knowledge of the epidemiology of EOD is the first step to understand its impact on patients, families, and society. This study complements current ongoing biomarker and clinical studies in filling the gap in the knowledge on an understudied face of dementia.

2 | METHODS

We conducted an epidemiological study in the province of Modena, Northern Italy, which encompasses an area of about 2689 square kilometers and includes 43 municipalities. It covers a mountain area in the Apennines and a plain area in the river Po valley (Pianura Padana). Modena (≈186,000 inhabitants) is the larger city in the province, followed by Carpi (≈72,000 inhabitants). On January 1, 2019, the area had a population of 347,146 people30 to 64 years of age and 211,043 people 45 to 64 years of age, over a total population of 701,896 inhabitants. Three years earlier, on January 1, 2016, there were 347,684 people 30 to 64 years of age and 200,402 people 45 to 64 years of age, over a total of 702,481 inhabitants.

We included in the study all the residents in the province of Modena alive on census day (June 30, 2019), who had received a diagnosis of dementia or major neurocognitive disorder with symptom onset before age 65 from January 1, 2006 to June 30, 2019. Exclusion criteria were co-existing diagnoses of developmental disorder (eg, Down syndrome or cerebral palsy), longstanding history of major psychiatric disorder (schizophrenia, bipolar disorder), cognitive impairment in the context of another neurological disorder in which severe disability was present due to non-cognitive symptoms (eg, multiple sclerosis, cerebrovascular disease with severe motor disability), age younger than 30, and residence outside the province of Modena on census day.

Patient recruitment involved the extended network of dementia services existing in the province of Modena, which includes two hospital-based outpatient cognitive neurology clinics in the two neurology services (Ospedale Civile di Baggiovara in Modena and Ospedale Ramazzini in Carpi, respectively) and eight outpatient geriatric memory clinics (all named "Centro per i Disturbi Cognitivi e le Demenze" [CDCD]). CDCDs reach patients living at home and in nursing homes, and coordinate the care of patients in daytime services and one special care unit for behavioral disturbances. Patients are followed periodically in their CDCD at least every 6 months (this is also related to the Italian regulation regarding prescription of cholinesterase inhibitor and neuroleptic medications that requires periodic medical checks). Because it is not infrequent that young patients with cognitive disorders and other neurological accompanying symptoms may be first referred to movement disorders or motor neuron disease clinics, all these clinics from the two neurology services of the province were also involved in the recruitment. All these services extensively cover the entire province and are part of the Italian National Health System (Sistema Sanitario Nazionale). Patients with cognitive symptoms who are younger than 65 years are usually referred to neurologic CDCDs, whereas older patients are referred to geriatric CDCDs. Referrals to CDCDs can be made by either general practitioners or specialists such as Psychiatrists (as frequently is the case for patients presenting with behavioral symptoms). The dementia care network is organized so that patients 65 and older can also be referred to neurologic CDCD (either by general

practitioners or geriatric CDCD) in case of diagnostic uncertainty, whereas EOD patients with severe functional impairment or living in nursing homes are referred to geriatric CDCD.

We identified retrospectively all EOD patients from January 1, 2006 to December 31, 2016, and prospectively all new EOD patients from January 1, 2017 to June 30, 2019. We adopted a mixed recruitment strategy because we were interested not only in EOD epidemiology, but also wanted to estimate the needs of all the living patients and their families with the ultimate aim of optimizing resource allocation. Therefore, after having received ethical approval for the current study, we commenced prospective recruitment of all new EOD cases but also searched retrospectively for all the living cases diagnosed in the previous 10 years. The definition of EOD cases and inclusion and exclusion criteria were consistent for the retrospective and the prospective parts of the study.

