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

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

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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 A β 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	I, P
	Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)	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]

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

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

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

42 Patient involvement is essential to ensure that NorCog is relevant to the population it will
43 impact. Therefore, it is stipulated in the articles of association for NorCog that users shall be
44 represented in the registry's Steering committee. The user representation is attended by The
45 Norwegian Health Association, a voluntary, humanitarian organization promoting the
46 interests of people with dementia and their carers. The members of the Steering committee
47 further include clinicians and managers from all health regions in Norway with backgrounds
48 from memory clinics or outpatient clinics in old-age psychiatric and geriatric units, of which
49 many have research competence. Furthermore, a patient advisory group, consisting of
50 people with dementia and/or their proxies, has been involved in several processes, such as
51 developing and pilot testing a PREM questionnaire, evaluating documents and information
52 sheets, as well as involvement in strategies for presenting studies based on NorCog data.
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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 (A β 42), 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 A β 42 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 A β 42 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]

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3 A complete list of research projects using data from NorCog, and their publications, can be
4 found on the website www.aldringoghelse.no/forskning/norkog.
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8 **STRENGTHS AND LIMITATIONS**

9 The main strengths of NorCog are the large sample size with extensive clinical data
10 combined with a research biobank, inclusion on a national level, and the opportunity to link
11 variables covering the most relevant domains of cognitive impairment or dementia with real-
12 world outcomes from national health registries, claims databases and chart records in
13 hospitals and nursing homes.
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17 The number of national registries specifically directed at persons with cognitive symptoms or
18 dementia worldwide is scarce, but such registries now exist in all three Scandinavian
19 countries.[32] The Swedish Dementia Registry (SveDem) has included a considerably larger
20 number of patients than NorCog and recruits patients from both specialist units and primary
21 care centers.[33] The Danish Dementia Registry (DanDem) has a similar profile as
22 SveDem.[34] SveDem and DanDem are quality registries for patients with dementia
23 disorders, and enrolment does not require written consent. NorCog is a combined quality
24 and research registry focusing on the extended assessment of cognitive symptoms in a
25 specialist setting that may or may not lead to a diagnosis of dementia, and it includes only
26 those patients who are able to give their informed consent. NorCog is, therefore, not a
27 dementia registry in the same sense as SveDem and DanDem, and it cannot be used to
28 generalize to the general dementia population in Norway. However, unlike SveDem and
29 DanDem, NorCog collects extensive data from all parts of the assessment with detailed
30 information about test results on cognition and neuropsychiatric symptoms, caregiver
31 situation, medications, medical history, and somatic status including results from blood
32 laboratory work-up and lumbar puncture. Few, if any, national registries have a similarly
33 broad spectrum of variables as NorCog, allowing for exploration of the main domains of
34 dementia and cognitive impairment. A number of people are referred to assessment
35 because of subjective memory complaints or mild cognitive impairment but do not fulfil the
36 criteria for dementia. By following these patients over time, we have a unique possibility to
37 identify risk factors for the development of dementia. The opportunity to link data with
38 medical records from later admissions to hospitals and nursing homes, as well as to national
39 registries, makes it possible to investigate predictors of real-world outcomes that are also
40 highly relevant to decision makers. Moreover, the collection of biomaterials in a general
41 research biobank can be used in research that aims to understand the aetiology of different
42 dementia disorders and to explore fluid biomarkers for prediction, diagnosis, and disease
43 progression.
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57 In contrast to the restricted setting of a clinical trial, NorCog is a clinical registry collecting
58 data as part of routine clinical practice and may, accordingly, be limited by lower data
59 quality, lack of adjudication, and missing data. Data not missing at random introduce bias
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3 and confounding that complicate statistical analyses. Nevertheless, the fact that the clinical
4 registries reflect populations that are representative of routine clinical practice is a strength,
5 increasing generalizability and external validity. The broad inclusion criteria for NorCog make
6 the sample representative for patients being referred for evaluation of cognitive symptoms
7 in a specialist setting. However, there are differences in the patient population depending on
8 the profile of the outpatient clinic. NorCog enrolls patients from memory clinics and
9 outpatient clinics in old-age psychiatry and geriatric medicine, but thus far, no neurological
10 departments have joined the registry. The representativeness is, thereby, somewhat
11 uncertain, although very few neurological departments conduct diagnostic assessments of
12 dementia in Norway.
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18 **FUTURE PLANS**

