BMJ Open

Cohort Profile: The Norwegian Registry of Persons Assessed for Cognitive Symptoms (NorCog) – a national research and quality registry with a biomaterial collection

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058810
Article Type:	Cohort profile
Date Submitted by the Author:	31-Oct-2021

Complete List of Authors:	Medbøen, Ingrid; Norwegian National Advisory Unit on Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital Persson, Karin; Norwegian National Advisory Unit on Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital Nåvik, Marit; Norwegian National Advisory Unit on Ageing and Health, Vestfold Hospital Trust; Department of Psychiatry, Telemark Hospital Totland, Torunn; Department of Chronic Diseases and Ageing, Norwegian Institute of Public Health Bergh, Sverre; Norwegian National Advisory Unit on Ageing and Health, Vestfold Hospital Trust; Research centre for Age-related Functional Decline and Disease, Innlandet Hospital trust Treviño, Cathrine; Norwegian National Advisory Unit on Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital Ulstein, Ingun; Department of Geriatric Medicine, Oslo University Hospital Engedal , Knut ; Norwegian National Advisory Unit on Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital Knapskog, Anne-Brita; Department of Geriatric Medicine, Oslo University Hospital Brækhus, Anne; Norwegian National Advisory Unit on Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital Øksengård, Anne; The Norwegian Health Association; Bærum Hospital, Vestre Viken Hospital Trust Horndalsveen, Peter; Department of Old Age Psychiatry, Innlandet Hospital trust Saltvedt, Ingvild; Department of Geriatrics, St. Olav's Hospital, Trondheim University Hospital; Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology Lyngroth, Anne; Department of Geriatrics, Sorlandet Hospital Arendal Ranhoff, Anette ; Department of Medicine, Diakonhjemmet Hospital; Department of Clinical Science, University of Bergen, Skrettingland, Dagny; Department of Geriatrics, Stavanger University Hospital Naik, Mala; Department of Clinical Science, University of Bergen, ;

	Department of Medicine, Haraldsplass Deaconess Hospital Soares, Jelena; Medical Department, Section of Geriatrics, Lovisenberg Diaconal Hospital Johnsen, Bente; Department of Geriatric Medicine, University Hospital of North Norway Selbaek, Geir; Norwegian National Advisory Unit on Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital
Keywords:	Dementia < NEUROLOGY, Delirium & cognitive disorders < PSYCHIATRY, GERIATRIC MEDICINE, Old age psychiatry < PSYCHIATRY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Cohort Profile: The Norwegian Registry of Persons Assessed for Cognitive Symptoms (NorCog) – a national research and quality registry with a biomaterial collection

Ingrid Tøndel Medbøen,[1,2] Karin Persson,[1,2] Marit Nåvik,[1,3] Torunn H. Totland,[4] Sverre Bergh,[1,5] Cathrine Selnes Treviño[1,2] Ingun Dina Ulstein,[2] Knut Engedal,[1,2] Anne-Brita Knapskog,[2] Anne Brækhus,[1,2] Anne Rita Øksengård,[6,7] Peter O Horndalsveen,[8] Ingvild Saltvedt,[9,10] Anne Liv Lyngroth,[11] Anette Hylen Ranhoff,[12,13] Dagny Bekkeheien Skrettingland,[14] Mala Naik,[13,15] Jelena Zugic Soares,[16] Bente Johnsen,[17] Geir Selbæk,[1,2]*

[1]Norwegian National Advisory Unit on Ageing and Health, Vestfold Hospital Trust, Tønsberg, Norway, [2]Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway, [3]Department of Psychiatry, Telemark Hospital, Skien, Norway, [4]Department of Chronic Diseases and Ageing, Norwegian Institute of Public Health, Oslo, Norway, [5]Research centre for Age-related Functional Decline and Disease, Innlandet Hospital trust, Ottestad, Norway, [6]The Norwegian Health Association, Oslo, Norway, [7]Bærum Hospital, Vestre Viken Hospital Trust, Drammen, Norway, [8]Department of Old Age Psychiatry, Innlandet Hospital trust, Ottestad, Norway, [9]Department of Geriatrics, St. Olav's Hospital, Trondheim University Hospital, Trondheim, Norway, [10]Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway, [11]Department of Geriatrics, Sorlandet Hospital Arendal, Arendal, Norway, [12]Department of Medicine, Diakonhjemmet Hospital, Oslo, Norway, [13]Department of Clinical Science, University of Bergen, Bergen, Norway, [14]Department of Geriatrics, Stavanger University Hospital, Stavanger, Norway, [15]Department of Medicine, Haraldsplass Deaconess Hospital, Bergen, Norway, [16]Medical Department, Section of Geriatrics, Lovisenberg Diaconal Hospital, Oslo, Norway, [17]Department of Geriatric Medicine, University Hospital of North Norway, Tromsø, Norway.

*Corresponding author. Norwegian National Advisory Unit on Ageing and Health, Vestfold Hospital Trust, Pb 2136, 3103 Tønsberg, Norway. Email: geir.selbaek@aldringoghelse.no

Word count: 3505 (excluding title page, abstract, strengths and limitations of this study, references, figures and tables)

ABSTRACT

Purpose: NorCog was established to harmonize and improve the quality of diagnostic practice across clinics assessing persons with cognitive symptoms in Norwegian specialist health care units and to establish a large research cohort with extensive clinical data.

Participants: The registry recruits patients who are referred for assessment of cognitive symptoms and suspected dementia at outpatient clinics in Norwegian specialist health care units. In total, 15 372 patients have been included in NorCog during the period 2009–2020. The average age at inclusion was 73.6 years. About half of the patients (47%) were diagnosed with dementia at the baseline assessment, 34% with mild cognitive impairment, 13% with no or subjective cognitive impairment; 7% received other specified diagnoses, such as mood disorders.

Findings to date: All patients have a detailed baseline characterization involving lifestyle and demographic variables; activities of daily living; caregiver situation; medical history; medication; psychiatric, physical and neurological examination; neurocognitive testing; blood laboratory work-up; and structural or functional brain imaging. Diagnoses are set according to standardized diagnostic criteria. The general research biobank of NorCog stores DNA and blood samples from 3000 to 4000 patients as well as cerebrospinal fluid from 750 patients. Data from NorCog have been used in a wide range of research projects evaluating and validating dementia-related assessment tools, identifying patient characteristics, symptoms, functioning and needs as well as caregiver burden and requirement of available resources.

Future plans: Data collection in NorCog will continue in coming years and data will be kept for as long as is necessary to achieve the purpose of the registry. During the year of 2021, the registry will undergo major changes. Paper-based data collection will be replaced with digital registration, and the number of variables collected will be reduced. Future plans also involve expanding the registry to include patients from primary care centers.

Strengths and limitations of this study

- A key strength of NorCog is the large sample size with extensive clinical data combined with a research biobank. Few, if any, national registries collect a similarly broad spectrum of variables as NorCog, allowing for exploration of the main domains of dementia and cognitive impairment.
- Patients consent to linkage of data with medical records from later admissions to hospitals and nursing homes, as well as to national health registries, making it possible to investigate predictors of real-world outcomes.
- NorCog only recruits patients who are referred for assessment in a specialist setting and cannot be used to generalize to the general dementia population in Norway.
- In contrast to the restricted setting of a clinical trial, NorCog is a clinical registry collecting data as part of routine clinical practice and may, accordingly, be limited by lower data quality, lack of adjudication, and missing data.

INTRODUCTION

Cognitive symptoms, such as problems with memory, reasoning, and language skills, as well as emotional and behavioural changes, may signal pathological changes in the brain that can cause dementia. The term dementia denotes a category of diseases, normally leading to progressive loss of brain function and, ultimately, resulting in complete dependence in regard to functions of daily living and premature death.[1]

In Norway, the municipalities are responsible for primary care, including the assessment of cognitive impairment in older patients with uncomplicated dementia symptoms. Specialist care is administered by four regional health authorities that are responsible for the assessment of younger patients with cognitive decline, patients with coexisting psychiatric, neurological, or somatic problems, atypical dementia disorders, and patient groups with complex disorders. For these groups, an extended assessment protocol is available.[2]

Recently, research including real-world outcome data has been requested.[3] Although consensus on the definition of real-world data is lacking, the term is most often defined as data used for coverage and payment decisions collected outside the constraints of conventional randomized controlled trials (RCTs).[4] Observational registries represent one type of sources for real-world data, typically including a larger and more diverse group of patients than generally studied in RCTs and, thereby, better reflecting populations that are representative of routine clinical practice.[5]

The Norwegian Registry of Persons Assessed for Cognitive Symptoms (NorCog) was established in 2008 with two main aims:

1. To harmonize and improve the quality of diagnostic practice across outpatient clinics assessing persons with cognitive symptoms in specialist care units.
2. To establish a large research cohort with extensive clinical data and provide an opportunity to link baseline data to important real-world outcomes in regional and national registries.

Oslo University Hospital has the overall responsibility for the registry data, and the Norwegian National Advisory Unit on Ageing and Health is managing the registry.

COHORT DESCRIPTION

NorCog has an observational design and recruits patients who are referred for assessment of cognitive symptoms and suspected dementia at outpatient clinics in Norwegian specialist health care units, provided that they are able to give informed consent. Patients are encouraged to bring their next of kin or another person who knows them well, referred to hereafter as the informant.

NorCog was originally established as a regional quality and research registry in 2008. During the first year of data collection, in 2009, seven outpatient clinics from the South-Eastern

Norway Regional Health Authority participated. Since then, outpatient clinics from all four regional health authorities in Norway have joined, and the registry received status as a national quality registry in 2013. Most of the clinics are referred to as memory clinics or outpatient clinics in old-age psychiatric and geriatric units.[6] In December 2020, a total of 47 outpatient clinics were participating.

The number of included patients per year has increased in line with the recruitment of new clinics, from 462 patients in 2009 to 2434 in 2019 (Figure 1). Because of the COVID-19 pandemic, the number of included patients in 2020 (N=2027) was somewhat lower than could be expected under normal circumstances. In total, 15 372 patients have been included in NorCog during the period 2009–2020. Table 1 shows some of the demographic, clinical, and social characteristics of the included patients at baseline. The average age at inclusion was 73.6 years with an age range of 26 to 99 years. Reports from 11 781 informants showed that memory problems were, by far, the most frequently reported first symptoms of the patient, as stated by 63% of the informants.

Table 1. A selection of demographic, social, and clinical characteristics of patients included in the NorCog cohort at baseline. Numbers of patients with missing data are shown in the far right column.

	Patients included in NorCog during 2009–2020					*Missing data total cohort, n (%)*
	Total cohort	NCI/SCI	MCI	Dementia	Other diagnoses	
n (%)	15 271 (100)	1936 (12.7)	5215 (34.1)	7113 (46.6)	1007 (6.6)	
Age (years), mean (SD)	73.6 (10.0)	67.1 (11.8)	73.0 (9.8)	76.2 (8.3)	70.5 (11.0)	*0*
Sex (female), n (%)	8006 (52.4)	1007 (52.0)	2569 (49.3)	3931 (55.3)	499 (49.6)	*0*
Education (years), mean (SD)	11.3 (3.7)	12.5 (4.0)	11.5 (3.7)	10.8 (3.5)	11.4 (3.9)	*1223 (8.0)*
Married/cohabiting, n (%)	8953 (58.6)	1171 (60.5)	3134 (60.1)	4065 (57.1)	583 (57.9)	*590 (3.9)*
Living alone, n (%)	5598 (36.7)	648 (33.5)	1892 (36.3)	2686 (37.8)	372 (36.9)	*625 (4.1)*
Public care, n (%)	4757 (31.2)	328 (16.9)	1351 (25.9)	2777 (39.0)	301 (29.9)	*526 (3.4)*
MMSE score, mean (SD)	23.6 (4.6)	27.1 (3.3)	25.3 (3.3)	21.1 (4.4)	26.0 (3.9)	*376 (2.5)*
Information from informant obtained, n (%)	14475 (94.8)	1684 (87.0)	4865 (93.3)	7025 (98.8)	901 (89.5)	

Abbreviations: MCI=mild cognitive impairment, MMSE=Mini-Mental State Examination, NCI=no cognitive impairment, SCI=subjective cognitive impairment, SD=Standard Deviation

During 2009–2020, about half of the patients (47%) were diagnosed with dementia at the baseline assessment, 34% with mild cognitive impairment (MCI), 13% with no or subjective cognitive impairment (NCI/SCI), and 7% received other specified diagnoses such as mood disorders. The diagnostic criteria will be explained in a separate paragraph below. Figure 2 shows the frequency of the different etiological dementia diagnoses.

Dementia severity was assessed with the Clinical Dementia Rating Scale (CDR), a global rating scale covering six domains of cognitive and functional performance.[7] The CDR is

scored according to an algorithm that gives precedence to the memory domain, with a total score of 0 (no cognitive impairment), 0.5 (questionable dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia). In NorCog, 81% of patients who were diagnosed with dementia at baseline during 2009–2020 had a score of 0.5 or 1, corresponding to a very mild or mild stage of dementia. Furthermore, 17% had a score of 2 (moderate dementia) and 2% a score of 3 (severe dementia).

Patients not included in NorCog

Beginning in 2016, all participating clinics have recorded the age and sex of patients who were not included in NorCog. During 2016-2020, a total of 542 patients lacked competence to give consent and were, therefore, not eligible for inclusion in NorCog. The total number of patients eligible for inclusion at the participating clinics during 2016-2020 was 14 277, whereof 71% of patients (n=10 095) were included and 29% (n=4182) were not included. The average age and the proportion of females were higher among the non-included patients compared to the included patients (Table 2). Among the patients that were not included, some were not asked to join the registry due to capacity considerations at the clinic (22%) or because the clinician perceived that the situation/condition of the patient did not allow it (31%). In other cases, patients were asked to participate, but declined (20%). In 27% of cases, the cause of non-inclusion was unknown, or another test battery was used due to language issues.

Table 2. The number of included and non-included patients eligible for inclusion at the participating outpatient clinics registered during 2016-2020

	Patients eligible for inclusion in NorCog in 2016-2020	
	Included patients (n=10 095)	Non-included patients (n=4182)
Age (years), mean (SD)	74.3 (9.5)	75.7 (10.8)
Sex (female), n (%)	5157 (51.6)	2264 (54.6)

Follow-up data

No predetermined follow-up schedule has been established for the registry. However, a registration form for assessment at follow-up according to clinical indication was implemented in 2015 (Table 3). Thus far, the clinics are encouraged but not obliged to deliver follow-up data to the registry. In several sub-studies, selected patients have been invited to receive additional examinations or follow-ups in compliance with specific research protocols. In 2017, a large research project began collecting follow-up data from patients in the registry. The project is called “Trajectories and risk factors of dementia – TRAIL-DEM” and involves linking data from the patients in NorCog with medical records in hospitals and nursing homes as well as national health registries (Table 3). The project investigates trajectories from dementia onset until nursing home admission and death, providing a

unique opportunity to investigate dementia aetiology and progression.[1 8-10] TRAIL-DEM will provide an extensive database that will form the basis for future projects.

Table 3. Overview of the samples/phases, measurements, biomaterial collection and linkages in the registry

Sample/Phase	Measurements	Biomaterial Collection/ Linkage
Baseline assessment NorCog 2009–2020 N=15 372 Ongoing in 2021	A comprehensive clinical assessment including lifestyle and demographic variables; activities of daily living; caregiver situation; medical history; current medication; psychiatric, physical, and neurological examination; neurocognitive testing; blood laboratory work-up; and routine MRI. When indicated: lumbar puncture for the measurement of Aβ and tau proteins and/or functional brain imaging.	EDTA-whole blood, n=3809 Serum, n=4215 Plasma, n=4002 CSF, n=754 PAXgene RNA, n=3308 DNA, n=3714
Follow-up NorCog patients by clinical indication 2015–2020 N=3008* Ongoing in 2021	A shorter set of registration forms including living situation, care resource use, sum score on neurocognitive tests, Clinical Dementia Rating scale, NPI-Q, blood pressure and pulse, clinical evaluation of change from baseline, clinical diagnosis, and recommended follow-up.	
The TRAIL-DEM study conducted during 2017-2021 Follow-up of patients in NorCog included during 2009–2016. New linkage in 2021 for patients included during 2017–2021.	Baseline data from NorCog and follow-up data from medical records of NorCog patients have been merged with clinical data from the NPR (any hospital admittance during lifetime) prior to and after the baseline investigation. Furthermore, patients from NorCog have been traced by the CoDR to examine time and cause of death and by the NPoR to learn which patients have been admitted to nursing homes. Clinical data on level of functioning, level of dementia, neuropsychiatric symptoms and drug use have been retrieved from nursing home records or from interviews with nursing home staff, by visiting the nursing homes or by phone.	Linkage to: Norwegian Patient Registry (NPR) Cause of Death Registry (CoDR) National Population Registry (NPoR) Norwegian Prescription Database (NorPD)

*Number of patients with data from at least one registered follow-up using the short registration form

Standardized dementia assessment

All patients have a detailed baseline characterization. The baseline data were collected using a standardized dementia assessment protocol developed in an interdisciplinary collaboration between geriatricians, psychiatrists, neurologists, other clinicians, and researchers. The assessment protocol is designed as a paper-based case report form that can be optically scanned and includes questionnaires, a battery of tests, and forms on which relevant measures can be added. The scales are in accordance with the recommendations of the Norwegian national guidelines on dementia.[2] Usually, the patient is followed by the person who is defined as the closest proxy and serves as the key informant. As a rule, the patient and informant are interviewed separately. Some of the variables, depending on the level of cognitive impairment, are collected from both the patient and the informant. If an informant

is not able to accompany the patient to the assessment, information is usually collected by phone interviews.

