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Marte Kvello-Alme

Young Onset Dementia in Central Norway

Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of Philosophiae Doctor
Faculty of Medicine and Health Sciences
Department of Neuromedicine and Movement Science

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Levanger, June 2021

Marte Kvello-Alme

3 LIST OF PAPERS

Paper I

Marte Kvello-Alme, Geir Bråthen, Linda R. White, Sigrid Botne Sando.

The Prevalence and Subtypes of Young Onset Dementia in Central Norway: A Population-Based Study.

JAD 2018

Paper II

Marte Kvello-Alme, Geir Bråthen, Linda R. White, Sigrid Botne Sando.

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

JAD 2019

Paper III

Marte Kvello-Alme, Geir Bråthen, Linda R. White, Sigrid Botne Sando.

Time to Diagnosis in Young Onset Alzheimer's Disease in Central Norway: A Population-Based Study.

JAD 2021

4 SUMMARY IN ENGLISH

Background and objectives

Dementia is one of the most frequent causes of illness and death in the world, and has social and economic impact on people and communities worldwide. Alzheimer's disease is the leading cause of all dementia, a syndrome caused by cognitive impairment interfering with the performance of everyday activities. It is characterized by a slowly progressive deterioration of cognitive functions such as memory, orientation and speech. As is the case for all neurodegenerative dementia disorders, Alzheimer's disease develops over decades before eventually disrupting a person's independency. Alzheimer pathology progresses in the brain at least a decade before signs of cognitive impairment appear. Often, several years pass before symptoms are recognized as such. For many years, the presence of dementia was obligatory for the diagnosis of Alzheimer's disease. More recent diagnostic criteria have made it possible to diagnose the disease in the stage of mild cognitive impairment, a pre-dementia phase characterized by cognitive impairment with preserved independency. In this stage, application of biomarkers was of particular importance. Diagnostic criteria for other neurodegenerative cognitive disorders have since developed in a similar way, with the positive effects of patients being recognized in an earlier phase, and researchers being able to identify dementing pathology at less advanced stages. Identification of disease as early as possible will be crucial in the event of medical treatment emerging in the future.

Research on the epidemiological aspects of cognitive disorders can be challenging. As age is the major risk factor for dementia, the majority of research on cognitive disorders has focused on late onset dementia, characterized by symptoms appearing after the age of 65. However, dementia is not limited to older populations. Although research is scarce, younger persons can also be affected. Young onset dementia is defined as dementia occurring before the age of 65.

As young onset dementia is a low frequency condition, research on epidemiological aspects is especially laborious, and requires a larger catchment area compared to studies on older populations. A majority of studies presenting epidemiological estimates of dementia have typically been designed to target disabilities among persons above the age of 60 to 70 years, leading to the specific bias of low numbers in younger subgroups. The estimates of young onset dementia provided in these studies are therefore of lower precision, though frequently cited in research, and by governments budgeting the costs of healthcare.

There have only been a few publications focusing on the prevalence and incidence of dementia in younger persons. In these studies, estimates vary substantially. Differences in study design, cultural attitudes, as well as disparities within the healthcare systems, account for most of the discrepancies. Importantly, some studies are based on high quality dementia

registries or tertiary clinics, others are community based; the former providing better diagnostics and higher specificity, the latter a lower level of diagnostic verification but higher sensitivity. Though young patients are likely to be assessed in hospitals, consensus exists that a population-based approach is preferred.

The main object of "UngDemens I Trøndelag" was to explore epidemiological aspects of young onset dementia in a defined catchment area in central Norway (Trøndelag). A large population, in combination with a multiple sourced case ascertainment process, the routine employment of biomarkers such as magnetic resonance imaging and cerebrospinal fluid analysis in hospitals, and a meticulous review of every participant included, provided us with a relatively large dataset of high clinical accuracy.

The first and second publication provided estimates on the prevalence, incidence and subtypes of dementia, while the third article focused on the diagnostic delays and the pathway to diagnosis for young onset Alzheimer's disease, a frequent cause of dementia among people under the age of 65.

Material and methods

The project was performed in Trøndelag, a geographically and administratively defined area with a population of almost 450 000. Trøndelag is heterogeneous in the distribution of urban and rural areas, hospital sizes, and the population is representative of that of the rest of the country.

Healthcare in Norway is largely publicly organized, and readily accessible. All patients are assigned to a general practitioner, usually responsible for all referrals to hospitals. Though a diagnosis of dementia in the elderly is frequently made by community healthcare services, patients with suspected cognitive impairment under the age of 65 are evaluated by a qualified hospital physician.

The primary source of patient identification was the Department of Neurology, University Hospital of Trondheim, and the memory clinic of the Department of Psychiatry, Levanger Hospital. Both departments are main referral sites of YOD in their catchment area, covering over 90 % of the target area. Secondary sources were hospital records from all three hospitals in the target area, specialized outpatient services for individuals with intellectual disabilities in both Trondheim and Levanger, and collaborating physicians in relevant hospital departments in Trøndelag. At a community level we worked closely with dementia coordinators and other relevant healthcare workers in frequent contact with young patients with cognitive disorders. Healthcare workers at every nursing home were individually contacted by telephone to ensure patients at all stages of the disease were identified. A regional centre for Huntington's disease provided information on patients with dementia. The inclusion period was between July 2014 and July 2018.

The project accepted all patients diagnosed with young onset dementia or mild cognitive impairment due to Alzheimer's disease. Patients were individually verified by researchers either by personal assessment, or by reviewing referrals from the general practitioner and relevant hospital notes. A telephone interview with a close family member was conducted. The project collected various data on demographics, time lags, initial symptoms, and results of hospital investigations. Included patients were either consenting or non-consenting. In cases where patients did not consent, the Regional Committee for Medical and Health Research Ethics allowed the project to include participants to the extent that we only collected data on age, sex and diagnosis. Validated diagnostic criteria were applied for all diagnoses.

Results

The project identified a total of 410 patients who met the inclusion criteria. Of these, 390 patients had a diagnosis of dementia on census day. Close to 80 % of dementias were caused by a neurodegenerative disease in an otherwise heterogeneous group of dementia subtypes, identifying 17 different causes in total. Alzheimer's disease was the most frequent cause of dementia, accounting for approximately 55 % of all dementias. There were no significant differences in sex.

A total of 171 of the prevalent cases were between the age of 30 and 64 on census date, yielding a prevalence of 85.5 per 100 000 persons at risk in the age category of 30-64 years, and 143.1 per 100 000 in the age category of 45-64 years. The prevalence of the most common subtypes of dementia were calculated, Alzheimer's disease being the largest displaying a prevalence of 37.0 and 65.4 per 100 000 persons at risk in the respective age categories. The project also produced prevalence rates for both dementia and most prevalent subtypes according to age (in five-year bands) and sex.

To provide incidence rates for the same age groups, we identified patients diagnosed with dementia in the years 2015, 2016 and 2017. A total of 89 incident cases of dementia were identified, resulting in an incidence of 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 per 100 000 person-years. The distribution of subtypes was similar to the prevalent cases; diverse, dominated by neurodegenerative disease, and AD causing almost half of all dementias. A total of 41 males and 48 females were identified, resembling the sex distribution in the prevalence study.

A total of 223 patients diagnosed with typical young onset Alzheimer's disease were included in a study of the diagnostic delays among these patients. Patients with mild cognitive impairment were included if biomarkers displayed signs of Alzheimer's pathology, fulfilling 2007 International Work Group criteria for Alzheimer's disease. The diagnosis of mild cognitive impairment due to Alzheimer's disease was more frequent after 2012, accounting for 43 of the total 45 patients who received a diagnosis in the pre-dementia phase. Time from onset of symptoms to diagnosis was 5.5 years. The time from onset to initial contact with the healthcare system, mainly through the general practitioner, was almost three and a half years. Time from contact to first visit at the hospital exceeded ten months, resulting in a period of almost 15 months of clinical investigations, and over five visits, before AD was diagnosed. Mini Mental Status Evaluation was normal in most patients, or only marginally pathological when performed for the first time. The analysis of cerebrospinal fluid core biomarkers was performed eight months after the patient's first visit to the hospital.

5 SUMMARY IN NORWEGIAN

Bakgrunn og målsetning

Demenssykdommer er en av de viktigste årsakene til sykdom og død, og har sosiale og økonomiske konsekvenser for mennesker og samfunn verden over. Alzheimers sykdom er den vanligste årsaken til demens i alle aldersgrupper. Tilstanden karakteriseres av gradvis økende reduksjon av kognitive funksjoner som hukommelse, orienteringsevne, språk, og evnen til å utføre sammensatte oppgaver.

Forløpet av Alzheimers sykdom er betydelig lengre enn tidligere antatt, og strekker seg over flere tiår. Den første tiden utvikler de sykelige forandringene seg i hjernen uten at man har symptomer. Overgangen til symptomgivende fase er oftest så umerkelig at det kan være vanskelig å tidfeste når symptomene startet. Det er ikke uvanlig at det tar lang tid før pasienter og pårørende innser at forandringene skyldes begynnende demenssykdom. Når symptomene melder seg er de milde i begynnelsen, men blir etter hvert mer uttalte. Så lenge symptomene ikke medfører et hjelpebehov kaller vi tilstanden mild kognitiv svikt. Demens defineres som tilstand der de kognitive problemene er så fremtredende at de påvirker pasientens evne til å ivareta dagliglivets funksjoner. Det tar vanligvis minst ti til tjue år fra hjernen rammes til man utvikler demens.

Fram til for ca. 10 år siden kunne man ikke diagnostisere Alzheimers sykdom før pasientene var hjelpetrengende og fylte kriteriene for demens. Forskning på nye biologiske markører (biomarkører) har gjort det mulig å diagnostisere sykdommen tidligere. Nye diagnosekriterier er også utarbeidet for å kunne identifisere sykdom på et tidligere stadium ved andre nevrodegenerative sykdommer (sykdommer der hjerneceller dør). Tidlig diagnostikk er viktig for pasienter og pårørende, som ofte opplever tiden før diagnosen som vanskelig. Når nye behandlingsmetoder blir tilgjengelig, er det også svært viktig at behandlingen kan igangsettes så tidlig som mulig.

Epidemiologi er læren om hvordan sykdom opptrer i befolkningen. Fordi alder er viktigste risikofaktor for demens rammes eldre hyppigere enn yngre. Epidemiologisk forskning på vanlige sykdommer kan gjøres i små befolkningsgrupper. Sjeldnere tilstander krever større populasjoner for å gi pålitelig informasjon. De aller fleste epidemiologiske studier på demens kartlegger forekomst blant eldre og er derfor for små til å gi gode og presise estimater blant yngre. Disse studiene har likevel blitt brukt som informasjonsgrunnlag. Dette er uheldig. Mest mulig presis kunnskap om forekomst er viktig for forskning og klinisk virksomhet, og helt avgjørende for at myndighetene skal kunne dimensjonere helsetilbudet for denne spesielt sårbare gruppen av pasienter.

Det har så langt vært få studier i verden som har kartlagt prevalens (hvor mange som lever med tilstanden) og insidens (hvor mange som får tilstanden hvert år) av demens hos yngre

(definert som symptomstart før 65 år). Fordi studiene har benyttet seg av ulike metoder og kildematerialer, og fordi den diagnostiske prosessen påvirkes av kultur og organisering av helsevesenet, har resultatene vært sprikende. Noen av studiene har benyttet kvalitetsregistre og data fra spesialisthelsetjenesten, mens andre studier baserer seg på populasjonsbaserte kilder fra førstelinjetjenesten. Det er ulemper og fordeler ved begge fremgangsmåter. Studier basert på data fra spesialisthelsetjenesten står i fare for å ikke rapportere pasienter som er utredet i andre deler av helsevesenet, men gir større sikkerhet for at de inkluderte personene virkelig har demens. Populasjonsbaserte studier identifiserer vanligvis flere pasienter, men sannsynligheten for at man også inkluderer pasienter som i virkeligheten ikke har demens er høyere. Selv om yngre pasienter oftest blir utredet i andrelinjetjenesten, har populasjonsbaserte metoder tradisjonelt vært foretrukket.

Hovedformålet med «UngDemens i Trøndelag» var å undersøke epidemiologiske aspekter ved demens og demenssykdom hos yngre personer i Midt-Norge (Trøndelag). Kombinasjonen av en stor populasjon, bruk av ulike kilder for å identifisere pasienter, rutinemessig bruk av biomarkører i spesialisthelsetjenesten og individuell verifisering av samtlige inkluderte pasienter har resultert i et stort datasett med høy grad av diagnostisk kvalitet og sikkerhet. Det finnes få tilsvarende materialer i verden.

Første og andre artikkel gir estimater på prevalens og insidens av tidligdebuterende demens i Trøndelag og beskriver årsakene til demensutviklingen hos de inkluderte pasientene. Tredje artikkel beskriver tid fra symptom til diagnose hos yngre pasienter med Alzheimers sykdom.

Materiale og metode

Forskningsprosjektet ble utført i Trøndelag. Trøndelag er et veldefinert geografisk og administrativt område med om lag 450 000 innbyggere. Trøndelag består av både byer og spredt befolkede områder, har sykehus av ulike størrelser, og populasjonen er representativ for resten av landet.

Norge har et offentlig helsevesen som er lett tilgjengelig for innbyggerne. Alle pasienter har fastleger som primærkontakt i førstelinjetjenesten, og det er fastlegen som i de fleste tilfeller sørger for henvisning til videre utredning og behandling på sykehusene i andrelinjetjenesten. Demens og demenssykdommer hos eldre diagnostiseres ofte i førstelinjetjenesten, mens yngre utredes i andrelinjetjenesten.

Hovedkilden til rekruttering av pasienter til prosjektet var Avdeling for nevrologi og klinisk nevrofysiologi ved St. Olavs hospital i Trondheim og Hukommelsesklinikken ved Psykiatrisk avdeling, Sykehuset Levanger. Begge avdelingene har hovedansvar for utredning av demenssykdom hos yngre i sine respektive nedslagsfelt, og dekker til sammen om lag 90 % av Trøndelags befolkning. Andre kilder til rekruttering var Habiliteringstjenesten for voksne

og andre samarbeidende sykehusavdelinger. Det ble også gjort søk på relevante diagnoser i sykehusregistre. Identifiserte pasienter og deres pårørende ble kontaktet med spørsmål om deltagelse. I kommunehelsetjenesten samarbeidet vi tett med lokale hukommelseskoordinatorer og annet relevant helsepersonell som har kontakt med yngre pasienter med kognitive vansker. Alle sykehjem, omsorgsboliger o.l. ble kontaktet per telefon med spørsmål om å identifisere aktuelle pasienter. Et regionalt senter for Huntingtons sykdom ga informasjon om pasientene med demens. Inklusjonsperioden var fra juli 2014 til juli 2018.

Prosjektet inkluderte pasienter diagnostisert med tidligdebuterende demens eller demenssykdom. Pasientene ble utredet og rekruttert av leger/forskere gjennom klinisk arbeid. Dersom pasienten var utredet av andre instanser ble diagnosen vurdert og verifisert av forskerne ved journalgjennomgang. Det ble også gjennomført telefonintervju av en nær pårørende. Regional komité for medisinsk og helsefaglig forskningsetikk ga prosjektet tillatelse til å inkludere pasienter som ikke ga samtykke til deltagelse. I slike tilfeller registrerte man kun informasjon om diagnose, kjønn og alder. Validerte diagnosekriterier ble anvendt på alle inkluderte pasienter.

Resultater

Prosjektet identifiserte 410 pasienter der symptomene debuterte før fylte 65 år. Av disse hadde 390 pasienter demens per 1. juli 2016. Vi identifiserte 17 ulike årsaker til demens, hvorav 80 % av tilfellene skyldtes degenerativ hjernesykdom. Litt over halvparten (ca. 55 %) av pasientene hadde Alzheimers sykdom. Det var signifikant forskjell i kjønn blant alle inkluderte (56 % kvinner og 44 % menn; p = 0.02), men ikke blant pasientene som hadde demens per 1. juli 2016 (52 % kvinner og 48 % menn, p = 0.52).

Totalt 171 pasienter med demens var mellom 30 og 64 år per 1. juli 2016. Disse ble inkludert i prevalensstudien. Dette ga en forekomst på 85.5 per 100 000 personer i aldersgruppen 30 - 64 år, og 143.1 per 100 000 i aldersgruppen 45-64 år. Forekomsten og årsaken til demens, ble kartlagt i ulike aldersgrupper hos begge kjønn. Forekomsten steg med økende alder. Det var ingen signifikant forskjell på forekomst hos menn og kvinner. Alzheimers sykdom var vanligste årsak til demens med 37.0 og 65.4 per 100 000 personer i de respektive aldersgruppene.

Prosjektet identifiserte 89 pasienter mellom 30 og 64 år som ble diagnostisert med demens i årene 2015, 2016 og 2017. Disse ble inkludert i insidensstudien. Insidens for aldersgruppen 30 til 64 år var 14.8 per 100 000 personer og 25.0 for aldersgruppen 45-64 år. Også i denne studien ble insidens kartlagt i ulike aldersgrupper hos menn og kvinner. Funnene viste samme mønster som i prevalensstudien. Insidens for Alzheimers sykdom var 6.7 og 11.8 per 100 000 personer. Man identifiserte flere underliggende tilstander, men de fleste av

tilfellene var forårsaket av degenerativ hjernesykdom. Halvparten av pasientene hadde Alzheimers sykdom. Man fant ingen signifikante kjønnsforskjeller.

Totalt 223 pasienter med typisk Alzheimers sykdom ble inkludert i studien der man kartla tidsforløpet i den diagnostiske prosessen. Studien omfattet også pasienter med mild kognitiv svikt dersom disse hadde typiske biomarkører som verifiserte Alzheimers sykdom. 43 av 45 av disse pasienten ble diagnostiert etter 2012. Tiden fra symptomene debuterte til pasientene ble diagnostisert med Alzheimers sykdom var fem og et halvt år. Pasientene hadde hatt kognitive symptomer i nesten tre og halvt år før helsevesenet ble kontaktet (vanligvis fastlegen) og det gikk ytterligere ti måneder før pasientene ble utredet på sykehus. Sykehusene brukte om lag 15 måneder og mer enn fem konsultasjoner på utredningen. Kognitiv screening med Mini Mental Status viste ingen eller minimal svikt ved første gangs administrasjon. Analyse av biomarkører i ryggmargsvæsken viste sykdomsaktivitet da analysen ble gjort, men undersøkelsen ble utført først åtte måneder ut i utredningsforløpet.

6 ABBREVIATIONS

AAO	Age at onset
AD	Alzheimer's disease
ARD	Alcohol-related dementia
CSF	Cerebrospinal fluid
CT	Computed tomography
DLB	Dementia with Lewy Bodies
DSM	The Diagnostic and Statistical Manual of Mental Disorders
FTD	Frontotemporal dementia
GP	General practitioner
HD	Huntington's disease
ICD-10	International Statistical Classification of Diseases and Related Health Problems (10^{th} Edition)
IWG	International Working Group
LOD	Late Onset Dementia
MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
NINDCDS-ADRDA	The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NIA-AA	The National Institute of Aging - Alzheimer's Association
PET	Positron emission tomography
PD	Parkinson's disease
SPECT	Single photon emission CT
VaD	Vascular dementia
YOD	Young onset dementia

7 GENERAL INTRODUCTION

7.1 YOUNG ONSET DEMENTIA

Dementia is cognitive impairment characterized by difficulties with normal thought processes, challenging the ability to perform daily life activities. It includes problems with memory, orientation, speech, attention, speed, the ability to use tools and perform complex tasks. It can also impact higher cognitive functioning such as reasoning, abstract thinking, and problem-solving. Cognitive impairment may have multiple causes, not all of them pathological [1]. Some forms of cognitive impairment are benign and reversible, others are signs of an underlying condition. Depression is a major cause of cognitive difficulties, but such situations are reversible when the affective symptoms go into remission [2].

Cognitive impairment can be classified according to the degree of severity. Subtle symptoms, not detectable in neuropsychological testing, are classified as subjective cognitive decline [3]. More pronounced symptoms, verifiable in neuropsychological testing, are classified as mild cognitive impairment (MCI) [4, 5]. MCI is strongly associated with neurodegenerative dementia disorders and other conditions affecting intellectual capacity, i.e. cerebrovascular disease and traumatic brain injury. In cases of neurodegeneration, subjective cognitive decline and MCI display phases in the development of clinical dementia, a condition defined as global impairment of intellectual function, impacting the activities of daily life, see Figure 1 [3, 6]. Preceding the clinical phases, neurodegenerative diseases such as Alzheimer's disease (AD) have a prolonged pre-clinical phase in which pathology develops in the brain in the absence of symptoms [7-11].

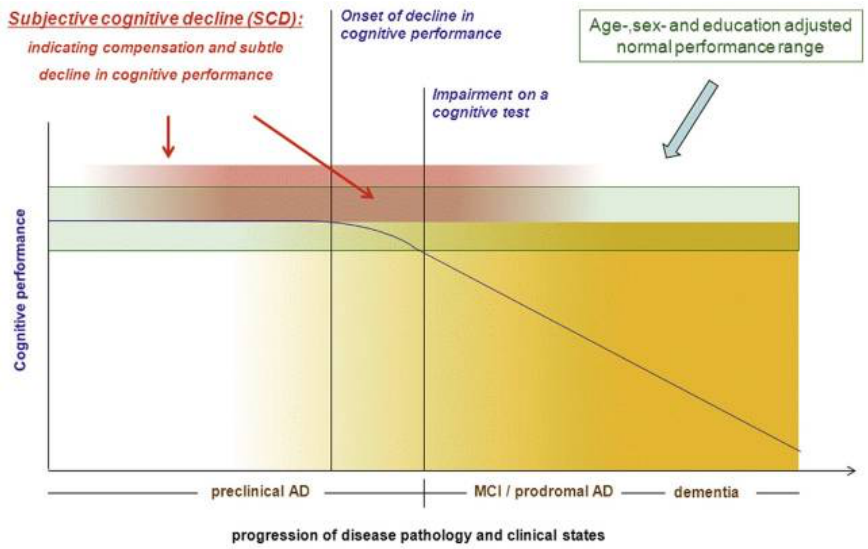
Symptoms of dementia occurring before the age of 65 is defined as young onset dementia (YOD), though other definitions exist [12, 13]. When symptoms debut after the age of 65, the condition is classified as late onset dementia (LOD).

Despite there being mainly historical and socioeconomic reasons for the dichotomisation of YOD and LOD, they also differ in other aspects, such as genetics, clinical presentation and underlying causes [13-20]. In young patients, genetic involvement is higher and more diverse, pathology more likely to debut in atypical regions causing atypical symptoms, and underlying conditions are more heterogeneous compared to older patients. Additionally, patients with YOD have a higher degree of awareness than older patients, especially in earlier phases, and are more likely to experience depression and other neuropsychiatric symptoms [21-23]. Younger patients with dementia also differ in other aspects, such as the level of medical treatment, physical activity, functional level, activities of daily living, and risk profiles, though the latter has very rarely been assessed [24-29]. Additionally, they are more educated, and less impaired at the time of diagnosis, demonstrating a well-established association between education and cognitive reserve [16, 17, 30, 31].

Older individuals are more prone to frailty and comorbidities compared to younger individuals [32-35]. If symptoms of dementia emerge at a high age, non-related disabilities and death might occur before severe dementia develops [36]. For patients with YOD, the risk of dying from other causes is lower, and they are more likely to experience the end-stages of dementia [37, 38].