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

52 The use of data and biological material from NorCog is subject to strict ethical and legal
53 regulations. All research projects must be approved by the Regional Committees for Medical
54 and Health Research Ethics in Norway and by the Steering committee for NorCog. Oslo
55 University Hospital has the overall responsibility for the data, and the Norwegian National
56 Advisory Unit on Ageing and Health is managing the registry. Applicants from outside
57 Norway are advised to identify a Norwegian collaborator. Enquiries can be submitted to the
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3 corresponding author, Geir Selbæk. An application form may be found at
4 <https://www.aldringoghelse.no/forskning/norkog>.

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12 **COMPETING INTERESTS**

13 ABK was/is the principal investigator of three drug trials (ROCHE BN29553, Boehringer-
14 Ingelheim 1346.23 and Novo Nordisk NN6535-4730). KP was/is rater in the ROCHE BN29553
15 and Novo Nordisk NN6535-4730 trials and IS was investigator in the Boehringer-Ingelheim
16 1346.23 trial.

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27 **CONTRIBUTORS**

28 ITM prepared the initial draft of the manuscript in collaboration with GS, KP, THT, SB, MNå
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30 All authors provided critical review of the manuscript and approved the final version.

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3 **Figure 1.** Number of outpatient clinics and number of included patients at baseline in NorCog per
4 year during 2009–2020 (N=15 372). In December 2020, 47 clinics from all four regional health
5 authorities in Norway participated
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9 **Figure 2.** Frequency of different types of dementia diagnoses registered in NorCog at baseline during
10 2009–2020 (n = 7113 dementia cases)
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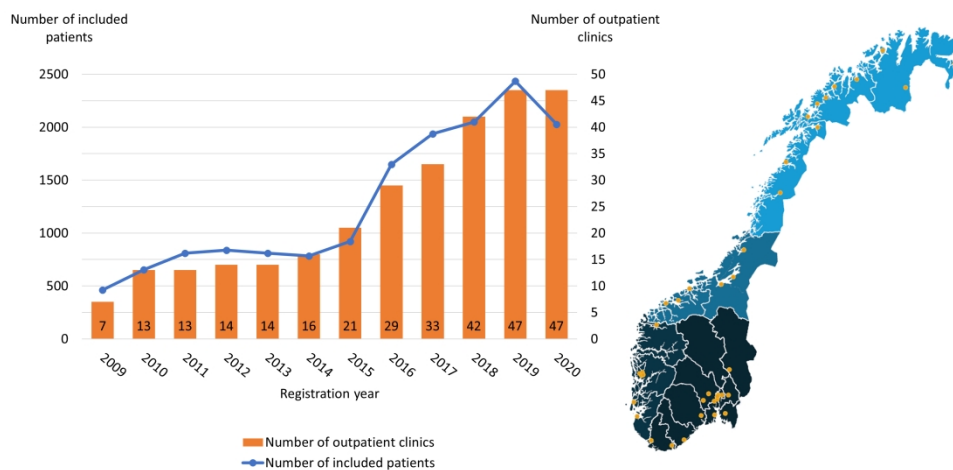


Figure 1. Number of outpatient clinics and number of included patients at baseline in NorCog per year during 2009–2020 (N=15 372). In December 2020, 47 clinics from all four regional health authorities in Norway participated