In the retrospective part of the study we identified all patients with a diagnosis of dementia occurring in the 2006 to 2016 period with an onset of cognitive or behavioral symptoms before age 65 seen in the neurologic CDCDs, geriatric CDCDs, movement disorders clinics, and motor neuron disease clinics, by review of their medical records and, whenever possible, by direct assessment of the patients. This allowed us to confirm a diagnosis of dementia or major neurocognitive disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5),[10] as well as to ascertain the specific clinical diagnosis and the date of onset of symptoms. The review of the clinical records and/or assessment of patients was performed by three neurologists (AC, GV, and MT) with clinical expertise in cognitive disorders. Each case was collegially discussed to reach consensus on the diagnosis. In the prospective part of the study we recruited all patients with onset of cognitive or behavioral symptoms before age 65 referred to the aforementioned facilities between January 1, 2017 and June 30, 2019. All these patients were assessed by a neurologist with clinical expertise in cognitive disorders of the two neurologic CDCDs (AC, GV, MT, GZ, MC). The diagnostic workup included neurological examination, extended neuropsychological assessment, and structural brain imaging with magnetic resonance imaging (MRI) for all patients (computerized tomography [CT] scan was performed only if MRI was contraindicated). In addition, when clinically indicated, patients also underwent lumbar puncture for measurement of cerebrospinal fluid (CSF) total tau, phosphorylated tau, and 1-42 amyloid beta ([Aβ], routinely performed at the two hospital-based cognitive neurology clinics in Modena Province since 2007), fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging or amyloid PET imaging (performed since 2006 and 2013, respectively), and genetic analysis (performed since 2006).

For each EOD case, diagnosis of the specific type of dementia was established through the use of most recent clinical criteria for each dementia syndrome, including AD,[11] vascular dementia (VaD),[12,13] behavioral variant of frontotemporal dementia (bvFTD),[14] primary progressive aphasia (PPA) and its variants,[15] posterior cortical atrophy (PCA),[16] Lewy body dementia (LBD),[17] Parkinson disease dementia,[18] dementia in Huntington disease (HD),[19] progressive supranuclear palsy (PSP),[20] corticobasal syndrome (CBS),[20] dementia in Creutzfeldt-Jakob Disease (JCD),[21] leukoencephalopathy,[22] and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).[23] The diagnosis of AD was supported by at least one biomarker suggestive of amyloid deposition (either CSF or amyloid-PET) in the large majority of cases. The macro-classification of different syndromes was based on Elahi and Miller.[24] Because clinical criteria may have evolved over time, for the retrospective part of the study the diagnoses were systematically assessed and harmonized according to the most recent criteria, upon consensus between the neurologists reviewing the cases. As an example, living cases of the logopenic variant of PPA (or lvPPA), which would have been included in the FTD spectrum prior to 2011, upon review were reclassified as a variant of dementia due to AD. Dementia cases that did not meet criteria for a specific type of dementia were classified as "not otherwise specified" (or NOS).

We collected demographic and clinical characteristics for each EOD case. Education was defined as the number of years of education. Age at symptom onset was defined as the referred age (by patient or caregiver) when the first cognitive or behavioral symptom had been observed by the patient themselves or by the caregiver. Age at diagnosis was defined as the age when the patient was diagnosed with dementia for the first time, irrespective of the specific type of dementia syndrome. For patients with a clinical diagnosis of mild cognitive impairment (MCI) or mild neurocognitive disorder (ie, presence of measurable deficit on at least one cognitive domain that does not affect everyday functioning) the age at diagnosis was the age when they converted to dementia, regardless of the fact that biomarkers suggestive of a specific underlying neurodegenerative pathophysiology may have also been available in the MCI phase (eg, MCI with evidence of underlying AD pathophysiology).[25]

We computed both crude and age- and sex-adjusted incidence rates with reference to the entire period January 1, 2016 through June 30, 2019, and to each of these years. For both calculations, we used the Modena province resident population on January 1 of each year from 2016 to 2019,[26] after exclusion of previously diagnosed EOD cases from the denominators. The rate was then directly standardized to the 2013 European standard population,[27] taking into account age and sex. We focused on the most recent years to avoid biases due to possible changes in diagnostic sensitivity over time.

We computed the crude and age- and sex-adjusted prevalence rate at census date (June 30, 2019), using as denominator the residing population on January 1, 2019, which was the most recent available.