With the prospects of living through the devastating phases of dementia, initially often fully aware of the consequences, the psychological and economic burden of battling progressive cognitive deterioration during midlife years is substantial [39-42]. The needs of younger patients with dementia and their families are therefore more complex, challenging healthcare organizations that typically are modelled for older individuals [43-47]. YOD constitutes less than 10 % of the total population with dementia, but the global costs and economic burden are significant, though probably underestimated [38, 48].

Figure 1. Illustration from Jessen et al. 2014 [3].



7.2 NEURODEGENERATIVE DISORDERS

Neuropathology

The aging brain is increasingly susceptible to cerebral damage and degeneration [49-52]. The presence of several co-existing neuropathological processes in late life infers that mixed pathologies might be the predominant cause in the oldest populations, while pure pathology is more likely to cause dementia in younger individuals [52, 53]. Increasing age is also strongly associated with the *clinical* syndrome of neurodegenerative dementia, of which AD is the most prevalent, followed by Parkinson's disease (PD), dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD) [54]. Age is also an essential risk factor for non-degenerative brain disorders such as cerebrovascular disease, which is regularly associated with cognitive impairment and dementia, and may coexist with degenerative changes [52, 54-56].

Neurodegenerative dementia disorders are slowly progressive and irreversible diseases that ultimately lead to cognitive symptoms and dementia. Though symptoms overlap, the various disorders display a heterogeneous clinical course, depending on the timely distribution of the affected brain regions. Motor symptoms often coincide with cognitive decline, parkinsonism being the most frequent [57].

Subtypes

The numerous subtypes of neurodegenerative disorders are associated with various underlying pathologies. In the case of AD, the accumulation of misfolded amyloid beta and hyperphosphorylated tau protein are the leading constituents of the pathogenetic plaques and tangles causing neuronal damage, although evidence also points to a more complex and multifactorial process [56, 58-60]. The neuropathology of FTD is complex and heterogeneous. The transactive response DNA-binding protein (TDP-43) accounts for up to 50 % of cases, while tau and fused in sarcoma (FUS) proteins are the remaining major pathological subtypes [61-66]. Lewy bodies, consisting mainly of α-synuclein, are the main contributing factors in the pathology of both DLB and PD [67, 68]. Evidence indicates overlapping pathological mechanisms between the various neurodegenerative disorders [67-70].

Genetics

AD is a multifactorial disease associated with both environmental and genetic factors [71]. Autosomal dominant young onset AD may be caused by mutations in the apolipoprotein (APP) or presenilin 1 and 2 (PSEN1/ PSEN2) genes, in some studies reported to account for 5 % of young patients [72]. Although they constitute a small proportion, genetic cases have provided valuable insight to many aspects of AD. The contribution of a genetic component to late onset AD is less clear, though the common allele *APOE ε4*, has been identified as the main genetic risk factor [73, 74]. A similar association of the *APOE ε4* allele has also been found in young patients, and also augments risk in carriers [75, 76].

Genetic causes are frequent in FTD. Up to 40 % have close relatives with dementia, psychiatric illness, or motor symptoms, and approximately 10 % are caused by an autosomal dominant genetic mutation, usually in the *C9ORF72* gene, the microtubule-associated protein (*MAPT*), or progranulin (*GRN*) [77-79].

The genetics of the various neurodegenerative diseases may overlap, especially concerning AD and DLB/PD(D) [80, 81].

7.2.1 Alzheimer's Disease

Since the pathology of AD in most cases emerges in the medial temporal lobe, cognitive symptoms correspondent to the disruption of these regions are typically seen at debut. Deterioration of the entorhinal cortex and hippocampus lead to disorientation to place and time, and memory impairment, of which the latter is a dominant feature in all stages of the disease. The topographical breakdown is reflected in characteristic histopathological changes in temporoparietal cortex, also detectable on neuroimaging [82-88].

AD dominated by memory impairment is referred to as amnestic or typical AD. Cases where AD pathology originally develops in other brain regions, causing non-memory symptoms, are referred to as non-amnestic or atypical AD [72].

Approximately 4-5 % of the total AD population develop symptoms before the age of 65 [72, 89, 90]. In younger patients, levels of acetylcholine neurotransmitters are lower, AD-pathology might be more pronounced, and tend to develop more frequently in posterior and parietal regions compared to older patients [72, 91-95]. Therefore, non-amnestic AD, such as posterior cortical atrophy and logopenic aphasia, are not infrequent presentations of the disorder in younger patients [72, 75, 96]. AD can also mimic clinical FTD with predominantly behavioural symptoms, largely affecting frontal and temporal lobes before impacting other regions [97, 98]. Aphasia, apraxia, visuospatial and executive dysfunction, and dyscalculia are more prevalent in young onset AD compared to late onset AD,

corresponding to the more frequent affection of posterior and parietal regions, one study demonstrating that even amnesic symptoms might follow different patterns [19, 99-104].

Over time, all AD pathologies will spread to other brain regions, causing progressive cognitive symptoms and cognitive decline, ultimately resulting in dementia. The rate of disease progression when compared to older patients remains unclear, but many studies show a more rapid clinical decline in younger patients [105-108]. Despite a greater pathological burden, younger patients are less impaired at presentation compared to patients with late onset, possibly due to a higher level of education and cognitive reserve capacity [109-111].

7.2.2 Frontotemporal dementia

FTD is a heterogeneous group of progressive neurodegenerative dementia disorders caused by neuropathology arising in the temporal and/or frontal lobes, disproportionally affecting younger patients [112, 113]. Neuroimaging displays characteristic changes in corresponding brain regions [86, 87, 114]. The clinical manifestations of FTD are categorized by a breakdown of social skills and affect, or by aphasia. These are designated as behavioural variant and primary progressive aphasia, respectively, in the setting of relatively preserved memory and visuospatial skills [115]. Of these, the behavioural variant is the most prevalent [96, 115, 116]. Although the clinical entities are associated with the involvement of distinct topographical areas, phenotypes can overlap [117]. Conditions such as corticobasal degeneration (or syndrome) and progressive supranuclear palsy, previously categorized as parkinsonism plus-disorders, are now commonly regarded as part of the clinicopathological spectrum of FTD [62, 118-123].

Behavioural variant FTD

Behavioural variant FTD is a condition primarily affecting social cognition in early stages. As with all neurodegenerative disorders, the onset is insidious, but with inexorable, progressive decline. Key features are personality changes and behavioural disturbances, subtle at first, but eventually causing devastating symptoms and dementia. It is associated with a distinct distribution of neuropathology in the anterior temporal lobe, and/or frontal lobe (symmetrical or right-sided) [112, 124]. Symptoms are a typically altered sense of social norms, emotional blunting, loss of empathy, apathy, neglect of personal hygiene, eating disturbances, and lack of insight [125, 126]. Studies suggest the possibility of several other clinical and neuropathological phenotypes, such as apathetic, disinhibited, or stereotype-

compulsive variants, but defined clinical criteria have not yet been presented, and evidence of the clinical usefulness is insufficient [127, 128]. Behavioural variant FTD is clinically and genetically associated with motoneuron disease, characterized by the progressive loss of upper and lower motoneurons resulting in the weakening and atrophy of muscles [129-131]. Though there are cases with overlapping phenotype, a clear association with amyotrophic lateral sclerosis has not been reported in other variants of FTD [132].

Primary progressive aphasia

Primary progressive aphasia can be further categorized according to symptoms and topographical involvement. Semantic dementia is characterized by reduced single-word comprehension and deterioration of semantic memory, with preserved fluency of speech [115, 133]. Progressive non-fluent aphasia is characterized by altered fluency of speech, either as apraxia of speech or agrammatism, or both, while comprehension is largely preserved [115, 133]. Semantic dementia may display behavioural symptoms such as loss of empathy and compulsiveness, and reduced facial recognition (prosopagnosia) [134, 135]. Topographically, semantic dementia is associated with dysfunction in anterior parts of the temporal lobe(s), typically on the left side, while non-fluent aphasia involves both frontal and temporal lobes on the left side [112].

7.3 NON-DEGENERATIVE DISORDERS

Several non-degenerative brain disorders are associated with cognitive impairment, especially in younger populations [136-140]. Though the underlying neuropathological processes differ, excessive alcohol consumption, head injuries, inflammatory and metabolic diseases, commonly lead to cellular dysfunction and cell loss, potentially causing cognitive symptoms corresponding to the affected brain areas. Not infrequently, cognitive decline is so severe as to be classified as dementia.

In the case of alcohol-related dementia (ARD), though nosology, neuropathology and relation to thiamine deficiency and Wernicke-Korsakoff syndrome are all unclear, the progressive deterioration of cognitive, neurological and psychiatric sequelae of prolonged exposure to alcohol is well established [141-145]. Symptoms are potentially reversible if alcohol withdrawal is sustained [146].

Severe head trauma can cause acute clinical symptoms of cognitive impairment, and if debilitating and persistent over 6 months, the condition may be classified as dementia. There is also emerging evidence of a neuropathological and clinical correlation between traumatic brain injury and a later development of dementia, such that head trauma is now a well-known risk factor for AD, lowering the age of onset [147-150].

Multiple sclerosis is an inflammatory disease with average onset in young adulthood [151]. Executive dysfunction is associated with progressive disease in late stages, a high lesion load and atrophy on magnetic resonance imaging (MRI), and axonal damage [152-154].

Wilson's disease is a rare genetic disease, primarily affecting copper metabolism in the liver of young adults, but often leads to cerebral damage and cognitive symptoms [155].

7.4 DIAGNOSTIC CRITERIA

Diagnostic criteria for dementia and dementia subtypes are complex for multiple reasons.

Since the earliest diagnostic criteria for AD were published in 1984, the diagnosis has been approached in a two-step manner. The first step was to establish the presence of dementia, the second step to identify the underlying cause. Consequently, the diagnosis of AD required the disease to progress to dementing stages. These phases occur several years after symptom debut, and even longer if preclinical phases are included. Because milder stages could be caused by benign, and potentially reversible conditions, the two-step process was a necessary precaution. This is also the reason why the diagnosis of AD and dementia became intertwined, and arguably, conflated, effectively requiring memory impairment for the diagnosis of any subtype of dementia. Furthermore, there has historically been a mismatch between the neuropathological disease and the clinical manifestations of it, such as MCI and dementia.

DSM & ICD-10

In the early days of Alois Alzheimer, dementia was regarded as a psychiatric illness, and this view influenced medicine for over a century. This is also why dementia diagnoses have largely been driven by criteria according to a manual of mental disorders (the Diagnostic and Statistical Manual of Mental Disorders (DSM)) [6]. The syndrome of dementia was referred to as "age psychosis" in publications extending in to the mid-eighties [156].

DSM-IV, which is the most frequently implemented edition in studies relevant to this thesis, regards dementia as impairment in memory and one additional cognitive domain causing disruption of social or occupational functioning. The International Statistical Classification of Diseases and Related Health Problems (10^{th} Edition) (ICD-10) requires a decline in memory and other cognitive abilities such as reasoning and abstract thinking, planning and organizing and in general processing of information, affecting emotional control and/or social behaviour. Though discrepancies exist, possibly causing differences in frequency studies, both regard the core syndrome of dementia as cognitive symptoms affecting daily life activities leading to a loss of independency [157, 158]. A decline in occupational abilities is a diagnostic criterium in DSM-IV but not in ICD-10.

In DSM-V, dementia is replaced by the term 'major cognitive disorder'. Six key cognitive domains are outlined; learning and memory, language, perceptual-motor function, executive function, complex attention and social cognition, of which only *one* domain must be affected. Memory impairment is for the first time not a requirement.

NINCDS-ADRDA criteria for Alzheimer's Disease

In 1984, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) published clinical diagnostic criteria for AD, prompting the emergence of modern research within the field of dementia [159]. In epidemiological research, these criteria still represent the gold standard for the diagnosis of both AD and dementia. The presence of dementia was compulsory, consolidating the two-step process. Despite not providing specific criteria, dementia was described as a "decline of memory and other cognitive functions" impairing "activities of daily living," and altering "patterns of behaviour".

Definite AD required histopathological evidence, while probable AD could be diagnosed if there was a typical insidious onset with progression, and other causes could be excluded. It also required a deficit in minimum two cognitive domains. Single domain cases of dementia were classified as possible AD.

The NINCDS-ADRDA criteria rested on the assumption that AD was a *clinical-pathological* entity, and that clinical symptoms corresponded to the underlying process of AD pathology. Decades of clinical research have since made it evident that this assumption was false, prompting two sets of revisions aimed at integrating the advanced knowledge and rectifying the discrepancies; The International Working Group (IWG), set in Europe, and the National Institute of Aging - Alzheimer's Association (NIA-AA), set in the US.

The IWG-criteria

- IWG criteria of 2007 (The IWG-I criteria): New criteria for *probable* AD were published in 2007 [160]. These criteria highlight the evolution of biological markers, such as cerebrospinal fluid (CSF) core biomarkers, medial temporal lobe atrophy on imaging (MRI) and typical findings on positron emission tomography (PET). In the clinical context of episodic memory impairment evidenced on testing, AD can be diagnosed in earlier, pre-dementia stages if a biomarker is present, designated MCI due to AD, parting from the two-step process.
- IWG criteria of 2010: In the revision of 2010, the work group allows for the diagnosis of non-amnestic AD, addressing patients with typical AD-pathology emerging in other regions than the medial temporal lobe, producing non-memory symptoms [161]. These disorders are referred to as atypical AD. Importantly, these changes harmonize the previous disparities between the neuropathological and clinical entities. In 2014, the criteria of typical and atypical AD are simplified, maintaining the need for a pathophysiological biomarker (The IWG-2 criteria) [162]. Typical forms are further classified into posterior, logopenic, frontal, and Down's syndrome variant.
- IWG criteria of 2016: In 2016 Dubois et al. published criteria for preclinical AD, finalizing the conceptual framework for all stages of the disorder [163].

The NIA-AA criteria

In 2011, the National Institute of Aging - Alzheimer's Association (NIA-AA) published three sets of criteria corresponding to three stages of AD, defined as preclinical, predementia and dementia phases, marking AD as a clinicopathological continuum [10, 164, 165].

The group introduces a broader definition of dementia, implying that the impairment of memory is not a mandatory feature. Cases of a single domain deficit, categorized as possible AD in the original criteria of NINDCS-ARDRA of 1984, and not further addressed in the IWG revisions, are classified as MCI in the NIA-AA criteria, (although if the impairment is sufficient to interfere with daily life activities, it can also be defined as dementia). In the diagnosis of probable MCI, a mild dependency is allowed, departing from to the NINCDS-ADRDA criteria for this stage in which level of functioning is described as independent. If cognitive symptoms interfere with work, patients are regarded as demented.

The emphasis of biomarkers is softened, aiming to provide guidance in a clinical setting.

7.5 EPIDEMIOLOGY IN YOD, PREVIOUS LITERATURE

The following section is a review of previous literature on epidemiological aspects relevant to this thesis.

7.5.1 Prevalence

Definition

Prevalence is defined as the proportion of a population who are affected by a medical condition at a specific time. It is derived by comparing the number of affected people to the total number of people at risk, and is usually expressed as a fraction, a percentage, or as the number of cases per 1 000, 10,000 or 100,000 people at risk. Low-frequency conditions, such as YOD, are typically expressed as the number of cases per 100 000 persons at risk. High-frequency conditions such as LOD, and their most frequent subtypes, are typically expressed as percentages. Prevalence can be estimated during a specific time, or on a specific date (often referred to as census date), commonly designated as point-prevalence.

7.5.1.1 Dementia

Population-based studies

LOD is more prevalent than YOD [31, 54, 166-170], and is far more researched. Population-based studies on the epidemiology of low-frequency conditions are costly and laborious, and there were only four studies with a comparable study design, and multiple case ascertainment processes, aimed specifically at assessing the prevalence YOD [137, 171-173]. Table 1 gives an overview of these studies. Three of them published rates in five-year intervals, while the remaining study gave rates in the total age group of 45-64. A study with a similar case ascertainment process but primarily assessing the needs in YOD, also provided rates in the age category of 45-64 (not shown in Table 1) [174].

The studies indicate increasing prevalence according to age within the group of YOD, roughly doubling for every five years after the age of 40. This pattern has previously been shown for LOD [54, 166, 168]. For the age group of 30-64, prevalence varies from 42 to 68

per 100 000 persons at risk, rising to 78 to 133 per 100 000 persons at risk for the age group of 45-64. Approximately half of patients with YOD are between the age of 60-64.

The effect of study design

Though discrepancies exist, studies presented in Table 1 provide estimates roughly in the same range. In addition to an elaborate effort to identify patients with YOD in the community as well as in secondary healthcare institutions, these studies had extensive processes in place for diagnosis validation and verification of dementia. The level of clinical accuracy is likely to have direct impact on the prevalence estimation. A population-based study from Scotland with a substantially larger study population (approximately 1.7 million), used a national data set based on general practitioner (GP) registered data to identify cases of dementia [175]. To examine the accuracy of the diagnoses, the researchers conducted a detailed evaluation of registered diagnoses in a cohort of approximately 50 000 people. The prevalence for persons in the age category of 40-64 in this cohort was 86.5 per 100 000 persons at risk. The corresponding estimate in the total study was over double of that in the smaller, verified cohort, estimated at 172 per 100 000 persons at risk. On the other hand, larger population sizes *are* advantageous with regards to the *precision* of the estimates, confidence intervals narrowing substantially for the estimates in the total population compared to the smaller cohort (161-82 vs 51-122, respectively).

Other studies

Several other studies have reported prevalence figures in younger persons. Typically, these studies target patients with LOD, and are not specifically designed for identifying patients under the age of 65. An overview of a variety of such reports is shown in Table 2. Prevalence figures for dementia in younger categories in these studies are generally higher compared to studies limited to assessing the prevalence of YOD. The discrepancy might partly result from smaller population sizes and fewer cases identified, increasing the possibility of selection bias. Within these studies, confidence intervals with respect to patients under the age of 65 are wider when compared to the corresponding intervals for patients over 65 (not shown). They are also wider compared to confidence intervals in studies aiming specifically at detecting YOD.

Table 1. Prevalence of young onset dementia in population-based studies.

Study	***Withall et al. [137]***	***Ikejima et al. [172]***	***Harvey et al. [173]***	***Ratnavalli et al. [171]***
Year	2014	2009	2003	2002
Country	Australia	Japan	UK	UK
Urban/ rural	Urban	Urban+rural	Urban	Urban + rural
Pop. size	-	2 966 000	567 500	326 019
Diagnostic criteria:				
Dementia	DSM-IV	DSM-III	DSM-IV	DSM-III
AD	NINCDS-ADRDA	DSM-IV	NINCDS-ADRDA	NINCDS-ADRDA
Sources:				
Hospital:	Questionnaires to hospitals Hospital records	Questionnaire to medical institutions	Relevant departments contacted Hospital records	Memory clinic database Hospital records
Community:	Dementia care facilities	Questionnaire to medical institutions	Relevant entities GP	Relevant entities GP
Diagnosis verification	Available documents individually evaluated by researches	Evaluated by responders; case control re-evaluation of 50 %	Hierarchical diagnostic algorithm; 3 stages	Available documents individually evaluated by researches
Biomarkers	NR	Case control (n=286): MRI+SPECT: 180 CT/MRI: 106	Stage 3: 83 % CT or MRI	NR
N (YOD)	141	761	185	108
N (30-64)	88	752	130	59*
Prevalence estimates				
30 - 34	3.8	4.2	12.7	-
35 - 39	8.8	4.9	8.0	-
40 - 44	25.5	11.9	15.5	-
45 - 49	69.3	24.3	33.0	-
50 - 54	102.7	50.0	62.5	-
55 - 59	131.2	94.3	152.1	-
60 - 64	265.2	163.3	166.3	-
30 - 64	*68.2*	*51.7*	*54.0*	-
45 - 64	*132.9*	*83.3*	*98.1*	*81.0*

Prevalence per 100 000 persons at risk
**N (45-64)*
NR= Not reported
Ikejima: Prevalence was adjusted (estimated) according to the response rate for each institutional group

Table 2. Prevalence of young onset dementia in various studies.

Study	Mölsä et al. [176]	Schoenberg et al.* [177]	Sulkava et al.* [169]	Kokmen et al. [178]	Coria et al. [179]	Ohshiro et al. [180]	Ott et al. [181]
Country	Finland	US	Finland	US	Spain	Japan	Netherlands
Year	1982	1985	1985	1989	1993	1994	1995
Age	>45	>40	>30	All ages	>40	40-64	>55
Pop-based	Y	Y	Y	Y	Y	N	Y
Pop. size	164 568	23 842	6 120	NR	1 011	209 621	7 528
N (<65)	34	NR	16	10	2	100	11
Prevalence:							
40-44	-	-	-	0	0	-	-
45-49	-	-	-	77	0	-	-
50-54	-	-	-	40	0	-	-
55-59	-	-	-	86	-	423.0	423.4
60-64	-	-	-	249	-	-	419.0
50-59	-	-	-	-	-	-	-
60-69	-	351.3	-	-	-	-	645.0
0-44	-	-	-	0	-	-	-
30-44	-	-	-	0	-	-	-
30-64	-	-	*260*	-	-	-	-
40-59	-	45.2	-	-	-	-	-
40-64	-	-	-	-	682.6	81.4	-
45-54	51	-	-	-	-	-	-
45-64	*93*	-	-	-	-	-	-
55-64	144	-	-	-	1418.4	-	421.0

Prevalence per 100 000 persons at risk
**Severe dementia*
NR = Not reported

7.5.1.2 Alzheimer's Disease

Only a few studies have published data on the prevalence of AD in patients under 65 years, Table 3 providing an overview of some of them. The occurrence before the age of 50 is minimal, with rates increasing in the years thereafter. Prevalence in the age category of 45-64 varies from 15 to 35 per 100 000 persons at risk.

Table 3. Prevalence of young onset Alzheimer's disease in various studies.

Study	Country	Year	Age	Pop-based	N	45-64	45-49	50-54	55-59	60-64
Withall et al. [137]	Australia	2014	30-64	Y	12	19.9	0.0	6.4	13.1	74.6
Ikejima et al. [172]	Japan	2009	20-64	Y	191	22.3	0.8	9.8	28.0	49.5
Harvey et al. [173]	UK	2003	30-64	Y	42	35.0	6.0	16.4	50.7	77.3
Ratnavalli et al.[171]	UK	2002	45-64	Y	11	15.1	-	-	-	-
Newens et al. [182]	UK	1993	<65	Y	227	34.6	2.4	11.8	35.6	87.3
Kokmen et al. [178]	US	1989	All ages	Y	3	-	0	0	86	50
Ohshiro et al. [180]	Japan	1994	40-64	N	-	-	-	-	-	47.5
Andreasen et al. [183]	Sweden	1999	All ages	Y	6		*40-64:* 28.0			-
Campion et al. [184]	France	1999	41-60	Y	39		*41-64:* 41.2			-
Ott et al. [181]	The Netherlands	1995	>55	Y	4		55-64: 153.1			-

Prevalence per 100 000 persons at risk

7.5.2 Incidence

Definition

Incidence can be defined as a measure of the probability of a given medical condition occurring in a population during a specified period of time. There are several types of incidence.

Incidence proportion is a measure of risk, or a probability, for developing a disease within a group of people. Incidence rate measures the disease occurrence as it relates to time. The numerators are the same, whereas the denominator in incidence proportion is the number of people in the group, and the total time the group is followed is the denominator in

incidence rate. Incidence rates are typically expressed as the number of cases per 100 000 person-years.

Incidence rates are commonly used when measuring the number of new cases in a population.

