Incidence of Young Onset Dementia in Central Norway: A Population-Based Study

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Abstract.
Background: The epidemiology of young onset dementia is little researched compared to late onset dementia. Information on incidence rates is vital for medical professionals, and for government planning purposes.
Objective: To determine the incidence of young onset dementia in a defined catchment area of central Norway.
Methods: The target area was Trøndelag county in central Norway with a total population of 449,796 inhabitants per January 1, 2016. We applied multiple case ascertainment strategies with sources from both primary and secondary healthcare facilities. Included patients received a diagnosis of dementia according to DSM-IV in the ages 30 to 64 years during the years 2015–2017. Subtypes of dementia were diagnosed according to standardized criteria. Incidence rates for dementia and Alzheimer's disease with dementia were calculated according to age and sex.
Results: A total of 89 incident cases were included. Incidence rates for dementia were 14.8 and 25.0 per 100,000 person-years for the age range 30–64 and 45–64, respectively. Corresponding incidence rates for Alzheimer's disease were 6.7 and 11.8. Alzheimer's disease represented half of all dementias. A majority of patients above the age of 50 had neurodegenerative disease, whereas non-degenerative disorders were more prevalent in younger patients.
Conclusion: Young onset dementia is a significant contributor to the overall occurrence of dementia in central Norway, and Alzheimer's disease is by far the most common diagnosis.

Keywords: Alzheimer's disease, early onset dementia, epidemiology, frequency, incidence, occurrence, young onset dementia

INTRODUCTION

There has been extensive research on the epidemiology of late onset dementia, and growing evidence of an increasing incidence of dementia with increasing age [1, 2]. In contrast, the epidemiology of young onset dementia (YOD) is little researched, particularly regarding the incidence [3].

YOD, also known as early onset dementia, is commonly defined as dementia occurring before the age of 65. Although it is relatively uncommon when compared to late onset dementia, it poses different challenges not only to the patients, their families and caregivers, but also to medical professionals and healthcare services in general. Politicians and governing institutions should have reliable and updated data on the occurrence of YOD when planning for the expenses and relevant healthcare provisions for this particularly vulnerable group of patients.

To our knowledge, only two research groups have researched the incidence of dementia in persons

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younger than 65 years in Scandinavia. Hagnell et al. prospectively investigated a population of approximately 2,500 people, and gave incidence rates of dementia over two periods (1947–1957 and 1957–1972) [4]. However, the sample size was too small to give reliable estimates on the incidence of dementia under the age of 65. Andreasen et al. reported incidence rates on the various subtypes of dementia in the years 1990–1995, but provided no data on the overall incidence of dementia [5]. Both studies were performed in Sweden, and the majority of patients included were older than 64 years. We have not been able to identify any published epidemiological data from Scandinavia focusing solely on the incidence of YOD.

Even outside Scandinavia, the number of studies on this topic is remarkably low and has shown varying incidence rates of YOD. In the UK, Mercy et al. found rates of 11.5 cases per 100,000 person-years for the age range 45–64, while in Argentina, Abraham Sanchez et al. found 11 cases per 100,000 in the age range 21–64 [6, 7]. In Spain, Garre-Olmo et al. reported incidence rates of 13.4 in the age category 30–64 years [8]. Other groups have reported various rates, possibly due to differences in study design [9–13].

We have recently published a report on the prevalence of YOD in central Norway [14]. The main findings were that the prevalence figures were higher than previous estimates from the UK and Japan, but similar to a study from Australia, with the prevalence of Alzheimer's disease (AD) being particularly high [15–18]. In the present report, we give data on the incidence of YOD and young onset AD based on the same material.

MATERIAL AND METHODS

Population base and patients

The current study was performed in the county of Trøndelag in central Norway, consisting of both rural and urban areas with a population of 449,769 as of January 1, 2016.

We identified patients based on the same multiple case ascertainment as previously reported, and for details on the population base, sources, case ascertainment, and clinical assessment of the participants, we refer to Kvello-Alme et al. [14]. Incidence rates were calculated based on the three years 2015, 2016, and 2017.

Incident cases were patients in the age range 30–64 years residing in Trøndelag when receiving a diagnosis of dementia during the study period. Patients with Huntington's disease, and patients who had received a clinical diagnosis of mild cognitive impairment due to AD, were especially challenging as dementia in such cases is not always formally diagnosed in hospital records. In order to avoid bias in the calculations, we only included patients for whom the age of dementia diagnosis could be ascertained.