To allow comparison with previous studies, we computed incidence and prevalence rates for the age groups 30 to 44 and 45 to 64 years, and for the entire population at risk, 30 to 64 years.

When reporting incidence and prevalence rates on 100,000 *inhabitants*, we considered as denominator the entire population of Modena province from age 0, whereas when reporting incidence and prevalence rates on 100,000 *persons at risk*, we used as denominators the resident population in the corresponding age subgroups (30 to 44, 45 to 64, and 30 to 64 years). Subjects who did not meet inclusion criteria because the predominant etiology of their disability was a developmental disorder, or a longstanding history of major psychiatric

TABLE 1 Prevalence of all-cause EOD at census date by range of age at onset and sex

	Prevalent cases at June 30, 2019			Age and sex specific prevalence at June 30, 2019 (per 100.000 inhabitants)		
Age range (year)	Total	M	F	Total	M	F
30-34	0	0	0	0	0	0
35-39	1	0	1	2.3	0	4.6
40-44	4	1	3	7.4	3.7	11.1
45-49	10	7	3	16.9	23.5	10.2
50-54	29	11	18	50.8	38.4	63.2
55-59	84	44	40	164.5	177.1	152.5
60-64	130	60	70	296.4	285.3	306.7

disorder, or another neurological disorder such as multiple sclerosis or cerebrovascular accident, were not removed from the population on which prevalence and incidence were calculated. The study was conducted in accordance with local clinical research regulations, and conformed to the Declaration of Helsinki (Study Number 186/2016 approved by the local ethical committee).

3 | RESULTS

3.1 | EOD incidence

From January 1, 2016 to June 30, 2019, we identified 160 incident cases of EOD, with a median age of onset of 60 years (interquartile range [IQR] 58 to 63). All-cause EOD **annual crude incidence** rate was 6.48 cases/100,000 inhabitants and annual **age- and sex-adjusted incidence** was 6.49 (95% confidence interval [CI] 6.46, 6.52) during the 2016 to 2019 period, corresponding to 46 new cases per year in the overall Modena province population. Considering **each year** separately, age- and sex-adjusted incidence was 5.98 cases/100,000 inhabitants (95% CI 5.93, 6.04) in 2016, 5.80 (95% CI 5.75, 5.86) in 2017, 7.52 (95% CI 7.46, 7.58) in 2018, and 6.81 (95% CI 6.72, 6.89) in 2019. When the analyses for **age group** were stratified, annual age- and sex-adjusted incidence rate was 2.94/100,000 (95% CI 2.81, 3.07) in the 30 to 44 age group, 22.06 (95% CI 21.96, 22.15) in the 45 to 64 age group, and 13.19 (95% CI 13.13, 13.25) in the whole 30 to 64 age group. Notably, the rate increased with age from 1.0 in the 40 to 44 age group, to 6.7 in the 50 to 54 group, to 59.8 in the 60 to 64 group.

3.2 | EOD prevalence

We identified 258 patients with a clinical diagnosis of EOD (male/female: 123/135) in Modena province at June 30, 2019. Thirty-one patients did not meet inclusion criteria because the predominant etiology of their disability was a developmental disorder (n = 3), a longstanding history of major psychiatric disorder (n = 11), or another neurological disorder such as multiple sclerosis (n = 4) or cerebrovascular accident (n = 13).

The resulting EOD **crude prevalence** was 36.43/100,000 inhabitants and the **age- and sex-adjusted prevalence** was 36.41/100,000 inhabitants (95% CI 35.01, 37.81). Stratifying the analyses for **age group**, EOD age- and sex-adjusted incidence prevalence was 3.69/100,000 (95% CI 2.67, 4.71) in the 30 to 44 age group, 119.85 (95% CI 115.20, 124.49) in the 45 to 64 age group, and 74.30 (95% CI 71.45, 77.16) in the whole 30 to 64 age group. Table 1 reports prevalence of all-cause EOD by age and sex.