7.5.2.1 Dementia

Prevalence and incidence rates relative to each other depend on the duration and mortality of the condition in question. They tend to merge in cases with short survival such as amyotrophic lateral sclerosis and pancreatic cancer, and deviate in chronic conditions with substantial longevity. Dementia disorders would be characterized by the latter, resulting in high prevalence rates relative to incidence rates. The practical consequence in the field of epidemiology is that studying incidence requires an even larger population size, possibly accounting for research on the incidence of YOD being particularly scarce [170].

Only two reports focusing solely on the incidence in younger categories have been published [185, 186]. Another report published rates comparing incidence in YOD and LOD [17]. A few studies have included patients under 65 years when assessing incidence rates in older communities. An overview over studies providing incidence rates in patients under the age of 65 is shown Table 4. Because studies have reported incidence rates in varying age brackets, they are less suitable for comparison. Mercy et al. and Garre-Olmo et al. both reported on the incidence in the category 45-64, estimating 11.5 and 22.8 per 100 000 person-years, respectively [17, 185].

As for the prevalence figures, incidence rates increase with age. Although incremental according to age within the same cohort, rates diverge significantly between studies, likely due to differing study design affecting incidence estimates in the same way as they affect prevalence estimates. Surveys of incidence vary in study design both regarding case identification processes and populations sizes, some studies screening the population in small geographical and administrational areas, prospectively following participants to identify incident cases. Although prospective studies have a high degree of clinical accuracy, they are very costly and comprehensive, significantly limiting population sizes to a few thousand, likely compromising the precision of the estimates (though CIs are not always published). Retrospective studies are less extensive, and may cover larger populations, improving precision of the estimates, but case verification is less rigorous, and therefore more susceptible to selection bias.

Table 4. Incidence of young onset dementia in various studies.

Study	Abraham Sanches et al. [186]	Garre-Olmo et al. [17]	Mercy et al. [185]	Knopman et al. [187]	Edland et al. [188]	Ruitenberg et al. [189]	Ott et al. [190]	Mölsä et al. [176]
Country	Argentina	Spain	UK	US	US	Netherlands	Netherlands	Finland
Year	2015	2010	2008	2006	2002	2001	1998	1982
Age	21-64	30-64	<65	>40	>50	>55	>55	All ages
Criteria:								
Dementia	NR	DSM-IV	NR	DSM-IV	DSM-IV	DSM-III-R	DSM-III-R	NR
AD	NINCDS-ADRDA	DSM-IV	NINCDS-ADRDA	DSM-IV	DSM-IV	NINCDS-ADRDA	NINCDS-ADRDA	NR
FTD	L-M	L-M+ Neary	Neary	Neary	-	-	DSM-III	NR
Source(s)	Hospital	Hospital	Hospital	Pop.based	Pop.based	Pop.based	Pop.based	Pop.based
Design	P	R	R	R	R	P	P	R
Point of detection	AAO	AAD	AAD	AAO	AAO	AAO*	Age of dementia	AAO
Pop.size	17 614	690 207	326 200	-	70 745	7 046	7 528	164 568
N (<65)	14	144	54	26	24	5	4	26
Incidence:								
30-34	0	0.5	-	-	-	-	-	-
35-39	0	1.1	-	-	-	-	-	-
40-44	0	2.9	-	-	-	-	-	-
45-49	-	5.1	-	-	-	-	-	-
50-54	-	14.8	-	-	35.6	-	-	-
55-59	-	32.0	-	-	40.2	40	59.0	-
60-64	-	67.7	-	125.9	129.2	50	109.0	-
21-55	3	-	-	-	-	-	-	-
21-64	11	-	-	-	-	-	-	-
30-64	-	*13.4*	-	-	-	-	-	-
40-49	-	-	-	8.8	-	-	-	-
40-64	-	-	-	29.6	-	-	-	-
45-54	8	-	-	-	-	-	-	10.2
45-64	-	*22.8*	*11.5*	-	-	-	-	-
50-59	-	-	-	22.9	-	-	-	-
55-64	22	-	-	-	-	-	-	27.0

Incidence per 100 000 person-years
NR = Not reported
AAO = Age at onset, AAD = Age at diagnosis
**Age at onset was determined as the midpoint between the last known date when a person was not demented and the first date of dementia diagnosis*
L-M: The Manchester-Lund criteria of 1994
R = Retrospective, P = Prospective

7.5.2.2 Alzheimer's disease

A number of incidence studies on YOD also provided rates on the incidence AD, demonstrating significantly less impact in younger populations compared to older populations [17, 177, 185, 189-193]. A few studies presented incidence estimates for AD and not for YOD [182, 183, 194]. An overview is provided in Table 5. As for the literature on the incidence of YOD, publications on the incidence of young onset AD are equally rare. With the exception of two, studies are small, and incidence rates are based on 9 to 61 patients. Two studies did not list the number of participants; one of them a small prospective study of approximately 7 000, the other scrutinized the entire population of Scotland from 1974 to 1988. A study from the UK covered a larger area, identifying 317 patients and estimated an additional 43, totalling 360 as basis for the incidence rates. The rates in this study are somewhat comparable to two other studies from Spain and the UK, both of them large register-based, the latter including diagnosis among GPs and primarily assessed survival and mortality [17, 105]. Incidence rates in the age bracket 45-64 were 7.2, 11.9 and 6.2 per 100 000 person-years, respectively. The national study from Scotland reported consistently higher incidence rates compared to all other studies, but the level of clinical accuracy was lower. Another national study from Israel, reported an incidence rate substantially lower for AD dementia aged 60 and lower, compared to the study from Scotland (2.4 vs 22.6 per 100 000 person-years for probable and 40.5 per 100 000 person-years for broad/possible) AD [194]. Smaller studies reported diverging rates.

Four studies reported incidence rates in five-year intervals indicating an incremental distribution after the age of 50, confirming that AD is uncommon in very young individuals [136, 182, 189, 191, 195].

Table 5. Incidence of young onset Alzheimer's disease in various studies.

Study	***Garre-Olmo et al. [17]***	***Mercy et al. [185]***	***Edland et al. [188]***	***Ruitenberg et al. [189]***	***Andreasen et al. [183]***	***Newens et al. [182]***	***McGonial et al. [195]***
Country	Spain	UK	US	Netherlands	Sweden	UK	Scotland
Year	2010	2008	2002	2001	1999	1993	1993
Ages	>30	<65	>50	>55	>40	<65	40-64
Criteria	DSM-IV	NINCDS-ADRDA	DSM-IV	NINCDS-ADRDA	NINCDS-ADRDA	NINCDS-ADRDA	NINCDS-ADRDA
Pop.size	690 207	326 200	70 745	7 046	61 874	45-65: 655 800	Entire pop. of Scotland
N (<64)	61	19	9	NR	15	360	NR
Design	R	R	R	P	R	R	R
Incidence:							
30-34	-	-	-	-	-	-	-
35-39	-	-	21.3	-	-	-	-
40-44	-	-	16.1	-	-	0.0	1.4
45-49	-	-	36.9	-	-	0.9	8.1
50-54	-	-	-	-	-	4.9	27.6
55-59	-	-	-	0	-	8.1	39.7
60-64	-	-	-	10	-	14.5	37.8
30-59	-	-	-	-	-	2.1	-
30-64	*5.7*	-	-	-	-	-	-
40-64	-	-	-	-	13.0	-	22.6
45-54	-	-	-	-	-	2.9	-
45-64	*11.9*	*4.2*	-	-	-	*7.2*	-
55-64	-	-	-	-	-	11.3	-

Incidence per 100 000 person-years
NR = Not reported
R = Retrospective, P = Prospective

7.5.3 Time trends

To establish trends over time, researchers must rely on population-based materials, collected with similar design, preferably in the same area [196]. Research is therefore scarce and conflicting, studies prior to the 1990s likely being compromised by differences in terminology, diagnostic criteria, and case ascertainment processes. Although there is evidence of a declining incidence of dementia in recent years, presumably connected to cardiovascular risk reduction in the 1980s, very few surveys covered younger populations [196-202]. Results from the Framingham Heart Study showed a progressive decline of incidence of dementia in the years 1977 to 2008, linked to improved cardiovascular health in higher educated subgroups, but only included individuals above the age of 60 [199]. Patients in the youngest cohort (60-69) showed a declining trend, though slightly less

compared to older subgroups. A reduction in these age group was also shown in the Rotterdam study, but findings did not reach the level of significance [203].

The Rochester Epidemiological Project in Minnesota, US, has published epidemiological data on dementia over decades, but population size and study design compromise trend analysis in YOD, (see Table 6). Kokmen et al. compared incidences in three quinquennial periods from 1960-1974, and later reanalysed the data five years later (including the years 1975-84), showing stable incidence rates, though the use of records linkages rather than standardised protocols might have introduced bias [192, 204]. A small population size (2 500), and lack of validated criteria, also limited validity of data for YOD in a prospective study in the years 1947-1972 in Lundby, Sweden [205].

Phung et al. conducted a large survey on the incidence of registered hospital dementia diagnosis over time in the entire nation of Denmark, and included patients > 40 [206]. Authors found increasing incidences in all age categories but could not exclude bias of differences in clinical dementia care practices.

Table 6. Incidence of dementia <65 in The Rochester Epidemiology project.

Study	***Schoenberg et al.* *[177]***	***Kokmen et al.***		***Rocca et al.***	***Edland et al.***	***Knopman et al.***
		[192]		***[207]***	***[188]***	***[187]***
Year	1987	1988		1998	2002	2006
Years investigated	1960-64	1965-69	1970-74	1975-84	1985-89	1990-94
Pop. size	42 000	55 000		-	70 745	-
N	22	-	-	11	24	26
Incidence:						
0-29	-	0.0	0.0	-	-	-
30-59	19.2	1.3	2.4	-	-	-
50-54	-	-	-	17.3	35.6	-
55-59	-	-	-	9.5	40.2	-
60-64	-	-	-	90.0	129.2	125.9
40-49	-			-	-	8.8
50-59	-			-	-	22.9
60-69	130.0	-	-	-	-	-

Incidence per 100 000 person-years

7.5.4 Relative frequency of YOD

The reported frequency of YOD relative to LOD ranges from 7 % to 48 %, depending on sources and methods [16, 17, 138, 208-211]. A majority of studies recruited patients from hospital registers, tertiary clinics or other specialized institutions. Due to selection bias, they presumably do not reflect the true proportion of YOD in the community but demonstrate that physicians assessing patients with cognitive symptoms regularly come in contact with young patients.

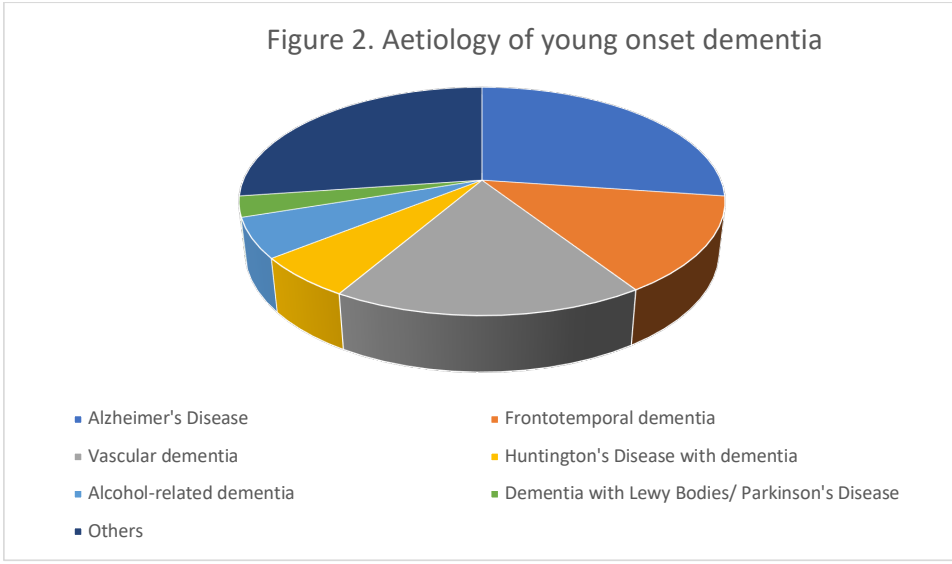
7.5.5 Aetiology

There have been several studies on the aetiology of YOD. Table 7 and Figure 2 give an overview. The proportion of AD varies from 1 to 55 %. The aetiologies in younger patients are more heterogenous than in older patients for whom AD accounts for approximately two thirds of the dementias [17, 166]. Non-degenerative dementias, such as traumatic brain injury and ARD are more frequent in younger individuals [137, 138, 187, 210, 212]. In a study of patients under the age of 45, neurodegenerative disorders only accounted for 31 %, whereas autoimmune and inflammatory aetiologies, including multiple sclerosis, were the cause in 21 %, and metabolic disease was the underlying condition in 11 % [136].

Table 7. The aetiology of young onset dementia in various studies (after 2000).

			Diagnosis (%)						
	N	Age	AD	FTD	HDD	PBD/ PDD	VaD	ARD	AD: FTD ratio
Study:									
Konijnenberg et al. [211]	1 325	<65	55	14	-	5	7	-	4:1
Withall et al. [137]	141	YOD	18	11	6	5	13	18	2:1
	88	30-64	14	8	-	-	11	24	2:1
Picard et al. [16]	811	<65	22	10	3*	5	16	10	2:1
Garre-Olmo et al. [17]	144	30-64	42	10	2	2	14	3	4:1
Ikejima et al. [172]	761	20-64	26	3	-	6	43	-	9:1
Papageorgiou et al. [209]	114	<65	27	25	3	4	6	-	1:1
Kelley et al. [136]	235	<45	1	13	8	-	6	<1	1:13
Mercy et al. [185]	54	<65	35	27	17	-	11	-	2:1
Shinagawa et al. [212]	185	<65	39	21	-	-	13	-	2:1
McMurtray et al. [138]	278	<65	17	3	1	3	29	5	6:1
Yokota et al. [210]	34	<65	38	15	-	-	24	-	2:1
Fujihara et al. [208]	141	<65	21	5	-	-	21	-	4:1
Sundar et al. [213]	76	30-64	13	-	-	-	44	-	-
Harvey et al. [173]	130	30-64	42	18	-	-	21	16	2:1
Ratnavalli et al. [171]	108	YOD	25	16	20	-	16	6	2:1
	59	45-64	11	11	14	-	6	-	1:1
Williams et al. [174]	132	<65	45	7	-	-	12	14	6:1

** Presence of dementia not specified*



Approximate proportions based on the studies in Table 7

7.5.6 Time to diagnosis

Few studies have explored the diagnostic challenges associated with YOD [106, 174, 211, 214-218]. A consistent finding is that the condition is difficult to diagnose, probably due to heterogeneity of causes and presentation. Depression and other mood disturbances, and/or behavioural changes, which are frequent features in younger patients, may obscure symptoms in early phases [22, 215, 219-221]. FTD can be especially challenging, indications are that young and late onset disease might even present differently, though some studies have suggested that having AD or FTD shortens the duration of disease before diagnosis [214-217, 222]. There is also the potential of over-diagnosing younger patients if algorithms for LOD are applied [223, 224].

Diagnostic delays might be longer for YOD compared to LOD, younger patients frequently enduring a higher number of consultations, often in multiple departments, and they are subjected to more extensive clinical investigations before a correct diagnosis is made [174, 214, 217, 218, 225]. Patients commonly receive more than one diagnoses of dementia subtype, although one study showed that this was less the case for patients with AD [215, 216]. Consequentially, there are multiple clinical pathways to obtaining a diagnosis of YOD. With regards to young onset AD, time to diagnosis has varied between 1.5 to 4.2 years, though reports are limited [96, 214-217].

In addition to aspects within the healthcare community, an important time lag in the pathway to diagnosis is the time from onset of cognitive symptoms to patients contacting the medical services. Associated factors were assessed in an Australian study, indicating that young age, but not dementia type or psychiatric history, contributed to an average delay of 2.3 years from onset to contact [215]. When this time lag was calculated in *median* time, time from onset to consultation was reported as 15 months for all types, and a few months earlier for patients with AD. This is similar to a study from Norway, in which young patients with AD presented to the healthcare services 13 months after symptom debut, a caveat being that the time lags in the latter publication were reported as a mean. Furthermore, upon contacting medical services for the first time, they may experience a substantial delay before they are referred to a hospital specialist [216]. Stigma among GPs and other professionals, may be a significant impediment to the timely diagnosis in older populations, though not investigated in younger individuals [226].

The timely diagnosis of dementia and AD is important for several reasons. The pre-diagnostic period is associated with considerable psychological stress in patients and their families [227-229]. Diagnostic delay postpones adequate treatment and support, and ultimately, a more efficient diagnostic pathway could also reduce healthcare resources and costs associated with the condition.

8 AIMS OF THE PRESENT STUDY

1. To study the following epidemiologic aspects of YOD in a population of central Norway:

    a. *Prevalence*
    b. *Incidence*
    c. *Aetiology*

2. To study the diagnostic pathway and time lags in young onset AD with early and dominant memory impairment.

9 MATERIAL AND METHODS

9.1 THE POPULATION OF TRØNDELAG

Trøndelag is a county in central Norway with a total population of 449 769 as of census date, July 1st, 2016. It represents almost 10 percent of the total population in Norway, including both urban and rural populations. The largest municipality includes the city of Trondheim with a population around 188 000. The populations in the remaining 48 municipalities range from 469 to 23 308 inhabitants. Trøndelag has slightly fewer immigrants than the national average (10.5 % v. 16.3 %), but the level of education, unemployment rate and general health do not differ significantly [230].

9.2 HEALTHCARE ORGANIZATION IN NORWAY

Norwegian healthcare is organized in a two-step hierarchical manner. The primary level consists of municipal-based services of GPs, home nursing care, day care centres and nursing homes. Hospitals and other specialist facilities form the secondary level. GPs are the physicians usually issuing referrals to hospitals. The system assumes close communication between the two levels, ensuring patient follow-up and transparency.

Healthcare in Norway is largely financed by public means, and private healthcare in the field of dementia is negligible outside the family environment.

9.3 EVALUATION OF PATIENTS WITH SUSPECTED COGNITIVE IMPAIRMENT

In Norway, patients with suspected LOD should primarily by evaluated by the GP but are regularly referred to hospitals due to uncertainty of the diagnosis and/or the management of the disorder. Dementia is primarily assessed in departments of neurology, geriatrics or psychiatry. Local preferences determine the distribution of the patients. Often, patients with predominantly psychiatric manifestations are evaluated by psychiatrists, patients with neurological manifestations are seen at departments of neurology, and multimorbidity patients are frequently evaluated by geriatricians. Some departments have multi- or unidisciplinary memory clinics. Patients with intellectual disabilities (including patients with Down's syndrome) and dementia are evaluated by specialized hospital departments. The

municipalities are urged to provide the services of a dementia team, which frequently also assist GPs in evaluating dementia diagnoses [231].

According to national guidelines, individuals with cognitive symptoms under the age of 65 should be referred to a specialist clinic for diagnostic work-up.

9.3.1 Evaluation of patients with suspected YOD in Trøndelag

There are three hospitals in Trøndelag; one University Hospital in Trondheim (for the larger southern district of Trøndelag), and two local hospitals in Levanger and Namsos (for the northern district).

In Trondheim, the Department of Neurology is the main referral site for suspected YOD in the southern district of Trøndelag. However, young patients with concomitant psychiatric symptoms are also assessed by psychiatrists, along with older patients with dominating neuropsychiatric manifestations. The Department of Geriatrics primarily evaluates older patients.

Throughout Trøndelag, patients with Huntington's disease (HD) regularly receive services from a regional centre situated in Trondheim.

In Levanger, the memory clinic at the Department of Psychiatry (geriatric psychiatry unit) is the corresponding main site of referral for YOD in the hospital's target area, covering approximately 75 % of the northern district. The memory clinic consists only of psychiatrists. As in Trondheim, a geriatrics unit evaluates older patients, but the Department of Neurology does not evaluate patients with dementia. A similar situation exists at Namsos Hospital. Although the Department of Psychiatry in Namsos does not have a memory clinic, psychiatrists routinely evaluate patients with dementia.

9.4 INCLUSION CRITERIA

- Individuals with YOD, defined as symptom onset before the age of 65.
- Individuals with MCI due to AD with symptom onset before the age of 65.

Age at onset

Age at onset (AAO) was defined as the age in which the earliest symptom appeared, as determined by hospital notes, patients or by a close family member (in a telephone interview performed in connection with admission to the study), or by a combination of these. If conflicting, the earliest time of symptom onset was noted.

9.5 CASE IDENTIFICATION

MKA and SBS were the lead researchers in this study. Except for cases identified by SBS at the Department of Neurology in Trondheim, all steps in the case ascertainment process were conducted by MKA over a period of four years between July 2014 and July 2018. Census date for the prevalence study was set in the middle of the inclusion period (1st July 2016) to minimize the time between inclusion and census date.

A small sample of three patients made known to us clinically were included in the days following the end of the recruitment period.

9.5.1 Primary sources

Primary sources were the hospital databases at The Department of Neurology, University Hospital of Trondheim, and the memory clinic of the Department of Psychiatry, Levanger Hospital. All patients who received a diagnosis of dementia or MCI due to AD with onset < 65 years were included.

9.5.2 Secondary sources

Hospital-based sources

Computerized hospital records from all three hospitals were searched for potential patients with a diagnosis of dementia according to ICD-10. Patients were categorized into two

groups: 1. Patients who received any diagnosis of dementia, (including G30.1 Alzheimer's disease (AD) with late onset and/or F00.1 Dementia in AD with late onset) before the age of 70, and 2. Patients who had received a diagnosis of AD with early onset (G30.0) and/or dementia in AD with early onset (F00.0). Potential patients and/or their caregiver, received a letter requesting them to participate in the study, and notifying them that they would receive a telephone from the researcher.

Specialized outpatient services for individuals with intellectual disabilities, (including Down's syndrome), identified patients who had received a diagnosis of YOD.

Physicians at other departments working in close collaboration with our research group were informed about the study and assisted with the identification of patients with YOD.

Community-based sources

Dementia teams in all municipalities were personally contacted by telephone and asked to scan their municipality for possible candidates. In municipalities without specialized dementia teams, the heads of home nursing services were contacted. It was emphasized that all causes of dementia were eligible, and that patients currently older than 65 years also could meet inclusion criteria depending on the duration of symptoms.

If the dementia teams did not have extensive knowledge of the patients in day care centres and sheltered housing or nursing homes in their area, the facilities themselves were directly contacted and asked to identify potential candidates.

The regional centre for HD provided basic information on patients with dementia.

9.6 CASE VERIFICATION

9.6.1 Consenting patients

All consenting patients had relevant hospital records that were reviewed for the purpose of precise diagnosis, AAO and other relevant data.

A telephone interview with a close family member was conducted by MKA. The main objects of the interview were to determine the accuracy of diagnosis, chronology of symptoms, time lags in the diagnostic process, and also to correctly estimate the true AAO, benefitting from hindsight and guidance from a physician with experience in diagnosing dementia.

9.6.2 Non-consenting patients

Throughout the clinical work and investigatory process, we identified patients with YOD who were reluctant to participate in a medical research study. To limit inclusion bias, the Regional Committee for Medical and Health Research Ethics accepted our request to count these individuals, hence contributing to a truer prevalence rate. Patients who did not provide formal consent are referred to as 'non-consenting' patients. Only information on age, gender and diagnosis was available for this group.

As patients with intellectual disabilities and dementia, and patients with HD dementia were identified through reliable and collaborating sources, we did not seek further confirmation of these diagnoses.