The interviews include demographic and lifestyle variables, measures of care resource use, physical and social activities, activities of daily living (ADL), caregiver distress, medical history, current medications, and neuropsychiatric symptoms. Further examination of the patient includes an evaluation and testing of cognitive function, a psychiatric evaluation with an emphasis on comorbid depression, and an assessment of somatic status including a physical and neurological examination, blood laboratory work-up, and structural brain imaging using CT or magnetic resonance imaging (MRI). A spinal fluid examination and/or functional brain imaging such as positron emission tomography (PET) are performed in sub-groups, according to clinical indication. See Table 4 for a summary of the measures and scales registered in NorCog at baseline. The assessment protocol is a valuable tool for the participating clinics. To optimize and update the protocol, revisions have been made over the years. The revision process is comprehensive and carefully considers variables that should be added, modified, or removed. All revisions must be approved by the Steering committee for NorCog.

Table 4. Measures and scales registered in NorCog at baseline and source of information

Main test domain	Measures and scales registered in NorCog	Source*
Lifestyle/ Background		
Demographic	Age, gender, education, occupational activity, marital status, children, living condition, informant (yes/no), relation to informant	I, P
Care resource use	Care provided by the municipality (hours per week) Private or family care (hours per week)	I, P
Activities	Physical activity (hours per week and intensity) Social and cultural activity (hours per week)	I, P
Stimulant use	Tobacco, alcohol, other substances	I, P
Safety	Driving, access to weapons, falls	I, P
Nutrition & natural functions	Involuntary weight loss? Unsatisfactory food intake? Incontinence?	I, P
Activities of Daily Living (ADL)		
Personal ADL	Physical Self-Maintenance Scale (PSMS)	I
Instrumental ADL	The Lawton Instrumental Activities of Daily Living Scale (IADL)	I
Patient-Reported Outcome Measures (PROM) and caregiver situation		
Caregiver distress	Relatives' Stress Scale (RSS)	I
Patient experience	Do you think your memory is worse than before? If yes, does this worry you?	P
Fatigue	Do you mostly feel strong and rested or tired?	P
Medical history		
Present symptoms	Onset, course, type of symptoms Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)	I, P I
Family history	Dementia, other disorders of the central nervous system (CNS)	I, P
Present or previous physical and/or psychiatric disease	Cerebrovascular, other CNS-disorders, cancer, arthritis, cardiovascular, endocrine, kidney, Chronic Obstructive Pulmonary Disease, psychiatric disease	I, P
Medication		

Current medication	ATC code and defined daily dose of regular medication	I, P
Neuropsychiatric symptoms (NPS)		
Overall NPS	Neuropsychiatric Inventory Questionnaire (NPI-Q)	I
Depression	Cornell Scale for Depression in Dementia (CSDD)	I
	Montgomery and Aasberg Depression Rating Scale (MADRS)	P
Neurocognitive tests		
Global cognition	Mini-Mental State Examination (MMSE)	P
	Clock Drawing Test (CDT)	P
	Clinical Dementia Rating (CDR)	C
Memory	Ten-word recall test	P
Attention	Trail Making Test A and B	P
Fluency	Controlled Oral Word Association Test (COWA)	P
Constructional praxis	CERAD figure copying (including recall)	P
Word retrieval	The Boston Naming Test	P
Insight	Reed Scale for evaluation of anosognosia (lack of insight)	C
Somatic status		
Physical and neurological examination	Blood pressure, pulse, weight, height, gait speed, chair stand, balance test, vision, hearing, auscultation of neck, central facial paresis, plantar reflex, gait, rigidity, spasticity, hypokinesia, tremor, Romberg's test	D
Blood test results	Hemoglobin, thrombocytes, CRP, s-cholesterol, Na, K, Ca, S-folate, homocysteine, vitamin B12, TSH, T4, ALP, SR, ALAT, G-GT, albumin, creatinine, vitamin D, HbA1C	D
CSF test results	Beta-amyloid, total tau, phosphorylated tau	D
Brain imaging	Structural and functional (yes/no): CT, MRI, PET, DAT, SPECT, EEG	D
Clinical evaluation		
Baseline diagnosis	ICD-10 codes/ SCI, MCI, dementia (AD, VaD, FTD, DLB, PDD, unspecified), other	C
Recommended follow-up	Specialist health care, primary health care, support for caregivers	C

*I=informant, P=patient, D=direct test, C=clinical evaluation
Abbreviations: AD=Alzheimer's disease, ALAT=alanine aminotransferase, ALP=alkaline phosphatase, ATC=Anatomical therapeutic chemical, Ca=calcium, CRP=C-reactive protein, CT=computed tomography, DAT=dopamine transporter, DLB = dementia with Lewy bodies, EEG=electroencephalogram, FTD = frontotemporal dementia, G-GT=gamma-glutamyl transferase, HbA1C= hemoglobin A1c, K=potassium, MCI=mild cognitive impairment, MRI=magnetic resonance imaging, Na=sodium, PDD = Parkinson's disease dementia, PET=positron emission tomography, SCI=subjective cognitive impairment, SPECT=single photon emission computerized tomography, SR=sedimentation rate, T4=thyroxine, TSH=thyroid stimulating hormone, VaD=vascular dementia

Diagnostic criteria

The patients have been diagnosed according to standardized diagnostic criteria. Clinical diagnoses are registered according to the 10th revision of the International Classification of Diseases (ICD-10) for research.[11] The clinicians also draw a conclusion on one of the following categories for each patient: dementia (ICD-10), MCI according to the Winblad criteria,[12] SCI defined as a subjective experience of cognitive problems in the absence of objectively measured cognitive deficits, or the category "other" for patients who do not fulfil the criteria for the previous categories. If dementia is present, an aetiological diagnosis according to ICD-10 is registered. Furthermore, the clinicians are encouraged to make a more specific sub-classification according to a number of research diagnostic criteria. Here, the NIA/AA criteria are used for Alzheimer's disease (AD),[13] the Sachdev/VASCOG for vascular dementia (VaD),[14] the McKeith criteria for dementia with Lewy bodies (DLB),[15]

the Emre criteria for Parkinson's disease dementia (PDD),[16] the Rascovsky criteria for frontotemporal dementia (FTD) behavioural variant,[17] and the Gorno-Tempini criteria for the language variants of FTD.[18] In addition, the NIA/AA criteria are used for the subclassification of MCI.[19]

Biomaterial collection

A subsample of the participating clinics collects blood and cerebrospinal fluid (CSF) for a general research biobank for NorCog. Blood samples include serum, ethylenediaminetetraacetic acid (EDTA) plasma, EDTA whole blood, as well as whole blood in PAXgene RNA tubes. Genomic DNA has been isolated from EDTA whole blood. The samples are collected, processed, and temporarily stored at the respective units according to a standard operating protocol before shipment to the central biobank for NorCog in Oslo. The central research biobank for NorCog currently stores DNA and blood samples from approximately 4000 patients as well as CSF from 750 patients. The samples have been stored for up to 12 years at -80˚C. Samples are collected once, at baseline, but follow-up projects have collected follow-up samples from sub-groups. Approximately 400-500 patients are recruited to the biobank yearly, and collection is ongoing.

Quality indicators and patient-reported measures

As a national quality registry, a principal aim of NorCog is to contribute to better quality of, and reduce unwarranted variation in, diagnostic practice in the specialist health services in Norway. Indicators to evaluate the quality of the dementia assessments across different hospitals were developed in 2017 and are reported annually in a national, publicly available report (written in Norwegian and can be found at www.kvalitetsregistre.no). Moreover, patient-reported outcome measures (PROM) are registered in NorCog, and patient-reported experience measures (PREM) will be implemented during 2021.

Patient and public involvement

Patient involvement is essential to ensure that NorCog is relevant to the population it will impact. Therefore, it is stipulated in the articles of association for NorCog that users shall be represented in the registry's Steering committee. The user representation is attended by The Norwegian Health Association, a voluntary, humanitarian organization promoting the interests of people with dementia and their carers. The members of the Steering committee further include clinicians and managers from all health regions in Norway with backgrounds from memory clinics or outpatient clinics in old-age psychiatric and geriatric units, of which many have research competence. Furthermore, a patient advisory group, consisting of people with dementia and/or their proxies, has been involved in several processes, such as developing and pilot testing a PREM questionnaire, evaluating documents and information sheets, as well as involvement in strategies for presenting studies based on NorCog data.

FINDINGS TO DATE

Data from NorCog have been used in a wide range of research projects within the field of cognitive impairment and dementia, incorporating geriatric medicine, psychology, pharmacy, nursing, occupational therapy, and basic research. Up to December 2020, more than 90 scientific papers, 22 PhDs, and 18 postdoctoral studies were fully or partially based on data from NorCog.

Studies have been conducted to evaluate and validate dementia-related assessment tools. One study compared the validity of the Cornell Scale for Depression in Dementia (CSDD) and the Montgomery-Aasberg Depression Rating Scale (MADRS) among memory clinic patients and concluded that both scales are suitable as screening tools. The prevalence of depressive symptoms was shown to be high among memory clinic patients, as measured by the CSDD.[20] Caregiver burden and the patients' neuropsychiatric symptoms have been shown to be important biasing factors when caregivers report on patients' cognitive functioning and instrumental activities of daily living (IADL).[21] Caregiver distress as measured by the Relatives' Stress Scale (RSS) was shown to be higher in people caring for someone with DLB compared with people caring for someone with AD.[22]

Biomarkers that can aid in the diagnostic work-up of patients suspected of having a dementia disorder have become increasingly important in research, clinical trials, and clinical practice. A number of studies have shown that the CSF biomarkers amyloid-β 42 (Aβ42), total tau, and phosphorylated tau can be used to distinguish patients with AD from healthy controls.[23] However, when analyzed in a heterogeneous memory clinic population of patients enrolled in NorCog, the authors found a much lower discriminating power for CSF biomarkers than previously reported.[24] In June 2017, the Aβ42 cut-off level for a pathologic test result was revised at the Norwegian laboratory analyzing the CSF markers, while the methodological routines remained unchanged. The change in the Aβ42 cut-off for the diagnosis of AD nearly doubled the sensitivity of the CSF biomarkers, from 31.9% to 60.9%.[25] Another study evaluated the clinical usefulness of automatic MRI assessment using NeuroQuant (NQ) and found that NQ measures could distinguish AD dementia from non-dementia fairly well but were generally poorer in regard to distinguishing AD dementia from non-AD dementia.[26] Furthermore, biological material from the research biobank has been used in studies identifying previously unknown genetic variants conferring a risk of AD.[27-30]

A recent study described patients assessed for cognitive decline in primary health care, compared to patients assessed in specialist health care that have been included in NorCog. The study found that patients assessed in primary health care were older, less educated, had poorer cognitive functioning and activity limitations, more often lived alone, and had more behavioural and psychological symptoms of dementia and depression.[31]

A complete list of research projects using data from NorCog, and their publications, can be found on the website www.aldringoghelse.no/forskning/norkog.

STRENGTHS AND LIMITATIONS

The main strengths of NorCog are the large sample size with extensive clinical data combined with a research biobank, inclusion on a national level, and the opportunity to link variables covering the most relevant domains of cognitive impairment or dementia with real-world outcomes from national health registries, claims databases and chart records in hospitals and nursing homes.

The number of national registries specifically directed at persons with cognitive symptoms or dementia worldwide is scarce, but such registries now exist in all three Scandinavian countries.[32] The Swedish Dementia Registry (SveDem) has included a considerably larger number of patients than NorCog and recruits patients from both specialist units and primary care centers.[33] The Danish Dementia Registry (DanDem) has a similar profile as SveDem.[34] SveDem and DanDem are quality registries for patients with dementia disorders, and enrolment does not require written consent. NorCog is a combined quality and research registry focusing on the extended assessment of cognitive symptoms in a specialist setting that may or may not lead to a diagnosis of dementia, and it includes only those patients who are able to give their informed consent. NorCog is, therefore, not a dementia registry in the same sense as SveDem and DanDem, and it cannot be used to generalize to the general dementia population in Norway. However, unlike SveDem and DanDem, NorCog collects extensive data from all parts of the assessment with detailed information about test results on cognition and neuropsychiatric symptoms, caregiver situation, medications, medical history, and somatic status including results from blood laboratory work-up and lumbar puncture. Few, if any, national registries have a similarly broad spectrum of variables as NorCog, allowing for exploration of the main domains of dementia and cognitive impairment. A number of people are referred to assessment because of subjective memory complaints or mild cognitive impairment but do not fulfil the criteria for dementia. By following these patients over time, we have a unique possibility to identify risk factors for the development of dementia. The opportunity to link data with medical records from later admissions to hospitals and nursing homes, as well as to national registries, makes it possible to investigate predictors of real-world outcomes that are also highly relevant to decision makers. Moreover, the collection of biomaterials in a general research biobank can be used in research that aims to understand the aetiology of different dementia disorders and to explore fluid biomarkers for prediction, diagnosis, and disease progression.

In contrast to the restricted setting of a clinical trial, NorCog is a clinical registry collecting data as part of routine clinical practice and may, accordingly, be limited by lower data quality, lack of adjudication, and missing data. Data not missing at random introduce bias

and confounding that complicate statistical analyses. Nevertheless, the fact that the clinical registries reflect populations that are representative of routine clinical practice is a strength, increasing generalizability and external validity. The broad inclusion criteria for NorCog make the sample representative for patients being referred for evaluation of cognitive symptoms in a specialist setting. However, there are differences in the patient population depending on the profile of the outpatient clinic. NorCog enrols patients from memory clinics and outpatient clinics in old-age psychiatry and geriatric medicine, but thus far, no neurological departments have joined the registry. The representativeness is, thereby, somewhat uncertain, although very few neurological departments conduct diagnostic assessments of dementia in Norway.

FUTURE PLANS

Data collection in NorCog will continue in the coming years and data will be kept for as long as is necessary to achieve the purpose of the registry. During the year of 2021, the registry will undergo major changes. Paper-based data collection will be replaced with digital registration, and the number of variables collected will be reduced. To ensure the quality of the assessment and data collection, the registry will continue to provide the participating clinics with validated screening and diagnostic tools in accordance with the recommendations of the Norwegian national guidelines on dementia. In the paper-based version of NorCog, the registry has provided, and collected data on, a fixed set of measures and scales, shown in Table 4. The new digital version of NorCog developed during 2021 will allow for a more individualized assessment, to be able to include all groups of patients in NorCog regardless of linguistic and cultural background as well as degree and type of dementia. A core set of variables will be collected for each patient, but beyond this the clinicians may choose the screening tools that are most appropriate based on the background and symptoms of the individual patient. Therefore, the participating clinics will be provided with a selection of additional validated tools in line with national and international guidelines. All follow-up assessments will be registered in the digital platform. Future plans also involve expanding the registry to include patients from additional Norwegian specialist clinics as well as including patients from primary care centers. Moreover, patients that have reduced or lost their capacity to provide informed consent will be recruited based on proxy consent. The registry will continue to serve as a combined quality and research registry with biomaterial collection for years to come.

COLLABORATION

The use of data and biological material from NorCog is subject to strict ethical and legal regulations. All research projects must be approved by the Regional Committees for Medical and Health Research Ethics in Norway and by the Steering committee for NorCog. Oslo University Hospital has the overall responsibility for the data, and the Norwegian National Advisory Unit on Ageing and Health is managing the registry. Applicants from outside Norway are advised to identify a Norwegian collaborator. Enquiries can be submitted to the

corresponding author, Geir Selbæk. An application form may be found at https://www.aldringoghelse.no/forskning/norkog.

ACKNOWLEDGEMENTS

The authors thank all patients and informants for providing information. We are grateful for the efforts done by the reporting outpatient clinics and the Steering committee for NorCog.

COMPETING INTERESTS

ABK was/is the principal investigator of three drug trials (ROCHE BN29553, Boehringer-Ingelheim 1346.23 and Novo Nordisk NN6535-4730). KP was/is rater in the ROCHE BN29553 and Novo Nordisk NN6535-4730 trials and IS was investigator in the Boehringer-Ingelheim 1346.23 trial.

FUNDING

NorCog is funded by the South-Eastern Norway Regional Health Authority and the Norwegian National Advisory Unit on Ageing and Health (grant number not applicable).

CONTRIBUTORS

ITM prepared the initial draft of the manuscript in collaboration with GS, KP, THT, SB, MNå and CST. ABK, AB, POH, IS, ALL, AHR, DBS, MNa, JZS and BJ contributed with data resources. All authors provided critical review of the manuscript and approved the final version.