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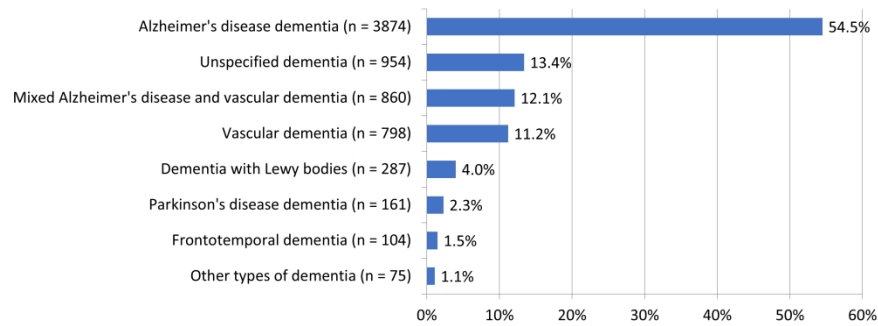


Figure 2. Frequency of different types of dementia diagnoses registered in NorCog at baseline during 2009–2020 (n = 7113 dementia cases)

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BMJ Open

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

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Secondary Subject Heading:	Geriatric medicine, Mental health, Neurology
Keywords:	Dementia < NEUROLOGY, Delirium & cognitive disorders < PSYCHIATRY, GERIATRIC MEDICINE, Old age psychiatry < PSYCHIATRY

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

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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 reformed 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	
<i>n</i> (%)	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
<i>n</i> (%)	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), <i>n</i> (%)	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, <i>n</i> (%)	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, <i>n</i> (%)	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, <i>n</i> (%)	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

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3 participation in the registry means. During 2009-2021, NorCog has only recruited patients
4 that have the capacity to give informed consent. However, from January 2022, patients who
5 are unable, or have reduced capacity, to provide informed consent can also be included in
6 NorCog based on proxy consent.
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10 **Patients not included in NorCog**

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

33 No predetermined follow-up schedule has been established for the registry. However, a
34 registration form for assessment at follow-up according to clinical indication was
35 implemented in 2015 (Table 3). Thus far, the clinics are encouraged but not obliged to
36 deliver follow-up data to the registry. In several sub-studies, selected patients have been
37 invited to receive additional examinations or follow-ups in compliance with specific research
38 protocols. In 2017, a large research project began collecting follow-up data from patients in
39 the registry. The project is called "Trajectories and risk factors of dementia – TRAIL-DEM"
40 and involves linking data from the patients in NorCog with medical records in hospitals and
41 nursing homes as well as national health registries (Table 3). The project investigates
42 trajectories from dementia onset until nursing home admission and death, providing a
43 unique opportunity to investigate dementia aetiology and progression.[1 8-10] TRAIL-DEM
44 will provide an extensive database that will form the basis for future projects.
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52 **Table 3.** Overview of the samples/phases, measurements, biomaterial collection and linkages in the
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Sample/Phase	Measurements	Biomaterial Collection/ Linkage
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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 A β 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