Among the 258 prevalent cases, median age at onset of the first cognitive or behavioral symptom was 60 years (IQR 56 to 63). Median age at dementia diagnosis was 63 years (IQR 59 to 66). Table 2 reports demographic characteristics of the **prevalent** cases. Ninety-nine patients (38.4%) were first cognitively assessed when they were still in the MCI stage. The remaining 159 patients were assessed when a dementia syndrome could already be diagnosed. Of all cases, 157 had been retrospectively identified. Of these, 89 were referred to one of the two recruiting neurologic CDCDs and examined by one of the study neurologists, whereas 68 were first seen in geriatric CDCDs and then referred to the neurology clinics, where they were directly examined by one of the study neurologists (n = 10) or received careful review of medical records (n = 58). The remaining 101 patients were prospectively identified and examined by one of the study neurologists. Among all cases, 47 had been seen previously in a psychiatric clinic and then referred to one of the CDCDs. Of these, 10 eventually received a diagnosis of AD dementia, 31 of a disease of the FTD spectrum, and 7received other dementia diagnoses.

All identified patients underwent brain imaging either with structural MRI (n = 206) or CT scan (n = 52). Among all cases, 131 also had lumbar puncture for measurement of CSF biomarkers, 51 had PET imaging (48 FDG, 3 amyloid), and 41 genetic analysis leading to the identification of a genetic cause in 14 cases (4 AD, 4 FTD spectrum, one hereditary diffuse leukoencephalopathy with spheroids [HDLS], 2 CADASIL, and 3HD). At the last visit performed within 6 months before census date, 88 patients (34.1%) had had a dementia of mild severity (defined as having Mini-Mental State Examination score[MMSE] >21), 83 (32.1%) had dementia of moderate severity (MMSE 10 to 20), 50 (19.3%) had dementia of advanced severity (MMSE <10), and for 37 patients (14.3%) MMSE was not available.

TABLE 2 Demographic and clinical characteristics of the 258 prevalent cases at census date

Characteristics of study subjects	Total (n = 258)		Male (n = 123)		Female (n = 135)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Age at onset, years	58.8 (5.0)	60 (56–63)	58.8 (4.9)	59 (57–63)	58.8 (5.2)	60 (56–63)
Age at diagnosis, years	62.0 (5.5)	63 (59–66)	62 (5.5)	63 (59–66)	62.1 (5.6)	63 (59–66)
Months between onset and diagnosis	38.7 (29.2)	31 (18–51)	37.9 (30.0)	29 (17–50)	39.5 (25.5)	33 (18–52)
Years of education[a]	9.0 (3.8)	8 (5–13)	9.3 (3.6)	8 (7–13)	8.8 (4.0)	8 (5–13)
MMSE score at diagnosis[a]	22.0 (5.2)	23 (19–26)	22.7 (5.5)	24 (20–26)	21.5 (4.8)	22 (19–26)

IQR, interquartile range; MMSE, Mini-Mental State Examination; SD, standard deviation.
[a]Years of education and MMSE score available in 224 (male/female: 110/114) and 189 (male/female: 88/101) patients, respectively.

TABLE 3 Clinical diagnoses of prevalent cases

Clinical diagnosis	N	%	M/F
Total	258	100	123/135
AD	113	43.8	36/77
FTD spectrum	78	30.2	44/34
Vascular dementia	24	9.3	16/8
Lewy body dementia	9	3.5	5/4
Leukoencephalopathy	7	2.7	5/2
Parkinson disease dementia	7	2.7	6/1
Alcoholic dementia	4	1.5	3/1
Cerebral amyloid angiopathy	3	1.2	2/1
Dementia in Huntington disease	3	1.2	2/1
NOS	10	3.9	4/6

AD, Alzheimer's dementia; FTD, frontotemporal dementia; NOS, dementia not otherwise specified.

3.3 | Clinical variants

AD was the most frequent clinical diagnosis, followed by clinical syndromes of the FTD spectrum, VaD, and LBD (Table 3). Other pathologies such as leukoencephalopathies including one case of HDLS and two cases of CADASIL, three cases of HD, and one case of JCD were also found.