REFERENCES

1. Strand BH, Knapskog AB, Persson K, et al. Survival and years of life lost in various aetiologies of dementia, mild cognitive impairment (MCI) and subjective cognitive decline (SCD) in Norway. *PloS one* 2018;13(9):e0204436. doi: 10.1371/journal.pone.0204436 [published Online First: 2018/09/22]
2. Norwegian Directorate of Health. The Norwegian national guideline on dementia, IS-2658: Helsedirektoratet; 2017 [updated 2020 Jan 3; cited 20 Jan 15]. Available from: https://www.helsedirektoratet.no/retningslinjer/demens accessed 2017 Aug 16.
3. Gallacher J, de Reydet de Vulpillieres F, Amzal B, et al. Challenges for Optimizing Real-World Evidence in Alzheimer's Disease: The ROADMAP Project. *Journal of Alzheimer's disease : JAD* 2019;67(2):495-501. doi: 10.3233/jad-180370 [published Online First: 2018/12/26]
4. Makady A, de Boer A, Hillege H, et al. What Is Real-World Data? A Review of Definitions Based on Literature and Stakeholder Interviews. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2017;20(7):858-65. doi: 10.1016/j.jval.2017.03.008 [published Online First: 2017/07/18]
5. Garrison LP, Jr., Neumann PJ, Erickson P, et al. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2007;10(5):326-35. doi: 10.1111/j.1524-4733.2007.00186.x [published Online First: 2007/09/25]

6. Braekhus A, Ulstein I, Wyller TB, et al. The Memory Clinic--outpatient assessment when dementia is suspected. *Tidsskr Nor Laegeforen* 2011;131(22):2254-7. doi: 10.4045/tidsskr.11.0786 [published Online First: 2011/11/17]
7. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. *The British journal of psychiatry : the journal of mental science* 1982;140:566-72. doi: 10.1192/bjp.140.6.566 [published Online First: 1982/06/01]
8. Edwin TH, Henjum K, Nilsson LNG, et al. A high cerebrospinal fluid soluble TREM2 level is associated with slow clinical progression of Alzheimer's disease. *Alzheimer's & dementia (Amsterdam, Netherlands)* 2020;12(1):e12128. doi: 10.1002/dad2.12128 [published Online First: 2020/12/15]
9. Edwin TH, Strand BH, Persson K, et al. Trajectories and risk factors of dementia progression: a memory clinic cohort followed up to 3 years from diagnosis. *International psychogeriatrics* 2020:1-11. doi: 10.1017/s1041610220003270 [published Online First: 2020/11/21]
10. Mjørud M, Selbæk G, Bjertness E, et al. Time from dementia diagnosis to nursing-home admission and death among persons with dementia: A multistate survival analysis. *PloS one* 2020;15(12):e0243513. doi: 10.1371/journal.pone.0243513 [published Online First: 2020/12/05]
11. Organization WH. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic criteria for research. Geneva, 1993.
12. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of internal medicine* 2004;256(3):240-6. doi: 10.1111/j.1365-2796.2004.01380.x [published Online First: 2004/08/25]
13. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 2011;7(3):263-9. doi: 10.1016/j.jalz.2011.03.005 [published Online First: 2011/04/26]
14. Sachdev P, Kalaria R, O'Brien J, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer disease and associated disorders* 2014;28(3):206-18. doi: 10.1097/wad.0000000000000034 [published Online First: 2014/03/19]
15. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* 2017;89(1):88-100. doi: 10.1212/wnl.0000000000004058 [published Online First: 2017/06/09]
16. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society* 2007;22(12):1689-707; quiz 837. doi: 10.1002/mds.21507 [published Online First: 2007/06/02]
17. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain : a journal of neurology* 2011;134(Pt 9):2456-77. doi: 10.1093/brain/awr179 [published Online First: 2011/08/04]
18. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology* 2011;76(11):1006-14. doi: 10.1212/WNL.0b013e31821103e6 [published Online First: 2011/02/18]

19. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 2011;7(3):270-9. doi: 10.1016/j.jalz.2011.03.008 [published Online First: 2011/04/26]
20. Knapskog AB, Barca ML, Engedal K. A comparison of the validity of the Cornell Scale and the MADRS in detecting depression among memory clinic patients. *Dementia and geriatric cognitive disorders* 2011;32(4):287-94. doi: 10.1159/000334983 [published Online First: 2012/01/21]
21. Persson K, Braekhus A, Selbaek G, et al. Burden of Care and Patient's Neuropsychiatric Symptoms Influence Carer's Evaluation of Cognitive Impairment. *Dementia and geriatric cognitive disorders* 2015;40(5-6):256-67. doi: 10.1159/000437298 [published Online First: 2015/08/26]
22. Svendsboe E, Terum T, Testad I, et al. Caregiver burden in family carers of people with dementia with Lewy bodies and Alzheimer's disease. *International journal of geriatric psychiatry* 2016;31(9):1075-83. doi: 10.1002/gps.4433 [published Online First: 2016/01/15]
23. Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *The Lancet Neurology* 2016;15(7):673-84. doi: 10.1016/s1474-4422(16)00070-3 [published Online First: 2016/04/14]
24. Knapskog AB, Engedal K, Braekhus A. Performance of Cerebrospinal Fluid Biomarkers of Alzheimer Disease in a Memory Clinic in Norway. *Alzheimer disease and associated disorders* 2016;30(1):8-14. doi: 10.1097/wad.0000000000000126 [published Online First: 2015/12/03]
25. Knapskog AB, Braekhus A, Engedal K. The Effect of Changing the Amyloid beta42 Cut-off of Cerebrospinal Fluid Biomarkers on Alzheimer Disease Diagnosis in a Memory Clinic Population in Norway. *Alzheimer disease and associated disorders* 2019;33(1):72-74. doi: 10.1097/wad.0000000000000268 [published Online First: 2018/08/15]
26. Persson K, Selbaek G, Braekhus A, et al. Fully automated structural MRI of the brain in clinical dementia workup. *Acta radiologica (Stockholm, Sweden : 1987)* 2017;58(6):740-47. doi: 10.1177/0284185116669874 [published Online First: 2016/10/01]
27. Jonsson T, Stefansson H, Steinberg S, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. *The New England journal of medicine* 2013;368(2):107-16. doi: 10.1056/NEJMoa1211103 [published Online First: 2012/11/16]
28. Steinberg S, Stefansson H, Jonsson T, et al. Loss-of-function variants in ABCA7 confer risk of Alzheimer's disease. *Nature genetics* 2015;47(5):445-7. doi: 10.1038/ng.3246 [published Online First: 2015/03/26]
29. Witoelar A, Rongve A, Almdahl IS, et al. Meta-analysis of Alzheimer's disease on 9,751 samples from Norway and IGAP study identifies four risk loci. *Scientific reports* 2018;8(1):18088. doi: 10.1038/s41598-018-36429-6 [published Online First: 2018/12/29]
30. Jansen IE, Savage JE, Watanabe K, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nature genetics* 2019;51(3):404-13. doi: 10.1038/s41588-018-0311-9 [published Online First: 2019/01/09]

31. Michelet M, Lund A, Strand BH, et al. Characteristics of patients assessed for cognitive decline in primary healthcare, compared to patients assessed in specialist healthcare. *Scand J Prim Health Care* 2020;38(2):107-16. doi: 10.1080/02813432.2020.1753334 [published Online First: 2020/05/05]
32. Krysinska K, Sachdev PS, Breitner J, et al. Dementia registries around the globe and their applications: A systematic review. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 2017;13(9):1031-47. doi: 10.1016/j.jalz.2017.04.005 [published Online First: 2017/06/04]
33. Religa D, Fereshtehnejad SM, Cermakova P, et al. SveDem, the Swedish Dementia Registry - a tool for improving the quality of diagnostics, treatment and care of dementia patients in clinical practice. *PloS one* 2015;10(2):e0116538. doi: 10.1371/journal.pone.0116538 [published Online First: 2015/02/20]
34. Johannsen P, Jorgensen K, Korner A, et al. Development of a dementia assessment quality database. *Aging & mental health* 2011;15(1):40-6. doi: 10.1080/13607863.2010.508769 [published Online First: 2011/01/29]

Figure 1. Number of outpatient clinics and number of included patients at baseline in NorCog per year during 2009–2020 (N=15 372). In December 2020, 47 clinics from all four regional health authorities in Norway participated

Figure 2. Frequency of different types of dementia diagnoses registered in NorCog at baseline during 2009–2020 (n = 7113 dementia cases)

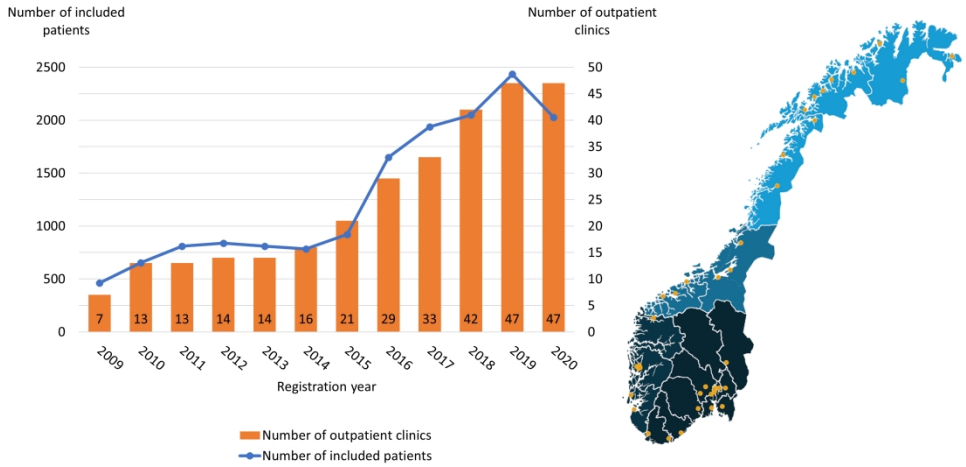

Figure 1. Number of outpatient clinics and number of included patients at baseline in NorCog per year during 2009–2020 (N=15 372). In December 2020, 47 clinics from all four regional health authorities in Norway participated

338x190mm (300 x 300 DPI)

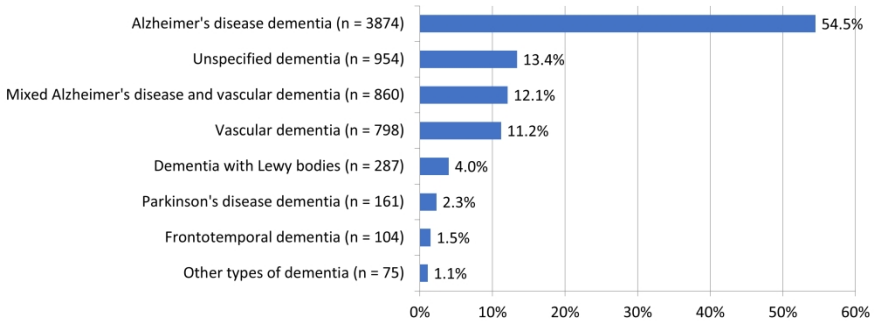

Figure 2. Frequency of different types of dementia diagnoses registered in NorCog at baseline during 2009–2020 (n = 7113 dementia cases)

338x129mm (300 x 300 DPI)

BMJ Open

Cohort Profile: The Norwegian Registry of Persons Assessed for Cognitive Symptoms (NorCog) – a national research and quality registry with a biomaterial collection

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058810.R1
Article Type:	Cohort profile
Date Submitted by the Author:	09-May-2022

Complete List of Authors:	Medbøen, Ingrid; Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital Persson, Karin; Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital Nåvik, Marit; Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust; Department of Psychiatry, Telemark Hospital Totland, Torunn; Department of Chronic Diseases and Ageing, Norwegian Institute of Public Health Bergh, Sverre; Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust; Research centre for Age-related Functional Decline and Disease, Innlandet Hospital trust Treviño, Cathrine; Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital Ulstein, Ingun; Department of Geriatric Medicine, Oslo University Hospital Engedal , Knut ; Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital Knapskog, Anne-Brita; Department of Geriatric Medicine, Oslo University Hospital Brækhus, Anne; Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital Øksengård, Anne; The Norwegian Health Association; Bærum Hospital, Vestre Viken Hospital Trust Horndalsveen, Peter; Department of Old Age Psychiatry, Innlandet Hospital trust Saltvedt, Ingvild; Department of Geriatrics, St. Olav's Hospital, Trondheim University Hospital; Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology Lyngroth, Anne; Department of Geriatrics, Sorlandet Hospital Arendal Ranhoff, Anette ; Department of Medicine, Diakonhjemmet Hospital; Department of Clinical Science, University of Bergen, Skrettingland, Dagny; Department of Geriatrics, Stavanger University Hospital Naik, Mala; Department of Clinical Science, University of Bergen, ;

	Department of Medicine, Haraldsplass Deaconess Hospital Soares, Jelena; Medical Department, Section of Geriatrics, Lovisenberg Diaconal Hospital Johnsen, Bente; Department of Geriatric Medicine, University Hospital of North Norway Selbaek, Geir; Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital
Primary Subject Heading:	Diagnostics
Secondary Subject Heading:	Geriatric medicine, Mental health, Neurology
Keywords:	Dementia < NEUROLOGY, Delirium & cognitive disorders < PSYCHIATRY, GERIATRIC MEDICINE, Old age psychiatry < PSYCHIATRY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Cohort Profile: The Norwegian Registry of Persons Assessed for Cognitive Symptoms (NorCog) – a national research and quality registry with a biomaterial collection

Ingrid Tøndel Medbøen,[1,2] Karin Persson,[1,2] Marit Nåvik,[1,3] Torunn H. Totland,[4] Sverre Bergh,[1,5] Cathrine Selnes Treviño[1,2] Ingun Dina Ulstein,[2] Knut Engedal,[1,2] Anne-Brita Knapskog,[2] Anne Brækhus,[1,2] Anne Rita Øksengård,[6,7] Peter O Horndalsveen,[8] Ingvild Saltvedt,[9,10] Anne Liv Lyngroth,[11] Anette Hylen Ranhoff,[12,13] Dagny Bekkeheien Skrettingland,[14] Mala Naik,[13,15] Jelena Zugic Soares,[16] Bente Johnsen,[17] Geir Selbæk,[1,2]*

[1]The Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust, Tønsberg, Norway, [2]Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway, [3]Department of Psychiatry, Telemark Hospital, Skien, Norway, [4]Department of Chronic Diseases and Ageing, Norwegian Institute of Public Health, Oslo, Norway, [5]Research centre for Age-related Functional Decline and Disease, Innlandet Hospital trust, Ottestad, Norway, [6]The Norwegian Health Association, Oslo, Norway, [7]Bærum Hospital, Vestre Viken Hospital Trust, Drammen, Norway, [8]Department of Old Age Psychiatry, Innlandet Hospital trust, Ottestad, Norway, [9]Department of Geriatrics, St. Olav's Hospital, Trondheim University Hospital, Trondheim, Norway, [10]Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway, [11]Department of Geriatrics, Sorlandet Hospital Arendal, Arendal, Norway, [12]Department of Medicine, Diakonhjemmet Hospital, Oslo, Norway, [13]Department of Clinical Science, University of Bergen, Bergen, Norway, [14]Department of Geriatrics, Stavanger University Hospital, Stavanger, Norway, [15]Department of Medicine, Haraldsplass Deaconess Hospital, Bergen, Norway, [16]Medical Department, Section of Geriatrics, Lovisenberg Diaconal Hospital, Oslo, Norway, [17]Department of Geriatric Medicine, University Hospital of North Norway, Tromsø, Norway.

*Corresponding author. Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust, Pb 2136, 3103 Tønsberg, Norway. Email: geir.selbaek@aldringoghelse.no

Word count: 4013 (excluding title page, abstract, strengths and limitations of this study, references, figures and tables)

ABSTRACT

Purpose: NorCog was established to harmonize and improve the quality of diagnostic practice across clinics assessing persons with cognitive symptoms in Norwegian specialist health care units and to establish a large research cohort with extensive clinical data.

Participants: The registry recruits patients who are referred for assessment of cognitive symptoms and suspected dementia at outpatient clinics in Norwegian specialist health care units. In total, 18 120 patients have been included in NorCog during the period 2009–2021. The average age at inclusion was 73.7 years. About half of the patients (46%) were diagnosed with dementia at the baseline assessment, 35% with mild cognitive impairment, 13% with no or subjective cognitive impairment; 7% received other specified diagnoses, such as mood disorders.

Findings to date: All patients have a detailed baseline characterization involving lifestyle and demographic variables; activities of daily living; caregiver situation; medical history; medication; psychiatric, physical and neurological examination; neurocognitive testing; blood laboratory work-up; and structural or functional brain imaging. Diagnoses are set according to standardized diagnostic criteria. The research biobank stores DNA and blood samples from 4000 patients as well as cerebrospinal fluid from 800 patients. Data from NorCog have been used in a wide range of research projects evaluating and validating dementia-related assessment tools, identifying patient characteristics, symptoms, functioning and needs as well as caregiver burden and requirement of available resources.

Future plans: The finish date of NorCog was originally in 2029. In 2021, the registry's legal basis was reformalized and NorCog got approval to collect and keep data for as long as is necessary to achieve the purpose of the registry. In 2022, the registry underwent major changes. Paper-based data collection was replaced with digital registration, and the number of variables collected were reduced. Future plans involve expanding the registry to include patients from primary care centers.

Strengths and limitations of this study

- A key strength of NorCog is the large sample size with extensive clinical data combined with a research biobank. Few, if any, national registries collect a similarly broad spectrum of variables as NorCog, allowing for exploration of the main domains of dementia and cognitive impairment.
- Patients consent to linkage of data with medical records from later admissions to hospitals and nursing homes, as well as to national health registries, making it possible to investigate predictors of real-world outcomes.
- NorCog only recruits patients who are referred for assessment in a specialist setting and cannot be used to generalize to the general dementia population in Norway.
- In contrast to the restricted setting of a clinical trial, NorCog is a clinical registry collecting data as part of routine clinical practice and may, accordingly, be limited by lower data quality, lack of adjudication, and missing data.

INTRODUCTION

Cognitive symptoms, such as problems with memory, reasoning, and language skills, as well as emotional and behavioural changes, may signal pathological changes in the brain that can cause dementia. Dementia is the deterioration of cognitive functions to an extent that impedes a person's ability to perform functions of daily living and, ultimately, resulting in premature death.[1]

In Norway, the municipalities are responsible for primary care, including the assessment of cognitive impairment in older patients with uncomplicated dementia symptoms. In more complicated cases, the recommendation of the Norwegian national guideline on dementia is to refer patients to specialist health care units for an extended assessment.[2] In Norway, specialist care is administered by four regional health authorities. According to the national guideline on dementia, cases that are appropriate to refer to specialist health care units may include younger patients with cognitive decline, patients with coexisting psychiatric, neurological, or somatic problems, atypical dementia disorders, and patient groups with complex disorders.

Recently, research including real-world outcome data has been requested.[3] Although consensus on the definition of real-world data is lacking, the term is most often defined as data used for coverage and payment decisions collected outside the constraints of conventional randomized controlled trials (RCTs).[4] Observational registries represent one type of sources for real-world data, typically including a larger and more diverse group of patients than generally studied in RCTs and, thereby, better reflecting populations that are representative of routine clinical practice.[5]

The purpose of this Cohort Profile is to describe the background, methods, baseline data and future plans of the Norwegian Registry of Persons Assessed for Cognitive Symptoms (NorCog). NorCog was established in 2008 with two main aims:

1. To harmonize and improve the quality of diagnostic practice across outpatient clinics assessing persons with cognitive symptoms in specialist care units.
2. To establish a large research cohort with extensive clinical data and provide an opportunity to link baseline data to important real-world outcomes in regional and national registries.