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

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

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

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

15 Data from NorCog have been used in a wide range of research projects within the field of
16 cognitive impairment and dementia, incorporating geriatric medicine, psychology,
17 pharmacy, nursing, occupational therapy, and basic research. Up to December 2021, more
18 than 100 scientific papers, 22 PhDs, and 18 postdoctoral studies were fully or partially based
19 on data from NorCog. A complete list of research projects using data from NorCog, and their
20 publications, can be found on the website www.aldringoghelse.no/forskning/norkog. Below
21 is a short description of results from a few of the published studies based on data from
22 NorCog.
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28 Studies have been conducted to evaluate and validate dementia-related assessment tools.
29 One study compared the validity of the Cornell Scale for Depression in Dementia (CSDD) and
30 the Montgomery-Aasberg Depression Rating Scale (MADRS) among memory clinic patients
31 and concluded that both scales are suitable as screening tools. The prevalence of depressive
32 symptoms was shown to be high among memory clinic patients, as measured by the
33 CSDD.[21] Caregiver burden and the patients' neuropsychiatric symptoms have been shown
34 to be important biasing factors when caregivers report on patients' cognitive functioning
35 and instrumental activities of daily living (IADL).[22] Caregiver distress as measured by the
36 Relatives' Stress Scale (RSS) was shown to be higher in people caring for someone with DLB
37 compared with people caring for someone with AD.[23]
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44 Biomarkers that can aid in the diagnostic work-up of patients suspected of having a
45 dementia disorder have become increasingly important in research, clinical trials, and clinical
46 practice. A number of studies have shown that the CSF biomarkers amyloid- β 42 (A β 42),
47 total tau, and phosphorylated tau can be used to distinguish patients with AD from healthy
48 controls.[24] However, when analyzed in a heterogeneous memory clinic population of
49 patients enrolled in NorCog, the authors found a much lower discriminating power for CSF
50 biomarkers than previously reported.[25] In June 2017, the A β 42 cut-off level for a
51 pathologic test result was revised at the Norwegian laboratory analyzing the CSF markers,
52 while the methodological routines remained unchanged. The change in the A β 42 cut-off for
53 the diagnosis of AD nearly doubled the sensitivity of the CSF biomarkers, from 31.9% to
54 60.9%.[26] Another study evaluated the clinical usefulness of automatic MRI assessment
55 using NeuroQuant (NQ) and found that NQ measures could distinguish AD dementia from
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3 non-dementia fairly well but were generally poorer in regard to distinguishing AD dementia
4 from non-AD dementia.[27] Furthermore, biological material from the research biobank has
5 been used in studies identifying previously unknown genetic variants conferring a risk of
6 AD.[28-31]
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10 A recent study described patients assessed for cognitive decline in primary health care,
11 compared to patients assessed in specialist health care that have been included in NorCog.
12 The study found that patients assessed in primary health care were older, less educated, had
13 poorer cognitive functioning and activity limitations, more often lived alone, and had more
14 behavioural and psychological symptoms of dementia and depression.[32]
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19 **STRENGTHS AND LIMITATIONS**

20 The main strengths of NorCog are the large sample size with extensive clinical data
21 combined with a research biobank, inclusion on a national level, and the opportunity to link
22 variables covering the most relevant domains of cognitive impairment or dementia with real-
23 world outcomes from national health registries, claims databases and chart records in
24 hospitals and nursing homes.
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29 The number of national registries specifically directed at persons with cognitive symptoms or
30 dementia worldwide is scarce, but such registries now exist in all three Scandinavian
31 countries.[33] The Swedish Dementia Registry (SveDem) has included a considerably larger
32 number of patients than NorCog and recruits patients from both specialist units and primary
33 care centers.[34] The Danish Dementia Registry (DanDem) has a similar profile as
34 SveDem.[35] SveDem and DanDem are quality registries for patients with dementia
35 disorders, and enrolment does not require written consent. NorCog is a combined quality
36 and research registry focusing on the extended assessment of cognitive symptoms in a
37 specialist setting that may or may not lead to a diagnosis of dementia, and from 2009-2021,
38 it included only those patients who were able to give their informed consent. NorCog is,
39 therefore, not a dementia registry in the same sense as SveDem and DanDem, and it cannot
40 be used to generalize to the general dementia population in Norway. However, unlike
41 SveDem and DanDem, NorCog collects extensive data from all parts of the assessment with
42 detailed information about test results on cognition and neuropsychiatric symptoms,
43 caregiver situation, medications, medical history, and somatic status including results from
44 blood laboratory work-up and lumbar puncture. Few, if any, national registries have a
45 similarly broad spectrum of variables as NorCog, allowing for exploration of the main
46 domains of dementia and cognitive impairment. A number of people are referred to
47 assessment because of subjective memory complaints or mild cognitive impairment but do
48 not fulfil the criteria for dementia. By following these patients over time, we have a unique
49 possibility to identify risk factors for the development of dementia. The opportunity to link
50 data with medical records from later admissions to hospitals and nursing homes, as well as
51 to national registries, makes it possible to investigate predictors of real-world outcomes that
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3 are also highly relevant to decision makers. Moreover, the collection of biomaterials in a
4 general research biobank can be used in research that aims to understand the aetiology of
5 different dementia disorders and to explore fluid biomarkers for prediction, diagnosis, and
6 disease progression.
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10 In contrast to the restricted setting of a clinical trial, NorCog is a clinical registry collecting
11 data as part of routine clinical practice and may, accordingly, be limited by lower data
12 quality, lack of adjudication, and missing data. Data not missing at random introduce bias
13 and confounding that complicate statistical analyses. Nevertheless, the fact that the clinical
14 registries reflect populations that are representative of routine clinical practice is a strength,
15 increasing generalizability and external validity. The broad inclusion criteria for NorCog make
16 the sample representative for patients being referred for evaluation of cognitive symptoms
17 in a specialist setting. However, there are differences in the patient population depending on
18 the profile of the outpatient clinic. NorCog enrolls patients from memory clinics and
19 outpatient clinics in old-age psychiatry and geriatric medicine, but thus far, no neurological
20 departments have joined the registry. The representativeness is, thereby, somewhat
21 uncertain.
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28 **FUTURE PLANS**