Among all AD dementia patients, 69.9% had amnestic onset, 17.7% had lvPPA, 7.9% had PPA, and 4.4% had behavioral/dysexecutive variant AD. Among all FTD spectrum patients, 62.8% had the bvFTD, 15.3% semantic variant of primary progressive aphasia (svPPA), 2.5% had agrammatic/non-fluent primary progressive aphasia (nfvPPA), 7.6% had FTD with amyotrophic lateral sclerosis (FTD-ALS) either with behavioral or non-fluent onset, 6.4% had CBS, and 5.3% had PSP. When looking at all the clinical variants together, the most frequent clinical presentation of EOD was the amnestic variant of AD, followed by bvFTD, lvPPA, svPPA, and PCA. There were no significant differences in diagnostic delay between the different clinical syndromes ($P = .252$). As expected, CSF Aβ 1-42 median value was 445 pg/mL in AD dementia patients (IQR 154), whereas it was 865 pg/mL in non-AD dementia patients (IQR 452). CSF total-tau median value was 567 pg/mL in AD (IQR 426) and 265 pg/mL in non-AD (IQR 257). Phospho-tau median value was 79 pg/mL in AD (IQR 44) and 44 pg/mL in non-AD (IQR 32).

Prevalence of AD dementia only was 32.55/100,000 in the whole 30 to 64 age group and 53.07 in the 45 to 64 age group. Prevalence of syndromes of the FTD spectrum was 22.47/100,000 in the whole 30 to 64 age group and 36.49 in the 45 to 64 age group. Prevalence calculated considering these two common neurodegenerative dementia syndromes (AD dementia and FTD) together was 55.02/100,000 in the whole 30 to 64 age group and 89.56/100,000 in the 45 to 64 age group. Table 4 reports the case number, prevalence, and incidence of the different clinical variants of AD and FTD spectrum.

4 | DISCUSSION

We report the incidence and prevalence of all the phenotypes of EOD including different variants of AD and FTD by conducting a population-based study of all the cases of dementia with onset before age 65 in the province of Modena, Northern Italy. We specifically aimed to investigate the epidemiology of all the different clinical presentations of dementia in young patients, including clinical variants of both AD and FTD, which—to the best of our knowledge—have never been investigated all together. We found that, among all the presentations, the most frequent is the amnestic variant of AD, followed by the behavioral variant of FTD, and by the logopenic variant of AD. This observation may have important clinical implications, since knowing the relative frequency of presentations will directly benefit the reasoning of clinicians faced with young patients with cognitive symptoms.

We found an overall EOD incidence of 6.5/100,000 inhabitants per year by adjusting for the demographical features (sex and age) of the European standard population. To our knowledge, no previous studies have corrected incidence for the demographic features of the specific populations in which they were carried out, limiting the possibility to truly compare results among different studies. We found a crude incidence of EOD of 13.2/100,000 persons at risk in the age range 30 to 64, and 22.1/100,000 persons at risk in the age range 45 to 64. These data are consistent with those reported by the most recent incidence study on EOD conducted in the Girona region of Spain using a dementia

TABLE 4 AD and FTD presentations: crude incidence (period January 1, 2016 to June 30, 2019) and crude prevalence on census day (June 30, 2019) per 100,000 persons 30 to 64 years of age

Clinical subtypes	Prevalent clinical subtypes N (%)	Prevalence on June 30, 2019	Incident clinical subtypes N (%)	Incidence (January 1, 2016-June 30, 2019)
AD	113 (100)	32.6	61 (100)	5.0
Amnestic	77 (68.1)	22.2	45 (73.8)	3.7
Posterior cortical atrophy (PCA)	8 (7.1)	2.3	2 (3.3)	0.16
Logopenic variant (lvPPA)	20 (17.8)	5.8	10 (16.4)	0.8
Behavioral/dysexecutive	4 (3.5)	1.2	/	/
NOS	4 (3.5)	1.2	4 (6.5)	0.3
FTD SPECTRUM	78 (100)	22.5	52 (100)	4.3
Behavioral variant (bvFTD)	49 (62.8)	14.1	32 (61.5)	2.6
Semantic variant (svPPA)	11 (14.1)	3.2	9 (17.3)	0.74
Non-fluent primary progressive aphasia (nfvPPA)	2 (2.6)	0.6	2 (3.8)	0.16
FTD-ALS	6[a] (7.7)	1.7	4[b] (7.7)	0.32
Corticobasal syndrome (CBS)	5 (6.4)	1.4	2 (3.8)	0.16
Progressive supranuclear palsy (PSP)	4 (5.1)	1.2	3 (5.9)	0.25
NOS	1 (1.3)	0.3	/	/