9.6.3 Patients included in paper I

Included patients met the clinical criteria for dementia according to DSM-IV, and were alive and residing within the catchment area on census date [6]. Dementia on census date was systematically verified either through personal telephone interview with a close family member or hospital records, or both.

9.6.4 Patients included in paper II

Included participants were diagnosed with YOD as classified in DSM-IV in the years of 2015, 2016 or 2017 [6].

9.6.5 Patients included in paper III

Included participants were consenting patients diagnosed with MCI or dementia due to Alzheimer's disease according to the clinical criteria of Dubois 2007 (the IWG-I criteria) and of NINCDS-ARDRA 1984 [159, 160].

9.7 DIAGNOSTIC VALIDATION

Validated diagnostic criteria were applied for the diagnosis of dementia, and the various underlying neurodegenerative diseases, vascular dementia (VaD) and ARD [159, 232-239]. Cases that did not meet a specific set of criteria were classified as “unspecified”.

Diagnostic consensus meeting of neurologists, geriatrics, psychiatrists and (neuro-) psychologists settled cases of unclear aetiology.

9.8 ETHICS

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK Midt 2014/487).

10 RESULTS

10.1 REVIEW OF PAPER I

The Prevalence and Subtypes of Young Onset Dementia

Marte Kvello-Alme, Geir Bråthen, Linda R. White, Sigrid Botne Sando

Background: Although battling progressive cognitive decline during midlife is a substantial burden for affected individuals, and poses significant societal and health care costs, the frequency and aetiology of young onset dementia has been little researched. The object of this study was to determine the prevalence and subtypes of young onset dementia in central Norway.

Methods: Multiple sources was used to identify eligible patients within the catchment area of Trøndelag. Primary source was the databases of The Department of Neurology, University Hospital of Trondheim (St. Olavs Hospital) and The Department of Psychiatry, Levanger Hospital, both main site of referrals of young onset dementia in the region. Other hospital-based sources included geriatric and psychiatric departments and specialised outpatient services for patients with intellectual disabilities, as well as computerised search in hospital records from all three hospitals. Community-based sources were relevant key persons in frequent contact with young patients with dementia, such as day-care centres and nursing homes. A telephone interview with a close family member was conducted. Participants met the DSM-IV criteria for dementia. The prevalence of dementia and most frequent subtypes was calculated by sex and age.

Results: A total of 390 patients with young onset dementia on census date was included in the study. Patients aged between 30 and 65 years were included in the prevalence calculations, yielding a prevalence of 85.5 and 143.1 per 100 000 persons at risk in the age category of 30-64 and 45-64, respectively. Though aetiology was heterogeneous, approximately two thirds of patients were diagnosed with a neurodegenerative disease of which Alzheimer's disease was the most frequent subtype, accounting for half of all dementias.

Conclusions: Young onset dementia affects a significant number of patients in central Norway. Alzheimer's disease is the most frequent subtype.

10.2 REVIEW OF PAPER II

The Incidence of Young Onset Dementia

Marte Kvello-Alme, Geir Bråthen, Linda R. White, Sigrid Botne Sando

Background: The research on the epidemiology of young onset dementia is limited, and incidence estimates particularly scarce. The number of new patients affected by the condition is an important aspect for clinicians, researchers and healthcare authorities responsible for these patients. The object of this study was to determine the incidence of young onset dementia in central Norway.

Methods: A total of 390 patients with young onset dementia were identified in a previous study on the prevalence in central Norway. Patients in the 30-64 age group, receiving the diagnosis dementia during the years 2015, 2016 and 2017 were included in the present study. Incidence rates for dementia and Alzheimer's dementia were calculated according to age and sex.

Results: A total of 89 patients met inclusion criteria, and were included in the incidence calculations. Incidence rates 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. The pattern of distribution was similar to the prevalence study, consolidating Alzheimer's disease as the major subtype. A plurality of patients over the age of 50 were diagnosed with neurodegenerative diseases, whereas non-degenerative disorders were more frequent in younger patients.

Conclusions: A significant number of patients are diagnosed with young onset dementia per year in central Norway. Alzheimer' disease represents most of these diagnoses.

10.3 REVIEW OF PAPER III

Time to Diagnosis in Young Onset Alzheimer's Disease

Marte Kvello-Alme, Geir Bråthen, Linda R. White, Sigrid Botne Sando

Background: The variety of underlying conditions and heterogeneous clinical presentation are factors associated with the challenging process of diagnosing young onset dementia. Indications are that younger patients are subjected to longer diagnostic delays compared to older patients, though to a lesser extent in cases of classic Alzheimer's disease - the major cause of dementia in all ages. The object of this study was to determine the pathway, and major time lags, in diagnosing typical young onset Alzheimer's disease in central Norway.

Methods: Patients with young onset dementia were identified in an epidemiological survey in central Norway. Patients diagnosed with young onset Alzheimer's disease with early and dominant memory impairment were included in the present study. Information on symptoms, age of onset, time lags, and the clinical assessment, including the use of biomarkers, were collected from hospital notes, and by conducting telephone interviews with a family member.

Results: A total of 223 patients were included in the study. Time from onset to contact with healthcare services (usually a GP) was 3.4 years. Time from contact with healthcare services to the first visit at a hospital was 10.3 months. Time from first visit at a hospital to diagnosis was 14.8 months. This equals a total diagnostic delay of 5.5 years from onset to diagnosis.

Conclusions: Typical Alzheimer's disease is associated with a substantial diagnostic delay in younger patients. There are obstacles in the diagnostic pathways. Raising public awareness, and education of healthcare professionals on the aspects of young onset Alzheimer's disease may be potential points of target.

11 DISCUSSION

Trøndelag has several desirable attributes for investigating epidemiological aspects of YOD. It is a well-defined geographical and administrational region, representative of the country in important areas, and includes both rural and urban districts with hospitals of different sizes and competence levels. Estimates derived from this region should therefore be largely applicable to other parts of Norway, as well as the rest of the world with a similar healthcare system. The challenge was to correctly identify every patient diagnosed with YOD in the area, rendering a time-consuming and meticulous process, extending over four years, but of vital importance for the reliability of estimates and overall quality of the study.

11.1 MATERIAL AND METHODS

11.1.1 Diagnostic criteria

Diagnostic criteria regarding dementia and subtypes were carefully selected.

Dementia

Several definitions of dementia have been published over the last forty years, of which DSM-IV and ICD-10 are the dominating sets of criteria [6]. In Europe, ICD-10 is widely used in clinical settings, but researchers worldwide until recently usually reported on dementia according to the DSM-IV criteria.

Impairment of occupational functioning, (regarded as dementia in DSM-IV), have less significance in LOD but is salient in YOD as a plurality of younger patients in Norway is employed when symptoms emerge. In the present survey, symptoms commonly affected work-related arenas before causing social dysfunction, implying a chronological “two-step ladder” of affected arenas in younger, employed patients, to which DSM-IV criteria are more sensitive. Twenty-seven patients in the prevalence study, and a third of patients in the incidence study met DSM-IV criteria for dementia due to occupational impairment. These patients could not have been included if the ICD-10 criteria had been applied in which occupational abilities are not a diagnostic determinant. It substantially increased the incidence rates, yet less impact on the prevalence figures was observed.

DSM-V criteria for major cognitive disorder (published in 2013) had yet to be used in population-based prevalence studies on YOD when the present project was executed. Since then, two studies have implemented them in relative large epidemiological studies on YOD [96, 240]. Estimates for prevalence and incidence were relatively comparable to the present figures in one of the studies, but incidence was lower than the current findings in the other. More studies are required to evaluate the potential bias between DSM-IV and DSM-V.

Subtypes

- Alzheimer's disease

The original criteria of NINCDS-ADRDA are known to have relatively high sensitivity (66-98 %), but lower specificity (23-75 %) for AD, the latter increasing substantially as criteria for other neurodegenerative disorders became available during the nineties [241-248]. Specificity increased to approximately 95 % in the 2011 NIA-AA criteria, likely at the expense of sensitivity (65.6 and 79.5 % for probable and possible, respectively) [249]. Though biomarkers, as introduced in 2007 (Dubois et al.), are likely to be influential in the future, they have yet to be implemented in population-based studies on the prevalence and incidence of young onset AD [160]. Because frequency in younger populations is little researched, it has been necessary to compare estimates with older publications, predating biomarkers, effectively limiting the introduction of biomarkers in later epidemiological studies. For the purposes of comparison, the current project also adopted this approach when estimating occurrences, though routinely analysing CSF core biomarkers and MRI in our daily clinical work-up.

Focusing on the diagnostic challenges facing patients and physicians in clinical practice, wherein the advantages of biomarkers are readily acknowledged, such considerations were less important in paper III. Our survey showed that physicians in Trøndelag increasingly diagnosed MCI due to AD throughout the period 2012-2019, while only two cases were identified in the years prior to 2012. To reflect the advancing diagnostics within the medical community, the NINCDS-ADRDA 2007 criteria for the early stages of AD were a necessary supplement [160].

On a historical note, biomarkers were primarily introduced originally for the purpose of research. The implementation in every day clinical work conceptualises a merging of research and clinical practice, and a harmonisation of clinical phenotype with the underlying neuropathology, both of which were previously lacking in the field of AD and dementia.

- Dementia with Lewy Bodies

The advancement of sophisticated technologies has also influenced diagnostic criteria for several other neurodegenerative disorders, such as FTD and DLB [126, 250]. Due to purposes described for AD, we selected older, clinical criteria for both of these conditions [232, 234]. For DLB, the implementation of neuroimaging (dopamine transporter scan) in diagnostic criteria postdated the recruitment period of the project, (though regularly used by clinicians in Trøndelag), and was therefore not an option for this project. Diagnostic criteria for prodromal DLB was published in 2020 [251].

- Frontotemporal dementia

In the case of FTD, there were three suitable sets of criteria [115, 126, 232]. In 1994 the Lund-Manchester Group published clinical and neuropathological criteria in the first attempt to separate patients with early behavioural disturbances but relatively preserved memory, from AD. These criteria did not distinguish aphasic dementias from the behavioural variant. Four years later, Neary et al. revised these criteria and proposed new and more detailed clinical criteria, recognising three separate entities: behavioural variant, and two variants of primary progressive aphasia [115]. Neither the Lund-Manchester Group, nor Neary et al. implemented neuroimaging or other biomarkers.

In an attempt to implement new knowledge, harmonise the clinical and neuropathological criteria, and provide guidelines to physicians in clinical practice, the Work Group on Frontotemporal Dementia and Pick's disease published clinical and neuropathological criteria in 2001 [252]. To our knowledge, these guidelines have not been implemented in any prevalence or incidence studies in young populations.

The 1998 criteria were later criticised, in part for the large number of features, limiting the sensitivity. The two definitions have not significantly impacted prevalence figures in studies of FTD in younger populations, (see Table 8) [253, 254]. (As a point of curiosity, the prevalence study that did apply the much narrower criteria of 1998, found figures in the upper ranges compared to studies adopting the older, broader definition of 1994.)

Neuroimaging for all three variants of FTD was implemented in 2011 [126]. These new and revised criteria had nevertheless rarely been applied in relevant studies, rendering strong support for the older criteria to serve as basis for FTD diagnoses in the project, although the main researchers otherwise seldom diagnose FTD without typical findings on neuroimaging in clinical practice. Attitudes regarding this may vary among physicians, as there is evidence of a clinical "phenocopy variant" of behavioural FTD in which patients display no or minimal atrophy on imaging, and slower symptomatic progression [255].

As most relevant studies for this project applied the Lund-Manchester criteria, and because hospital notes were insufficient to accurately evaluate the detailed criteria of Neary, the oldest criteria were chosen.

- Frontotemporal dementia, and dementia

Neither the Lund-Manchester criteria nor Neary explicitly require the presence of dementia. This did not affect the prevalence or incidence rates in the current project, nor was it a source of bias between studies, as all of them investigated dementia according to various criteria. However, it is likely that frequency of FTD is underestimated in such studies. A study of 85 year-olds in Sweden showed that only five of 14 patients fulfilling the Lund-Manchester criteria were not demented according to DSM-III-R [256].

- Alzheimer's disease vs frontotemporal dementia

The distribution of pathological change should, by inference, be predictive of the underlying pathology and clinical manifestations, but has proven complex to encapsulate in diagnostic criteria for the various neurodegenerative disorders. The differentiation of AD and FTD has been especially challenging as the syndromes have overlapping phenotypes, FTD not infrequently presenting with amnesia, and AD with predominantly behavioural disturbances, or progressive aphasia [257-262]. The possibility of misdiagnosis is a caveat in any survey of frequencies of dementia, even more so in population-based studies, such as the present case, in which pathological confirmations are mostly lacking.

Atypical AD with AD-pathology and dominant behavioural disturbances in early stages, would be classified as FTD as defined by the Lund-Manchester Group. This could imply an overrepresentation of FTD in studies assigning these criteria, especially when compared to the Neary criteria, which might be more likely to exclude these patients. Differing criteria for FTD would also potentially affect the AD to FTD ratio, presumably skewing it towards FTD. Though prevalence studies without pathological confirmation are not designed to explore such aspects, studies of YOD at least do not seem to offer support of these hypotheses (see Table 8). Studies with otherwise similar study design, and definition of AD, showed on average a lower prevalence rate than the study from England applying the more specific criteria of Neary. The latter study also reported an AD to FTD ratio of 1:1, which is higher than studies based on the Lund-Manchester criteria. A variety of factors would contribute to these figures, and conclusions regarding sensitivity and specificity of diagnostic criteria should not be drawn from these deliberations.

Table 8. Prevalence of young onset frontotemporal dementia, and Alzheimer's disease to frontotemporal dementia ratio, in various population-based studies.

Study	Norway (Current study)	Australia [137]	Japan [172]	England [173]	England [171]
Criteria	*Lund-Manchester*	*Lund-Manchester*	*Lund-Manchester*	*Lund-Manchester*	*Neary et al.*
50-54	3.4	6.4	1.5	3.3	-
55-59	26.0	26.2	1.7	25.4	-
60-64	25.6	8.3	4.4	23.2	-
30-64	*5.4*	*5.4*	*1.2*	*7.5*	-
45-64	*10.6*	*11.6*	*2.0*	*15.4*	*15.1*
AD:FTD*	6.2:1	1.7:1	11.2:1	2.3:1	1:1

*Age 45-64

Effect of biomarker-supported criteria

A recent study from Italy reported a prevalence of 14.1 per 100 000 at risk for behavioural FTD according to criteria requiring typical atrophy on imaging (Rascovsky et al.), which is higher than any of the previous population-based studies [96, 126]. This is interesting because patients with behavioural variant AD would be classified as FTD in the current report (and other similar surveys), potentially increasing the bias toward a higher prevalence for FTD. The Italian study would exclude these patients from the FTD spectrum, having the opposite effect. This is the first study to implement these new criteria, and more research is needed to explore the impact on prevalence estimates.

Definition of young onset dementia

The nosology of YOD can be confusing. At least two terms exist, YOD and early onset dementia [12]. While early onset dementia is a more frequent term, the project chose YOD to avoid confusion with dementia in earlier phases.

A majority of reports define YOD, or early onset dementia, as symptoms of dementia occurring before the age of 65. For the prevalence study we adopted this definition. There is, however, some inclination to regard YOD as dementia *diagnosed* before the age of 65, especially in incidence studies [17, 185, 186]. In prospective studies of incidence, onset as the defining term could be useful, but is less favourable in retrospective studies, in which

the time of diagnosis is an easier mark to detect. For these purposes, the project chose to define YOD as dementia diagnosed before the age of 65 in the (retrospective) incidence study, though aware of the fact that this would exclude a number of patients. One study on the prevalence of YOD reported that 20 of 108 patients became symptomatic before the age of 65 but were diagnosed during the three years thereafter [171]. This project did not evaluate the number of patients that would have been included in the incidence report if a different definition had been applied but acknowledges that this is a source of bias. In the third paper, young onset AD was defined by onset of symptoms as the information was available for this group of patients.

11.1.2 Case ascertainment process

11.1.2.1 Subtypes and methodology

The project carried out a case ascertainment process based on multiple sources from hospitals, and from within the communities, detecting more cases of AD relative to population size than other studies with a similar approach [137, 171-173]. There might be several reasons for this. Sources and methods are only one part of the equation, the healthcare system wherein it is performed, is another. As the commonest dementia disorder, we suspect that AD might have shaped cultural and medical attitudes within the field of dementia in Norway. Reciprocally, such a system would also be more likely to identify patients with AD, and less inclined to detect patients with other types of dementia, especially dementias occurring in the context of non-cognitive symptoms, creating a bias in epidemiological data.

At hospitals, cognitive impairment due to other causes is frequently overlooked, and/or often not coded in notes or records. Even neurologists treating patients with Parkinson's disease and multiple sclerosis have been less motivated to assess cognitive symptoms.

In the computerised output of hospital records, we searched for ICD-10 codes of brain injuries. The sheer number of them eventually made it too comprehensive to investigate, and the effort was rejected early in the process. Though these patients were cognitively evaluated later in departments of rehabilitation, dementia was seldom coded in the hospital records. In a similar way, patients with alcohol substance abuse are treated in other departments not specialised in cognitive assessments. The follow-up of these patients is often accommodated through other trajectories within the system, and they are less often referred to dementia services in the communities. Thus, an underestimation of dementia among these patients is likely. A study from Australia confirms that a different approach to detecting ARD might be warranted [137]. This is probably also the case for other secondary

dementias. The underestimation of these is especially relevant for prevalence studies of YOD as younger individuals are disproportionally affected by these disorders.

In conclusion, medical tradition and cultural aspects could explain the low frequency of non-AD dementia, relative to AD, in our material. Other studies based on multiple sources have shown similar frequencies of non-AD dementias, but lower rates of AD, so the full effect of cultural attitudes and organization of patient-flow within hospitals, nevertheless remains unclear.

11.1.2.2 The approach to community sources

When searching for YOD within the communities, the project contacted relevant personnel by telephone rather than sending questionnaires. This way, we were able to search through every nursing home and any other relevant entity in Trøndelag. It is our belief that this approach increased detection rates in nursing homes, in day-care centres, and among patients receiving home care services. Many of the patients identified by the community employees were already known to the researchers, but 61 patients were not, increasing the total basis for calculations by 15.6 %.

11.1.2.3 Non-consenting patients

The Regional Ethics Committee allowed the project to include patients that did not consent to participation, a bias in any study on frequency in which the ability to identify all and every candidate is vital for a correct estimate. A total of 89 patients were non-consenting. Of these, 29 were aged 30-64 on census date, increasing the prevalence estimate from 71.0 to 76.3 persons at risk. As the survey only collected age, gender and diagnosis in these patients, they were excluded in Paper III on diagnostic delay, for which participation required more detailed information.

11.1.2.4 Assessing age at onset

Paper III

In paper III, the time from onset of symptoms to patients, or others, contacted their GPs, was 3.4 years, which is substantially longer than reported by other authors [215, 216]. There might be at least two explanations for this. One argument, though less likely, might be that patients in Trøndelag *are* more hesitant to contact medical services compared to patients

studied elsewhere. Another would relate to the study design, and specifically to the assessment of age at onset. For this, the present study relied on hospital notes and in-depth, loosely structured interviews conducted by the main researcher with a mean time of 3.1 years after the diagnosis. It was a consistent finding that family members reported a shorter duration of symptoms in the hospital notes compared to their assessments later on, leaving the impression that patients failed to recognise the earliest phases of AD during the diagnostic process. By educating the proxy on the facets of the disease, and benefitting from the time that had elapsed since diagnosis, this approach seemed to limit the potential bias of delayed recognition if the hospital notes had been left unchecked.

It is therefore our hypothesis that the assessment of age at onset in this project contributed to a more accurate assessment of onset of symptoms. The approach benefitted both from hindsight, and guidance from the researcher, possibly compensating for family members' failure to attribute symptoms to dementia. By consequence, duration of illness before contacting medical services was protracted, resulting in a longer diagnostic delay overall than previously reported.

Despite limited research, other surveys on time to diagnosis may offer some insight. Though assessment of age at onset has been approached in similar ways, there are a few important distinctions. To remove confounding factors of age, subtype of dementia, and delay within the healthcare system, studies providing information on the time from onset to contact in a cohort of young onset AD, would presumably be best suited for comparisons, of which there are only two. One study performed telephone interviews with a family caregiver, but very soon (1.9 months) after the diagnosis [216]. The time from onset to contact in this material was approximately one year, almost two and a half years less than the current finding. Authors of the other simply noted that patients and/or carers were asked about the earliest symptom of dementia, without specifying how or when [215]. This study also reported a time lag of approximately one year.

Although insufficient for conclusions, various other publications may provide additional support: one study demonstrated that caregivers estimated longer duration and earlier onset proportional to the time that had passed since the diagnosis [263]. Proxy informants have been shown to be more reliable than medical notes alone, and in-depth interviews improved the estimate when compared to a single-question method, especially in later stages, although responses might be less valid corresponding to a long duration of illness [263, 264]. Although retrospective studies may be prone to recall bias, retrospective reports by proxies have been shown to be reliable [265-267]. If anything, they might be more likely to underreport, rather than exaggerate the cognitive decline over time, favouring an underestimation of symptom debut [266, 267]. Furthermore, accuracy of onset was improved when assessed by a trained physician, increasing the duration of the illness, which would seem to offer direct support for our hypothesis [268]. These studies, however, were performed in the setting of LOD, and the relevance for YOD is indeed unclear, and on a general note, studies on the validity of assessing age at onset will always be limited by the lack of a "gold standard" for the true age at onset.

Paper I

The approach to assessing age at onset also increased the number of patients identified as YOD in the total project, providing a larger cohort in which to assess the aetiology of dementia in a younger population. Many patients coded as late onset in hospital records, were reclassified as young onset upon scrutiny of the telephone interview, enhancing the precision and quality of the presented data. One epidemiological study on YOD (AD) reported that an upper age limit of 73 in hospital records identified over 97% of those with onset before the age of 65 [195].

11.2 RESULTS

11.2.1 Prevalence

11.2.1.1 Dementia

The project identified 390 patients with YOD alive and residing within the study area at census day, of which 171 were in age group of 30-64, yielding a prevalence rate of 85.5 per 100 000 persons at risk in the this age group, and 143.1 among persons aged 45-64. This would correspond to approximately 2 000 persons living with YOD in Norway. Prevalence increased according to age, roughly doubling for every five years after the age of 50, a pattern of distribution previously shown for LOD [168].

Included patients were thoroughly investigated. A preponderance of cases were subjected to cognitive tests and the evaluation of biomarkers.