29 Originally, the finish date of NorCog was set to the year of 2029. However, the legal basis of
30 NorCog was reformed in 2021 according to the Norwegian Regulations relating to
31 medical quality registries (FOR-2019-06-21-789), and the registry got approval to collect and
32 keep data as long as is necessary to achieve the purpose of the registry. Thus, data collection
33 in NorCog will continue in the coming years without a specific finish date. In the spring of
34 2022, the registry underwent major changes. Paper-based data collection was replaced with
35 digital registration, and the number of variables collected were reduced. To ensure the
36 quality of the assessment and data collection, the registry will continue to provide the
37 participating clinics with validated screening and diagnostic tools in accordance with the
38 recommendations of the Norwegian national guidelines on dementia. In the paper-based
39 version of NorCog, the registry has provided, and collected data on, a fixed set of measures
40 and scales, shown in Table 4. The new digital version of NorCog, starting in 2022, will allow
41 for a more individualized assessment, to be able to include all groups of patients in NorCog
42 regardless of linguistic and cultural background as well as degree and type of dementia. A
43 core set of variables will be collected for each patient, but beyond this the clinicians may
44 choose the screening tools that are most appropriate based on the background and
45 symptoms of the individual patient. Therefore, the participating clinics will be provided with
46 a selection of additional validated tools in line with national and international guidelines. All
47 follow-up assessments will be registered in the digital platform. Future plans also involve
48 expanding the registry to include patients from additional Norwegian specialist clinics as well
49 as including patients from primary care centers. Moreover, patients that have reduced or
50 lost their capacity to provide informed consent will be recruited based on proxy consent. The
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3 registry will continue to serve as a combined quality and research registry with biomaterial
4 collection for years to come.
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7 **COLLABORATION AND ACCESS TO DATA AND BIOMATERIAL**

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

31 ABK was/is the principal investigator of three drug trials (ROCHE BN29553, Boehringer-
32 Ingelheim 1346.23 and Novo Nordisk NN6535-4730). KP was/is rater in the ROCHE BN29553
33 and Novo Nordisk NN6535-4730 trials and IS was investigator in the Boehringer-Ingelheim
34 1346.23 trial.
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45 **CONTRIBUTORS**