N, number of subjects.
NOS, not otherwise specified.
[a] N = 4 bvFTD and N = 2 nfvPPA variants.
[b] N = 3 bvFTD and N = 1 nfvPPA variants.

registry, which found incidences of 13.4/100,000 person-years in the age group 30 to 64 and 22.8/100,000 person-years in the age group 45 to 64.[8] They are also comparable but slightly smaller to those obtained from the Rochester Epidemiology Project,[28] which also included cases with cognitive impairment secondary to brain tumors or chronic mental illness that, instead, we purposefully excluded from our study. Our crude incidence for the 45 to 64 age group (22.1/100,000) is almost twofold higher than the incidence of 11.5/100,000 reported by a study of all cases seen in an hospital-based study in the UK,[29] possibly reflecting a higher rate of physician consultation and specialist referral in Italy compared to other European countries.[29]

We found a prevalence of all-cause EOD of 74.3/100,000 persons at risk in the age range 30 to 64 and 119.9/100,000 persons at risk in the age range 45 to 64. This prevalence overlaps with those obtained in two recent studies conducted in Norway[7] and Australia[30] but is greater than those reported in older studies conducted in the UK[31] and Japan.[32] Of interest, even when considering the diagnoses of AD and FTD dementia only, we found a greater prevalence compared to that reported by the only prevalence study on EOD conducted in Italy, in the Brescia province.[33] That we found greater prevalence relative to older studies may reflect the general improvement in dementia identification and diagnosis seen over the past decade worldwide, which is a consequence not only of educational interventions to improve primary care practice,[34] but also of the general improvement in the diagnostic ability through the use of biomarkers, which were not easily available in clinical practices a decade ago. In addition, the high prevalence reported in the present study may be related to the high level of diagnostic accuracy and to the widespread recruitment based on an inclusive and easily accessible dementia care network. Alternatively, the greater prevalence may reflect a really larger incidence and/or survival in our population.

We found that the most frequent cause of EOD is AD dementia. This is consistent with previous epidemiological studies on EOD incidence[8,35] and with most studies on EOD prevalence.[7,36] The few prevalence studies that found that AD dementia was the second prevalent cause of EOD after VaD were either not population-based but conducted on hospital-based cohorts,[37,38] or carried out in countries such as Japan,[32] with a known greater incidence of stroke relative to the Caucasian population in presenile ages.[39] A recent EOD prevalence study, which found AD second to alcohol-related dementia, may have been biased by over-diagnosis of the latter by clinicians who were not dementia specialists, as stated by the authors.[30] Of interest, in our series, there were no differences in diagnostic delay between the different clinical syndromes, suggesting that even challenging cases such as those presenting with behavioral symptoms were identified promptly by the study network.

With regard to the clinical variants of AD dementia, their incidence or prevalence has not been investigated in population-based studies yet, possibly because their characterization is relatively recent and only subsequent to the advent of AD biomarkers.[15,16] In our population-based study the non-amnestic variants represented 34% of all AD dementia cases, with lvPPA being the most frequent. This is

comparable to one of the two previous hospital-based studies conducted on cohorts of patients referred to dementia clinics, which reported a relative proportion of non-amnestic presentations of 32%,[40] but is lower than the one conducted on consecutive cases seen at a specialist dementia center, which reported a proportion of non-amnestic presentations of 64%[6] and might have been biased by a focus on atypical presentations. As for the FTD spectrum, one previous study conducted in 2007-2009 reported the incidence of bvFTD, svPPA, CBS, and PSP, but not of nfvPPA and ALS-FTD.[8] Our incidence values are consistent for CBS and PSP, but higher for bvFTD and svPPA, possibly reflecting the fact that the refinement of diagnostic criteria for the latter variants was subsequent to that study and that our diagnosis was based on an in-depth clinical assessment and supported by the use of biomarkers. There are no comprehensive studies on prevalence of the clinical presentations of the FTD spectrum.