Oslo University Hospital has the overall responsibility for the registry data, and the Norwegian National Centre for Ageing and Health is managing the registry.

COHORT DESCRIPTION

NorCog has an observational design and recruits patients who are referred for assessment of cognitive symptoms and suspected dementia at outpatient clinics in Norwegian specialist

health care units. Patients are encouraged to bring their next of kin or another person who knows them well, referred to hereafter as the informant.

NorCog was originally established as a regional quality and research registry in 2008. During the first year of data collection, in 2009, seven outpatient clinics from the South-Eastern Norway Regional Health Authority participated. Since then, outpatient clinics from all four regional health authorities in Norway have joined, and the registry received status as a national quality registry in 2013. Most of the clinics are referred to as memory clinics or outpatient clinics in old-age psychiatric and geriatric units.[6] There is no clear consensus for which type of outpatient clinics that should be assessing dementia in Norway and there are variations between regions. To be eligible for data collection in NorCog, the outpatient clinics need to have a specialist as part of their interdisciplinary staff. Some clinics have had staffing problems and have stopped or paused data collection in NorCog until specialists are rehired. In December 2021, 45 out of 49 eligible outpatient clinics (memory clinics or outpatient clinics in old-age psychiatric and geriatric units) participated with data collection in NorCog.

The number of included patients per year has increased in line with the recruitment of new clinics, from 462 patients in 2009 to 2414 in 2021 (Figure 1). Because of the COVID-19 pandemic, the number of included patients in 2020 (N=2293) was somewhat lower than could be expected under normal circumstances. In total, 18 120 patients have been included in NorCog during the period 2009–2021. Table 1 shows some of the demographic, clinical, and social characteristics of the included patients at baseline. The average age at inclusion was 73.7 years with an age range of 26 to 99 years. Reports from 13 615 informants showed that memory problems were, by far, the most frequently reported first symptoms of the patient, as stated by 63% of the informants.

Table 1. A selection of demographic, social, and clinical characteristics of patients included in the NorCog cohort at baseline. Numbers of patients with missing data are shown in the far right column.

	Patients included in NorCog during 2009–2021					*Missing data total cohort, n (%)*
	Total cohort	NCI/SCI	MCI	Dementia	Other diagnoses	
n (%)	18 120 (100)	2258 (12.5)	6307 (34.8)	8368 (46.2)	1187 (6.6)	
Age (years), mean (SD)	73.7 (9.9)	67.3 (11.7)	73.1 (9.7)	76.3 (8.2)	70.5 (10.9)	*0*
Sex (female), n (%)	9443 (52.1)	1167 (51.7)	3097 (49.1)	4599 (55.0)	580 (48.9)	*0*
Education (years), mean (SD)	11.3 (3.8)	12.5 (3.9)	11.5 (3.8)	10.8 (3.6)	11.3 (3.9)	*1521 (8.4)*
Married/cohabiting, n (%)	10 709 (61.6)	1402 (65.0)	3800 (62.7)	4812 (59.9)	695 (61.2)	*729 (4.0)*
Living alone, n (%)	6589 (36.4)	737 (32.6)	2284 (36.2)	3135 (37.5)	433 (36.5)	*687 (3.8)*
Public care, n (%)	5639 (32.1)	388 (18.1)	1626 (26.6)	3260 (40.0)	356 (31.6)	*597 (3.3)*
MMSE score, mean (SD)	23.6 (4.6)	27.1 (3.3)	25.2 (3.4)	21.0 (4.4)	26.2 (3.8)	*478 (2.6)*
Information from informant obtained, n (%)	17234 (95.1)	1983 (87.8)	5907 (93.7)	8275 (98.9)	1069 (90.1)	

Abbreviations: MCI=mild cognitive impairment, MMSE=Mini-Mental State Examination, NCI=no cognitive impairment, SCI=subjective cognitive impairment, SD=Standard Deviation

During 2009–2021, about half of the patients (46%) were diagnosed with dementia at the baseline assessment, 35% with mild cognitive impairment (MCI), 13% with no or subjective cognitive impairment (NCI/SCI), and 7% received other specified diagnoses such as mood disorders. The diagnostic work-up and criteria will be explained in a separate paragraph below. Table 2 shows the frequency of the different etiological dementia diagnoses and a selection of characteristics by dementia diagnoses.

Table 2. Demographic characteristics by etiological dementia diagnoses registered in NorCog at baseline during 2009-2021.

	AD dementia	Mixed AD and VaD	VaD	DLB	PDD	FTD	Unspecified dementia	Other dementia types
n (%)	4481 (53.5)	1047 (12.5)	925 (11.1)	343 (4.1)	199 (2.4)	131 (1.6)	1154 (13.8)	88 (1.1)
Age (years), mean (SD)	75.9 (8.3)	79.0 (6.7)	78.4 (7.2)	74.3 (8.2)	75.0 (6.5)	66.8 (10.9)	75.9 (8.1)	70.6 (9.1)
Sex (female), n (%)	2750 (61.4)	552 (52.7)	411 (44.4)	140 (40.8)	70 (35.2)	61 (46.6)	574 (49.7)	40 (45.5)
Education (years), mean (SD)	10.9 (3.5)	10.6 (4.1)	10.3 (3.4)	11.3 (3.6)	11.4 (3.8)	12.3 (3.6)	10.5 (3.5)	11.5 (3.3)
Married/ cohabiting, n (%)	2606 (60.3)	569 (57.1)	505 (56.7)	223 (67.4)	151 (77.8)	97 (77.6)	610 (55.7)	51 (61.4)
Living alone, n (%)	1676 (38.8)	428 (41.9)	371 (41.5)	98 (29.4)	42 (22.0)	30 (23.8)	461 (41.4)	28 (32.9)
Public care, n (%)	1429 (32.7)	516 (50.4)	510 (56.5)	123 (37.3)	96 (50.0)	32 (25.4)	517 (46.0)	36 (43.4)
MMSE score, mean (SD)	20.8 (4.4)	20.7 (4.2)	21.4 (4.3)	21.5 (4.5)	21.7 (4.3)	24.1 (3.7)	20.9 (4.6)	23.7 (4.0)

Abbreviations: AD=Alzheimer's disease, DLB=Dementia with Lewy bodies, FTD=Frontotemporal dementia, MMSE=Mini-Mental State Examination, PDD=Parkinson's disease dementia, SD=Standard Deviation, VaD=Vascular dementia

Dementia severity was assessed with the Clinical Dementia Rating Scale (CDR), a global rating scale covering six domains of cognitive and functional performance.[7] The CDR is scored according to an algorithm that gives precedence to the memory domain, with a total score of 0 (no cognitive impairment), 0.5 (questionable dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia). In NorCog, 81% of patients who were diagnosed with dementia at baseline during 2009–2021 had a score of 0.5 or 1, corresponding to a very mild or mild stage of dementia. Furthermore, 17% had a score of 2 (moderate dementia) and 2% a score of 3 (severe dementia).

Informed consent

Participation in NorCog is voluntary and enrolment require written informed consent. To give informed consent, a person must have the ability to fully understand what the

participation in the registry means. During 2009-2021, NorCog has only recruited patients that have the capacity to give informed consent. However, from January 2022, patients who are unable, or have reduced capacity, to provide informed consent can also be included in NorCog based on proxy consent.

Patients not included in NorCog

The number of non-included patients during 2009-2015 has not been registered. Beginning in 2016, all participating clinics have recorded the age and sex of patients who were not included in NorCog. During 2016-2021, a total of 613 patients lacked competence to give consent and were, therefore, not eligible for inclusion in NorCog. The total number of patients eligible for inclusion at the participating clinics during 2016-2021 was 17 597, whereof 73% of patients (n=12 845) were included and 27% (n=4752) were not included. The average age and the proportion of females were higher among the non-included patients (76 years and 55% females) compared to the included patients (74 years and 51% females). Among the patients that were not included, some were not asked to join the registry due to capacity considerations at the clinic (22%) or because the clinician perceived that the situation/condition of the patient did not allow it (31%). In other cases, patients were asked to participate, but declined (21%). In 26% of cases, the cause of non-inclusion was unknown, or another test battery was used due to language issues.

Follow-up data

No predetermined follow-up schedule has been established for the registry. However, a registration form for assessment at follow-up according to clinical indication was implemented in 2015 (Table 3). Thus far, the clinics are encouraged but not obliged to deliver follow-up data to the registry. In several sub-studies, selected patients have been invited to receive additional examinations or follow-ups in compliance with specific research protocols. In 2017, a large research project began collecting follow-up data from patients in the registry. The project is called “Trajectories and risk factors of dementia – TRAIL-DEM” and involves linking data from the patients in NorCog with medical records in hospitals and nursing homes as well as national health registries (Table 3). The project investigates trajectories from dementia onset until nursing home admission and death, providing a unique opportunity to investigate dementia aetiology and progression.[1 8-10] TRAIL-DEM will provide an extensive database that will form the basis for future projects.

Table 3. Overview of the samples/phases, measurements, biomaterial collection and linkages in the registry

Sample/Phase	Measurements	Biomaterial Collection/ Linkage

Baseline assessment NorCog 2009–2021 N=18 120	A comprehensive clinical assessment including lifestyle and demographic variables; activities of daily living; caregiver situation; medical history; current medication; psychiatric, physical, and neurological examination; neurocognitive testing; blood laboratory work-up; and routine MRI. When indicated: lumbar puncture for the measurement of Aβ and tau proteins in cerebrospinal fluid (CSF) and/or functional brain imaging.	EDTA-whole blood, n=4342 Serum, n=4509 Plasma, n=4293 CSF, n=800 PAXgene RNA, n=3544 DNA, n=3714
Follow-up NorCog patients by clinical indication 2015–2021 N=3656*	A shorter set of registration forms including living situation, care resource use, sum score on neurocognitive tests, Clinical Dementia Rating scale, NPI-Q, blood pressure and pulse, clinical evaluation of change from baseline, clinical diagnosis, and recommended follow-up.	
The TRAIL-DEM study conducted during 2017-2022 Follow-up of patients in NorCog included during 2009–2016. New linkage in 2022 for patients included during 2017–2021.	Baseline data from NorCog and follow-up data from medical records of NorCog patients have been merged with clinical data from the NPR (any hospital admittance during lifetime) prior to and after the baseline investigation. Furthermore, patients from NorCog have been traced by the CoDR to examine time and cause of death and by the NPoR to learn which patients have been admitted to nursing homes. Clinical data on level of functioning, level of dementia, neuropsychiatric symptoms and drug use have been retrieved from nursing home records or from interviews with nursing home staff, by visiting the nursing homes or by phone.	Linkage to: Norwegian Patient Registry (NPR) Cause of Death Registry (CoDR) National Population Registry (NPoR) Norwegian Prescription Database (NorPD)

*Number of patients with data from at least one registered follow-up using the short registration form

Standardized dementia assessment

All patients have a detailed baseline characterization. The baseline data were collected using a standardized dementia assessment protocol developed in an interdisciplinary collaboration between geriatricians, psychiatrists, neurologists, other clinicians, and researchers. The assessment protocol is designed as a paper-based case report form that can be optically scanned and includes questionnaires, a battery of tests, and forms on which relevant measures can be added. The scales are in accordance with the recommendations of the Norwegian national guidelines on dementia.[2] Usually, the patient is followed by the person who is defined as the closest proxy and serves as the key informant. As a rule, the patient and informant are interviewed separately. Some of the variables, depending on the level of cognitive impairment, are collected from both the patient and the informant. If an informant is not able to accompany the patient to the assessment, information is usually collected by phone interviews.

The interviews include demographic and lifestyle variables, measures of care resource use, physical and social activities, activities of daily living (ADL), caregiver distress, medical history, current medications, and neuropsychiatric symptoms. Further examination of the patient includes an evaluation and testing of cognitive function, a psychiatric evaluation with an emphasis on comorbid depression, and an assessment of somatic status including a

physical and neurological examination, blood laboratory work-up, and structural brain imaging using CT or magnetic resonance imaging (MRI). A spinal fluid examination and/or functional brain imaging such as positron emission tomography (PET) are performed in sub-groups, according to clinical indication. See Table 4 for a summary of the measures and scales registered in NorCog at baseline. The assessment protocol is a valuable tool for the participating clinics. To optimize and update the protocol, revisions have been made over the years. The revision process is comprehensive and carefully considers variables that should be added, modified, or removed. All revisions must be approved by the Steering committee for NorCog.

Table 4. Measures and scales registered in NorCog at baseline and source of information

Main test domain	Measures and scales registered in NorCog	Source*
Lifestyle/ Background		
Demographic	Age, gender, education, occupational activity, marital status, children, living condition, informant (yes/no), relation to informant	I, P
Care resource use	Care provided by the municipality (hours per week) Private or family care (hours per week)	I, P
Activities	Physical activity (hours per week and intensity) Social and cultural activity (hours per week)	I, P
Stimulant use	Tobacco, alcohol, other substances	I, P
Safety	Driving, access to weapons, falls	I, P
Nutrition & natural functions	Involuntary weight loss? Unsatisfactory food intake? Incontinence?	I, P
Activities of Daily Living (ADL)		
Personal ADL	Physical Self-Maintenance Scale (PSMS)	I
Instrumental ADL	The Lawton Instrumental Activities of Daily Living Scale (IADL)	I
Patient-Reported Outcome Measures (PROM) and caregiver situation		
Caregiver distress	Relatives' Stress Scale (RSS)	I
Patient experience	Do you think your memory is worse than before? If yes, does this worry you?	P
Fatigue	Do you mostly feel strong and rested or tired?	P
Medical history		
Present symptoms	Onset, course, type of symptoms Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)	I, P I
Family history	Dementia, other disorders of the central nervous system (CNS)	I, P
Present or previous physical and/or psychiatric disease	Cerebrovascular, other CNS-disorders, cancer, arthritis, cardiovascular, endocrine, kidney, Chronic Obstructive Pulmonary Disease, psychiatric disease	I, P
Medication		
Current medication	ATC code and defined daily dose of regular medication	I, P
Neuropsychiatric symptoms (NPS)		
Overall NPS	Neuropsychiatric Inventory Questionnaire (NPI-Q)	I
Depression	Cornell Scale for Depression in Dementia (CSDD)	I
	Montgomery and Aasberg Depression Rating Scale (MADRS)	P
Neurocognitive tests		
Global cognition	Mini-Mental State Examination (MMSE)	P
	Clock Drawing Test (CDT)	P
	Clinical Dementia Rating (CDR)	C
Memory	Ten-word recall test	P
Attention	Trail Making Test A and B	P

Fluency	Controlled Oral Word Association Test (COWA)	P
Constructional praxis	CERAD figure copying (including recall)	P
Word retrieval	The Boston Naming Test	P
Insight	Reed Scale for evaluation of anosognosia (lack of insight)	C
Somatic status		
Physical and neurological examination	Blood pressure, pulse, weight, height, gait speed, chair stand, balance test, vision, hearing, auscultation of neck, central facial paresis, plantar reflex, gait, rigidity, spasticity, hypokinesia, tremor, Romberg's test	D
Blood test results	Hemoglobin, thrombocytes, CRP, s-cholesterol, Na, K, Ca, S-folate, homocysteine, vitamin B12, TSH, T4, ALP, SR, ALAT, G-GT, albumin, creatinine, vitamin D, HbA1C	D
CSF test results	Beta-amyloid, total tau, phosphorylated tau	D
Brain imaging	Structural and functional (yes/no): CT, MRI, PET, DAT, SPECT, EEG	D
Clinical evaluation		
Baseline diagnosis	ICD-10 codes/ SCI, MCI, dementia (AD, VaD, FTD, DLB, PDD, unspecified), other	C
Recommended follow-up	Specialist health care, primary health care, support for caregivers	C

*I=informant, P=patient, D=direct test, C=clinical evaluation

Abbreviations: AD=Alzheimer's disease, ALAT=alanine aminotransferase, ALP=alkaline phosphatase, ATC=Anatomical therapeutic chemical, Ca=calcium, CRP=C-reactive protein, CSF=cerebrospinal fluid, CT=computed tomography, DAT=dopamine transporter, DLB = dementia with Lewy bodies, EEG=electroencephalogram, FTD = frontotemporal dementia, G-GT=gamma-glutamyl transferase, HbA1C= hemoglobin A1c, K=potassium, MCI=mild cognitive impairment, MRI=magnetic resonance imaging, Na=sodium, PDD = Parkinson's disease dementia, PET=positron emission tomography, SCI=subjective cognitive impairment, SPECT=single photon emission computerized tomography, SR=sedimentation rate, T4=thyroxine, TSH=thyroid stimulating hormone, VaD=vascular dementia

Diagnostic work-up and criteria

The diagnostic workups are conducted by specialists (e.g., physicians or psychologists) at the outpatient clinics. Diagnoses are discussed in interdisciplinary consensus meetings and are based on all available data from the assessment, including biological markers such as imaging, blood tests and cerebrospinal fluid (CSF) biomarkers. The specialists at the outpatient clinics conclude on a diagnosis according to standardized diagnostic criteria. ICD-10 is the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD), a medical classification list by the World Health Organization. In Norway, ICD-10 is established in clinical practice. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is widely used in clinical practice in the US and internationally, wherein the terms mild neurocognitive disorder and major neurocognitive disorder have largely supplanted the term dementia.[11] DSM-5 is not widely used in Norwegian clinical practice, but ICD-11, which is more similar to DSM-5 than ICD-10, will be implemented in the near future. Clinical diagnoses in NorCog are registered according to the ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic criteria for research.[12] The clinicians also draw a conclusion on one of the following categories for each patient: dementia (ICD-10), MCI according to the Winblad criteria,[13] SCI defined as a subjective experience of cognitive problems in the absence of objectively measured cognitive deficits, or the category "other" for patients who do not fulfil the criteria for the

previous categories. If dementia is present, an aetiological diagnosis according to ICD-10 is registered in NorCog.