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK Midt 2014/487). The research group was allowed to include patients who did not sign a formal consent, but in such cases only information on date of birth, time, and age at diagnosis and subtype of dementia were collected. The accuracy of the diagnoses was individually evaluated by MKA and SBS.

Diagnosis

All patients met the clinical criteria for dementia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. [19]. Subtype of dementia was determined based on all available information, consistent with validated clinical diagnostic criteria for dementia disorders as previously described [20–29]. Details regarding the validation of diagnoses are given in Kvello-Alme et al. 2019 [14]. Despite the presence of biomarkers, diagnoses were based on clinical criteria, including the diagnosis of AD.

Patients with Huntington's disease with dementia, and patients with intellectual disability with dementia were recruited through specialized care units. The diagnoses of these patients were not subjected to further evaluation by the research team, and none of them signed a formal consent.

Analysis

Incidence rates of dementia for both sexes were calculated in five-year bands from 30–64 years, as well as for the total age groups of 30–64 and 45–64 years, consistent with the prevalence figures. For the clinical diagnosis of AD, we also calculated incidence rates for the age category 50–64 years. The denominator and total number of person-years were calculated by adding all person-years aged between 30 and 64 from 2015 to the end of 2017. We did not adjust the denominator for prevalent cases of YOD

due to the low frequency of the condition, as it was unlikely to affect the results [6, 8]. The Poisson distribution served as the basis for 95 % confidence interval calculations. Mean age at diagnosis was calculated for every subtype of dementia. Differences in age at diagnosis between subtypes and gender were explored with a two-sample *t*-test with equal variances, Wilcoxon rank-sum test or one-way ANOVA, all with a significance level of 0.05.

RESULTS

A total of 89 patients met the inclusion criteria for this study. Thirty-seven patients were non-consenting and mainly made known to us through our clinical work and/or by collaborating physicians in other departments. The distribution of diagnoses among non-consenting patients was as follows: 15 intellectual disability with dementia, 5 AD, 3 vascular dementia, 3 alcohol-related dementia, 2 Parkinson's disease with dementia/dementia with Lewy bodies, 1 frontotemporal dementia (FTD), 1 progressive supranuclear palsy, 1 acquired brain injury, 1 metabolic encephalopathy, 1 normal pressure hydrocephalus, 1 Huntington's disease with dementia, and 3 unspecified.

Every patient received their diagnosis at hospital level, so all had relevant hospital records that were reviewed in the diagnostic process. Among 52 consenting patients, 48 (92%) had performed Mini-Mental Status Examination and a Clock Drawing Test, 39 (75%) had performed a Trail Making Test, and 34 (65%) a CERAD Ten Word Test. Furthermore, 49 patients (94%) underwent cerebral MRI, 39 (75%) were evaluated by lumbar puncture with the analysis of core biomarkers for AD, and 38 (73%) were examined with both MRI and cerebrospinal fluid (CSF) analysis. Among patients with clinical AD the corresponding figures for the performance of biomarkers (MRI, CSF, or both) were 34 (97%), 33 (94%), and 32 (91%). An interview with a close caregiver was performed in 88% of consenting cases.

Table 1 provides information on the diagnoses by gender and age at diagnosis for incident cases. As expected from our prevalence analysis, neurodegenerative disease constituted the main category of dementia, accounting for roughly two thirds of all dementias. The clinical diagnosis of AD was the most incident subtype of dementia representing 74% of the neurodegenerative diseases, and nearly half of all

Table 1
Diagnoses and age at diagnosis (AAD) for incident cases of young onset dementia in Trøndelag 2015–2017

DIAGNOSIS	Total			Male		Female	
	N	%	AAD	N	AAD	N	AAD
Degenerative dementias	54	60.7	59.2	23	59.3	31	59.2
AD	40	44.9	60.0	16	59.4	24	60.3
FTD	5	5.6	57.0	2	60.0	3	55.0
HD with dementia	1	1.1	42.0	–	–	1	42.0
PDD/DLB	5	5.6	58.8	4	58.5	1	60.0
PCA	1	1.1	60.0	1	60.0	–	–
PSP	1	1.1	62.0	–	–	1	62.0
CJD	1	1.1	57.0	–	–	1	57.0
Vascular dementia	7	7.9	52.6	3	53.3	4	52.0
ARD	6	6.7	58.8	4	59.8	2	57.0
NPH	1	1.1	58.0	1	58.0	–	–
ID with dementia	15	16.9	53.3	4	54.8	11	52.8
Secondary dementias	2	2.2	51.0	2	51.0	–	–
Unspecified	4	4.5	60.0	4	60.0	–	–
All	*89*	*100*	*57.5*	*41*	*58.1*	*48*	*57.0*