Population-based studies

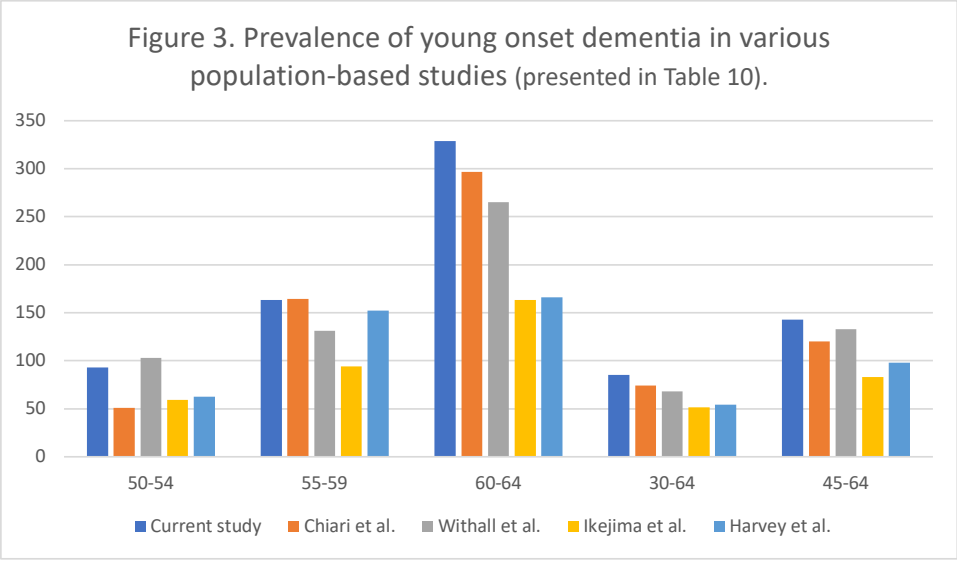
Though more aligned with the recent study from Australia, this project found a higher prevalence of YOD compared to three other matching population-based studies with similar study design and criteria, (see Table 10 and Figure 3). CIs in Ikejima et al. are narrower, while remaining studies report CIs within the same range, indicating a more precise estimate in the larger study, (though only half of diagnoses were individually reviewed). Only the current study reported a high frequency of dementia in patients with intellectual disability, contributing to a higher overall prevalence.

Since the present study was published, Chiari et al. reported prevalence rates of YOD and subtypes according to DSM-V for dementia, the NIA-AA for AD, and biomarker-mandated criteria for FTD and DLB in a large, population-based study of approximately 700 000 inhabitants in Italy (shown in Table 10) [96]. The rates where slightly less but comparable with the present study. The study excluded patients with Down's syndrome and secondary dementia with significant non-cognitive manifestations.

Table 10. Prevalence of young onset dementia in various population-based studies.

Study	***Current***		***Chiari et al. [96]***		***Withall et al. [137]***		***Ikejima et al. [172]***		***Harvey et al. [173]***		***Ratnavalli et al. [171]***	
	Rate*	95% CI	Rate*	95% CI	Rate*	95% CI	Rate*	95% CI	Rate*	95% CI	Rate*	95% CI
N	171		258		88		752		130		59	
30-34	6.9	1.0 - 25.0	0.0	NR	3.8	0.2 - 17.9	4.2	2.3 - 8.0	12.7	4.7 - 26.7	-	-
35-39	3.6	1.0 - 20.2	2.3	NR	8.8	1.3 - 28.3	4.9	2.7 - 9.1	8.0	1.6 - 23.3	-	-
40-44	19.8	7.3 - 43.0	7.4	NR	25.5	9.0 - 55.5	11.9	7.8 - 18.1	15.5	5.7 - 33.8	-	-
45-49	22.2	8.9 - 45.6	16.9	NR	69.3	37.0 - 116.7	24.3	18.1 - 32.4	33.0	16.5 - 59.0	-	-
50-54	92.9	61.3 - 135.2	50.8	NR	102.7	60.1 - 161.8	50.0	41.5 - 60.3	62.5	37.6 - 97.5	-	-
55-59	163.2	118.6 - 219.0	164.5	NR	131.2	81.5 - 197.6	94.3	83.1 - 107.0	152.1	110 - 206	-	-
60-64	328.6	262.2 - 406.7	296.4	NR	265.2	183.5 - 368.1	163.3	146.3 - 182.4	166.3	120 - 224	-	-
30-64	*85.5*	*73.2 - 99.3*	*74.3*	*NR*	*68.2*	*54.9 - 83.4*	-	- - -	*54.0*	*45.1 - 64.1*	-	-
45-64	*143.1*	*122.0 - 166.9*	*119.0*	*NR*	*132.9*	*105.8 - 164.2*	*83.3*	*77.4 - 89.6*	*98.1*	*81.1 - 118*	*81.0*	*62.8 - 104.5*

**Per 100 000 persons at risk*



Prevalence per 100 000 persons at risk

Other studies

Various other studies with differing study designs have published prevalence figures for dementia at age <65, (see Table 11). Aside from a pattern of increasing rates according to age, (small studies generally reporting higher prevalence than larger ones), estimates fluctuate between studies, challenging further inference.

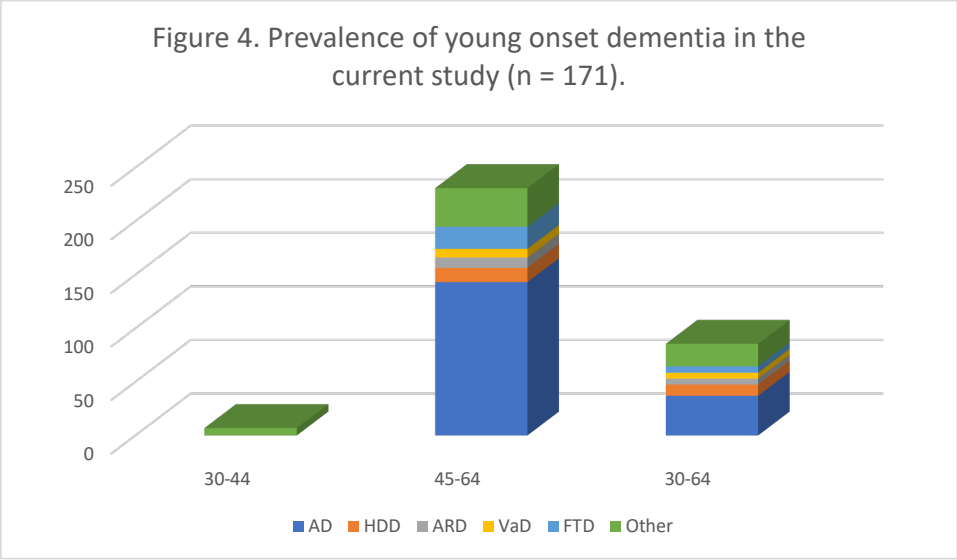
Table 11. Prevalence of young onset dementia in various studies.

Study	*Current study*	*Ott et al. [181]*	*Ohshiro et al. [180]*	*Coria et al. [179]*	*Kokmen et al. [178]*	*Sulkava et al.* [169]*	*Schoenberg et al.* [177]*	*Mölsä et al. [176]*
Country	Norway	The Netherlands	Japan	Spain	US	Finland	US	Finland
Year	2019	1995	1994	1993	1989	1985	1985	1982
Age	30-64	>55	40-64	>40	All ages	>30	>40	All ages
Pop.based	Y	Y	N	Y	Y	Y	Y	Y
Pop.size	449 769	7 528	209 621	1 011		6 120	23 842	164 568
N (<65)	171	11	100	2	10	24	3	68
Prevalence:								
40-44	19.8	-	-	0	0	-	-	-
45-49	22.2	-	-	0	77	-	-	-
50-54	92.9	-	-	0	40	-	-	-
55-59	163.2	423.4	423.0	-	86	-	-	-
60-64	328.6	419.0	-	500	249	-	-	-
40-49	21.0	-	-	0	-	-	-	-
50-59	126.8	-	-	-	-	-	-	-
60-69	-	645.0	-	-	-	-	351.0	-
30-44	10.4	-	-	-	0	-	-	-
30-64	85.5	-	-	-	-	260	-	-
40-59	71.2	-	-	-	-	-	45.2	-
40-64	117.1	-	81.4	700	-	-	-	-
45-54	56.1	-	-	-	-	-	-	51
45-64	143.1	-	-	-	-	-	18.2	93
55-64	243.7	421.0	-	1400	-	-	-	144

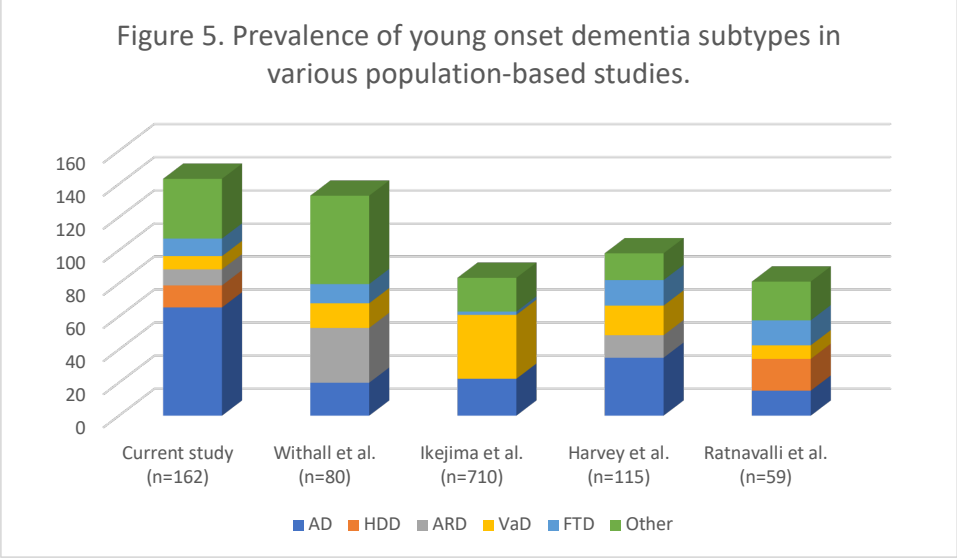
Prevalence per 100 000 persons at risk
**Severe dementia*

11.2.1.2 Subtypes

The most prevalent disorders among persons aged 30-64 were AD, HD with dementia, FTD, VaD and ARD (37.0, 10.5, 6.0, 5.5 and 5.5 per 100 000 persons at risk, respectively, see Figure 4). Neurodegenerative disorders were more frequent in older age brackets compared to a younger population. This is accordance with previous literature [136].



Prevalence per 100 000 persons at risk



Prevalence per 100 000 persons at risk in the age category 45-64

Prevalence rates of subtypes vary among population-based studies of YOD. An overview is presented in Figure 5., and further commented under the various subtypes.

Alzheimer's disease

The project identified a large number of prevalent cases of AD. As discussed in the case ascertainment section, abundance might be due to methodological aspects; identifying dementia in a system with particular competence in AD. Based on the findings in the present study, some inferences could be made:

1 AD vs. dementia in the current study (Figure 6):

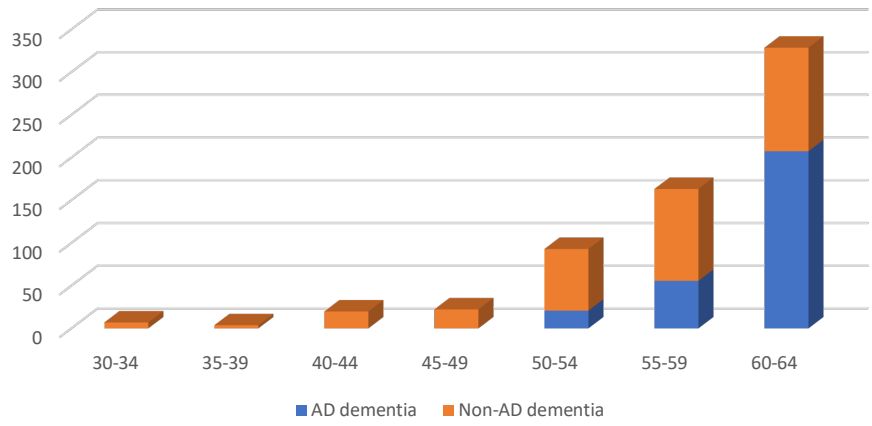
   a. High prevalence of dementia aged 30-64 in central Norway is largely driven by AD. Because AD is the major cause of YOD, a high frequency of this subtype will affect the overall prevalence more than other subtypes. Older brackets are larger than younger age groups, (the number of patients aged 60-64 is almost triple the number of younger patients combined (53 vs 21)). Therefore, an incremental prevalence of AD in these categories has a major impact on the overall prevalence of YOD.
   b. Above the age of 50, the distribution of YOD parallels the distribution of AD.

2 Prevalence of AD and dementia vs. other population-based studies (Figure 7 and 8)

   Prevalence of AD is higher in the present study compared to other population-based studies, (see Figure 7). Although AD is more frequent in all age categories in the current study, estimates become disproportionally higher as age increases, especially above the age of 50. A high proportion of prevalent AD may therefore explain why prevalence of all dementia is higher in the current study than in other population-based studies, (see Figure 8).

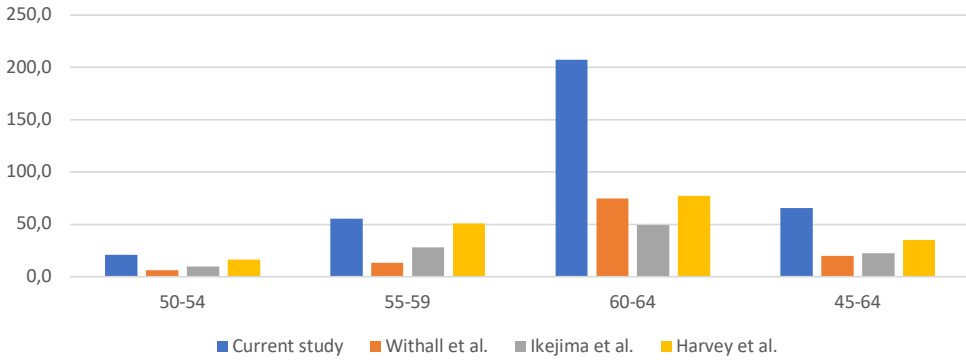
   A study from Italy, published in 2020, diagnosed AD dementia according to the revised criteria of NIA-AA, which allows for non-amnestic subtypes of AD to be included [96]. The prevalence for all variants of AD was remarkably similar to the present study (which including only the amnestic variant) (32.6 vs 33.0 per 100 000 persons at risk aged 30-64). The corresponding Italian figure was 22.2 per 100 000 persons at risk for the amnestic phenotype.

Figure 6. Alzheimer's dementia vs non-Alzheimer's dementia in central Norway (n=171).

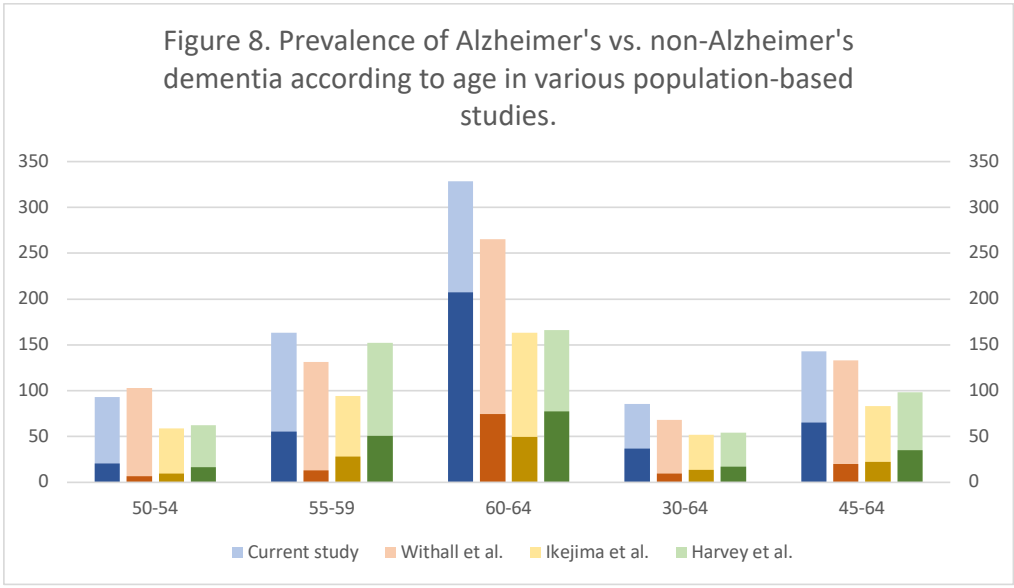


Prevalence per 100 000 persons at risk

Figure 7. Prevalence of Alzheimer's disease in various population-based studies.



Prevalence per 100 000 persons at risk



Dark colour: Alzheimer's dementia
Light colour: Non- Alzheimer's dementia

Other subtypes

An overview over FTD, VaD and ARD in various population-based studies is presented in Table 12.

Table 12. Prevalence of frontotemporal dementia, vascular dementia and alcohol-related dementia in studies.

Study		***Current* study**	***Withall et al. [137]***	***Ikejima et al. [172]***	***Harvey et al. [173]***	***Ratnavalli et al. [171]***
FTD		Rate*	Rate*	Rate*	Rate*	Rate*
	50-54	3.4	6.4	1.5	3.3	-
	55-59	26.0	26.2	1.7	25.4	-
	60-64	15.6	8.3	4.4	23.2	-
	30-64	*6.0*	*5.4*	*1.2*	*7.5*	-
	45-64	*10.6*	*11.6*	*2.0*	*15.4*	*15.1*
VaD						
	50-54	3.4	6.4	22.9	6.6	-
	55-59	11.1	13.1	42.2	32.6	-
	60-64	15.6	49.7	78.4	38.7	-
	30-64	*5.5*	*7.7*	*10.1*	*8.7*	-
	45-64	*8.0*	*14.9*	*38.6*	*17.9*	*8.2*
ARD						
	50-54	6.9	32.1	-	19.7	-
	55-59	7.4	32.8	-	18.1	-
	60-64	27.4	49.7	-	11.6	-
	30-64	5.5	16.3	-	6.6	-
	45-64	9.7	33.1	-	13.6	-

**Prevalence per 100 000 persons at risk*

- *Frontotemporal dementia*

Three population-based studies report similar prevalence of FTD as found in the current study, while one study reported significantly lower (see Table 12). The reason for the divergent figure in Ikejima et al. is unclear. All studies report increasing prevalence according to age.

A recent study from Italy, implementing imaging as a criterion for diagnosis, reported prevalence of 14.1 for behavioural FTD, which is higher than any of the previous population-based studies [96]. Furthermore, this is the only study reporting prevalence figures for the entire spectrum of FTD (22.5 per 100 000 persons at risk for the age group of 30-64), for which all subtypes fulfilled new and revised criteria, including biomarkers, for all subtypes.

Though FTD is known to have a debut also in the forties' age group, the project was not able to identify any patients younger than 50 on census day [136, 173]. A minimal occurrence at younger ages is relatively consistent with the findings in all studies in Table 12, except from Harvey et al. who found four patients with FTD younger than 50. As for other neurodegenerative disorders, all studies showed increasing prevalence of FTD in the fifth and sixth decade.

- *Huntington's disease and dementia*

The monogenetic autosomal dominant disorder of HD is characterized by a triad of progressive extrapyramidal, neuropsychiatric and cognitive symptoms in patients exceeding 35-39 CAG repetitions in the gene coding for huntingtin, though patients with less repetitions also exhibit diffuse symptoms in some cases [236, 269-272]. Depending on the number of repetitions, onset of motor manifestations and dementia is typically in the fourth decade [271, 273]. Very few studies have published prevalence rates for HD in younger patients with dementia; Ratnavalli et al. may be the only one apart from the present study [171]. Harvey et al. identified nine patients with early onset, Withall et al. found eight patients, while Ikejima et al. did not report any; none of them reporting prevalence figures [137, 172, 173]. Despite the fact that HD with dementia represented the second most prevalent disorder in the present study, our estimate was slightly lower compared to Ratnavalli et al. (13.3 vs 19.2 per 100 000 persons at risk, age category 45-64) [171]. Both of these study populations included a specialised treatment centre for HD, facilitating identification.

Though subtle, cognitive symptoms in patients with HD often precede motor manifestations but may go unrecognized for many years due to their non-AD nature. Early symptoms are related to executive dysfunction and poor judgement. The frequent disruption of the capability of distinguishing what is relevant from what is not is prominent, all of which ultimately affect the management of their lives [274]. As criteria and clinical practice focus mostly on motor symptoms, the prevalence of dementia in these patients is probably underestimated.

- *Vascular dementia*

The effect of cerebrovascular risk factors increases with age, inferring less cognitive impact in younger brains. Though prevalence of VaD varies between studies on YOD, all of them report lower prevalence compared to older populations (see Table 12). The study from Japan showed a higher prevalence of VaD than AD, which has been confirmed in another (hospital-based) study from Japan, indicating a different aetiological profile of YOD compared to Western countries [180]. (A recent study from Japan showed that AD had surpassed VaD as the most frequent cause of YOD but clinical accuracy of diagnoses was low [275].)

Similar to the distribution of VaD subtypes in Japanese YOD, our study found a higher relative frequency of stroke-related dementia compared to microvascular-related dementia, (11 of 16 cases), perhaps reflecting a common distribution of stroke and microvascular pathology in this age group [175, 276, 277]. Aside from the reports in Table 12, low prevalence of VaD in YOD may be supported in a few additional studies; one small prospective study of 7 528 in Rotterdam identified 5 patients with VaD aged 55-64 and one retrospective study of 164 000 in Piteå, Sweden identified one patient aged 40-64, yielding prevalence figures of 191.4 and 3 (age-adjusted) per 100 000 persons at risk [181, 183]. However, the low number of included patients discourages any conclusions.

The relatively low prevalence of VaD found in this project, though similar to other reports, might be partly caused by a separate patient-flow for acute vascular events within the Norwegian healthcare system. Stroke patients are mainly treated in rehabilitation institutions, and frequently cared for in other parts of community healthcare services, less scrutinized in the current project. The real prevalence of young onset VaD, at least in Norway, might be higher.

- *Alcohol-related dementia*

The survey from Australia reported a higher prevalence of ARD than AD, and significantly higher prevalence of ARD compared to all other studies, likely benefitting from a study designed specifically to detect this dementia subtype. Though they deviate from the rest, it is highly probable that the Australian estimates are more reliable than the others, including the current study. Aside from another survey of admission-diagnosis from a hospital in Australia, yielding similar results (referenced in the before mentioned article), and Harvey et al., there have not been other reports on the prevalence of ARD in younger populations [173, 278]. In general, ARD is challenging to assess in epidemiological studies, and even among the elderly it has not received particular attention, studies being too heterogeneous and results too fluctuating to yield a reliable estimate [279].

11.2.1.3 Conclusion

Though population-based studies yield somewhat comparable figures and rates for the total population of YOD, the prevalence of subtypes differs according to the sources and methods applied. Due to undetected cases, the figures should be regarded as minimum estimates.

11.2.2 Incidence of dementia and AD

Incidence of YOD was 14.8 and 25.0 per 100 000 person-years in the age categories 30-64 and 45-64, respectively. The rates are remarkably similar to two larger studies, one from Spain in 2010 and one from Italy in 2020 (13.4/13.2 and 22.8 per 100 000 person-years in the corresponding categories) [17, 96]. The incidence rates for AD in these studies were also similar (5.0-6.7 and 11.8-11.9 per 100 000 person-years, for the corresponding age categories). The current study, and the study from Spain applied DSM-IV criteria for dementia and 1984 NINSCD-ADRDA for AD, whereas the survey from Italy applied DSM-V criteria for major cognitive disorder (dementia) and NIA-AA criteria for AD as discussed earlier.

Other studies have published incidence rates of YOD and AD in various age categories, making inferences challenging, (see Table 13 and 14). There are very few comparable studies on the incidence of YOD, providing less basis for reliable estimates. The age of 50 emerges as a threshold age for the clinical development of neurodegenerative diseases, but apart from confirming lower estimates compared to LOD, and increasing prevalence according to age, further investigation is required, preferably with a similar study design.

Table 13. Incidence of young onset dementia in various studies.