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47 and CST. ABK, AB, ARØ, POH, IS, ALL, AHR, DBS, MNa, JZS and BJ contributed with data
48 resources. ARØ is also the user representative from The Norwegian Health Association. IDU
49 and KE were responsible for the initial design and creation of the registry. All authors
50 provided critical review of the manuscript and approved the final version.
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3 **Figure 1.** Number of outpatient clinics and number of included patients at baseline in NorCog per
4 year during 2009–2021 (N=18 120). In December 2021, 45 clinics from all four regional health
5 authorities in Norway participated
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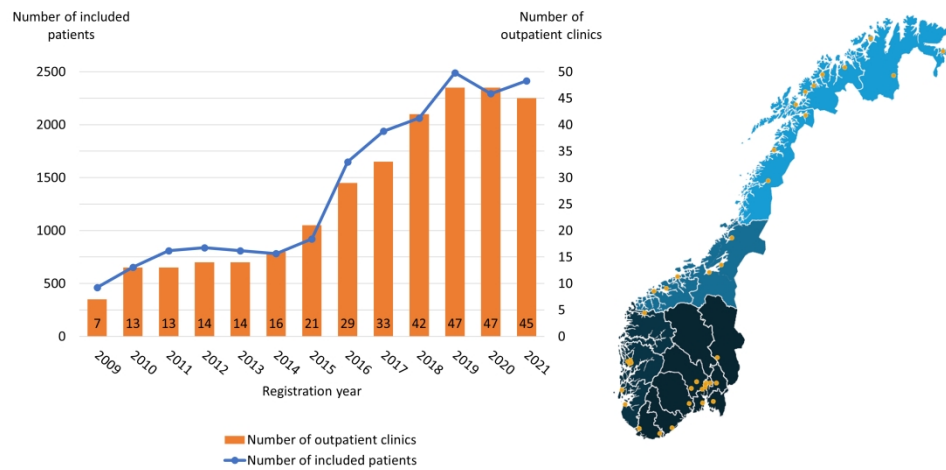


Figure 1. Number of outpatient clinics and number of included patients at baseline in NorCog per year during 2009–2021 (N=18 120). In December 2021, 45 clinics from all four regional health authorities in Norway participated

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

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

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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 reformed 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	
<i>n</i> (%)	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
<i>n</i> (%)	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), <i>n</i> (%)	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, <i>n</i> (%)	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, <i>n</i> (%)	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, <i>n</i> (%)	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

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

17 Participation in NorCog is voluntary and enrolment require written informed consent. To
18 give informed consent, a person must have the ability to fully understand what the
19 participation in the registry means. During 2009-2021, NorCog has only recruited patients
20 that have the capacity to give informed consent. However, from January 2022, patients who
21 are unable, or have reduced capacity, to provide informed consent can also be included in
22 NorCog based on proxy consent.
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28 **Patients not included in NorCog**

29 The number of non-included patients during 2009-2015 has not been registered. Beginning
30 in 2016, all participating clinics have recorded the age and sex of patients who were not
31 included in NorCog. During 2016-2021, a total of 613 patients lacked capacity to give consent
32 and were, therefore, not eligible for inclusion in NorCog. The total number of patients
33 eligible for inclusion at the participating clinics during 2016-2021 was 17 597, whereof 73%
34 of patients (n=12 845) were included and 27% (n=4752) were not included. The average age
35 and the proportion of females were higher among the non-included patients (76 years and
36 55% females) compared to the included patients (74 years and 51% females). Among the
37 patients that were not included, some were not asked to join the registry due to capacity
38 considerations at the clinic (22%) or because the clinician perceived that the
39 situation/condition of the patient did not allow it (31%). In other cases, patients were asked
40 to participate, but declined (21%). In 26% of cases, the cause of non-inclusion was unknown,
41 or another test battery was used due to language issues.
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49 **Follow-up data**

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

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3 disorder and major neurocognitive disorder have largely supplanted the term dementia.[13]
4 DSM-5 is not widely used in Norwegian clinical practice, but ICD-11, which is more similar to
5 DSM-5 than ICD-10, will be implemented in the near future. Clinical diagnoses in NorCog are
6 registered according to the ICD-10 Classification of Mental and Behavioural Disorders:
7 Diagnostic criteria for research.[14] The clinicians also draw a conclusion on one of the
8 following categories for each patient: dementia (ICD-10), MCI according to the Winblad
9 criteria,[15] SCI defined as a subjective experience of cognitive problems in the absence of
10 objectively measured cognitive deficits, or the category “other” for patients who do not fulfil
11 the criteria for the previous categories. If dementia is present, an aetiological diagnosis
12 according to ICD-10 is registered in NorCog.
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18 Furthermore, the specialists at the outpatient clinics are encouraged, but not obliged, to
19 make a more specific sub-classification according to a number of research diagnostic criteria.
20 Here, the NIA/AA criteria are used for Alzheimer’s disease (AD),[16] the Sachdev/VASCOG for
21 vascular dementia (VaD),[17] the McKeith criteria for DLB,[18] the Emre criteria for
22 Parkinson’s disease dementia (PDD),[19] the Rascovsky criteria for FTD behavioural
23 variant,[20] and the Gorno-Tempini criteria for the language variants of FTD.[21] In addition,
24 the NIA/AA criteria are used for the subclassification of MCI.[22] Since the specialists at the
25 outpatient clinics are not obliged to register diagnoses according to research criteria other
26 than ICD-10, research diagnoses are determined retrospectively in some research projects.
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32 **Biomaterial collection**