AD, Alzheimer's disease; FTD, frontotemporal dementia; HD, Huntington's disease with dementia; PDD, Parkinson's disease with dementia; DLB, dementia with Lewy bodies; PCA, posterior cortical atrophy; PSP, progressive supranuclear palsy; CJD, Creutzfeldt Jacob's disease; ARD, alcohol related dementia; NPH, normal pressure hydrocephalus; ID, intellectual disability.

dementias. There was a total of seven incident cases of vascular dementia. Of these, four were post stroke dementias of which one also experienced gradual progression after the stroke, and one with subarachnoid hemorrhage. We identified two patients with secondary dementia; one with metabolic disease, and one with acquired brain injury.

There were no significant differences in age at diagnosis between subtypes of dementia, except for AD versus either vascular dementia ($p = 0.01$) or intellectual disability with dementia ($p = 0.001$). Patients with non-degenerative diseases received their diagnoses at a significantly earlier age than patients with degenerative diseases (54.9 versus 59.2 years, $p = 0.0007$). The only patient with Huntington's disease with dementia was diagnosed at the age of 42, which is considerably lower than every other subgroup, but the low frequency does not provide for a meaningful comparison. There were no significant differences in age at diagnosis by gender.

Tables 2 and 3 give incidence rates of overall dementia and AD according to age and gender in the study population, displaying an incremental pattern with increasing age, especially after the age of 50. As no patient with AD received a diagnosis of dementia prior to this age, we only report five-year incidence rate bands of AD from the ages 50 to 64 years.

Table 2
Age- and gender-specific incidence rates of dementia 2015–2017

	Denominators (person-years)		All			Male			Female		
Age range	Male	Female	n	Rate*	95% CI	n	Rate*	95% CI	n	Rate*	95% CI
30–34	45 208	41 870	0	0.0	0.0–4.2**	0	0.0	0.0–8.2**	0	0.0	0.0–8.8**
35–39	43 328	39 666	2	2.4	0.3–8.7	1	2.3	0.1–12.9	1	2.5	0.1–14.1
40–44	46 767	43 948	2	2.2	0.3–8.0	0	0.0	0.0–7.9**	2	4.6	0.6–16.4
45–49	48 399	46 461	2	2.1	0.3–7.6	0	0.0	0.0–7.6**	2	4.3	0.5–15.6
50–54	44 655	42 448	18	20.7	12.3–32.7	10	22.4	10.7–41.2	8	18.9	8.1–37.1
55–59	41 357	39 621	23	28.4	18.0–42.6	8	19.3	8.4–38.1	15	37.9	21.2–62.4
60–64	38 414	38 200	42	54.8	39.5–74.1	22	57.3	35.9–86.7	20	52.4	32.0–80.9
30–64	*308 128*	*292 214*	*89*	*14.8*	*11.9–18.2*	*41*	*13.3*	*9.6–18.1*	*48*	*16.4*	*12.1–21.8*
45–64	*172 825*	*166 730*	*85*	*25.0*	*20.0–31.0*	*40*	*23.1*	*16.5–31.5*	*45*	*27.0*	*19.7–36.1*

*Rate per 100 000 person-years. **One-sided, 97.5% CI.

Table 3
Age- and gender-specific incidence rates of Alzheimer's disease 2015–2017

	All			Male			Female		
Age-range	N	Rate*	95 % CI	N	Rate*	95 % CI	N	Rate*	95 % CI
50–54	6	6.9	2.5–15.0	4	9.0	2.4–22.9	2	4.7	0.6–17.0
55–59	10	12.4	5.9–22.7	2	4.8	0.6–17.5	8	20.2	8.7–39.8
60–64	24	31.3	20.1–46.6	10	26.0	12.5–47.9	14	36.7	20.0–61.5
30–64	*40*	*6.7*	*4.8–9.1*	*16*	*5.2*	*3.0–8.4*	*24*	*8.2*	*5.3–12.2*
45–64	*40*	*11.8*	*8.4–16.0*	*16*	*9.3*	*5.3–15.0*	*24*	*14.4*	*9.2–21.4*
50–64	40	16.4	11.7–22.3	16	12.9	7.4–20.9	24	20.0	12.8–29.7

*Rate per 100 000 person-years.