Study	*Current study*	*Chiari et al. [96]*	*Edahiro et al. [240]*	*Abraham Sanches et al. [186]*	*Garre-Olmo et al. [17]*	*Mercy et al. [185]*	*Knopman et al. [187]*	*Edland et al. [188]*
Country	Norway	Italy	Japan	Argentina	Spain	UK	US	US
Year	2020	2020	2020	2015	2010	2008	2006	2002
Age	30-64	30-64	18-64	21-64	>30	<65	>40	>50
Criteria:								
Dementia	DSM-IV	DSM-V	DSM-V	-	DSM-IV	NR	DSM-IV	DSM-IV
AD	NINCDS-ADRDA	NIA-AA	DSM-V	NINCDS-ADRDA	DSM-IV	NINCDS-ADRDA	DSM-IV	DSM-IV
FTD	L-M	Rascovsky Gorno-Tempini	DSM-V	L-M	L-M+ Neary	Neary	Neary	-
Source(s)	Pop.based	Pop.based	Tertiary clinics	Hospital	Hospital	Hospital	Pop.based	Pop.based
Design	R	R+P	R	P	R	R	R	R
Point of detection	AAD	AAO	AAD	?	AAD(?)	AAD	AAO	AAO
Pop.size	449 796	702 481	National population	17 614	690 207	326 200	-	70 745
N (<65)	89	160	1733	14	144	54	26	24
Incidence:								
30-34	0.0	-	-	0	0.5	-	-	-
35-39	2.4	-	-	0	1.1	-	-	-
40-44	2.2	-	-	0	2.9	-	-	-
45-49	2.1	-	-	-	5.1	-	-	-
50-54	20.7	-	-	-	14.8	-	-	35.6
55-59	28.4	-	-	-	32.0	-	-	40.2
60-64	54.8	-	-	-	67.7	-	125.9	129.2
30-39	1.2	-		-				
40-49	2.2	-	-	-	-	-	8.8	-
50-59	24.4	-	-	-	-	-	22.9	-
21-54	-	-	-	3	-	-	-	-
18/21-64	-	-	2.5	11	-	-	-	-
30-64	*14.8*	*13.2*	-	-	*13.4*	-	-	-
40-64	20.2	-	-	-	-	-	29.6	-
45-54	50.6	-	-	8	-	-	-	-
45-64	*25.0*	-	-	-	*22.8*	*11.5*	-	-
55-64	41.2	-	-	22	-	-	-	-

Incidence per 100 000 person-years

Table 14. Incidence of Alzheimer's disease in various studies.

Study	***Current study***	***Chiari et al.***	***Garre-Olmo et al. [17]***	***Mercy et al. [185]***	***Edland et al. [188]***	***Ruitenberg et al. [189]***	***Andreasen et al. [183]***	***Newens et al. [182]***	***McGonial et al. [195]***
Country	Norway	Italy	Spain	UK	US	The Netherlands	Sweden	UK	Scotland
Year	2020	2020	2010	2008	2002	2001	1999	1993	1993
Ages	30-64	30-63	>30	<65	>50	>55	>40	<65	40-64
Criteria	NINCDS-ADRDA	NINCDS-ADRDA (2011)	DSM-IV	NINCDS-ADRDA	DSM-IV	NINCDS-ADRDA	NINCDS-ADRDA	NINCDS-ADRDA	NINCDS-ADRDA
Pop. size	449 796	702 481	690 207	326 200	70 745	7 046	61 874	45-65: 655 800	Entire pop. of Scotland
N (<64)	40	61	61	19	9	Not specified	15	360	Not specified
Design	R	R+P	R	R	R	P	R	R	R
Incidence:									
30-34	0.0	-	-	-	-	-	-	-	-
35-39	0.0	-	-	-	21.3	-	-	-	-
40-44	0.0	-	-	-	16.1	-	-	0.0	1.4
45-49	0.0	-	-	-	36.9	-	-	0.9	8.1
50-54	6.9	-	-	-	-	-	-	4.9	27.6
55-59	12.4	-	-	-	-	0	-	8.1	39.7
60-64	31.3	-	-	-	-	10	-	14.5	37.8
30-59	-	-	-	-	-	-	-	2.1	-
30-64	*6.7*	*5.0*	*5.7*	-	-	-	-	-	-
40-64	6.9	-	-	-	-	-	13.0	-	22.6
45-54	3.3	-	-	-	-	-	-	2.9	-
45-64	*11.8*	-	*11.9*	*4.2*	-	-	-	*7.2*	-
50-64	16.4	-	-	-	-	-	-	-	-
55-64	21.6	-	-	-	-	-	-	11.3	-

Incidence per 100 000 person-years

11.2.3 Aetiology

The aetiology of YOD was heterogeneous, as has been shown in several previous publications [137, 138, 173]. AD was the most frequent subtype, the proportion of which was in the upper range compared to other reports (56.2 vs 13.0-66.7 %) [208, 212, 213, 280]. The AD to FTD ratio was 7.3:1 in the total cohort of YOD (219 individuals aged > 65 on census date), lowering to 6.2:1 in patients younger than 65, agreeing with the high number of AD cases identified in the project. An overview of previous literature on the subject is given in Table 7. A study from Italy, published later (in 2020), reported proportions of the various phenotypes of AD and FTD not assessed in previous studies, confirming that the

amnestic variant of AD is the most frequent presentation, followed by behavioural variant of FTD, and the logopenic variant of AD [96].

A recent survey on the prevalence of LOD investigated almost 10 000 elderly individuals aged >70 in the northern district of Trøndelag (the HUNT-study) [281]. This study performed cognitive evaluations and interviews with caregivers, and diagnosed patients according to DSM-V criteria. Although widely differing study design, the proportion of AD was strikingly similar to the current study (both 57 %), of which the current study is in the upper ranges, whereas the HUNT-study is in the lower ranges of previous reports [282-284]. The authors ascertained that the low proportion of AD might have been caused by the large number of cases (17 %) in which the HUNT researchers could not identify a specific diagnosis. The present study had more detailed information available, allowing identification of a greater variety of diagnosis.

11.2.4 Time to diagnosis

Paper III is to date the largest survey on time to diagnosis in typical young onset AD. Time from symptom onset to diagnosis was 5.5 years. This is longer than previously reported in which diagnostic delay has ranged from 1.5 to 4.2 years for this subtype of YOD [214-217]. The longest time lag was from symptom onset to anyone contacting medical services, usually the GP. Aspects related to this were discussed in "Assessing age at onset".

Obstacles within the healthcare system were also identified. GPs postponed referrals to hospitals by 7.5 months. As 2.8 months elapsed from the issue of a referral to patients visiting the hospital for the first time, the total delay from alerting the GP to an adequate evaluation of symptoms exceeded 10 months. Even though patients recognized symptoms earlier than family members, the GP acted sooner if concern was raised by an employer or family member compared to the patient. Increased awareness in YOD compared to LOD, especially in earlier phases, has been previously shown [21]. Approximately a third of patients in the present study initiated an investigation of cognitive symptoms themselves.

Hospital evaluation lasted 15 months before the diagnosis could be made. Almost three months elapsed before hospital physicians attributed symptoms to dementia. Initial screening methods, such as Mini Mental Status Examination and MRI, were largely normal, possibly freezing further investigations. The Consortium to Establish a Registry for Alzheimer's Disease Word List Memory Task (Ten-word test) and analysis of CSF core biomarkers were performed with a substantial delay of 6.5 and 8.3 months, respectively, and most likely the precipitating factor for the diagnosis in the months thereafter. Time aspects regarding the clinical evaluation of young onset AD is within the range of previous studies reporting an average of 6-26 months, (the latter included time from referral to first visit) [215, 216]. None of these studies assessed the delay of lumbar puncture, which has become an increasingly essential diagnostic tool in AD. In vivo evidence of AD-pathology

allows for the diagnosis to be made in predementia phases, thus shortening the pre-diagnostic period which is disproportionally difficult in younger patients [227, 228].

The hypothesis of diagnostic delay being connected to the complexity of YOD does not fully apply for these patients, as all of them were dominated by impairment of memory. Age, lack of knowledge on prevalence and clinical presentation of young onset AD might therefore be major obstacles in the diagnostic pathway.

11.3 Conclusions

The project found that YOD affects a significant number of individuals in central Norway. AD was the most frequent subtype of dementia, more prevalent than previously shown. Nevertheless, the diagnostic delay for patients receiving a diagnosis of young onset AD is substantial.

Our aim was to identify every patient diagnosed with YOD in Trøndelag, always accepting that any frequency estimate, including the present one, is only approximate. Our project had both strengths and weaknesses, demonstrating ability for detecting the most common neurodegenerative disorder of AD, but the case ascertainment strategy proved less well-suited for identifying secondary subtypes. We only included diagnosed cases. A survey's ability to identify diagnosed and covert patients of the entire aetiological spectrum remains a major challenge but is necessary to assess the true epidemiology of YOD.

Reliable estimates are vital for the public, for healthcare authorities, and for physicians evaluating patients with YOD, ultimately benefitting the patients we are committed to serve.

12 REFERENCES

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Paper I

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The Prevalence and Subtypes of Young Onset Dementia in Central Norway: A Population-Based Study

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Abstract.
Background: Young onset dementia poses several challenges for the individual, health care, and society that are not normally relevant for late onset dementia, but is little researched.
Objective: To determine the prevalence and subtypes of young onset dementia in a defined catchment area in central Norway.
Methods: The main sources of patient identification were the databases at the Department of Neurology, University Hospital of Trondheim (St. Olav's Hospital), and Department of Psychiatry, Levanger Hospital. Both departments are the main sites for referral of young onset dementia (onset before age 65 years) in the county, covering approximately 90% of the catchment area of the study. Other sources included key persons in the communities, collaborating hospital departments examining dementia, and review of hospital records of all three hospitals in the area. Included patients met the DSM-IV criteria for dementia. The prevalence of dementias was calculated by sex and age.
Results: All patients identified with dementia and onset before 65 years on census date were included in the study ($n = 390$). Patients younger than 65 on census date were included in the calculation of prevalence, giving a result of 76.3 per 100 000 persons at risk in the age category of 30–65 years, and 163.1 per 100,000 for the category 45–64 years. Etiology was heterogeneous, but the main subtype of dementia was Alzheimer's disease.
Conclusions: Young onset dementia affects a significant number of people in central Norway. Prevalence figures are higher than previously reported from England and Japan, but are similar to a more recent study from Australia.

Keywords: Alzheimer's disease, early onset dementia, epidemiology, prevalence

INTRODUCTION

There has been extensive research on the prevalence of dementia in later stages of life, but few studies on the prevalence among younger patients, probably due to a considerably higher prevalence of dementia in the older population. Dementia is challenging in any case, but can be disastrous for patients and their families when it strikes at a young age. Young onset dementia (YOD), also known as early onset dementia, is commonly defined as dementia with onset before the age of 65 years. YOD impacts family, income, occupational and social life, and imposes an appreciable challenge to health care and dementia services [1–3]. These may be inexperienced

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in addressing the special needs of this younger group of patients [4].

Prevalence studies on YOD vary in design and the results are conflicting. In recent years, only four population-based reports have been published where the design is relatively comparable: two from England, one from Japan, and one from Australia [5–8]. All studies relied on multiple case ascertainment to identify patients diagnosed with YOD. The results in the studies from England and Japan are fairly consistent, whereas the report from Australia indicates a higher prevalence.

The prevalence of YOD in Scandinavia has not been well documented to date. A population-based Swedish study from the area of Lundby actually found no patients with dementia under the age of 60 when prospectively investigating the total population between 1957 and 1972, and only one patient under the age of 65 [9]. Two other hospital-based reports from Sweden and Denmark produced diverging, though higher prevalence estimates of YOD than the Lundby-study [10, 11]. There are currently no publications on the prevalence of YOD from Norway.

Reliable epidemiological data on the occurrence of YOD are vital for medical professionals, providers of health care and policy makers. The aim of this study was to provide an estimate of the prevalence and subtypes of YOD in central Norway.

MATERIAL AND METHODS

Population base

Trøndelag is a county in central Norway with a total population of 449,769 as of July 1, 2016, representing 9.8% of the total population. Trøndelag includes both urban and rural populations. By far the largest municipality is the city of Trondheim with a population around 188,000. The populations in the remaining 48 municipalities range from 469 to 23,308 inhabitants. Trøndelag has slightly fewer immigrants than the national average (10.5% versus 16.3%), but the level of education, unemployment rate and general health do not differ significantly [12].

Health care organization

Norwegian health care is organized in a dual system of primary and secondary services. Primary health care is a municipal responsibility and consists of general practitioners (GP) and general health care services such as home nursing care, day care centers, and nursing homes. Hospitals and other specialist facilities form the secondary level. Close communication between levels improves patient follow-up and increases transparency. There are three hospitals in Trøndelag: a University Hospital in Trondheim, and local hospitals in Levanger and Namsos. According to national guidelines, people under the age of 65 with symptoms indicating dementia should be referred to a specialist clinic for diagnostic work-up. Each municipality is urged to provide the services of a dementia team [13].

Health care in Norway is largely financed by public means, and private health care in the field of dementia is negligible outside the family environment.

Case identification

Primary sources

Primary sources were the hospital databases at the Department of Neurology, University Hospital of Trondheim, and the memory clinic of the Department of Psychiatry, Levanger Hospital. Both departments are main referral sites of YOD in their catchment area, covering over 90% of the target area. They constitute the leading research facilities in the study. All patients who received a diagnosis of dementia with onset < 65 years by the leading research facilities were included.

Secondary sources
Hospital based:

a. Computerized hospital records from all three hospitals were researched for potential patients with a diagnosis of dementia according to ICD-10. Patients were categorized into two groups: 1) Patients who received any diagnosis of dementia, (including G30.1 Alzheimer's disease (AD) with late onset and/or F00.1 Dementia in AD with late onset) before the age of 70, and 2) Patients who had received a diagnosis of AD with early onset (G30.0) and/or dementia in AD with early onset (F00.0). All patients and/or primary caregivers were contacted by mail and telephone in order to determine the accuracy of diagnosis, and to estimate the age at onset (AAO).

   Patients who were obviously miscoded were not included.
b. Specialized outpatient services for individuals with intellectual disabilities are located in both Trondheim and Levanger, but serve the entire catchment area, and enabled inclusion of all

patients who had received a diagnosis of YOD. These services routinely evaluate patients with Down's syndrome (trisomy 21).

c. Physicians at other departments working in close collaboration with our research group were informed about the study, and assisted with the inclusion of patients who met the criteria.

Community based

d. Dementia teams in all the 49 municipalities in the target area were personally contacted by telephone and asked to scan their municipality for candidates. In municipalities without specialized dementia teams, the heads of home nursing services were contacted. It was emphasized that all subtypes of dementia were eligible, and that patients currently older than 65 years also could meet inclusion criteria depending on the duration of symptoms.

e. If the dementia teams did not have extensive knowledge of the patients in day care centers and sheltered housing or nursing homes in their area, the facilities themselves were requested to identify potential candidates.

f. A regional center for Huntington's disease (HD) with extensive knowledge about patients throughout the entire target area with this condition provided basic information on patients with dementia.

MKA and SBS were the lead researchers in this study. Except for cases identified by SBS at the Department of Neurology in Trondheim, all the steps in case ascertainment were conducted by MKA over a period of four years between July 2014 and July 2018. Due to a lengthy investigatory process, census date was set in the middle of the inclusion period (July 1, 2016) to minimize the time between inclusion and census date. A small sample of three patients made known to us clinically were included in the days following the end of the recruitment period.

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK Midt 2014/487).

Case verification

Included patients met the clinical criteria for dementia according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. and were alive and residing within the catchment area on census date [14]. Dementia on census date was systematically verified either through personal telephone interview with caregivers or hospital records, or both.

Diagnostic validation

Validated diagnostic criteria were applied for the diagnosis of various neurodegenerative diseases [15–22], vascular dementia (VaD) [23], and alcohol-related dementia [14]. Diagnostic criteria for AD, frontotemporal dementia (FTD), VaD, and alcohol-related dementia are consistent with Harvey et al. [8], Ikejima et al. [7], and Withall et al. [5]. Patients with intellectual disability and dementia (mainly Down's syndrome) were not further classified. Secondary dementias were categorized according to the underlying disease. Cases that did not meet a specific set of criteria were classed as "unspecified". Challenging cases with unclear etiology were classified following consensus meetings with specialists in neurology, geriatrics, and psychiatry.

AAO was defined as the age at appearance of the first symptom as recognized by caregiver or patient.

Consenting patients

Consenting patients who had not personally been assessed and included by the lead researchers, were consecutively evaluated through hospital records as we were made aware of them through our various sources. A telephone interview with a close caregiver was conducted by MKA if possible.

Non-consenting patients

Throughout the clinical work and investigatory process, we identified patients with YOD who were reluctant to participate in a medical research study. To limit inclusion bias, the Regional Committee for Medical and Health Research Ethics accepted our request to count these individuals, hence contributing to truer prevalence figures. Patients who did not provide formal consent are referred to as 'non-consenting patients'. All non-consenting patients were evaluated by the lead researchers. Patients older than 65 years on census date were excluded due to uncertainty of AAO. Only information on age, gender, and diagnosis was available for this group.

As patients with intellectual disability and patients with HD dementia were identified through reliable and collaborating sources, we did not seek further confirmation of these diagnoses.

Table 1
Sources of identification

Source		*N* (%)
Primary		*248 (63.6)*
	Databases of:	
	Dept. of Neurology	161 (41.3)
	Dept. of Psychiatry	96 (24.6)
	Both	9 (2.3)
Secondary		*142 (36.4)*
	Hospital records	61 (15.6)
	SOSII*	13 (3.4)
	Other departments	7 (1.8)
	Community research**	61 (15.6)

*Specialized outpatient services for individuals with intellectual disabilities. **12 patients were identified through the regional center for HD.

RESULTS

Patients

We identified a total of 410 individuals with YOD, of which 390 patients had dementia on census date and were included in the study. A total of 171 of these cases were between the age of 30 and 64 on census date and constituted the basis for the prevalence calculations. Sources of identification are listed in Table 1.

Diagnosis verification

Consenting patients

A total of 301 patients were consenting participants and subjected to a detailed review of hospital records. Almost two thirds of these patients received their diagnosis in leading research facilities ($n = 180$).

Clinical work-up

With the exception of one patient with alcohol-related dementia and one with AD, all consenting patients underwent some form of cognitive assessment in a specialist setting. For the isolated case of alcohol-related dementia, the diagnosis was determined on the basis of relevant hospital records, CT scan, and interview with a close family member. For the isolated case of AD, the patient had received the diagnosis from the GP, which was then confirmed in hospital records and by a close family member who described symptom progression typical of AD. All but this latter patient had some form of neuroimaging available for review. Table 2 gives an overview of the clinical work-up for consenting patients.

Non-consenting patients

A total of 89 patients were non-consenting participants. Of these, 55 patients were diagnosed by lead researchers or physicians in collaborating hospital departments. Nine patients were initially identified by hospital records in which the subtype of dementia in four of the cases was confirmed by their closest caregivers (two with AD, one with alcohol-related dementia, and one with FTD), three by collaborating physicians (one with AD, one with VaD, and one with metabolic disease), and two by the patient's GP (both alcohol-related dementia). Diagnoses of 13 patients with intellectual disability and dementia, and 12 patients with HD dementia, were confirmed by specialized regional centers for these conditions.

Descriptives

The mean age of the total population of YOD was 63.6 years (SD 8.3, range 21–81) and 58.0 years for patients who were under 65 years (SD 8.0) on census date. There was a significant difference between males and females within the total population of YOD (43.8 and 56.2%, respectively; $p = 0.02$), but not among patients younger than 65 years on census date (47.7 and 52.3%; $p = 0.52$).

Consenting patients

Mean AAO for consenting patients with YOD was 56.7 years ($n = 295$, SD 6.7, range 18–64). Mean age at diagnosis was 62.1 years ($n = 296$, SD 6.7, range 20–73). Roughly half of the consenting population (46.2%) were residing in residential care with no significant differences in gender.

Etiology

Degenerative disease accounted for the majority of cases in the sample, with AD representing more than two thirds of the degenerative dementias, and over half of all dementias. Of the 16 cases of vascular dementia, 11 were post-stroke dementias whereof 3 were caused by subarachnoid hemorrhage. Table 3 gives an overview of the distribution of diagnoses in the total sample of YOD.

Prevalence

A total of 171 patients were aged between 30 and 64 years on census date and constituted the basis for prevalence calculations. Only nine of these patients were younger than age 45 years. About 50% of the

Table 2
Medical evaluation of consenting patients

				Cognitive tests			Biomarkers				
		Total	Interview with	MMSE	Clock	TMT-A	CERAD**	CSF	MRI	Both	DATscan
		n	caregiver*		drawing test	and/or -B		analysis		CSF&MRI	
All	*n*	301	279	278	265	224	156	212	278	207	17
	%	100	92.7	92.4	88.0	74.4	51.8	70.4	92.4	68.8	5.6
AD	*n*	205	195	203	198	172	118	170	195	165	2
	%	68.1	95.1	99.0	96.6	83.9	57.6	82.9	95.1	80.5	1.0
FTD	*n*	26	26	24	24	19	16	21	26	21	0
	%	8.6	100.0	92.3	92.3	73.1	61.5	80.8	100.0	80.8	0.0
DLB/	*n*	21	18	21	19	16	13	11	18	11	13
PDD	%	7.0	85.7	100.0	90.5	76.2	61.9	52.4	85.7	52.4	61.9
VaD	*n*	11	10	6	3	11	1	0	7	0	0
	%	3.7	90.9	54.5	27.3	100.0	9.1	0.0	63.6	0.0	0.0

*Telephone interview performed by MKA. **CERAD Word List Test.

Table 3
Primary diagnoses in the sample *(n = 390)*

	n	%	F/M
DEGENERATIVE DEMENTIAS	311	79.7	185/126
Alzheimer's disease	219	56.2	142/77
Huntington's disease with dementia	30	7.7	12/18
Frontotemporal dementia	30	7.7	20/10
Dementia with Lewy bodies	19	4.9	7/12
Parkinson's disease with dementia	6	1.5	1/5
Posterior cortical atrophy	5	1.3	1/4
Progressive supranuclear palsy	1	0.3	1/0
Corticobasal syndrome	1	0.3	1/0
VASCULAR DEMENTIA	16	4.1	6/10
MIXED VaD/AD	6	1.5	3/3
OTHERS	45	11.5	18/27
Alcohol-related dementia	15	3.9	6/9
Intellectual disability and dementia (mainly Down's syndrome)	13	3.3	7/6
Acquired brain injury	8	2.1	2/6
Multiple sclerosis	4	1.0	2/2
Metabolic encephalopathy	3	0.8	1/2
Normal pressure hydrocephalus	1	0.3	0/1
Encephalitis	1	0.3	0/1
UNSPECIFIED	12	3.1	7/5

patients under 65 years were aged between 60 and 64 years. Table 4 gives an overview of the prevalence according to age and gender.

AD was the most prevalent subtype of dementia among patients between 30 and 65 years of age, followed by HD dementia, alcohol-related dementia, VaD, and FTD. We did not identify any case of AD or FTD under 45 years of age. Age-specific prevalence figures for the most common diagnoses are shown in Table 5.

DISCUSSION

This is the first population-based study to investigate the prevalence of YOD in Norway, and the first of its kind in Scandinavia. The population base constitutes around 10% of the national population, and does not differ significantly from that of the rest of Norway. We identified 390 patients with YOD of whom 175 were younger than 65 on census date. This qualifies as a large cohort investigating the epidemiology of YOD [5, 6, 24].

We found an overall dementia prevalence of 76.3 per 100,000 persons at risk in the age group of 30–64 years, and 143.1 in the age group of 45–64 years. These figures are similar to those found in Australia, and considerably larger than the results from England and Japan [5, 7, 8]. For comparison, the prevalence figures of various subtypes of dementia in relevant population-based studies with similar design are shown in Table 6.