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

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

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

27 Data from NorCog have been used in a wide range of research projects within the field of
28 cognitive impairment and dementia, incorporating geriatric medicine, neurology, psychiatry,
29 psychology, pharmacy, nursing, occupational therapy, and basic research. Up to December
30 2021, more than 100 scientific papers, 22 Ph.D. dissertations, and 18 postdoctoral studies
31 were fully or partially based on data from NorCog. A complete list of research projects using
32 data from NorCog, and their publications, can be found on the website
33 www.aldringoghelse.no/forskning/norkog. Below is a short description of results from a few
34 of the published studies based on data from NorCog.
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40 Studies have been conducted to evaluate and validate dementia-related assessment tools.
41 One study compared the validity of the Cornell Scale for Depression in Dementia (CSDD) and
42 the Montgomery-Aasberg Depression Rating Scale (MADRS) among memory clinic patients
43 and concluded that both scales are suitable as screening tools. The prevalence of depressive
44 symptoms was shown to be high among memory clinic patients, as measured by the
45 CSDD.[23] Caregiver burden and the patients' neuropsychiatric symptoms have been shown
46 to be important biasing factors when caregivers report on patients' cognitive functioning
47 and instrumental activities of daily living (IADL).[24] Caregiver distress as measured by the
48 Relatives' Stress Scale (RSS) was shown to be higher in people caring for someone with DLB
49 compared with people caring for someone with AD.[25]
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55 Biomarkers that can aid in the diagnostic work-up of patients suspected of having a
56 dementia disorder have become increasingly important in research, clinical trials, and clinical
57 practice. A number of studies have shown that the CSF biomarkers amyloid- β 42 (A β 42),
58 total tau, and phosphorylated tau can be used to distinguish patients with AD from healthy
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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 A β 42 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 A β 42 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

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3 blood laboratory work-up and lumbar puncture. Few, if any, national registries have a
4 similarly broad spectrum of variables as NorCog, allowing for exploration of the main
5 domains of dementia and cognitive impairment. A number of people are referred to
6 assessment because of subjective memory complaints or mild cognitive impairment but do
7 not fulfil the criteria for dementia. By following these patients over time, we have a unique
8 possibility to identify risk factors for the development of dementia. The opportunity to link
9 data with medical records from later admissions to hospitals and nursing homes, as well as
10 to national registries, makes it possible to investigate predictors of real-world outcomes that
11 are also highly relevant to decision makers. Moreover, the collection of biomaterials in a
12 general research biobank can be used in research that aims to understand the aetiology of
13 different dementia disorders and to explore fluid biomarkers for prediction, diagnosis, and
14 disease progression.
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21 In contrast to the restricted setting of a clinical trial, NorCog is a clinical registry collecting
22 data as part of routine clinical practice and may, accordingly, be limited by lower data
23 quality, lack of adjudication, and missing data. Data not missing at random introduce bias
24 and confounding that complicate statistical analyses. Nevertheless, the fact that the clinical
25 registries reflect populations that are representative of routine clinical practice is a strength,
26 increasing generalizability and external validity. The broad inclusion criteria for NorCog make
27 the sample representative for patients being referred for evaluation of cognitive symptoms
28 in a specialist setting. However, there are differences in the patient population depending on
29 the profile of the outpatient clinic. NorCog enrolls patients from memory clinics and
30 outpatient clinics in old-age psychiatry and geriatric medicine, but thus far, no neurological
31 departments have joined the registry. The representativeness is, thereby, somewhat
32 uncertain.
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40 **FUTURE PLANS**