DISCUSSION

To our knowledge, this is the first population-based study providing incidence rates for YOD in Scandinavia, and among the few efforts to provide five-year age estimates of both YOD and young onset AD in the world.

The strengths of this study are several. The study population resides in a geographically well-defined catchment area with almost 10% of the Norwegian population. Trøndelag is representative for the national level with respect to important health, socioeconomic, and cultural aspects [30]. We made use of multiple case ascertainment, including sources from relevant primary and secondary health institutions. The departments investigating YOD in the area have a longstanding practice of comprehensive clinical assessment of patients with cognitive impairment, routinely implementing biomarkers as part of the diagnostic workup [14]. Standardized clinical criteria for the various diagnoses were applied for every case. We therefore consider this study to have a high level of clinical accuracy regarding both the presence of dementia and the categorization of subtypes.

For the age range of 30–64 and 45–64 years, the incidence rates of overall dementia were 14.8 and 25.0 per 100,000 person-years, respectively. This is remarkably similar to the corresponding rates of 13.4

and 22.8 in the study from Spain, and higher than the study from the UK (11.5 per 100,000 person-years for the latter category) [6, 8]. Our rates displayed a similar pattern to those in the Spanish study, and we confirm low rates in the 30–49 age group, followed by substantial increases in older groups.

Incidence rates for AD displayed a similar distribution as for overall dementia, but there were a few exceptions. We did not identify any patients with AD receiving a diagnosis of dementia younger than 50 years, but above this age incidence rates approximately doubled for every five years. A doubling of incidence rates of AD for every five years in these age categories has previously been shown in a large study on young onset AD from the UK, their rates being slightly lower than ours [31]. For the age category of 45–64 years we found an incidence rate of 11.8 per 100,000 person-years. This finding is similar to the study from Spain, which also provided an estimate for AD in this particular age range (11.9 per 100,000 person-years) [8].

Overall, our findings are in alignment with previous studies demonstrating that the clinical phase of neurodegeneration commonly debuts in the fifth decade, and therefore represents the majority of cases above this age, while dementia due to non-degenerative causes has a greater impact in those under the age of 50 [15, 32, 33]. This is also reflected

Table 4
Incidence rates per 100,000 person years of all dementia and Alzheimer's disease in various studies

	ALL DEMENTIA				
	Current study Norway (2019)	Garre-Olmo et al. Spain (2010)	Mercy et al. United Kingdom (2008)	Edland et al. USA (2002)	Ruitenberg et al. Netherland (2001)
30–34	0.0	0.5	–	–	–
35–39	2.4	1.1	–	–	–
40–44	2.2	2.9	–	–	–
45–49	2.1	5.1	–	–	–
50–54	20.7	14.8	–	35.6	–
55–59	28.4	32.0	–	40.2	40.0*
60–64	54.8	67.7	–	129.2	50.0*
30–64	*14.8*	*13.4*	*–*	*–*	*–*
45–64	*25.0*	*22.8*	*11.5*	*–*	*–*
N	*89*	*144*	*54*	*24*	*5*

	ALZHEIMER'S DISEASE					
	Current study Norway (2019)	Garre-Olmo et al. Spain (2010)	Mercy et al. United Kingdom (2008)	Edland et al. USA (2002)	Ruitenberg et al. Netherland (2001)	Newens et al. United Kingdom (1993)
50–54	6.7	–	–	21.3	–	4.9
55–59	12.4	–	–	16.1	0.0*	8.1
60–64	31.3	–	–	36.9	10.0*	14.5
30–64	*6.7*	*5.7*	*–*	*–*	*–*	*–*
45–64	*11.8*	*11.9*	*4.2*	*–*	*–*	*7.2*
N	*40*	*61*	*19*	*9*	*–*	*94*

*Calculated from 1000 person-years.

by a significantly lower age at diagnosis in non-degenerative dementias compared to degenerative dementias (54.9 versus 59.2 years). When examining results from earlier studies [10, 31, 32, 34], considered together with the present results, it seems there may be a "threshold age" of symptomatic neurodegeneration. However, there are a few exceptions: FTD, dementia in Huntington's disease, and AD in the context of Down's syndrome often start before the age of 50 [32, 35]. The distribution of diagnoses among the youngest illustrates this, two of them diagnosed with vascular dementia, two with dementia in connection with intellectual disability, one with FTD, and one with Huntington's disease with dementia. Table 4 lists incidence rates of YOD and AD in various studies for comparison.