Furthermore, the specialists at the outpatient clinics are encouraged, but not obliged, to make a more specific sub-classification according to a number of research diagnostic criteria. Here, the NIA/AA criteria are used for Alzheimer's disease (AD),[14] the Sachdev/VASCOG for vascular dementia (VaD),[15] the McKeith criteria for dementia with Lewy bodies (DLB),[16] the Emre criteria for Parkinson's disease dementia (PDD),[17] the Rascovsky criteria for frontotemporal dementia (FTD) behavioural variant,[18] and the Gorno-Tempini criteria for the language variants of FTD.[19] In addition, the NIA/AA criteria are used for the subclassification of MCI.[20] Since the specialists at the outpatient clinics are not obliged to register diagnoses according to research criteria other than ICD-10, research diagnoses are determined retrospectively in some research projects.

Biomaterial collection

A subsample of the participating clinics collects blood and CSF for a general research biobank for NorCog. Blood samples include serum, ethylenediaminetetraacetic acid (EDTA) plasma, EDTA whole blood, as well as whole blood in PAXgene RNA tubes. Genomic DNA has been isolated from EDTA whole blood. The samples are collected, processed, and temporarily stored at the respective units according to a standard operating protocol before shipment to the central biobank for NorCog in Oslo. The central research biobank for NorCog currently stores DNA and blood samples from over 4000 patients as well as CSF from 800 patients. The samples have been stored for up to 12 years at -80˚C. Samples are collected once, at baseline, but follow-up projects have collected follow-up samples from sub-groups. Approximately 400-500 patients are recruited to the biobank yearly, and collection is ongoing.

Quality indicators and patient-reported measures

As a national quality registry, a principal aim of NorCog is to contribute to better quality of, and reduce unwarranted variation in, diagnostic practice in the specialist health services in Norway. Indicators to evaluate the quality of the dementia assessments across different hospitals were developed in 2017 and are reported annually in a national, publicly available report (written in Norwegian and can be found at www.kvalitetsregistre.no). Moreover, patient-reported outcome measures (PROM) are registered in NorCog, and patient-reported experience measures (PREM) will be implemented during 2022.

Patient and public involvement

Patient involvement is essential to ensure that NorCog is relevant to the population it will impact. Therefore, it is stipulated in the articles of association for NorCog that users shall be represented in the registry's Steering committee. The user representation is attended by The Norwegian Health Association, a voluntary, humanitarian organization promoting the

interests of people with dementia and their carers. The members of the Steering committee further include clinicians and managers from all health regions in Norway with backgrounds from memory clinics or outpatient clinics in old-age psychiatric and geriatric units, of which many have research competence. Furthermore, a patient advisory group, consisting of people with dementia and/or their proxies, has been involved in several processes, such as developing and pilot testing a PREM questionnaire, evaluating documents and information sheets, as well as involvement in strategies for presenting studies based on NorCog data.

FINDINGS TO DATE

Data from NorCog have been used in a wide range of research projects within the field of cognitive impairment and dementia, incorporating geriatric medicine, psychology, pharmacy, nursing, occupational therapy, and basic research. Up to December 2021, more than 100 scientific papers, 22 PhDs, and 18 postdoctoral studies were fully or partially based on data from NorCog. A complete list of research projects using data from NorCog, and their publications, can be found on the website www.aldringoghelse.no/forskning/norkog. Below is a short description of results from a few of the published studies based on data from NorCog.

Studies have been conducted to evaluate and validate dementia-related assessment tools. One study compared the validity of the Cornell Scale for Depression in Dementia (CSDD) and the Montgomery-Aasberg Depression Rating Scale (MADRS) among memory clinic patients and concluded that both scales are suitable as screening tools. The prevalence of depressive symptoms was shown to be high among memory clinic patients, as measured by the CSDD.[21] Caregiver burden and the patients' neuropsychiatric symptoms have been shown to be important biasing factors when caregivers report on patients' cognitive functioning and instrumental activities of daily living (IADL).[22] Caregiver distress as measured by the Relatives' Stress Scale (RSS) was shown to be higher in people caring for someone with DLB compared with people caring for someone with AD.[23]

Biomarkers that can aid in the diagnostic work-up of patients suspected of having a dementia disorder have become increasingly important in research, clinical trials, and clinical practice. A number of studies have shown that the CSF biomarkers amyloid-β 42 (Aβ42), total tau, and phosphorylated tau can be used to distinguish patients with AD from healthy controls.[24] However, when analyzed in a heterogeneous memory clinic population of patients enrolled in NorCog, the authors found a much lower discriminating power for CSF biomarkers than previously reported.[25] In June 2017, the Aβ42 cut-off level for a pathologic test result was revised at the Norwegian laboratory analyzing the CSF markers, while the methodological routines remained unchanged. The change in the Aβ42 cut-off for the diagnosis of AD nearly doubled the sensitivity of the CSF biomarkers, from 31.9% to 60.9%.[26] Another study evaluated the clinical usefulness of automatic MRI assessment using NeuroQuant (NQ) and found that NQ measures could distinguish AD dementia from

non-dementia fairly well but were generally poorer in regard to distinguishing AD dementia from non-AD dementia.[27] Furthermore, biological material from the research biobank has been used in studies identifying previously unknown genetic variants conferring a risk of AD.[28-31]

A recent study described patients assessed for cognitive decline in primary health care, compared to patients assessed in specialist health care that have been included in NorCog. The study found that patients assessed in primary health care were older, less educated, had poorer cognitive functioning and activity limitations, more often lived alone, and had more behavioural and psychological symptoms of dementia and depression.[32]

STRENGTHS AND LIMITATIONS

The main strengths of NorCog are the large sample size with extensive clinical data combined with a research biobank, inclusion on a national level, and the opportunity to link variables covering the most relevant domains of cognitive impairment or dementia with real-world outcomes from national health registries, claims databases and chart records in hospitals and nursing homes.

The number of national registries specifically directed at persons with cognitive symptoms or dementia worldwide is scarce, but such registries now exist in all three Scandinavian countries.[33] The Swedish Dementia Registry (SveDem) has included a considerably larger number of patients than NorCog and recruits patients from both specialist units and primary care centers.[34] The Danish Dementia Registry (DanDem) has a similar profile as SveDem.[35] SveDem and DanDem are quality registries for patients with dementia disorders, and enrolment does not require written consent. NorCog is a combined quality and research registry focusing on the extended assessment of cognitive symptoms in a specialist setting that may or may not lead to a diagnosis of dementia, and from 2009-2021, it included only those patients who were able to give their informed consent. NorCog is, therefore, not a dementia registry in the same sense as SveDem and DanDem, and it cannot be used to generalize to the general dementia population in Norway. However, unlike SveDem and DanDem, NorCog collects extensive data from all parts of the assessment with detailed information about test results on cognition and neuropsychiatric symptoms, caregiver situation, medications, medical history, and somatic status including results from blood laboratory work-up and lumbar puncture. Few, if any, national registries have a similarly broad spectrum of variables as NorCog, allowing for exploration of the main domains of dementia and cognitive impairment. A number of people are referred to assessment because of subjective memory complaints or mild cognitive impairment but do not fulfil the criteria for dementia. By following these patients over time, we have a unique possibility to identify risk factors for the development of dementia. The opportunity to link data with medical records from later admissions to hospitals and nursing homes, as well as to national registries, makes it possible to investigate predictors of real-world outcomes that

are also highly relevant to decision makers. Moreover, the collection of biomaterials in a general research biobank can be used in research that aims to understand the aetiology of different dementia disorders and to explore fluid biomarkers for prediction, diagnosis, and disease progression.

In contrast to the restricted setting of a clinical trial, NorCog is a clinical registry collecting data as part of routine clinical practice and may, accordingly, be limited by lower data quality, lack of adjudication, and missing data. Data not missing at random introduce bias and confounding that complicate statistical analyses. Nevertheless, the fact that the clinical registries reflect populations that are representative of routine clinical practice is a strength, increasing generalizability and external validity. The broad inclusion criteria for NorCog make the sample representative for patients being referred for evaluation of cognitive symptoms in a specialist setting. However, there are differences in the patient population depending on the profile of the outpatient clinic. NorCog enrols patients from memory clinics and outpatient clinics in old-age psychiatry and geriatric medicine, but thus far, no neurological departments have joined the registry. The representativeness is, thereby, somewhat uncertain.

FUTURE PLANS

Originally, the finish date of NorCog was set to the year of 2029. However, the legal basis of NorCog was reformalized in 2021 according to the Norwegian Regulations relating to medical quality registries (FOR-2019-06-21-789), and the registry got approval to collect and keep data as long as is necessary to achieve the purpose of the registry. Thus, data collection in NorCog will continue in the coming years without a specific finish date. In the spring of 2022, the registry underwent major changes. Paper-based data collection was replaced with digital registration, and the number of variables collected were reduced. To ensure the quality of the assessment and data collection, the registry will continue to provide the participating clinics with validated screening and diagnostic tools in accordance with the recommendations of the Norwegian national guidelines on dementia. In the paper-based version of NorCog, the registry has provided, and collected data on, a fixed set of measures and scales, shown in Table 4. The new digital version of NorCog, starting in 2022, will allow for a more individualized assessment, to be able to include all groups of patients in NorCog regardless of linguistic and cultural background as well as degree and type of dementia. A core set of variables will be collected for each patient, but beyond this the clinicians may choose the screening tools that are most appropriate based on the background and symptoms of the individual patient. Therefore, the participating clinics will be provided with a selection of additional validated tools in line with national and international guidelines. All follow-up assessments will be registered in the digital platform. Future plans also involve expanding the registry to include patients from additional Norwegian specialist clinics as well as including patients from primary care centers. Moreover, patients that have reduced or lost their capacity to provide informed consent will be recruited based on proxy consent. The

registry will continue to serve as a combined quality and research registry with biomaterial collection for years to come.

COLLABORATION AND ACCESS TO DATA AND BIOMATERIAL

The use of data and biological material from NorCog is subject to ethical and legal regulations, including the General Data Protection Regulation, the Health Register Act, the Health Research Act, and the Register Regulations. The information and biomaterial collected in NorCog can be made available to researchers if access is permitted under these regulations. Applicants from outside Norway are advised to identify a Norwegian collaborator. Enquiries can be submitted to the corresponding author, Geir Selbæk. An application form in Norwegian and in English may be found at https://www.aldringoghelse.no/forskning/norkog. All research projects must be approved by the Regional Committees for Medical and Health Research Ethics in Norway and by the Steering committee for NorCog. Oslo University Hospital has the overall responsibility for the data, and the Norwegian National Centre for Ageing and Health is managing the registry.

ACKNOWLEDGEMENTS

The authors thank all patients and informants for providing information. We are grateful for the efforts done by the reporting outpatient clinics and the Steering committee for NorCog.

COMPETING INTERESTS

ABK was/is the principal investigator of three drug trials (ROCHE BN29553, Boehringer-Ingelheim 1346.23 and Novo Nordisk NN6535-4730). KP was/is rater in the ROCHE BN29553 and Novo Nordisk NN6535-4730 trials and IS was investigator in the Boehringer-Ingelheim 1346.23 trial.

FUNDING

NorCog is funded by the South-Eastern Norway Regional Health Authority and the Norwegian National Centre for Ageing and Health (grant number not applicable).

CONTRIBUTORS

ITM prepared the initial draft of the manuscript in collaboration with GS, KP, THT, SB, MNå and CST. ABK, AB, ARØ, POH, IS, ALL, AHR, DBS, MNa, JZS and BJ contributed with data resources. ARØ is also the user representative from The Norwegian Health Association. IDU and KE were responsible for the initial design and creation of the registry. All authors provided critical review of the manuscript and approved the final version.

REFERENCES

1. Strand BH, Knapskog AB, Persson K, et al. Survival and years of life lost in various aetiologies of dementia, mild cognitive impairment (MCI) and subjective cognitive decline (SCD) in Norway. *PloS one* 2018;13(9):e0204436. doi: 10.1371/journal.pone.0204436 [published Online First: 2018/09/22]

2. Norwegian Directorate of Health. The Norwegian national guideline on dementia, IS-2658: Helsedirektoratet; 2017 [updated 2020 Jan 3; cited 20 Jan 15]. Available from: https://www.helsedirektoratet.no/retningslinjer/demens accessed 2017 Aug 16.
3. Gallacher J, de Reydet de Vulpillieres F, Amzal B, et al. Challenges for Optimizing Real-World Evidence in Alzheimer's Disease: The ROADMAP Project. *Journal of Alzheimer's disease : JAD* 2019;67(2):495-501. doi: 10.3233/jad-180370 [published Online First: 2018/12/26]
4. Makady A, de Boer A, Hillege H, et al. What Is Real-World Data? A Review of Definitions Based on Literature and Stakeholder Interviews. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2017;20(7):858-65. doi: 10.1016/j.jval.2017.03.008 [published Online First: 2017/07/18]
5. Garrison LP, Jr., Neumann PJ, Erickson P, et al. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2007;10(5):326-35. doi: 10.1111/j.1524-4733.2007.00186.x [published Online First: 2007/09/25]
6. Braekhus A, Ulstein I, Wyller TB, et al. The Memory Clinic--outpatient assessment when dementia is suspected. *Tidsskr Nor Laegeforen* 2011;131(22):2254-7. doi: 10.4045/tidsskr.11.0786 [published Online First: 2011/11/17]
7. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. *The British journal of psychiatry : the journal of mental science* 1982;140:566-72. doi: 10.1192/bjp.140.6.566 [published Online First: 1982/06/01]
8. Edwin TH, Henjum K, Nilsson LNG, et al. A high cerebrospinal fluid soluble TREM2 level is associated with slow clinical progression of Alzheimer's disease. *Alzheimer's & dementia (Amsterdam, Netherlands)* 2020;12(1):e12128. doi: 10.1002/dad2.12128 [published Online First: 2020/12/15]
9. Edwin TH, Strand BH, Persson K, et al. Trajectories and risk factors of dementia progression: a memory clinic cohort followed up to 3 years from diagnosis. *International psychogeriatrics* 2020:1-11. doi: 10.1017/s1041610220003270 [published Online First: 2020/11/21]
10. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th edn. Washington, D.C: American Psychiatric Publishing 2013.
11. Mjørud M, Selbæk G, Bjertness E, et al. Time from dementia diagnosis to nursing-home admission and death among persons with dementia: A multistate survival analysis. *PloS one* 2020;15(12):e0243513. doi: 10.1371/journal.pone.0243513 [published Online First: 2020/12/05]
12. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic criteria for research. Geneva, 1993.
13. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of internal medicine* 2004;256(3):240-6. doi: 10.1111/j.1365-2796.2004.01380.x [published Online First: 2004/08/25]
14. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.

Alzheimer's & dementia : the journal of the Alzheimer's Association 2011;7(3):263-9. doi: 10.1016/j.jalz.2011.03.005 [published Online First: 2011/04/26]

15. Sachdev P, Kalaria R, O'Brien J, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer disease and associated disorders* 2014;28(3):206-18. doi: 10.1097/wad.0000000000000034 [published Online First: 2014/03/19]
16. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* 2017;89(1):88-100. doi: 10.1212/wnl.0000000000004058 [published Online First: 2017/06/09]
17. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society* 2007;22(12):1689-707; quiz 837. doi: 10.1002/mds.21507 [published Online First: 2007/06/02]
18. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain : a journal of neurology* 2011;134(Pt 9):2456-77. doi: 10.1093/brain/awr179 [published Online First: 2011/08/04]
19. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology* 2011;76(11):1006-14. doi: 10.1212/WNL.0b013e31821103e6 [published Online First: 2011/02/18]
20. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 2011;7(3):270-9. doi: 10.1016/j.jalz.2011.03.008 [published Online First: 2011/04/26]
21. Knapskog AB, Barca ML, Engedal K. A comparison of the validity of the Cornell Scale and the MADRS in detecting depression among memory clinic patients. *Dementia and geriatric cognitive disorders* 2011;32(4):287-94. doi: 10.1159/000334983 [published Online First: 2012/01/21]
22. Persson K, Braekhus A, Selbaek G, et al. Burden of Care and Patient's Neuropsychiatric Symptoms Influence Carer's Evaluation of Cognitive Impairment. *Dementia and geriatric cognitive disorders* 2015;40(5-6):256-67. doi: 10.1159/000437298 [published Online First: 2015/08/26]
23. Svendsboe E, Terum T, Testad I, et al. Caregiver burden in family carers of people with dementia with Lewy bodies and Alzheimer's disease. *International journal of geriatric psychiatry* 2016;31(9):1075-83. doi: 10.1002/gps.4433 [published Online First: 2016/01/15]
24. Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *The Lancet Neurology* 2016;15(7):673-84. doi: 10.1016/s1474-4422(16)00070-3 [published Online First: 2016/04/14]
25. Knapskog AB, Engedal K, Braekhus A. Performance of Cerebrospinal Fluid Biomarkers of Alzheimer Disease in a Memory Clinic in Norway. *Alzheimer disease and associated disorders* 2016;30(1):8-14. doi: 10.1097/wad.0000000000000126 [published Online First: 2015/12/03]
26. Knapskog AB, Braekhus A, Engedal K. The Effect of Changing the Amyloid beta42 Cut-off of Cerebrospinal Fluid Biomarkers on Alzheimer Disease Diagnosis in a Memory Clinic

Population in Norway. *Alzheimer disease and associated disorders* 2019;33(1):72-74. doi: 10.1097/wad.0000000000000268 [published Online First: 2018/08/15]