Other studies with a different approach to that used by us have demonstrated a wide range of dementia prevalence among patients younger than 65 [10,

Table 4
Age- and gender-specific prevalence figures in the study population

All causes of dementia											
Population			All			Male			Female		
Age range	Male (n)	Female (n)	*n*	Prev*	95% CI	*n*	Prev*	95% CI	*n*	Prev*	95% CI
30–34	14 955	13 956	2	6.9	(1.0–25.0)	2	13.4	(1.6–48.3)	0	–	–
35–39	14 451	13 145	1	3.6	(1.0–20.2)	0	–	–	1	7.6	(1.0–42.4)
40–44	15 656	14 683	6	19.8	(7.3–43.0)	5	31.9	(10.4–74.5)	1	6.8	(1.0–38.0)
45–49	16 094	15 507	7	22.2	(8.9–45.6)	5	31.1	(10.1–72.5)	2	12.9	(1.6–46.6)
50–54	14 908	14 146	27	92.9	(61.3–135.2)	11	73.8	(36.8–132.0)	16	113.1	(64.7–183.6)
55–59	13 762	13 199	44	163.2	(118.6–219.0)	21	152.6	(94.5–233.2)	23	174.3	(110.5–261.4)
60–64	12 830	12 732	84	328.6	(262.2–406.7)	42	327.4	(236.0–442.2)	42	329.9	(237.8–445.6)
30–44	45 062	41 784	9	10.4	(4.7–19.7)	7	15.5	(6.2–32.0)	2	4.8	(1.0–17.3)
30–64	102 656	97 368	171	76.3	(65.3–88,6)	86	74.9	(60.0–92.6)	85	77.7	(62.1–96.0)
45–64	57 594	55 584	162	143.1	(122.0–167.0)	79	137.2	(108.6–171.0)	83	149.3	(119.0–185.1)

*Prevalence proportion calculated per 100,000 people.

Table 5
Age-specific prevalence figures for the most common causes of YOD

Age range	Alzheimer's disease			Huntington's disease with dementia			Alcohol-related dementia			Vascular dementia			Frontotemporal		
	n	Prev*	95% CI	*n*	Prev*	95% CI	*n*	Prev*	95% CI	*n*	Prev*	95% CI	*n*	Prev*	95% CI
35–39										1	3.6	(1.0–20.2)			
40–44				5	16.5	(5.4–38.5)				1	3.3	(1.0–18.4)			
45–49				3	9.5	(2.0–27.7)				1	3.2	(1.0–17.6)			
50–54	6	20.7	(7.6–44.9)	4	13.8	(1.8–35.2)	2	6.9	(1.0–24.9)	1	3.4	(1.0–19.2)	1	3.4	(1.0–19.2)
55–59	15	55.6	(31.1–91.7)	3	11.1	(2.3–32.5)	2	7.4	(1.0–26.8)	3	11.1	(2.3–32.5)	7	26.0	(10.4–53.5)
60–64	53	207.3	(155.3–271.1)	5	19.6	(6.4–45.6)	7	27.4	(11.0–56.4)	4	15.6	(4.3–40.1)	4	15.6	(4.3–40.1)
30–64	74	33.0	(25.9–41.0)	21	9.4	(5.8–14.3)	11	4.9	(2.5–8.8)	11	4.9	(2.4–8.8)	12	5.4	(2.8–9.4)
45–64	74	65.4	(51.3–82.1)	15	13.3	(7.4–21.9)	11	9.7	(4.9–17.4)	9	7.1	(3.1–13.9)	12	10.6	(5.5–18.5)

*Prevalence proportion calculated per 100,000 people.

25–27]. It is commonly thought that such diverging results are due to variability of study design. Heterogeneous inclusion and diagnostic criteria, and deviating case ascertainment are well-known factors in this respect. Population-based studies are preferred to avoid selection bias, but are far more cost extensive, and often limited to small population sizes. Registry-based studies are traditionally thought to have a high level of case accuracy, and their ability to cover large areas increases the precision of the estimates. On the other hand, such studies are inevitably linked to the quality of the respective registry. The level of clinical assessment might vary and valid biomarkers are not always included. Studies based on a low level of clinical assessment favor sensitivity over specificity, and often tend to yield higher prevalence figures. This is often the case in studies where the entire study population is screened. These types of "screening-studies" also include patients that are undiagnosed and therefore unrecognized by the health care system in which the study is performed, both of which may contribute to higher prevalence. Studies based on identifying patients already diagnosed with dementia are dependent on the ability of the respective health care systems to do so, and differences in prevalence in the various studies might be a mere reflection of the health care systems in which they are operating.

The present study was performed in a well-organized and publicly-financed health care system easily accessible for patients of diverse socioeconomic background, presumably increasing the likelihood of contact with health services. The structure of small and distinct municipalities, and well-informed dementia coordinators, in turn facilitated the identification of the patients after they received their diagnosis. We consider it likely that the relatively high prevalence estimations presented in the current study are more accurate than previous reports conducted in populations with less organized health care systems.

However, all types of epidemiological studies are associated with some form of bias, with potential weaknesses and strengths depending on the approach. The main strength of this study is a relatively large sample size of high clinical accuracy, covering a geographically large area of both rural and urban

Table 6
Comparison of prevalence figures per 100,000 persons for YOD in various population-based studies

	ALL DEMENTIA				
	Norway (Current study)	Australia [5]	Japan [7]	England [8]	England [6]
Age:					
50–54	92.9	102.7	59.0	62.5	–
55–59	163.2	131.2	94.3	152.1	–
60–64	328.6	265.2	163.3	166.3	–
30–64	*76.3*	*68.2*	*51.7**	*54.0*	–
45–64	*143.1*	*132.9*	*83.3*	*98.1*	*81.0*

	DEMENTIA SUBTYPES									
	Norway (Current study)	Australia [5] AD	Japan [7]	England [8]	England [6]	Norway (Current study)	Australia [5] VaD	Japan [7]	England [8]	England [6]
Age:										
50–54	20.7	6.4	9.8	16.4	–	3.4	6.4	22.9	6.6	–
55–59	55.6	13.1	28.0	50.7	–	11.1	13.1	42.2	32.6	–
60–64	207.3	74.6	49.5	77.3	–	15.6	49.7	78.4	38.7	–
30–64	*33.0*	*9.3*	*13.4**	*17.4*	–	*4.9*	*7.7*	*10.1**	*8.7*	–
45–64	*65.4*	*19.9*	*22.3*	*35.0*	*15.1*	*7.1*	*14.9*	*38.6*	*17.9*	*8.2*
		FTD					ARD			
50–54	3.4	6.4	1.5	3.3	–	6.9	32.1	–	19.7	–
55–59	26.0	26.2	1.7	25.4	–	7.4	32.8	–	18.1	–
60–64	15.6	8.3	4.4	23.2	–	27.4	49.7	–	11.6	–
30–64	*5.4*	*5.4*	*1.2**	*7.5*	–	*4.9*	*16.3*	–	*6.6*	–
45–64	*10.6*	*11.6*	*2.0*	*15.4*	*15.1*	*9.7*	*33.1*	–	*13.6*	–

*Calculated. AD, Alzheimer's disease; VaD, vascular dementia; FTD, frontotemporal dementia; ARD, alcohol-related dementia.

districts, combined with case ascertainment based on multiple sources in the context of a well-organized health care system. We were able to evaluate every patient made known to us through our sources, including patients identified in the computerized search.

Nevertheless, cultural differences in the population bases and the organization of the health care system may affect which subtypes of dementia that are more likely to be diagnosed. The Norwegian health care system is largely adapted to recognize and care for dementia patients with AD, which is the dominant subtype of late onset dementia. This could explain why we found a higher prevalence of AD compared to most other reports. Our study was based on a comprehensive specialized clinical work-up for most patients, particularly for those with AD, where clinical findings have been routinely supplemented with MRI and/or cerebrospinal fluid (CSF) core biomarkers. Although clinical criteria were applied for the sake of general comparison, the vast majority of the patients diagnosed with AD also had at least one marker indicating AD-pathology. On the other hand, intellectual disability was mostly due to Down's syndrome and the subtype of their dementia was not further investigated. Although the likelihood of AD was high, these patients were not categorized as such, and therefore represent a potential source of underestimation. Overall, we believe the number of patients with AD to be fairly accurate, though like most neurodegenerative conditions, AD is a slow, progressive disease, so accurate assessment of dementia debut will at present remain a matter of judgement on the part of the physician.

AD represents 56.9 % of the total cohort of YOD. Other cohorts have shown varying proportions of AD, but most of the studies conclude that AD is the most prevalent subtype of dementia, even among younger patients [28–30]. We identified 17 different subtypes of dementia, confirming other reports on the heterogeneity of YOD etiology [5, 31, 32]. Neurodegenerative disease counted for almost 80 % of the cases. As neurodegenerative conditions are rare before the age of 45, our findings may be a reflection of the relatively high mean age of 63.6 years [33].

Despite the advantages of a well-organized health care system, even in Norway there are formal and tacit norms for identifying and diagnosing dementia subtypes. Unfortunately, there are certain conditions where dementia occurrence was difficult to identify from patient records as dementia is not commonly used as an identifier. This was essentially

the case for most secondary dementias, and other conditions where cognitive symptoms coincide with non-cognitive symptoms, such as in VaD, alcohol-related dementia, and acquired brain injury.

With respect to alcohol-related dementia, patients with alcohol dependencies are frequently treated in other parts of our health care system, and cases with dementia might to a lesser extent be referred to dementia care units in the communities. The study from Sydney, Australia, had a particular focus on alcohol-related dementia [5]. Their findings indicate that it is a significant subtype of YOD and that the prevalence could be underestimated in many studies, as is likely the case in the present one. It also shows the need for targeted methodological measures to identify alcohol-related dementia. Additionally, due to capacity limitations, patients with potential dementia from head injuries were not investigated during the computerized search at the hospitals, though emphasized when collaborating with dementia coordinators. Departments for rehabilitation or treating substance dependencies were not contacted. Similarly, PD has traditionally been diagnosed according to motor symptoms and the cognitive deficits have largely gone unrecognized until more recently, and we identified few PD-related cases here. For these reasons we believe our figures for such conditions, though similar to figures found in several other studies, are almost certainly underestimated in the current material.

However, there will always be patients that remain undetected regardless of the techniques employed. Future estimates for the prevalence of dementia would be improved by a comprehensive approach to detect all relevant types. Despite the high number of patients with AD, we believe that this reflects only a minimum of the true prevalence. Furthermore, old diagnostic criteria which were purposely applied for the sake of comparison, serve directly to affect the outcome and artificially reduce the prevalence figures. The ability of future studies to produce an accurate frequency of AD depends on how well the diagnostic criteria will be able to detect cognitive changes during the pre-dementia phase of the condition.

Taking these considerations into account, we believe that the current study provides valuable insight into the epidemiology of YOD, generating updated and improved estimations of the prevalence and etiology on an important and particularly vulnerable subgroup of patients with dementia.

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Erratum

The Prevalence and Subtypes of Young Onset Dementia in Central Norway: A Population-Based Study

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On page 1 and 6 incorrect values have been given. The correct values are given below.

On page 1, in line 2 of the Results section of the Abstract: 76.3 per 100,000 should be 85.5 per 100,000.

On page 1, in line 3 of the Results section of the Abstract: 163.1 per 100,000 should be 143.1 per 100,000.

On page 5, line 10 of the Discussion section: 76.3 per 100 000 should be 85.5 per 100 000.

On pages 484 and 485: Tables 4-6 contain incorrect values. The correct Tables 4-6 are listed below.

Table 4
Age and gender-specific prevalence rates in the study population

Population			All causes of dementia								
			All			Male			Female		
Age range	Male (n)	Female (n)	*n*	Rate*	95% CI	n	Rate*	95% CI	n	Rate*	95% CI
30–34	14 955	13 956	2	6.9	(1.0–25.0)	2	13.4	(1.6–48.3)	0	–	–
35–39	14 451	13 145	1	3.6	(1.0–20.2)	0	–	–	1	7.6	(1.0–42.4)
40–44	15 656	14 683	6	19.8	(7.3–43.0)	5	31.9	(10.4–74.5)	1	6.8	(1.0–38.0)
45–49	16 094	15 507	7	22.2	(8.9–45.6)	5	31.1	(10.1–72.5)	2	12.9	(1.6–46.6)
50–54	14 908	14 146	27	92.9	(61.3–135.2)	11	73.8	(36.8–132.0)	16	113.1	(64.7–183.6)
55–59	13 762	13 199	44	163.2	(118.6–219.0)	21	152.6	(94.5–233.2)	23	174.3	(110.5–261.4)
60–64	12 830	12 732	84	328.6	(262.2–406.7)	42	327.4	(236.0–442.2)	42	329.9	(237.8–445.6)
30–44	45 062	41 784	9	10.4	(4.7–19.7)	7	15.5	(6.2–32.0)	2	4.8	(1.0–17.3)
30–64	102 656	97 368	171	85.5	(73.2–99.3)	86	83.8	(67.0–103.5)	85	87.3	(69.7–107.9)
45–64	57 594	55 584	162	143.1	(122.0–166.9)	79	137.2	(108.6–170.9)	83	149.3	(119.0–185.1)

*Rate per 100 000 people at risk.

Table 5
Age specific prevalence rates for the most common causes of YOD

	Alzheimer's disease			HD dementia			Alcohol related dementia			Vascular dementia			Frontotemporal dementia		
Age range	n	Rate*	95% CI	N	Rate*	95% CI	n	Rate*	95% CI	n	Rate*	95% CI	n	Rate*	95% CI
35–39										1	3.6	(1.0–20.2)			
40–44				5	16.5	(5.4–38.5)				1	3.3	(1.0–18.4)			
45–49				3	9.5	(2.0–27.7)				1	3.2	(1.0–17.6)			
50–54	6	20.7	(7.6–44.9)	4	13.8	(3.8–35.2)	2	6.9	(1.0–24.9)	1	3.4	(1.0–19.2)	1	3.4	(1.0–19.2)
55–59	15	55.6	(31.1–91.7)	3	11.1	(2.3–32.5)	2	7.4	(1.0–26.8)	3	11.1	(2.3–32.5)	7	26.0	(10.4–53.5)
60–64	53	207.3	(155.3–271.1)	5	19.6	(6.4–45.6)	7	27.4	(11.0–56.4)	4	15.6	(4.3–40.1)	4	15.6	(4.3–40.1)
30–64	74	37.0	(29.1–46.4)	21	10.5	(6.5–16.0)	11	5.5	(2.7–9.8)	11	5.5	(2.7–9.8)	12	6.0	(3.1–10.5)
45–64	74	65.4	(51.3–82.1)	15	13.3	(7.4–21.9)	11	9.7	(4.9–17.4)	9	8.0	(3.6–15.1)	12	10.6	(5.5–18.5)

*Rate per 100 000 people at risk.

Table 6
Prevalence rates per 100,000 persons at risk of dementia and subtypes in various population-based studies

	All dementia				
	Norway (Current study)	Australia (Whithall et al., 2014)	Japan (Ikejima et al., 2009)	England (Harvey et. Al 2003)	England (Ratnavalli et al., 2002)
Age:					
50–54	92.9	102.7	59.0	62.5	–
55–59	163.2	131.2	94.3	152.1	–
60–64	328.6	265.2	163.3	166.3	–
30–64	*85.5*	*68.2*	*51.7**	*54.0*	–
45–64	*143.1*	*132.9*	*83.3*	*98.1*	*81.0*

	Dementia subtypes									
	Norway (Current study)	Australia (Whithall et al., 2014)	Japan (Ikejima et al., 2009)	England (Harvey et. Al 2003)	England (Ratnavalli et al., 2002)	Norway (Current study)	Australia (Whithall et al., 2014)	Japan (Ikejima et al., 2009)	England (Harvey et. Al 2003)	England (Ratnavalli et al., 2002)
	AD					VaD				
Age:										
50–54	20.7	6.4	9.8	16.4	–	3.4	6.4	22.9	6.6	–
55–59	55.6	13.1	28.0	50.7	–	11.1	13.1	42.2	32.6	–
60–64	207.3	74.6	49.5	77.3	–	15.6	49.7	78.4	38.7	–
30–64	*37.0*	*9.3*	*13.4**	*17.4*	–	*5.5*	*7.7*	*10.1**	*8.7*	–
45–64	*65.4*	*19.9*	*22.3*	*35.0*	*15.1*	*8.0*	*14.9*	*38.6*	*17.9*	*8.2*
	FTD					ARD				
50–54	3.4	6.4	1.5	3.3	–	6.9	32.1	–	19.7	–
55–59	26.0	26.2	1.7	25.4	–	7.4	32.8	–	18.1	–
60–64	15.6	8.3	4.4	23.2	–	27.4	49.7	–	11.6	–
30–64	6.0	5.4	1.2*	7.5	–	*5.5*	*16.3*	–	*6.6*	–
45–64	10.6	11.6	2.0	15.4	15.1	*9.7*	*33.1*	–	*13.6*	–

*Calculated.

Paper II

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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 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.

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

	Total			Male		Female	
DIAGNOSIS	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.

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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Paper III

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Time to Diagnosis in Young Onset Alzheimer's Disease: A Population-Based Study from Central Norway

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Abstract.
Background: Young onset dementia is associated with a longer time to diagnosis compared to late onset dementia. Earlier publications have indicated that atypical presentation is a key contributing factor to the diagnostic delay. Our hypothesis was that even the most common presentation of Alzheimer's disease is associated with a substantial diagnostic delay in patients < 65 years.
Objective: To determine the time to diagnosis, and time lags in the diagnostic pathway in typical young onset Alzheimer's disease in central Norway.
Methods: The main sources of patients were the databases at the Department of Neurology, University Hospital of Trondheim (St. Olav's Hospital), and Department of Psychiatry, Levanger Hospital. Other sources included key persons in the communities, collaborating hospital departments examining patients with suspected cognitive impairment, and review of hospital records of all three hospitals in the area. Information on the time lags, and the clinical assessment, including the use of biomarkers, was collected from hospital notes. Caregivers were interviewed by telephone.
Results: Time from first symptom to diagnosis in typical young onset Alzheimer's disease was 5.5 years ($n = 223$, SD 2.8). Time from onset to contact with healthcare services (usually a general practitioner) was 3.4 years (SD 2.3). Time from contact with healthcare services to the first visit at a hospital was 10.3 months (SD 15.5). Time from first visit at a hospital to diagnosis was 14.8 months (SD 22.6). The analysis of cerebrospinal fluid core biomarkers was performed after 8.3 months (SD 20.9).
Conclusion: Typical Alzheimer's disease is associated with a substantial diagnostic delay in younger patients. Raising public awareness, and education of healthcare professionals on the aspects of young onset Alzheimer's disease is warranted. CSF core biomarkers should be performed earlier in the hospital evaluation process.

Keywords: Clinical characteristics, delayed diagnosis, diagnosis, early onset Alzheimer's disease, early onset dementia, young onset dementia

INTRODUCTION

Young onset dementia (YOD) is a term used to denote dementia that develops before the age of 65 [1]. Although many types of dementia may start

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before the age of 65, the most common cause of YOD is Alzheimer's disease [2, 3]. Young onset AD, as in late onset dementia (onset over age 65), is characterized as a slow, progressive disease with preclinical and clinical phases, stretching over decades [4–6]. The prolonged nature, and resemblance to age-related slowing of cognition, hinder the recognition of symptoms as the disease develops from preclinical to clinical stages. The symptomatic period can be further divided into pre-dementia and dementia stages, where the latter is characterized by the disruption of daily life [7].

Objective symptoms of cognitive decline precede the diagnosis of dementia by up to 10 to 12 years, one study reporting the clinical pre-dementia phase as long as 18 years [8–10]. Until recently, the presence of dementia was required for the diagnosis of AD, prolonging the period of symptoms devoid of a proper explanation and diagnosis.

Time to diagnosis has been shown to be longer for patients with YOD when compared to late onset dementia [11]. Contributing factors to this include young age, having frontotemporal dementia, or any diagnosis other than AD [11–14]. A recent publication found that the total number of specialist services consulted increased the time to diagnosis, probably due to the complexity and diversity of young onset neurodegenerative disease and maybe also lack of competence even in specialist services [14–16].

The time from symptom onset to diagnosis is a difficult phase at any age, but additionally so when affecting persons under the age of 65 [17, 18]. Since the introduction of core biomarkers in cerebrospinal fluid (CSF), the diagnosis of AD can be made during the pre-dementia phase of the disease, allowing patients and carers to plan for the future at an earlier stage [19]. Reducing the time from symptom onset to diagnosis will be of importance at any age when treatment emerges.

Many studies of the time to diagnosis in YOD include patients with a heterogeneity of dementias, and studies of AD often include multiple AD variants, both of which are associated with diagnostic delay. As the amnestic type of AD is the typical and most frequent presentation, factors contributing to an increased time to diagnosis for this particular subgroup of patients is important from a public health perspective. The main objective of this study was therefore to determine time from symptom to diagnosis in young onset AD with a typical presentation, where amnesia will be predominant in most cases. Our hypothesis was that even the commonest presentation of AD is associated with a substantial diagnostic delay in young patients.

The diagnostic assessment at hospitals often extends to months, even years, before a correct diagnosis is made [14, 16]. It is crucial that clinicians identify patients with young onset AD without further delay. A secondary objective was therefore to provide clinical characteristics of these patients as they present themselves at the hospital for the first time, rather than at the time of diagnosis.

MATERIALS AND METHODS

Organization of healthcare services

Norway has a national health service that is readily accessible. All citizens are assigned to a general practitioner (GP), and access to hospital services is usually arranged through referrals by a GP. According to national guidelines, patients < 65 years with symptoms of dementia should be evaluated at an appropriate hospital department. In Norway, suspected cognitive impairment is commonly investigated in departments of neurology, geriatrics, or psychiatry.

The target area

The target area in the present study included both rural and urban areas whereof the city of Trondheim is the largest with approximately 200,000 people. There are three hospitals in Trøndelag; the University Hospital of Trondheim in which departments of neurology, geriatrics, and psychiatry see patients with symptoms of dementia, and two smaller hospitals in the northern region (the hospitals of Levanger and Namsos). These latter two hospitals have departments of neurology, geriatrics, and psychiatry, but patients with cognitive impairment are only evaluated at the Department of Geriatrics and Psychiatry. In Levanger, a memory clinic is situated at the Department of Psychiatry. The resident population of Trøndelag, consisting of approximately 470,000 people, does not differ significantly from that of the rest of the country [20].

Patients and recruitment process

Participants were recruited to the project "Young dementia in Trøndelag" (UngDemens i Trøndelag). The objective was to explore epidemiological aspects of YOD in a defined catchment area in central

Table 1
Collected data

	Onset	*Hospital*	*Inclusion in study*
Demographics	Age*	Age at diagnosis	Age at inclusion
	Number and age of children	Year of diagnosis	Gender
	Employment status	MCI or dementia at diagnosis?	Education
	Arena of symptom recognition		Marital status
			Community care
			Disability status
Symptoms	Symptoms during initial three years		
Diagnostic assessments		*Cognitive tests:*	
		MMSE, clock drawing test, CERAD ten-item word test, Trail Making Test A/B	
		Biomarkers:	
		CSF core biomarkers	
		MRI	
		Number of contacts:	
		Types of specialists involved	
		Psychiatric evaluation and/or treatment before diagnosis?	

*Assessed by a combination of interview with caregiver and hospital records. CERAD, the Consortium to Establish a Registry for Alzheimer's Disease.