A major strength of our study was the ability to merge several sources of health data from a capillary network of centers for the diagnosis and care of dementia, movement disorders and motor neuron disease, and residential care facilities, which allowed the identification of all EOD cases in a defined population. Another strength is that all cases underwent in-depth clinical assessment in which the diagnosis was often supported by the use of biomarkers thus improving diagnostic accuracy. Finally, all cases were either examined directly or reviewed by a team of neurologists of a third-level dementia center, to ensure consistency in the diagnosis.

The present study also has limitations. First, we used a mixed retrospective-prospective design for case inclusion, possibly leading to lower sensitivity in the earlier years of the study. For this reason, we purposefully decided to calculate incidence over the last 3.5 years of the study period, during which we detected stable incidence rates over time. Second, we acknowledge that we might have underestimated cases of alcoholic dementia because in the Modena province patients with suspected alcohol abuse are usually referred to specific psychiatric services and not to the dementia network. However, we did include those patients with alcoholic dementia in whom dementia was the principal consequence of alcohol abuse, that is, they had *pure* alcoholic dementia, not confounded by other comorbidities. Third, we purposefully excluded patients with cognitive impairment and a long history of psychiatric disorders; this might have led us to underestimate cases of neurodegenerative dementia syndromes possibly co-occurring in those patients. However, these patients were not included in previous studies.[8,30,33] In addition, psychiatric services generally refer to our dementia network patients with suspected neurocognitive disorders (for the present study 47 EOD were included from that source); therefore we do not expect to have substantially missed cases for this reason. Finally, we did not use cross-matching with data from other provinces of the Emilia Romagna region and may have missed patients referred to dementia centers outside of the Modena province. However, this is very unlikely, because dementia drug distribution and social care facilities in Italy are strictly linked to the place of residence.

The result of this population study may contribute to a better understanding of epidemiology and clinical management of EOD, and its different clinical presentations, thus helping to optimize cost-effective dementia care organization, and ultimately to improve quality of life for patients and caregivers.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest.

REFERENCES

1. Sikes P, Hall M. The impact of parental young onset dementia on children and young people's educational careers. *Br Educ Res J*. 2018;44:593-607.
2. Sakata N, Okumura Y. Job loss after diagnosis of early-onset dementia: a matched cohort study. *J Alzheimers Dis*. 2017;60:1231-1235.
3. Lambert MA, Bickel H, Prince M, et al. Estimating the burden of early onset dementia; systematic review of disease prevalence. *Eur J Neurol*. 2014;21:563-569.
4. Draper B, Cations M, White F, et al. Time to diagnosis in young-onset dementia and its determinants: the INSPIRED study. *Int J Geriatr Psychiatry*. 2016;31:1217-1224.
5. Mendez MF. Early-onset Alzheimer disease. *Neurol Clin*. 2017;35:263-281.
6. Mendez MF, Lee AS, Joshi A, Shapira JS. Nonamnestic presentations of early-onset Alzheimer's disease. *Am J Alzheimers Dis Other Demen*. 2012;27:413-420.
7. Kvello-Alme M, Brathen G, White LR, Sando SB. The prevalence and subtypes of young onset dementia in central norway: a population-based study. *J Alzheimers Dis*. 2019;69:479-487.
8. Garre-Olmo J, Genis Batlle D, del Mar Fernandez M, et al. Incidence and subtypes of early-onset dementia in a geographically defined general population. *Neurology*. 2010;75:1249-1255.