27. Persson K, Selbaek G, Braekhus A, et al. Fully automated structural MRI of the brain in clinical dementia workup. *Acta radiologica (Stockholm, Sweden : 1987)* 2017;58(6):740-47. doi: 10.1177/0284185116669874 [published Online First: 2016/10/01]
28. Jonsson T, Stefansson H, Steinberg S, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. *The New England journal of medicine* 2013;368(2):107-16. doi: 10.1056/NEJMoa1211103 [published Online First: 2012/11/16]
29. Steinberg S, Stefansson H, Jonsson T, et al. Loss-of-function variants in ABCA7 confer risk of Alzheimer's disease. *Nature genetics* 2015;47(5):445-7. doi: 10.1038/ng.3246 [published Online First: 2015/03/26]
30. Witoelar A, Rongve A, Almdahl IS, et al. Meta-analysis of Alzheimer's disease on 9,751 samples from Norway and IGAP study identifies four risk loci. *Scientific reports* 2018;8(1):18088. doi: 10.1038/s41598-018-36429-6 [published Online First: 2018/12/29]
31. Jansen IE, Savage JE, Watanabe K, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nature genetics* 2019;51(3):404-13. doi: 10.1038/s41588-018-0311-9 [published Online First: 2019/01/09]
32. Michelet M, Lund A, Strand BH, et al. Characteristics of patients assessed for cognitive decline in primary healthcare, compared to patients assessed in specialist healthcare. *Scand J Prim Health Care* 2020;38(2):107-16. doi: 10.1080/02813432.2020.1753334 [published Online First: 2020/05/05]
33. Krysinska K, Sachdev PS, Breitner J, et al. Dementia registries around the globe and their applications: A systematic review. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 2017;13(9):1031-47. doi: 10.1016/j.jalz.2017.04.005 [published Online First: 2017/06/04]
34. Religa D, Fereshtehnejad SM, Cermakova P, et al. SveDem, the Swedish Dementia Registry - a tool for improving the quality of diagnostics, treatment and care of dementia patients in clinical practice. *PloS one* 2015;10(2):e0116538. doi: 10.1371/journal.pone.0116538 [published Online First: 2015/02/20]
35. Johannsen P, Jorgensen K, Korner A, et al. Development of a dementia assessment quality database. *Aging & mental health* 2011;15(1):40-6. doi: 10.1080/13607863.2010.508769 [published Online First: 2011/01/29]

Figure 1. Number of outpatient clinics and number of included patients at baseline in NorCog per year during 2009–2021 (N=18 120). In December 2021, 45 clinics from all four regional health authorities in Norway participated

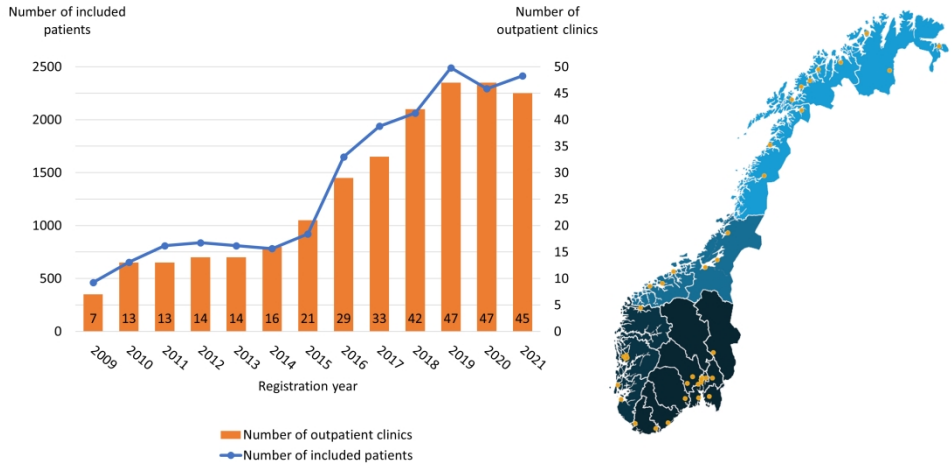

Figure 1. Number of outpatient clinics and number of included patients at baseline in NorCog per year during 2009–2021 (N=18 120). In December 2021, 45 clinics from all four regional health authorities in Norway participated

338x190mm (300 x 300 DPI)

BMJ Open

Cohort Profile: The Norwegian Registry of Persons Assessed for Cognitive Symptoms (NorCog) – a national research and quality registry with a biomaterial collection

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058810.R2
Article Type:	Cohort profile
Date Submitted by the Author:	17-Aug-2022

Complete List of Authors:	Medbøen, Ingrid; Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital Persson, Karin; Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital Nåvik, Marit; Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust; Department of Psychiatry, Telemark Hospital Totland, Torunn; Department of Chronic Diseases and Ageing, Norwegian Institute of Public Health Bergh, Sverre; Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust; Research centre for Age-related Functional Decline and Disease, Innlandet Hospital trust Treviño, Cathrine; Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital Ulstein, Ingun; Department of Geriatric Medicine, Oslo University Hospital Engedal , Knut ; Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital Knapskog, Anne-Brita; Department of Geriatric Medicine, Oslo University Hospital Brækhus, Anne; Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital Øksengård, Anne; The Norwegian Health Association; Bærum Hospital, Vestre Viken Hospital Trust Horndalsveen, Peter; Department of Old Age Psychiatry, Innlandet Hospital trust Saltvedt, Ingvild; Department of Geriatrics, St. Olav's Hospital, Trondheim University Hospital; Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology Lyngroth, Anne; Department of Geriatrics, Sorlandet Hospital Arendal Ranhoff, Anette ; Department of Medicine, Diakonhjemmet Hospital; Department of Clinical Science, University of Bergen, Skrettingland, Dagny; Department of Geriatrics, Stavanger University Hospital Naik, Mala; Department of Clinical Science, University of Bergen, ;

	Department of Medicine, Haraldsplass Deaconess Hospital Soares, Jelena; Medical Department, Section of Geriatrics, Lovisenberg Diaconal Hospital Johnsen, Bente; Department of Geriatric Medicine, University Hospital of North Norway Selbaek, Geir; Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust; Department of Geriatric Medicine, Oslo University Hospital
Primary Subject Heading:	Diagnostics
Secondary Subject Heading:	Geriatric medicine, Mental health, Neurology
Keywords:	Dementia < NEUROLOGY, Delirium & cognitive disorders < PSYCHIATRY, GERIATRIC MEDICINE, Old age psychiatry < PSYCHIATRY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Cohort Profile: The Norwegian Registry of Persons Assessed for Cognitive Symptoms (NorCog) – a national research and quality registry with a biomaterial collection

Ingrid Tøndel Medbøen,[1,2] Karin Persson,[1,2] Marit Nåvik,[1,3] Torunn H. Totland,[4] Sverre Bergh,[1,5] Cathrine Selnes Treviño[1,2] Ingun Dina Ulstein,[2] Knut Engedal,[1,2] Anne-Brita Knapskog,[2] Anne Brækhus,[1,2] Anne Rita Øksengård,[6,7] Peter O Horndalsveen,[8] Ingvild Saltvedt,[9,10] Anne Liv Lyngroth,[11] Anette Hylen Ranhoff,[12,13] Dagny Bekkeheien Skrettingland,[14] Mala Naik,[13,15] Jelena Zugic Soares,[16] Bente Johnsen,[17] Geir Selbæk,[1,2]*

[1]The Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust, Tønsberg, Norway, [2]Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway, [3]Department of Psychiatry, Telemark Hospital, Skien, Norway, [4]Department of Chronic Diseases and Ageing, Norwegian Institute of Public Health, Oslo, Norway, [5]Research centre for Age-related Functional Decline and Disease, Innlandet Hospital trust, Ottestad, Norway, [6]The Norwegian Health Association, Oslo, Norway, [7]Bærum Hospital, Vestre Viken Hospital Trust, Drammen, Norway, [8]Department of Old Age Psychiatry, Innlandet Hospital trust, Ottestad, Norway, [9]Department of Geriatrics, St. Olav's Hospital, Trondheim University Hospital, Trondheim, Norway, [10]Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway, [11]Department of Geriatrics, Sorlandet Hospital Arendal, Arendal, Norway, [12]Department of Medicine, Diakonhjemmet Hospital, Oslo, Norway, [13]Department of Clinical Science, University of Bergen, Bergen, Norway, [14]Department of Geriatrics, Stavanger University Hospital, Stavanger, Norway, [15]Department of Medicine, Haraldsplass Deaconess Hospital, Bergen, Norway, [16]Medical Department, Section of Geriatrics, Lovisenberg Diaconal Hospital, Oslo, Norway, [17]Department of Geriatric Medicine, University Hospital of North Norway, Tromsø, Norway.

*Corresponding author. Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust, Pb 2136, 3103 Tønsberg, Norway. Email: geir.selbaek@aldringoghelse.no

Word count: 4193

ABSTRACT

Purpose: NorCog was established to harmonize and improve the quality of diagnostic practice across clinics assessing persons with cognitive symptoms in Norwegian specialist health care units and to establish a large research cohort with extensive clinical data.

Participants: The registry recruits patients who are referred for assessment of cognitive symptoms and suspected dementia at outpatient clinics in Norwegian specialist health care units. In total, 18 120 patients have been included in NorCog during the period 2009–2021. The average age at inclusion was 73.7 years. About half of the patients (46%) were diagnosed with dementia at the baseline assessment, 35% with mild cognitive impairment, 13% with no or subjective cognitive impairment; 7% received other specified diagnoses, such as mood disorders.

Findings to date: All patients have a detailed baseline characterization involving lifestyle and demographic variables; activities of daily living; caregiver situation; medical history; medication; psychiatric, physical and neurological examination; neurocognitive testing; blood laboratory work-up; and structural or functional brain imaging. Diagnoses are set according to standardized diagnostic criteria. The research biobank stores DNA and blood samples from 4000 patients as well as cerebrospinal fluid from 800 patients. Data from NorCog have been used in a wide range of research projects evaluating and validating dementia-related assessment tools, identifying patient characteristics, symptoms, functioning and needs as well as caregiver burden and requirement of available resources.

Future plans: The finish date of NorCog was originally in 2029. In 2021, the registry's legal basis was reformalized and NorCog got approval to collect and keep data for as long as is necessary to achieve the purpose of the registry. In 2022, the registry underwent major changes. Paper-based data collection was replaced with digital registration, and the number of variables collected were reduced. Future plans involve expanding the registry to include patients from primary care centers.

Strengths and limitations of this study

- A key strength of NorCog is the large sample size with extensive clinical data combined with a research biobank. Few, if any, national registries collect a similarly broad spectrum of variables as NorCog, allowing for exploration of the main domains of dementia and cognitive impairment.
- Patients consent to linkage of data with medical records from later admissions to hospitals and nursing homes, as well as to national health registries, making it possible to investigate predictors of real-world outcomes.
- NorCog only recruits patients who are referred for assessment in a specialist setting and cannot be used to generalize to the general dementia population in Norway.
- In contrast to the restricted setting of a clinical trial, NorCog is a clinical registry collecting data as part of routine clinical practice and may, accordingly, be limited by lower data quality, lack of adjudication, and missing data.

INTRODUCTION

Cognitive symptoms, such as problems with memory, reasoning, and language skills, as well as emotional and behavioural changes, may signal pathological changes in the brain that can cause dementia. Dementia is the deterioration of cognitive functions to an extent that impedes a person's ability to perform functions of daily living and, ultimately, resulting in premature death.[1]

In Norway, the municipalities are responsible for primary care, including the assessment of cognitive impairment in older patients with uncomplicated dementia symptoms. In more complicated cases, the recommendation of the Norwegian national guideline on dementia is to refer patients to specialist health care units for an extended assessment.[2] In Norway, specialist care is administered by four regional health authorities. According to the national guideline on dementia, cases that are appropriate to refer to specialist health care units may include younger patients with cognitive decline, patients with coexisting psychiatric, neurological, or somatic problems, atypical dementia disorders, and patient groups with complex disorders.

Recently, research including real-world outcome data has been requested.[3] Although consensus on the definition of real-world data is lacking, the term is most often defined as data used for coverage and payment decisions collected outside the constraints of conventional randomized controlled trials (RCTs).[4] Observational registries represent one type of sources for real-world data, typically including a larger and more diverse group of patients than generally studied in RCTs and, thereby, better reflecting populations that are representative of routine clinical practice.[5]

The purpose of this Cohort Profile is to describe the background, methods, baseline data and future plans of the Norwegian Registry of Persons Assessed for Cognitive Symptoms (NorCog). NorCog was established in 2008 with two main aims:

1. To harmonize and improve the quality of diagnostic practice across outpatient clinics assessing persons with cognitive symptoms in specialist care units.
2. To establish a large research cohort with extensive clinical data and provide an opportunity to link baseline data to important real-world outcomes in regional and national registries.

Oslo University Hospital has the overall responsibility for the registry data, and the Norwegian National Centre for Ageing and Health is managing the registry.

COHORT DESCRIPTION

NorCog has an observational design and recruits patients who are referred for assessment of cognitive symptoms and suspected dementia at outpatient clinics in Norwegian specialist

health care units. Patients are encouraged to bring their next of kin or another person who knows them well, referred to hereafter as the informant.

NorCog was originally established as a regional quality and research registry in 2008. During the first year of data collection, in 2009, seven outpatient clinics from the South-Eastern Norway Regional Health Authority participated. Since then, outpatient clinics from all four regional health authorities in Norway have joined, and the registry received status as a national quality registry in 2013. Most of the clinics are referred to as memory clinics or outpatient clinics in old-age psychiatric and geriatric units.[6] There is no clear consensus for which type of outpatient clinics that should be assessing dementia in Norway and there are variations between regions. To be eligible for data collection in NorCog, the outpatient clinics need to have a specialist as part of their interdisciplinary staff. Some clinics have had staffing problems and have stopped or paused data collection in NorCog until specialists are rehired. In December 2021, 45 out of 49 eligible outpatient clinics (memory clinics or outpatient clinics in old-age psychiatric and geriatric units) participated with data collection in NorCog.

The number of included patients per year has increased in line with the recruitment of new clinics, from 462 patients in 2009 to 2414 in 2021 (Figure 1). Because of the COVID-19 pandemic, the number of included patients in 2020 (N=2293) was somewhat lower than could be expected under normal circumstances. In total, 18 120 patients have been included in NorCog during the period 2009–2021. Table 1 shows some of the demographic, clinical, and social characteristics of the included patients at baseline. The average age at inclusion was 73.7 years with an age range of 26 to 99 years. Reports from 13 615 informants showed that memory problems were, by far, the most frequently reported first symptoms of the patient, as stated by 63% of the informants.

Table 1. A selection of demographic, social, and clinical characteristics of patients included in the NorCog cohort at baseline. Numbers of patients with missing data are shown in the far right column.

	Patients included in NorCog during 2009–2021					*Missing data total cohort, n (%)*
	Total cohort	NCI/SCI	MCI	Dementia	Other diagnoses	
n (%)	18 120 (100)	2258 (12.5)	6307 (34.8)	8368 (46.2)	1187 (6.6)	
Age (years), mean (SD)	73.7 (9.9)	67.3 (11.7)	73.1 (9.7)	76.3 (8.2)	70.5 (10.9)	*0*
Sex (female), n (%)	9443 (52.1)	1167 (51.7)	3097 (49.1)	4599 (55.0)	580 (48.9)	*0*
Education (years), mean (SD)	11.3 (3.8)	12.5 (3.9)	11.5 (3.8)	10.8 (3.6)	11.3 (3.9)	*1521 (8.4)*
Married/cohabiting, n (%)	10 709 (61.6)	1402 (65.0)	3800 (62.7)	4812 (59.9)	695 (61.2)	*729 (4.0)*
Living alone, n (%)	6589 (36.4)	737 (32.6)	2284 (36.2)	3135 (37.5)	433 (36.5)	*687 (3.8)*
Public care, n (%)	5639 (32.1)	388 (18.1)	1626 (26.6)	3260 (40.0)	356 (31.6)	*597 (3.3)*
MMSE score, mean (SD)	23.6 (4.6)	27.1 (3.3)	25.2 (3.4)	21.0 (4.4)	26.2 (3.8)	*478 (2.6)*
Information from informant obtained, n (%)	17234 (95.1)	1983 (87.8)	5907 (93.7)	8275 (98.9)	1069 (90.1)	

Abbreviations: MCI=mild cognitive impairment, MMSE=Mini-Mental State Examination, NCI=no cognitive impairment, SCI=subjective cognitive impairment, SD=Standard Deviation

During 2009–2021, about half of the patients (46%) were diagnosed with dementia at the baseline assessment, 35% with mild cognitive impairment (MCI), 13% with no or subjective cognitive impairment (NCI/SCI), and 7% received other specified diagnoses such as mood disorders. The diagnostic work-up and criteria will be explained in a separate paragraph below. Table 2 shows the frequency of the different etiological dementia diagnoses and a selection of characteristics by dementia diagnoses. The frequency of dementia subtypes is similar to the distributions in the Swedish Dementia Registry (SveDem) and the Danish Dementia Registry (DanDem),[7] although these two registries recruit patients from both specialist units and primary care centres. Since NorCog only recruits from specialist units, one might have expected a higher share of the less frequent dementia subtypes such as dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD). The distribution of dementia subtypes in NorCog is also similar to the findings in a recent Norwegian population-based prevalence study.[8] The subtype of unspecified dementia is often used as a pending diagnosis when the etiological diagnosis is not yet confirmed at the time of baseline registration. It is possible that rarer or more complicated dementia subtypes are overrepresented in this diagnostic group. Better registry follow-up data in the future may reveal the etiological diagnoses in the unspecified dementia group.

Table 2. Demographic characteristics by etiological dementia diagnoses registered in NorCog at baseline during 2009-2021.