Norway. Main inclusion criteria were a diagnosis of dementia, or mild cognitive impairment (MCI) due to AD, with onset before the age of 65. The recruitment process was conducted from 2014 to 2018 making use of multiple case ascertainment, including community sources as well as multiple sources at hospital level. The main source of patients was the Department of Neurology at Trondheim University Hospital, and the Department of Psychiatry at the Hospital of Levanger, both main sites of referral for YOD in the target area. Additional sources included other hospitals and hospital units, and a wide range of community-based entities providing services to these patients. Information on the recruitment process is described elsewhere [3]. Data have already been published on the prevalence and incidence of YOD in the target area [2, 3]. A main finding of these studies was that almost every patient receiving a diagnosis of dementia was evaluated at a hospital.

Inclusion and exclusion criteria

In this study we included patients receiving a diagnosis of AD, regardless of the presence of dementia. Diagnoses were individually verified by researchers (MKA and SBS) as fulfilling criteria either for dementia or MCI due to AD [19, 21]. The verification process included both review of hospital notes and interview with a close caregiver.

Cases in which onset or time of the diagnosis could not be reliably identified were excluded.

Variables and data

Tables 1 and 2 give an overview of collected variables and recorded time lags in the diagnostic process.

Age at onset was defined as the age when the first symptom(-s) appeared and was determined based on a combination of hospital notes and interview with a caregiver (most often a family member). In the loosely structured interview (conducted by the main researcher), substantial effort was made to reliably determine when symptoms appeared. In cases where hospital notes revealed that patients had recognized symptoms earlier than the caregiver, the age of onset was determined based on the patients recorded statements.

Arena of symptom recognition was dichotomized into work related and/or non-work related arenas. Information on these variables were based on information provided by the caregiver in the interview, and if addressed, in hospital notes.

Symptoms of AD were defined by a decline in premorbid functioning in the respective cognitive domain, as reported by the patient, caregiver, and/or by cognitive tests. Presence of symptoms was determined by all available data (caregiver interview, hospital notes, and cognitive tests). Poor performance on cognitive tests was not a requirement, as these often are not performed during the initial years. Also, subjective symptoms naturally precede verification on cognitive tests.

Initial contact with healthcare services was defined as the first time the patient, or others, reported

Table 2
Time lags

- Time from disease onset to initial contact with a GP, or other healthcare professional.
- Time from the initial contact with a GP (or other) to a hospital referral.
- Time from a hospital referral to first consultation with a hospital physician.
- Time from first consultation with a hospital physician to recognition of a primary cognitive disorder.
- Time from recognition of a primary cognitive disorder to diagnosis of AD.
- Time from first consultation at a hospital to MMSE.
- Time from first consultation at a hospital to lumbar puncture and cerebral MRI.

symptoms to a physician. Recognition of a primary cognitive disorder by a hospital physician was defined as the moment the physician requested and/or performed an adequate examination of dementia symptoms.

Cognitive tests and MRIs were often conducted on multiple occasions during the hospital evaluation process. Only the first test score, and results from the first MRI, were registered in this study.

RESULTS

Demographics

A total of 223 patients met the inclusion criteria, whereof 142 (63.7%) were females and 81 (36.3%) males. Four patients with AD pathology in CSF core biomarkers, but atypical presentations were excluded; three patients with posterior cortical atrophy and one with frontotemporal dementia. Mean age at onset, age at diagnosis and age at study inclusion were 58.4 years (SD 4.3, range 47–64), 63.3 years (SD 4.7, range 50–73), and 66.4 years (SD 5.3, range 50–79), respectively. Patients received their diagnosis during the years 2001 to 2018, the majority between 2012 and 2017. Of the 45 patients (20.2%) who were diagnosed with MCI due to AD, 43 were diagnosed between 2012 and 2018. Interview with a close caregiver was performed in 211 (94.6%) of cases, with a mean time of 3.1 years post diagnosis.

Twenty-three patients (10.7%) had children under the age of 18, nine patients (4.2%) had children under the age of 12, and two (0.9%) had children under the age of six at the time of symptom onset (missing: eight). Almost two thirds of the patients ($n = 142$, 64.0%) were living at home, 43 (30.3%) of them receiving home care services. The rest of the patients ($n = 80$, 36.0%) were living in nursing homes. In one case the researchers were not able to determine the living situation.

Mean length of education was 11.5 years (SD 3.3, missing: two).

Almost a third of patients ($n = 72$, 32.4%) initiated medical evaluation themselves, while 18 (8.1%) did so in collaboration with their families. In other cases ($n = 82$, 36.9%), family members alone alerted the medical services. In 14 cases (6.3%) persons connected with the workplace (employer, co-workers, representatives from the Norwegian Labour and Welfare Administration) notified the GP. In 10 cases (4.5%) work-related persons contacted the GP in collaboration with family members, and in two cases they did so in collaboration with the patient. The GP suspected symptoms of dementia, and independently made the referral in only 11 cases (5.0%). In remaining cases ($n = 13$, 5.9%), others initiated the contact (such as friends, neighbors, hospital physicians). In one case, the researchers were not able to identify the initiating contact. Patients were referred to the hospital by their GP in 200 cases (89.7%).

A total of 156 patients (70.0%) were employed when symptoms emerged. Of these, 105 (67.3%) reported that symptoms of AD initially became apparent at work, before being observed in other arenas. Additionally, 26 patients (16.7%) reported symptoms emerging both at work and in non-work arenas concomitantly. In six cases (3.8%) the researchers were not able to identify the arena of debut.

More than six out of ten patients ($n = 143$, 65.0%) had public disability benefits at the time of study inclusion. Of these, only 80 (55.9%) were granted benefits because of acknowledged symptoms of AD, while 54 (37.8%) were on disability before they were diagnosed with AD, of which eight (14.8%) were granted benefits for non-AD symptoms that were later considered to be clearly AD-related. Four patients resigned from work due to covert symptoms of AD, resulting in financial loss. In three cases, the researchers were not able to determine the disability status.

Symptoms and diagnostic assessments

Table 3 shows symptoms during the initial three years of disease as reported by the patient, close family member, or by cognitive evaluation. Symptoms were typical for AD. In some patients, manifest amnesia was only evident subsequent to a period of diffuse symptoms.

Table 3
Symptoms during the initial three years

Symptom	Percentage of cases
Amnesia	94.6
Disorientation	58.5
Apathy	50.4
Depression	38.4
Apraxia	33.5
Aphasia	25.4
Emotional instability, irritability	18.3
Personality changes	15.2

Table 4
Cognitive tests and biomarkers

Cognitive test	*N*	%	Mean score	Range
MMSE	223	100	23.0* (SD 5.0)	8–30
			% pathological	
Clock drawing test	219	98.2	62.3	
CERAD ten-item word test				
Immediate recall	142	63.7	88.7	
Delayed recall	138	61.9	95.7	
Recognition	84	37.7	92.9	
Trail Making Test				
A	194	87.0	45.9	
B	191	85.7	76.3	
Biomarkers				
CSF core biomarkers	191	85.7		
$A\beta_{42}$			67.5	
Phosphorylated tau protein			61.8	
Total tau protein			73.8	
All three			39.8	
Cerebral MRI**	214	96.0	46.3	

*50.4% scored ≥ 26 points. **The remaining nine patients not receiving an MRI were evaluated by CT. CERAD, the Consortium to Establish a Registry for Alzheimer's Disease.

Table 4 gives an overview of details on cognitive tests, as well as biomarkers.

Number of contacts and psychiatric evaluation

The mean number of hospital evaluation points in the diagnostic workup is illustrated in Fig. 1. The mean number of visits before the physician acknowledged the symptoms as AD-related, and initiated investigation of a cognitive disorder, was 2.0 (SD 4.7, range 1–4). Eighteen patients (8.1%) received evaluation and/or treatment for psychiatric symptoms with a mean duration of 15.1 months (SD 16.4, range 1–48 months).

Types of specialists involved in assessing the diagnosis

A diagnosis of AD was made at a department of neurology ($n = 107$, 48.0%), psychiatry ($n = 67$, 30.0%), or internal medicine (mainly by geriatric physicians, $n = 49$, 22.0%). In 67 cases (30.0%) more than one department was involved in the diagnostic process (range 2–6).

Time lags

Mean time lags, and number of contacts at the hospital before the diagnosis was made, are visualized in Figs. 1 and 2. The time lags illustrate the pathway to diagnosis. In cases where the GP was not contacted, and he/she independently issued a referral to the hospital, the time from symptom debut to referral was 5.0 years ($n = 11$, range 5–204, SD 55.3, not illustrated in Fig. 2).

Mean time from first contact with a hospital to the performance on the Mini-Mental State Examination (MMSE) and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) ten-item word test was 2.8 months (range 0–109 months, SD 12.3) and 6.5 months (range 0–136, SD 19.5), respectively. A total of 191 patients (85.7%) were evaluated with MMSE at the first visit. The mean time from first visit to a hospital to the performance of MMSE for patients who received a psychiatric evaluation and/or treatment was 21.0 months (range 0–109, SD 29.3). Almost half of MRIs ($n = 104$, 48.6%) were performed before the first visit to a hospital. Of these, 47 (45.2%) were not pathological, and 22 (21.2%) only marginally pathological (medial temporal atrophy classified as Scheltens 2 [22]).

DISCUSSION

To our knowledge, this is the largest study on the time from symptom debut to diagnosis in patients with typical AD with young onset. Diagnoses were individually verified with a high level of clinical accuracy, including biomarkers in over 80% of the cases. The geographical target area covers both urban and rural areas, has three hospitals of varying sizes providing approximately equal access to healthcare, and the resident population is largely representative for that of the rest of the country [20]. In our opinion, the findings of this study are both relevant and applicable for other parts of the world with a similar healthcare system.

The main finding in this study is a substantial diagnostic delay of 5.5 years for patients with typical young onset AD. This is considerably longer than previous studies in which delays have ranged from 1.5

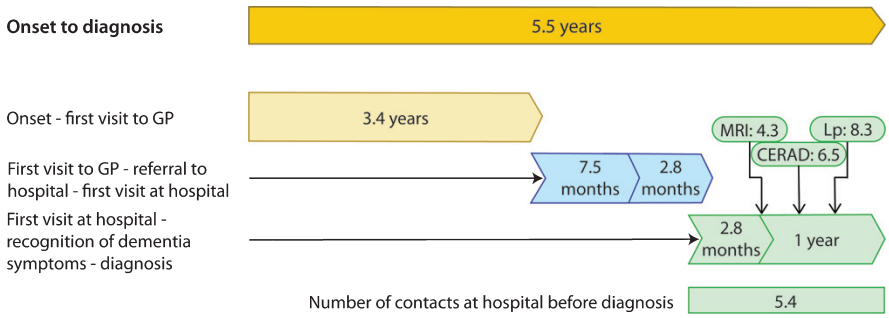

Fig. 1. Time lags from symptom to diagnosis of young onset Alzheimer's disease. GP, general practitioner; MRI, magnetic resonance imaging; Lp, Lumbar puncture; CERAD, Consortium. Time from onset to diagnosis; $n = 223$, range 2–17, SD 2.8 (years). Time from symptom to contact; $n = 188$, range 6–132, SD 2.3 (months). Time from contact to referral; $n = 182$, range 0–110, SD 15.2 (months). Time from referral to first visit at hospital; $n = 203$, range 0–52, SD 3.8 (months). Time from first visit to hospital to recognition of dementia symptoms; $n = 222$, range 0–109, SD 12.1, months). Time from primary recognition of dementia symptoms to diagnosis; $n = 223$, range 0–140, SD 20.1 (months). Time from first visit to hospital to MRI; $n = 214$, range 0–125, SD 13.8 (months). Time from first visit to hospital to CERAD; $n = 142$, range 0–136, SD 19.5 (months). Time from first visit to hospital to lumbar puncture; $n = 191$, range 0–139, SD 20.9 (months).

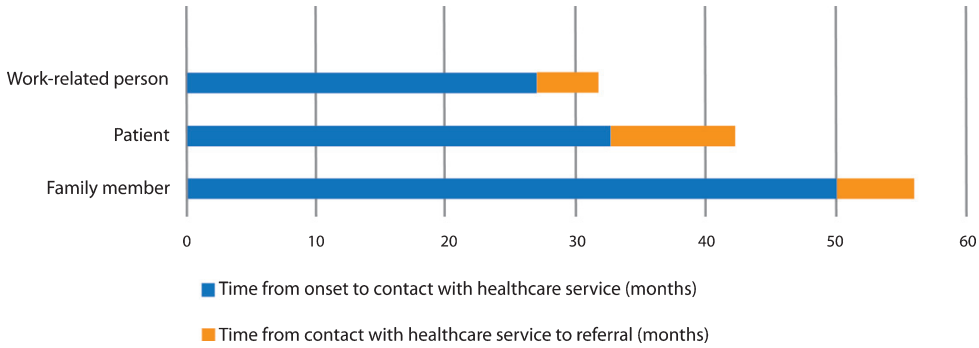

Fig. 2. Pre-hospital time lags according to person initiating contact with healthcare services. Work-related person: Time from onset to contact; $n = 13$, range 12–72, SD 19.4. Time from contact to referral; $n = 13$, range 0–12, SD 3.2. Patient: Time from onset to contact; $n = 68$, range 6–108, SD 21.5. Time from contact to referral; $n = 66$, range 0 –110, SD 20.5. Family member: Time from onset to contact; $n = 76$, range 12–132, SD 29.9. Time from contact to referral; $n = 75$, range 0–51, SD 9.1.

to 4.2 years (Table 5) [11–14]. Low age and clinical heterogeneity have been hypothesized to be factors associated with a longer time to diagnosis in patients under 65 years, but do not offer plausible explanations for the time to diagnosis in the present study [1, 16, 23]. Patients in both this and the previous studies had predominantly amnestic symptoms. In addition, age at onset and age at diagnosis were higher in the present study compared to the two studies that provided this information for typical AD [12, 14]. With the exception of one study from Australia, all studies were conducted in a population-based setting, indicating that healthcare capacity was not a source of bias between them [14].

There may be various factors underlying the delays in the diagnostic pathway. Segmentation of the time to diagnosis into time lags may offer greater insight for understanding the fundamentals of diagnostic delay.

Time lag prior to contact with medical services

A significant finding in our study was the prolonged time from onset of symptoms to the time that patients or their family requested a medical evaluation. On average, the symptoms had persisted for 3.4 years before contact with medical services was initiated, accounting for well over half the total delay. Although research on this time lag is scarce, it is substantially longer than two other studies (from Norway and Australia) reporting approximately 12–13 months (Fig. 3) [12, 13]. There could be several reasons for this. The slow and covert nature of the onset of symptoms impedes timely recognition. The actual

Table 5
Time to diagnosis in young onset AD with typical progression in various studies

Study	Country	Diagnosis	*N*	Mean time to diagnosis (y)
Current study	Norway	MCI/ dementia	223	5.5
Loi et al., 2020 [14]	Australia	Dementia	55	2.9
Draper et al., 2016 [13]	Australia	Dementia	47	1.5*
Van Vliet et al., 2013 [11]	The Netherlands	Dementia	139	4.2
Rosness et al., 2008 [12]	Norway	Dementia	37	3.3

*Median time.

debut of symptoms might therefore be easier to identify retrospectively after a diagnosis has been made, providing caregivers with the opportunity to reflect upon when symptoms first emerged. In the present study, the onset of symptoms was assessed by asking proxies at a later stage compared to the earlier study from Norway; 3.1 years versus 1.9 months after diagnosis [12]. It was a consistent finding in the current study that onset was considered to be earlier when caregivers were interviewed by the researcher during a later phase. Not infrequently a discrepancy of several years was reported when compared to the hospital notes, contributing to a significant increase both in the time before contact, and in consequence, to the total diagnostic delay. A study from the United States showed that time from onset to problem recognition in AD increased with the time that had passed since the diagnosis, caregivers reporting a mean time of 2.25 years if the diagnosis was made 49 months or more prior to the interview [24]. Methodological differences might therefore be a source of substantial bias between studies, those benefitting from hindsight perhaps providing a more accurate estimation.

In the effort to reduce time to diagnosis, this study demonstrates the relevance of raising public awareness of the *typical* symptoms of young onset AD. The amnestic variant of AD is the most common subtype of YOD, and any successful effort to diminish the burden of diagnostic delay in this group of patients is therefore likely to have a greater impact on public health. The beneficial effects of cholinesterase inhibitors in AD, especially if implemented in earlier phases, may additionally provide incentives for patients and caregivers to seek an early diagnosis [25–29]. Public knowledge on the availability of pharmacological treatment should therefore be an important priority for healthcare authorities.

Anosognosia is a common symptom in AD. Patients with young onset AD have a higher level of awareness of their symptoms in earlier stages than patients with late onset disease [30]. In the present study, approximately 40% of patients sought a medical opinion for their symptoms themselves, demonstrating that many patients do acknowledge emerging symptoms. Moreover, they recognize them significantly earlier than their family members. Almost 70% of patients were employed when symptoms appeared, and more than two thirds of these reported difficulty at work before symptoms became apparent elsewhere, consistent with the finding that persons related to the workspace acknowledged cognitive changes sooner than family members. However, only a small percentage of employers actually notified the GP, which was the initial point of contact in most cases. Consistent with the findings in this study, it has been shown that patients with AD have significantly more severe work-related difficulties compared to patients with frontotemporal dementia [12].

Only four patients described financial loss due to the diagnostic delay. The potential effects of economic considerations, and/or perceived stigma, both of which are aspects associated with a reluctance to pursue a diagnosis, were regrettably not explored in the current study. Previous studies have found an age-related association between YOD and these factors, and one study found that persons with YOD leave their jobs with a hazard ratio of 2.26 compared to healthy controls, but additional research is warranted [31–33].

Time lag following contact with medical services

After patients and/or others contact the healthcare services, the healthcare system is responsible for any subsequent delays. In the present study, physicians used more than two years to diagnose AD.

The role of the GP

The second step in the diagnostic pathway is the referring physician. Patients were referred to a hospital with a substantial delay of 7.5 months, occasionally stretching up to nine years. In the most extreme instances, the patients were mainly referred for the evaluation and treatment of behavioral disturbances during later stages of dementia, the underlying

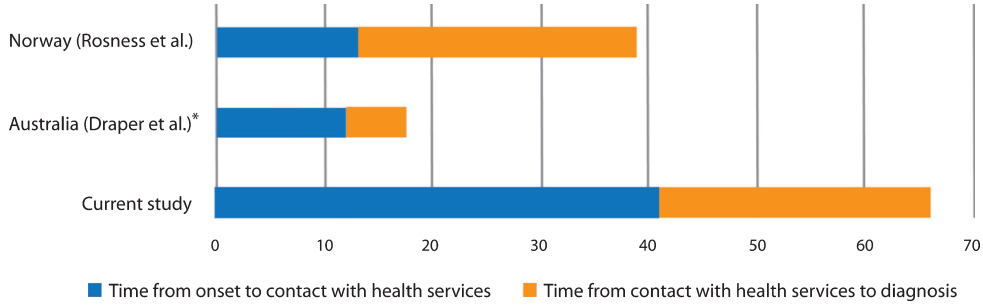

Fig. 3. Time lags in other studies. *Median.

diagnosis being a secondary objective. A prolonged period from presenting to a medical doctor until specialist referral has been previously shown in a study from Norway [12]. In this latter study the delay was even longer (19.1 months). It is worth noticing that less than 5% of the patients in the present study were independently recognized by the GP. In these cases, time from onset to referral was 5.0 years, indicating that GPs might not be trained to detect cognitive impairment at earlier stages. Interestingly, in cases where the patients themselves contacted the GP, the GP referred patients to the hospital later compared to cases where the GP was contacted by employers or family members. The reasons for this may be complex but indicate that GPs are less alert if patients report cognitive symptoms themselves. This contrasts with our findings that patients acknowledge symptoms earlier than their families.

Nevertheless, a time lag of seven months from the time of contact with the GP to the issuing of a referral, identifies an obstacle to early diagnosis. Educating GPs on the particular aspects of young onset AD, such as the increasing incidence from the threshold age of 50, symptom profile, a high level of patient awareness, arena of debut, and the positive effects of cholinesterase inhibitors might be warranted.

The role of the hospital

Patients were evaluated at the hospital three months after a referral was issued, such that it took as long as ten months from patient contact with medical services to receiving a clinical assessment of their symptoms. An additional three months passed before hospital physicians recognized the symptoms as being primarily cognitive, thus exceeding a year from initial contact to an adequate examination. In total, hospitals spent nearly one and a half years with over five points of contact with the patient, to correctly identify AD. This is less than a previous study from Norway, but more than a study from Australia (Fig. 3). Almost one third of patients were evaluated by physicians of different specialties, ranging from two to six departments, displaying a diagnostic pathway "from pillar to post", as characterized in an early study from England, and reaffirmed in a more recent study from Australia [14, 16]. In this respect, it is clear that there remains considerable room for improvement.

Cognitive tests are tools for documenting cognitive decline over time. As hospitals spent a substantial time evaluating these patients, occasionally extending over several years, rather than focusing on test scores at the time of diagnosis, as many studies do, this study provides data on test scores when conducted for the first time [11, 34]. Consistently, mean MMSE score was higher in the present study when compared to a study on young onset AD and a study of YOD in which MMSE scores were registered at the time of diagnosis (23.0 versus 21.3 and 21.1, respectively) [11, 12]. Test scores have previously been shown to be associated with age, younger patients doing better than older patients at the time of diagnosis [11, 34, 35]. MMSE was conducted relatively early in the investigatory process, and the majority of patients performed well at this point. MMSE therefore seemed to have the potential effect of freezing further investigations of cognitive impairment, and paradoxically, delaying the diagnosis. The CERAD ten-item word test was largely pathological when performed for the first time but was not performed until 6.5 months into the investigative process. Clock drawing test and Trail Making Tests were less sensitive, and not infrequently normal.

Relatively intact cognitive capabilities could partly be a reflection of the substantial portion of patients (20%, $n = 45$) who were diagnosed with MCI due to AD. The ability to diagnose AD in the predementia

stages of the condition according to new diagnostic criteria is a valuable step in reducing diagnostic delay.

As large parts of the world continue to develop as societies with high cognitive demands, it is possible to hypothesize that patients at all ages, younger and employed patients in particular, will present themselves to healthcare services at earlier, and less impaired phases in the future. Hospital physicians will need to adjust to this reality.

MRI scans were available to the hospital physician by the first visit in approximately half the cases, and they were often normal. A low diagnostic value of imaging in early stages of young onset AD agrees with previous studies [36]. The analysis of CSF core biomarkers was performed at a later stage (8.3 months), probably precipitating a diagnosis of AD in the months thereafter. CSF analysis, in combination with the CERAD ten-item word test, might therefore be the key to early diagnosis, and in our opinion should be a priority in the medical evaluation of suspected cognitive impairment.

In conclusion, the present study demonstrates the challenges of diagnosing patients with the most frequent subtype of YOD. A time to diagnosis of 5.5 years affects quality of life for patients and their families and impedes the success of any emerging pharmacological treatment in the future. The study identified several obstacles to the rapid diagnosis of young onset AD, some concerning public and family awareness, and multiple delays originating within the medical services, some of them overlapping. Public healthcare authorities could play a key role in educating the public and relevant parts of the medical community. A survey from Australia found a year's decrease in the diagnostic delay for patients evaluated in a specialized YOD service, calling for a more specialized assessment of young patients with cognitive symptoms [14]. Although there are several points of target, as the current study indicates, the current authors share this view.

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