The etiology in the current report is similar to that of the prevalence study carried out in the same geographical area [14], with neurodegenerative disease representing almost two-thirds of all dementias, and AD being the main subtype of dementia. AD accounted for almost half of all dementias. Although AD also represents the majority of YOD in other studies, the proportion of AD in our material is higher than that previously reported [36–38]. The reason is unclear, but there may be a bias in Norway toward diagnosing dementia due to AD rather than

lesser-known diagnoses such as FTD. Generally, and consistent with existing literature, the heterogeneity of YOD subtypes was high [39].

The proportion of cases due to intellectual disability was high. This might be due to an extensive collaboration with the two departments evaluating these patients in the target area. These specialized hospital units had comprehensive overview on their respective areas and were able to identify almost every patient they had diagnosed with dementia in the previous years. It is possible that other research groups publishing epidemiological data on YOD have focused less on persons with intellectual disability despite the substantially increased risk of AD among these patients. For this reason, we believe that the figures presented in this study are more reliable than similar reports displaying a lower frequency.

There are limitations to our study. Despite the setting of a well-organized and easily accessible healthcare system, the rates in this study are likely to be a minimum of the true incidence for several reasons. Importantly, a significant proportion of patients with dementia remain unrecognized by the healthcare services even in Norway, sometimes because dementia is not considered one of the cardinal symptoms of the condition, as in patients with traumatic brain injury or alcohol abuse. Various studies show

diverging results of undiagnosed dementia, ranging from 32 to 96% depending on study design, the organization and accessibility of the healthcare system, as well as cultural reasons that affect the degree to which patients and caregivers seek assistance from medical professionals when cognitive impairment is suspected [40–42]. However, there are important arguments as to why reports on this topic have less relevance for the current study, a key aspect being that many studies typically include late onset dementia. There are currently few estimates of the proportion of undetected dementia in younger patients. Although a meta-analysis on undetected dementia in the community suggested that the detection rate *is* lower for people with dementia at earlier ages; only five of the 23 studies cited actually included patients under the age of 65 [43]. The authors of the meta-analysis acknowledged that several studies drew conclusions contradictory to their overall results, and called for further investigations on the association with age. A healthcare system's ability to recognize and accurately diagnose dementia may be closely associated with the degree of the condition, especially in younger persons, such that early stages could be expected to be missed more often than in older individuals [40, 44]. However, the little that is to be found with relevance for younger patients indicated lower impairment at the time of diagnosis than in patients 65 years of age or older [8, 45]. Clearly, more research is warranted. Equally important, the rate of undetected dementia is lower in high-income countries, such as Norway [43].

Furthermore, studies on existing, though undiagnosed dementia are usually performed in a primary care setting. The case identification process in the current study included secondary, as well as primary healthcare sources. This is perhaps a more relevant approach when investigating the epidemiology of YOD, as studies show that most of these patients receive their diagnosis at hospitals [14, 46]. However, a study from Denmark found that a hospital-registered diagnosis of YOD could only be confirmed in 59% of cases, whereas the precision level for all dementia was 86% [47, 48]. It is therefore quite possible that dementia in younger patients may be over-, rather than underdiagnosed. Throughout our own investigatory process, numerous patients were discovered with a registered diagnosis of dementia, but who were clearly not demented. The potential uncertainty of such registered diagnoses, even at hospital level, in our opinion is an important aspect when evaluating the precision of research based solely on

information from registers, without the diagnoses being individually confirmed by researchers. This underlines how important it is to use a study design that will reduce undiagnosed and wrongly-diagnosed YOD to a minimum.

In summary, and with such concerns in mind, this report based on multiple case ascertainment and careful examination of every participant in the study, provides updated and minimum estimates of the incidence of YOD and young onset AD in Norway.

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