	AD dementia	Mixed AD and VaD	VaD	DLB	PDD	FTD	Unspecified dementia	Other dementia types
n (%)	4481 (53.5)	1047 (12.5)	925 (11.1)	343 (4.1)	199 (2.4)	131 (1.6)	1154 (13.8)	88 (1.1)
Age (years), mean (SD)	75.9 (8.3)	79.0 (6.7)	78.4 (7.2)	74.3 (8.2)	75.0 (6.5)	66.8 (10.9)	75.9 (8.1)	70.6 (9.1)
Sex (female), n (%)	2750 (61.4)	552 (52.7)	411 (44.4)	140 (40.8)	70 (35.2)	61 (46.6)	574 (49.7)	40 (45.5)
Education (years), mean (SD)	10.9 (3.5)	10.6 (4.1)	10.3 (3.4)	11.3 (3.6)	11.4 (3.8)	12.3 (3.6)	10.5 (3.5)	11.5 (3.3)
Married/ cohabiting, n (%)	2606 (60.3)	569 (57.1)	505 (56.7)	223 (67.4)	151 (77.8)	97 (77.6)	610 (55.7)	51 (61.4)
Living alone, n (%)	1676 (38.8)	428 (41.9)	371 (41.5)	98 (29.4)	42 (22.0)	30 (23.8)	461 (41.4)	28 (32.9)
Public care, n (%)	1429 (32.7)	516 (50.4)	510 (56.5)	123 (37.3)	96 (50.0)	32 (25.4)	517 (46.0)	36 (43.4)
MMSE score, mean (SD)	20.8 (4.4)	20.7 (4.2)	21.4 (4.3)	21.5 (4.5)	21.7 (4.3)	24.1 (3.7)	20.9 (4.6)	23.7 (4.0)

Abbreviations: AD=Alzheimer's disease, DLB=Dementia with Lewy bodies, FTD=Frontotemporal dementia, MMSE=Mini-Mental State Examination, PDD=Parkinson's disease dementia, SD=Standard Deviation, VaD=Vascular dementia

Dementia severity was assessed with the Clinical Dementia Rating Scale (CDR), a global rating scale covering six domains of cognitive and functional performance.[9] The CDR is scored according to an algorithm that gives precedence to the memory domain, with a total score of 0 (no cognitive impairment), 0.5 (questionable dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia). In NorCog, 81% of patients who were diagnosed with dementia at baseline during 2009–2021 had a score of 0.5 or 1, corresponding to a very mild or mild stage of dementia. Furthermore, 17% had a score of 2 (moderate dementia) and 2% a score of 3 (severe dementia).

Informed consent

Participation in NorCog is voluntary and enrolment require written informed consent. To give informed consent, a person must have the ability to fully understand what the participation in the registry means. During 2009-2021, NorCog has only recruited patients that have the capacity to give informed consent. However, from January 2022, patients who are unable, or have reduced capacity, to provide informed consent can also be included in NorCog based on proxy consent.

Patients not included in NorCog

The number of non-included patients during 2009-2015 has not been registered. Beginning in 2016, all participating clinics have recorded the age and sex of patients who were not included in NorCog. During 2016-2021, a total of 613 patients lacked capacity to give consent and were, therefore, not eligible for inclusion in NorCog. The total number of patients eligible for inclusion at the participating clinics during 2016-2021 was 17 597, whereof 73% of patients (n=12 845) were included and 27% (n=4752) were not included. The average age and the proportion of females were higher among the non-included patients (76 years and 55% females) compared to the included patients (74 years and 51% females). Among the patients that were not included, some were not asked to join the registry due to capacity considerations at the clinic (22%) or because the clinician perceived that the situation/condition of the patient did not allow it (31%). In other cases, patients were asked to participate, but declined (21%). In 26% of cases, the cause of non-inclusion was unknown, or another test battery was used due to language issues.

Follow-up data

No predetermined follow-up schedule has been established for the registry. However, a registration form for assessment at follow-up according to clinical indication was implemented in 2015 (Table 3). Thus far, the clinics are encouraged but not obliged to deliver follow-up data to the registry. In several sub-studies, selected patients have been invited to receive additional examinations or follow-ups in compliance with specific research protocols. In 2017, a large research project began collecting follow-up data from patients in the registry. The project is called “Trajectories and risk factors of dementia – TRAIL-DEM” and involves linking data from the patients in NorCog with medical records in hospitals and

nursing homes as well as national health registries (Table 3). The project investigates trajectories from dementia onset until nursing home admission and death, providing a unique opportunity to investigate dementia aetiology and progression.[1, 10-12] TRAIL-DEM will provide an extensive database that will form the basis for future projects.

Table 3. Overview of the samples/phases, measurements, biomaterial collection and linkages in the registry

Sample/Phase	Measurements	Biomaterial Collection/ Linkage
Baseline assessment NorCog 2009–2021 N=18 120	A comprehensive clinical assessment including lifestyle and demographic variables; activities of daily living; caregiver situation; medical history; current medication; psychiatric, physical, and neurological examination; neurocognitive testing; blood laboratory work-up; and routine MRI. When indicated: lumbar puncture for the measurement of Aβ and tau proteins in cerebrospinal fluid (CSF) and/or functional brain imaging.	EDTA-whole blood, n=4342 Serum, n=4509 Plasma, n=4293 CSF, n=800 PAXgene RNA, n=3544 DNA, n=3714
Follow-up NorCog patients by clinical indication 2015–2021 N=3656*	A shorter set of registration forms including living situation, care resource use, sum score on neurocognitive tests, Clinical Dementia Rating scale, NPI-Q, blood pressure and pulse, clinical evaluation of change from baseline, clinical diagnosis, and recommended follow-up.	
The TRAIL-DEM study conducted during 2017-2022 Follow-up of patients in NorCog included during 2009–2016. New linkage in 2022 for patients included during 2017–2021.	Baseline data from NorCog and follow-up data from medical records of NorCog patients have been merged with clinical data from the NPR (any hospital admittance during lifetime) prior to and after the baseline investigation. Furthermore, patients from NorCog have been traced by the CoDR to examine time and cause of death and by the NPoR to learn which patients have been admitted to nursing homes. Clinical data on level of functioning, level of dementia, neuropsychiatric symptoms and drug use have been retrieved from nursing home records or from interviews with nursing home staff, by visiting the nursing homes or by phone.	Linkage to: Norwegian Patient Registry (NPR) Cause of Death Registry (CoDR) National Population Registry (NPoR) Norwegian Prescription Database (NorPD)

*Number of patients with data from at least one registered follow-up using the short registration form

Standardized dementia assessment

All patients have a detailed baseline characterization. The baseline data were collected using a standardized dementia assessment protocol developed in an interdisciplinary collaboration among geriatricians, psychiatrists, neurologists, other clinicians, and researchers. The assessment protocol is designed as a paper-based case report form that can be optically scanned and includes questionnaires, a battery of tests, and forms on which relevant measures can be added. The scales are in accordance with the recommendations of the Norwegian national guidelines on dementia.[2] Usually, the patient is followed by the person who is defined as the closest proxy and serves as the key informant. As a rule, the patient and informant are interviewed separately. Some of the variables, depending on the level of

cognitive impairment, are collected from both the patient and the informant. If an informant is not able to accompany the patient to the assessment, information is usually collected by phone interviews.

The interviews include demographic and lifestyle variables, measures of care resource use, physical and social activities, activities of daily living (ADL), caregiver distress, medical history, current medications, and neuropsychiatric symptoms. Further examination of the patient includes an evaluation and testing of cognitive function, a psychiatric evaluation with an emphasis on comorbid depressive disorder, and an assessment of somatic status including a physical and neurological examination, blood laboratory work-up, and structural brain imaging using CT or magnetic resonance imaging (MRI). A spinal fluid examination and/or functional brain imaging such as positron emission tomography (PET) are performed in sub-groups, according to clinical indication. See Table 4 for a summary of the measures and scales registered in NorCog at baseline. The assessment protocol is a valuable tool for the participating clinics. To optimize and update the protocol, revisions have been made over the years. The revision process is comprehensive and carefully considers variables that should be added, modified, or removed. All revisions must be approved by the Steering Committee for NorCog.

Table 4. Measures and scales registered in NorCog at baseline and source of information

Main test domain	Measures and scales registered in NorCog	Source*
Lifestyle/ Background		
Demographic	Age, gender, education, occupational activity, marital status, children, living condition, informant (yes/no), relation to informant	I, P
Care resource use	Care provided by the municipality (hours per week) Private or family care (hours per week)	I, P
Activities	Physical activity (hours per week and intensity) Social and cultural activity (hours per week)	I, P
Stimulant use	Tobacco, alcohol, other substances	I, P
Safety	Driving, access to weapons, falls	I, P
Nutrition & natural functions	Involuntary weight loss? Unsatisfactory food intake? Incontinence?	I, P
Activities of Daily Living (ADL)		
Personal ADL	Physical Self-Maintenance Scale (PSMS)	I
Instrumental ADL	The Lawton Instrumental Activities of Daily Living Scale (IADL)	I
Patient-Reported Outcome Measures (PROM) and caregiver situation		
Caregiver distress	Relatives' Stress Scale (RSS)	I
Patient experience	Do you think your memory is worse than before? If yes, does this worry you?	P
Fatigue	Do you mostly feel strong and rested or tired?	P
Medical history		
Present symptoms	Onset, course, type of symptoms Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)	I, P I
Family history	Dementia, other disorders of the central nervous system (CNS)	I, P
Present or previous physical and/or psychiatric disease	Cerebrovascular, other CNS-disorders, cancer, arthritis, cardiovascular, endocrine, kidney, Chronic Obstructive Pulmonary Disease, psychiatric disease	I, P

Medication		
Current medication	ATC code and defined daily dose of regular medication	I, P
Neuropsychiatric symptoms (NPS)		
Overall NPS	Neuropsychiatric Inventory Questionnaire (NPI-Q)	I
Depression	Cornell Scale for Depression in Dementia (CSDD)	I
	Montgomery and Aasberg Depression Rating Scale (MADRS)	P
Neurocognitive tests		
Global cognition	Mini-Mental State Examination (MMSE)	P
	Clock Drawing Test (CDT)	P
	Clinical Dementia Rating (CDR)	C
Memory	Ten-word recall test	P
Attention	Trail Making Test A and B	P
Fluency	Controlled Oral Word Association Test (COWA)	P
Constructional praxis	CERAD figure copying (including recall)	P
Word retrieval	The Boston Naming Test	P
Insight	Reed Scale for evaluation of anosognosia (lack of insight)	C
Somatic status		
Physical and neurological examination	Blood pressure, pulse, weight, height, gait speed, chair stand, balance test, vision, hearing, auscultation of neck, central facial paresis, plantar reflex, gait, rigidity, spasticity, hypokinesia, tremor, Romberg's test	D
Blood test results	Hemoglobin, thrombocytes, CRP, s-cholesterol, Na, K, Ca, S-folate, homocysteine, vitamin B12, TSH, T4, ALP, SR, ALAT, G-GT, albumin, creatinine, vitamin D, HbA1C	D
CSF test results	Beta-amyloid, total tau, phosphorylated tau	D
Brain imaging	Structural and functional (yes/no): CT, MRI, PET, DAT, SPECT, EEG	D
Clinical evaluation		
Baseline diagnosis	ICD-10 codes/ SCI, MCI, dementia (AD, VaD, FTD, DLB, PDD, unspecified), other	C
Recommended follow-up	Specialist health care, primary health care, support for caregivers	C

*I=informant, P=patient, D=direct test, C=clinical evaluation
Abbreviations: AD=Alzheimer's disease, ALAT=alanine aminotransferase, ALP=alkaline phosphatase, ATC=Anatomical therapeutic chemical, Ca=calcium, CRP=C-reactive protein, CSF=cerebrospinal fluid, CT=computed tomography, DAT=dopamine transporter, DLB = dementia with Lewy bodies, EEG=electroencephalogram, FTD = frontotemporal dementia, G-GT=gamma-glutamyl transferase, HbA1C= hemoglobin A1c, K=potassium, MCI=mild cognitive impairment, MRI=magnetic resonance imaging, Na=sodium, PDD = Parkinson's disease dementia, PET=positron emission tomography, SCI=subjective cognitive impairment, SPECT=single photon emission computerized tomography, SR=sedimentation rate, T4=thyroxine, TSH=thyroid stimulating hormone, VaD=vascular dementia

Diagnostic work-up and criteria

The diagnostic workups are conducted by specialists (e.g., geriatricians, psychiatrists, neurologists or psychologists) at the outpatient clinics. Diagnoses are discussed in interdisciplinary consensus meetings and are based on all available data from the assessment, including biological markers such as imaging, blood tests and cerebrospinal fluid (CSF) biomarkers. The specialists at the outpatient clinics conclude on a diagnosis according to standardized diagnostic criteria. ICD-10 is the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD), a medical classification list by the World Health Organization. In Norway, ICD-10 is established in clinical practice.
The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is widely used in clinical practice in the US and internationally, wherein the terms mild neurocognitive

disorder and major neurocognitive disorder have largely supplanted the term dementia.[13] DSM-5 is not widely used in Norwegian clinical practice, but ICD-11, which is more similar to DSM-5 than ICD-10, will be implemented in the near future. Clinical diagnoses in NorCog are registered according to the ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic criteria for research.[14] The clinicians also draw a conclusion on one of the following categories for each patient: dementia (ICD-10), MCI according to the Winblad criteria,[15] SCI defined as a subjective experience of cognitive problems in the absence of objectively measured cognitive deficits, or the category "other" for patients who do not fulfil the criteria for the previous categories. If dementia is present, an aetiological diagnosis according to ICD-10 is registered in NorCog.

Furthermore, the specialists at the outpatient clinics are encouraged, but not obliged, to make a more specific sub-classification according to a number of research diagnostic criteria. Here, the NIA/AA criteria are used for Alzheimer's disease (AD),[16] the Sachdev/VASCOG for vascular dementia (VaD),[17] the McKeith criteria for DLB,[18] the Emre criteria for Parkinson's disease dementia (PDD),[19] the Rascovsky criteria for FTD behavioural variant,[20] and the Gorno-Tempini criteria for the language variants of FTD.[21] In addition, the NIA/AA criteria are used for the subclassification of MCI.[22] Since the specialists at the outpatient clinics are not obliged to register diagnoses according to research criteria other than ICD-10, research diagnoses are determined retrospectively in some research projects.

Biomaterial collection

A subsample of the participating clinics collects blood and CSF for a general research biobank for NorCog. Blood samples include serum, ethylenediaminetetraacetic acid (EDTA) plasma, EDTA whole blood, as well as whole blood in PAXgene RNA tubes. Genomic DNA has been isolated from EDTA whole blood. The samples are collected, processed, and temporarily stored at the respective units according to a standard operating protocol before shipment to the central biobank for NorCog in Oslo. The central research biobank for NorCog currently stores DNA and blood samples from over 4000 patients as well as CSF from 800 patients. The samples have been stored for up to 12 years at -80˚C. Samples are collected once, at baseline, but follow-up projects have collected follow-up samples from sub-groups. Approximately 400-500 patients are recruited to the biobank yearly, and collection is ongoing.

Quality indicators and patient-reported measures

As a national quality registry, a principal aim of NorCog is to contribute to better quality of, and reduce unwarranted variation in, diagnostic practice in the specialist health services in Norway. Indicators to evaluate the quality of the dementia assessments across different hospitals were developed in 2017 and are reported annually in a national, publicly available report (written in Norwegian and can be found at www.kvalitetsregistre.no). Moreover,

patient-reported outcome measures (PROM) are registered in NorCog, and patient-reported experience measures (PREM) will be implemented during 2022.

Patient and public involvement

Patient involvement is essential to ensure that NorCog is relevant to the population it will impact. Therefore, it is stipulated in the articles of association for NorCog that users shall be represented in the registry's Steering Committee. The user representation is attended by The Norwegian Health Association, a voluntary, humanitarian organization promoting the interests of people with dementia and their carers. The members of the Steering Committee further include clinicians and managers from all health regions in Norway with backgrounds from memory clinics or outpatient clinics in old-age psychiatric and geriatric units, of which many have research competence. Furthermore, a patient advisory group, consisting of people with dementia and/or their proxies, has been involved in several processes, such as developing and pilot testing a PREM questionnaire, evaluating documents and information sheets, as well as involvement in strategies for presenting studies based on NorCog data.

FINDINGS TO DATE

Data from NorCog have been used in a wide range of research projects within the field of cognitive impairment and dementia, incorporating geriatric medicine, neurology, psychiatry, psychology, pharmacy, nursing, occupational therapy, and basic research. Up to December 2021, more than 100 scientific papers, 22 Ph.D. dissertations, and 18 postdoctoral studies were fully or partially based on data from NorCog. A complete list of research projects using data from NorCog, and their publications, can be found on the website www.aldringoghelse.no/forskning/norkog. Below is a short description of results from a few of the published studies based on data from NorCog.