9. Newens AJ, Forster DP, Kay DW. Death certification after a diagnosis of presenile dementia. *J Epidemiol Community Health*. 1993;47:293-297.
10. Association AP. Diagnostic and statistical manual of mental disorders: DSM-5. 52013.
11. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:263-269.
12. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43:250-260.
13. Skrobot OA, Black SE, Chen C, et al. Progress toward standardized diagnosis of vascular cognitive impairment: guidelines from the Vascular Impairment of Cognition Classification Consensus Study. *Alzheimers Dement*. 2018;14:280-292.
14. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134:2456-2477.
15. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76:1006-1014.
16. Crutch SJ, Schott JM, Rabinovici GD, et al. Consensus classification of posterior cortical atrophy. *Alzheimers Dement*. 2017;13:870-884.
17. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. *Neurology*. 2017;89:88-100.
18. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord*. 2007;22:1689-1707; quiz 837.
19. Peavy GM, Jacobson MW, Goldstein JL, et al. Cognitive and functional decline in Huntington's disease: dementia criteria revisited. *Mov Disord*. 2010;25:1163-1169.
20. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology*. 1996;47:1-9.
21. Zerr I, Kallenberg K, Summers DM, et al. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. *Brain*. 2009;132:2659-2668.
22. Ahmed RM, Murphy E, Davagnanam I, et al. A practical approach to diagnosing adult onset leukodystrophies. *J Neurol Neurosurg Psychiatry*. 2014;85:770-781.
23. Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser MG. Cadasil. *Lancet Neurol*. 2009;8:643-653.
24. Elahi FM, Miller BL. A clinicopathological approach to the diagnosis of dementia. *Nat Rev Neurol*. 2017;13:457-476.
25. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7:270-279.
26. Emilia-Romagna R. Popolazione per sesso ed età. *Indici di stato*. 2020.
27. Eurostat. Revision of the European Standard Population - Report of Eurostat's task force. https://ec.europa.eu/eurostat/web/products-manuals-and-guidelines/-/KS-RA-13-0282013.
28. Knopman DS, Petersen RC, Cha RH, Edland SD, Rocca WA. Incidence and causes of nondegenerative nonvascular dementia: a population-based study. *Arch Neurol*. 2006;63:218-221.
29. Jakubowski E. Health care system in the EU: a compatative study. 1998.
30. Withall A, Draper B, Seeher K, Brodaty H. The prevalence and causes of younger onset dementia in Eastern Sydney, Australia. *Int Psychogeriatr*. 2014;26:1955-1965.
31. Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. *J Neurol Neurosurg Psychiatry*. 2003;74:1206-1209.
32. 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;40:2709-2714.
33. Borroni B, Alberici A, Grassi M, et al. Prevalence and demographic features of early-onset neurodegenerative dementia in Brescia County, Italy. *Alzheimer Dis Assoc Disord*. 2011;25:341-344.
34. International. AsD. *World Alzheimer Report 2011: The Benefits of Early Diagnosis and Intervention*. London: Alzheimer's Disease International; 2011.
35. Mercy L, Hodges JR, Dawson K, Barker RA, Brayne C. Incidence of early-onset dementias in Cambridgeshire, United Kingdom. *Neurology*. 2008;71:1496-1499.
36. Vieira RT, Caixeta L, Machado S, et al. Epidemiology of early-onset dementia: a review of the literature. *Clin Pract Epidemiol Ment Health*. 2013;9:88-95.
37. McMurtray A, Clark DG, Christine D, Mendez MF. Early-onset dementia: frequency and causes compared to late-onset dementia. *Dement Geriatr Cogn Disord*. 2006;21:59-64.
38. Fujihara S, Brucki SM, Rocha MS, Carvalho AA, Piccolo AC. Prevalence of presenile dementia in a tertiary outpatient clinic. *Arq Neuropsiquiatr*. 2004;62:592-595.
39. Aho K, Reunanen A, Aromaa A, Knekt P, Maatela J. Prevalence of stroke in Finland. *Stroke*. 1986;17:681-686.
40. Koedam EL, Lauffer V, van der Vlies AE, van der Flier WM, Scheltens P, Pijnenburg YA. Early-versus late-onset Alzheimer's disease: more than age alone. *J Alzheimers Dis*. 2010;19:1401-1408.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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