Studies have been conducted to evaluate and validate dementia-related assessment tools. One study compared the validity of the Cornell Scale for Depression in Dementia (CSDD) and the Montgomery-Aasberg Depression Rating Scale (MADRS) among memory clinic patients and concluded that both scales are suitable as screening tools. The prevalence of depressive symptoms was shown to be high among memory clinic patients, as measured by the CSDD.[23] Caregiver burden and the patients' neuropsychiatric symptoms have been shown to be important biasing factors when caregivers report on patients' cognitive functioning and instrumental activities of daily living (IADL).[24] Caregiver distress as measured by the Relatives' Stress Scale (RSS) was shown to be higher in people caring for someone with DLB compared with people caring for someone with AD.[25]

Biomarkers that can aid in the diagnostic work-up of patients suspected of having a dementia disorder have become increasingly important in research, clinical trials, and clinical practice. A number of studies have shown that the CSF biomarkers amyloid-β 42 (Aβ42), total tau, and phosphorylated tau can be used to distinguish patients with AD from healthy

controls.[26] However, when analyzed in a heterogeneous memory clinic population of patients enrolled in NorCog, the authors found a much lower discriminating power for CSF biomarkers than previously reported.[27] In June 2017, the Aβ42 cut-off level for a pathologic test result was revised at the Norwegian laboratory analyzing the CSF markers, while the methodological routines remained unchanged. The change in the Aβ42 cut-off for the diagnosis of AD nearly doubled the sensitivity of the CSF biomarkers, from 31.9% to 60.9%.[28] Another study evaluated the clinical usefulness of automatic MRI assessment using NeuroQuant (NQ) and found that NQ measures could distinguish AD dementia from non-dementia fairly well but were generally poorer in regard to distinguishing AD dementia from non-AD dementia.[29] Furthermore, biological material from the research biobank has been used in studies identifying previously unknown genetic variants conferring a risk of AD.[30-33]

A recent study described patients assessed for cognitive decline in primary health care, compared to patients assessed in specialist health care that have been included in NorCog. The study found that patients assessed in primary health care were older, less educated, had poorer cognitive functioning and activity limitations, more often lived alone, and had more behavioural and psychological symptoms of dementia and depression.[34]

STRENGTHS AND LIMITATIONS

The main strengths of NorCog are the large sample size with extensive clinical data combined with a research biobank, inclusion on a national level, and the opportunity to link variables covering the most relevant domains of cognitive impairment or dementia with real-world outcomes from national health registries, claims databases and chart records in hospitals and nursing homes.

The number of national registries specifically directed at persons with cognitive symptoms or dementia worldwide is scarce, but such registries now exist in all three Scandinavian countries.[35] The Swedish Dementia Registry (SveDem) has included a considerably larger number of patients than NorCog and recruits patients from both specialist units and primary care centers.[36] The Danish Dementia Registry (DanDem) has a similar profile as SveDem.[37] SveDem and DanDem are quality registries for patients with dementia disorders, and enrolment does not require written consent. NorCog is a combined quality and research registry focusing on the extended assessment of cognitive symptoms in a specialist setting that may or may not lead to a diagnosis of dementia, and from 2009-2021, it included only those patients who were able to give their informed consent. NorCog is, therefore, not a dementia registry in the same sense as SveDem and DanDem, and it cannot be used to generalize to the general dementia population in Norway. However, unlike SveDem and DanDem, NorCog collects extensive data from all parts of the assessment with detailed information about test results on cognition and neuropsychiatric symptoms, caregiver situation, medications, medical history, and somatic status including results from

blood laboratory work-up and lumbar puncture. Few, if any, national registries have a similarly broad spectrum of variables as NorCog, allowing for exploration of the main domains of dementia and cognitive impairment. A number of people are referred to assessment because of subjective memory complaints or mild cognitive impairment but do not fulfil the criteria for dementia. By following these patients over time, we have a unique possibility to identify risk factors for the development of dementia. The opportunity to link data with medical records from later admissions to hospitals and nursing homes, as well as to national registries, makes it possible to investigate predictors of real-world outcomes that are also highly relevant to decision makers. Moreover, the collection of biomaterials in a general research biobank can be used in research that aims to understand the aetiology of different dementia disorders and to explore fluid biomarkers for prediction, diagnosis, and disease progression.

In contrast to the restricted setting of a clinical trial, NorCog is a clinical registry collecting data as part of routine clinical practice and may, accordingly, be limited by lower data quality, lack of adjudication, and missing data. Data not missing at random introduce bias and confounding that complicate statistical analyses. Nevertheless, the fact that the clinical registries reflect populations that are representative of routine clinical practice is a strength, increasing generalizability and external validity. The broad inclusion criteria for NorCog make the sample representative for patients being referred for evaluation of cognitive symptoms in a specialist setting. However, there are differences in the patient population depending on the profile of the outpatient clinic. NorCog enrols patients from memory clinics and outpatient clinics in old-age psychiatry and geriatric medicine, but thus far, no neurological departments have joined the registry. The representativeness is, thereby, somewhat uncertain.

FUTURE PLANS

Originally, the finish date of NorCog was set to the year of 2029. However, the legal basis of NorCog was reformalized in 2021 according to the Norwegian Regulations relating to medical quality registries (FOR-2019-06-21-789), and the registry got approval to collect and keep data as long as is necessary to achieve the purpose of the registry. Thus, data collection in NorCog will continue in the coming years without a specific finish date. In the spring of 2022, the registry underwent major changes. Paper-based data collection was replaced with digital registration, and the number of variables collected were reduced. To ensure the quality of the assessment and data collection, the registry will continue to provide the participating clinics with validated screening and diagnostic tools in accordance with the recommendations of the Norwegian national guidelines on dementia. In the paper-based version of NorCog, the registry has provided, and collected data on, a fixed set of measures and scales, shown in Table 4. The new digital version of NorCog, starting in 2022, will allow for a more individualized assessment, to be able to include all groups of patients in NorCog regardless of linguistic and cultural background as well as degree and type of dementia. A

core set of variables will be collected for each patient, but beyond this the clinicians may choose the screening tools that are most appropriate based on the background and symptoms of the individual patient. Therefore, the participating clinics will be provided with a selection of additional validated tools in line with national and international guidelines. All follow-up assessments will be registered in the digital platform. Future plans also involve expanding the registry to include patients from additional Norwegian specialist clinics as well as including patients from primary care centers. Moreover, patients that have reduced or lost their capacity to provide informed consent will be recruited based on proxy consent. The registry will continue to serve as a combined quality and research registry with biomaterial collection for years to come.

COLLABORATION AND ACCESS TO DATA AND BIOMATERIAL

The use of data and biological material from NorCog is subject to ethical and legal regulations, including the General Data Protection Regulation, the Health Register Act, the Health Research Act, and the Register Regulations. The information and biomaterial collected in NorCog can be made available to researchers if access is permitted under these regulations. Applicants from outside Norway are advised to identify a Norwegian collaborator. Enquiries can be submitted to the corresponding author, Geir Selbæk. An application form in Norwegian and in English may be found at https://www.aldringoghelse.no/forskning/norkog. All research projects must be approved by the Regional Committees for Medical and Health Research Ethics in Norway and by the Steering Committee for NorCog. Oslo University Hospital has the overall responsibility for the data, and the Norwegian National Centre for Ageing and Health is managing the registry.

ACKNOWLEDGEMENTS

The authors thank all patients and informants for providing information. We are grateful for the efforts done by the reporting outpatient clinics and the Steering Committee for NorCog.

COMPETING INTERESTS

ABK was/is the principal investigator of three drug trials (ROCHE BN29553, Boehringer-Ingelheim 1346.23 and Novo Nordisk NN6535-4730). KP was/is rater in the ROCHE BN29553 and Novo Nordisk NN6535-4730 trials and IS was investigator in the Boehringer-Ingelheim 1346.23 trial.

FUNDING

NorCog is funded by the South-Eastern Norway Regional Health Authority and the Norwegian National Centre for Ageing and Health (grant number not applicable).

CONTRIBUTORS

ITM prepared the initial draft of the manuscript in collaboration with GS, KP, THT, SB, MNå and CST. ABK, AB, ARØ, POH, IS, ALL, AHR, DBS, MNa, JZS and BJ contributed with data

resources. ARØ is also the user representative from The Norwegian Health Association. IDU and KE were responsible for the initial design and creation of the registry. All authors provided critical review of the manuscript and approved the final version.

REFERENCES

1. Strand BH, Knapskog AB, Persson K, et al. Survival and years of life lost in various aetiologies of dementia, mild cognitive impairment (MCI) and subjective cognitive decline (SCD) in Norway. *PloS one* 2018;13(9):e0204436. doi: 10.1371/journal.pone.0204436 [published Online First: 2018/09/22]
2. Norwegian Directorate of Health. The Norwegian national guideline on dementia, IS-2658: Helsedirektoratet; 2017 [updated 2020 Jan 3; cited 20 Jan 15]. Available from: https://www.helsedirektoratet.no/retningslinjer/demens accessed 2017 Aug 16.
3. Gallacher J, de Reydet de Vulpillieres F, Amzal B, et al. Challenges for Optimizing Real-World Evidence in Alzheimer's Disease: The ROADMAP Project. *Journal of Alzheimer's disease : JAD* 2019;67(2):495-501. doi: 10.3233/jad-180370 [published Online First: 2018/12/26]
4. Makady A, de Boer A, Hillege H, et al. What Is Real-World Data? A Review of Definitions Based on Literature and Stakeholder Interviews. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2017;20(7):858-65. doi: 10.1016/j.jval.2017.03.008 [published Online First: 2017/07/18]
5. Garrison LP, Jr., Neumann PJ, Erickson P, et al. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2007;10(5):326-35. doi: 10.1111/j.1524-4733.2007.00186.x [published Online First: 2007/09/25]
6. Braekhus A, Ulstein I, Wyller TB, et al. The Memory Clinic--outpatient assessment when dementia is suspected. *Tidsskr Nor Laegeforen* 2011;131(22):2254-7. doi: 10.4045/tidsskr.11.0786 [published Online First: 2011/11/17]
7. Fereshtehnejad SM, Johannsen P, Waldemar G, et al. Dementia Diagnosis, Treatment, and Care in Specialist Clinics in Two Scandinavian Countries: A Data Comparison between the Swedish Dementia Registry (SveDem) and the Danish Dementia Registry. *J Alzheimers Dis* 2015*;48*(1), 229-239. doi:10.3233/jad-150144
8. Gjøra L, Strand BH, Bergh S, et al. Current and Future Prevalence Estimates of Mild Cognitive Impairment, Dementia, and Its Subtypes in a Population-Based Sample of People 70 Years and Older in Norway: The HUNT Study. *J Alzheimers Dis* 2021*;79*(3), 1213-1226. doi:10.3233/jad-201275
9. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. *The British journal of psychiatry: the journal of mental science* 1982;140:566-72. doi: 10.1192/bjp.140.6.566 [published Online First: 1982/06/01]
10. Edwin TH, Henjum K, Nilsson LNG, et al. A high cerebrospinal fluid soluble TREM2 level is associated with slow clinical progression of Alzheimer's disease. *Alzheimer's & dementia (Amsterdam, Netherlands)* 2020;12(1):e12128. doi: 10.1002/dad2.12128 [published Online First: 2020/12/15]
11. Edwin TH, Strand BH, Persson K, et al. Trajectories and risk factors of dementia progression: a memory clinic cohort followed up to 3 years from diagnosis.

International psychogeriatrics 2020:1-11. doi: 10.1017/s1041610220003270 [published Online First: 2020/11/21]
12. Mjørud M, Selbæk G, Bjertness E, et al. Time from dementia diagnosis to nursing-home admission and death among persons with dementia: A multistate survival analysis. *PloS one* 2020;15(12):e0243513. doi: 10.1371/journal.pone.0243513 [published Online First: 2020/12/05]
13. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th edn. Washington, D.C: American Psychiatric Publishing 2013.
14. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic criteria for research. Geneva, 1993.
15. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of internal medicine* 2004;256(3):240-6. doi: 10.1111/j.1365-2796.2004.01380.x [published Online First: 2004/08/25]
16. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 2011;7(3):263-9. doi: 10.1016/j.jalz.2011.03.005 [published Online First: 2011/04/26]
17. Sachdev P, Kalaria R, O'Brien J, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer disease and associated disorders* 2014;28(3):206-18. doi: 10.1097/wad.0000000000000034 [published Online First: 2014/03/19]
18. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* 2017;89(1):88-100. doi: 10.1212/wnl.0000000000004058 [published Online First: 2017/06/09]
19. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society* 2007;22(12):1689-707; quiz 837. doi: 10.1002/mds.21507 [published Online First: 2007/06/02]
20. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain : a journal of neurology* 2011;134(Pt 9):2456-77. doi: 10.1093/brain/awr179 [published Online First: 2011/08/04]
21. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology* 2011;76(11):1006-14. doi: 10.1212/WNL.0b013e31821103e6 [published Online First: 2011/02/18]
22. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 2011;7(3):270-9. doi: 10.1016/j.jalz.2011.03.008 [published Online First: 2011/04/26]
23. Knapskog AB, Barca ML, Engedal K. A comparison of the validity of the Cornell Scale and the MADRS in detecting depression among memory clinic patients. *Dementia and geriatric cognitive disorders* 2011;32(4):287-94. doi: 10.1159/000334983 [published Online First: 2012/01/21]

24. Persson K, Braekhus A, Selbaek G, et al. Burden of Care and Patient's Neuropsychiatric Symptoms Influence Carer's Evaluation of Cognitive Impairment. *Dementia and geriatric cognitive disorders* 2015;40(5-6):256-67. doi: 10.1159/000437298 [published Online First: 2015/08/26]
25. Svendsboe E, Terum T, Testad I, et al. Caregiver burden in family carers of people with dementia with Lewy bodies and Alzheimer's disease. *International journal of geriatric psychiatry* 2016;31(9):1075-83. doi: 10.1002/gps.4433 [published Online First: 2016/01/15]
26. Olsson B, Lautner R, Andreasson U, et al. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *The Lancet Neurology* 2016;15(7):673-84. doi: 10.1016/s1474-4422(16)00070-3 [published Online First: 2016/04/14]
27. Knapskog AB, Engedal K, Braekhus A. Performance of Cerebrospinal Fluid Biomarkers of Alzheimer Disease in a Memory Clinic in Norway. *Alzheimer disease and associated disorders* 2016;30(1):8-14. doi: 10.1097/wad.0000000000000126 [published Online First: 2015/12/03]
28. Knapskog AB, Braekhus A, Engedal K. The Effect of Changing the Amyloid beta42 Cut-off of Cerebrospinal Fluid Biomarkers on Alzheimer Disease Diagnosis in a Memory Clinic Population in Norway. *Alzheimer disease and associated disorders* 2019;33(1):72-74. doi: 10.1097/wad.0000000000000268 [published Online First: 2018/08/15]
29. Persson K, Selbaek G, Braekhus A, et al. Fully automated structural MRI of the brain in clinical dementia workup. *Acta radiologica (Stockholm, Sweden : 1987)* 2017;58(6):740-47. doi: 10.1177/0284185116669874 [published Online First: 2016/10/01]
30. Jonsson T, Stefansson H, Steinberg S, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. *The New England journal of medicine* 2013;368(2):107-16. doi: 10.1056/NEJMoa1211103 [published Online First: 2012/11/16]
31. Steinberg S, Stefansson H, Jonsson T, et al. Loss-of-function variants in ABCA7 confer risk of Alzheimer's disease. *Nature genetics* 2015;47(5):445-7. doi: 10.1038/ng.3246 [published Online First: 2015/03/26]
32. Witoelar A, Rongve A, Almdahl IS, et al. Meta-analysis of Alzheimer's disease on 9,751 samples from Norway and IGAP study identifies four risk loci. *Scientific reports* 2018;8(1):18088. doi: 10.1038/s41598-018-36429-6 [published Online First: 2018/12/29]
33. Jansen IE, Savage JE, Watanabe K, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nature genetics* 2019;51(3):404-13. doi: 10.1038/s41588-018-0311-9 [published Online First: 2019/01/09]
34. Michelet M, Lund A, Strand BH, et al. Characteristics of patients assessed for cognitive decline in primary healthcare, compared to patients assessed in specialist healthcare. *Scand J Prim Health Care* 2020;38(2):107-16. doi: 10.1080/02813432.2020.1753334 [published Online First: 2020/05/05]
35. Krysinska K, Sachdev PS, Breitner J, et al. Dementia registries around the globe and their applications: A systematic review. *Alzheimer's & dementia : the journal of the Alzheimer's Association* 2017;13(9):1031-47. doi: 10.1016/j.jalz.2017.04.005 [published Online First: 2017/06/04]

36. Religa D, Fereshtehnejad SM, Cermakova P, et al. SveDem, the Swedish Dementia Registry - a tool for improving the quality of diagnostics, treatment and care of dementia patients in clinical practice. *PloS one* 2015;10(2):e0116538. doi: 10.1371/journal.pone.0116538 [published Online First: 2015/02/20]
37. Johannsen P, Jorgensen K, Korner A, et al. Development of a dementia assessment quality database. *Aging & mental health* 2011;15(1):40-6. doi: 10.1080/13607863.2010.508769 [published Online First: 2011/01/29]

Figure 1. Number of outpatient clinics and number of included patients at baseline in NorCog per year during 2009–2021 (N=18 120). In December 2021, 45 clinics from all four regional health authorities in Norway participated

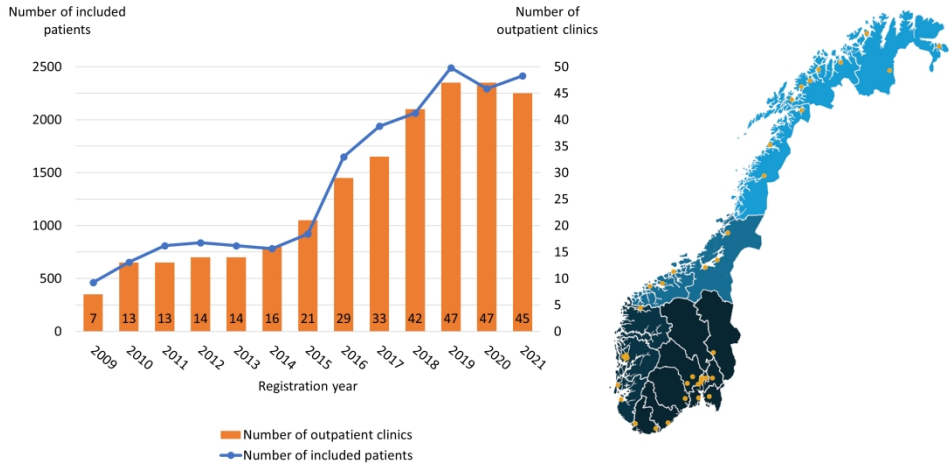

Figure 1. Number of outpatient clinics and number of included patients at baseline in NorCog per year during 2009–2021 (N=18 120). In December 2021, 45 clinics from all four regional health authorities in Norway participated

338x190mm (300 x 300 DPI)