41 Originally, the finish date of NorCog was set to the year of 2029. However, the legal basis of
42 NorCog was reformed in 2021 according to the Norwegian Regulations relating to
43 medical quality registries (FOR-2019-06-21-789), and the registry got approval to collect and
44 keep data as long as is necessary to achieve the purpose of the registry. Thus, data collection
45 in NorCog will continue in the coming years without a specific finish date. In the spring of
46 2022, the registry underwent major changes. Paper-based data collection was replaced with
47 digital registration, and the number of variables collected were reduced. To ensure the
48 quality of the assessment and data collection, the registry will continue to provide the
49 participating clinics with validated screening and diagnostic tools in accordance with the
50 recommendations of the Norwegian national guidelines on dementia. In the paper-based
51 version of NorCog, the registry has provided, and collected data on, a fixed set of measures
52 and scales, shown in Table 4. The new digital version of NorCog, starting in 2022, will allow
53 for a more individualized assessment, to be able to include all groups of patients in NorCog
54 regardless of linguistic and cultural background as well as degree and type of dementia. A
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3 core set of variables will be collected for each patient, but beyond this the clinicians may
4 choose the screening tools that are most appropriate based on the background and
5 symptoms of the individual patient. Therefore, the participating clinics will be provided with
6 a selection of additional validated tools in line with national and international guidelines. All
7 follow-up assessments will be registered in the digital platform. Future plans also involve
8 expanding the registry to include patients from additional Norwegian specialist clinics as well
9 as including patients from primary care centers. Moreover, patients that have reduced or
10 lost their capacity to provide informed consent will be recruited based on proxy consent. The
11 registry will continue to serve as a combined quality and research registry with biomaterial
12 collection for years to come.

17 18 **COLLABORATION AND ACCESS TO DATA AND BIOMATERIAL**

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

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41 42 **COMPETING INTERESTS**

43 ABK was/is the principal investigator of three drug trials (ROCHE BN29553, Boehringer-
44 Ingelheim 1346.23 and Novo Nordisk NN6535-4730). KP was/is rater in the ROCHE BN29553
45 and Novo Nordisk NN6535-4730 trials and IS was investigator in the Boehringer-Ingelheim
46 1346.23 trial.

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54 55 **CONTRIBUTORS**

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

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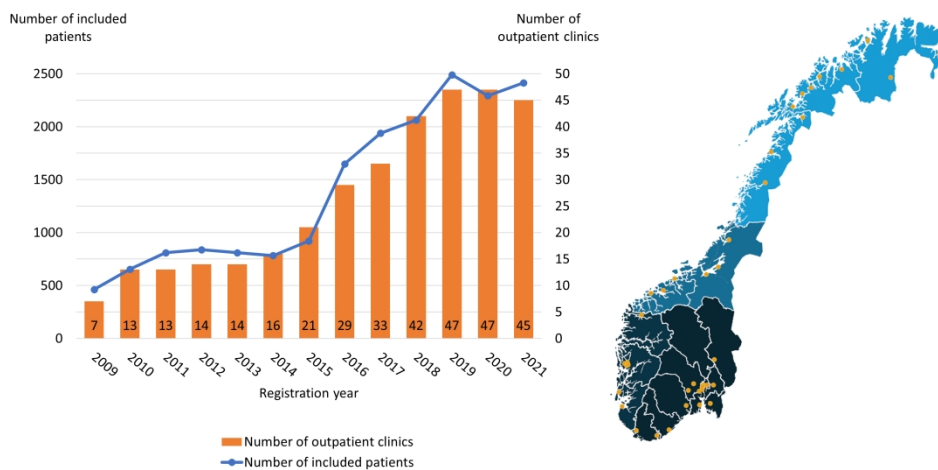


Figure 1. Number of outpatient clinics and number of included patients at baseline in NorCog per year during 2009–2021 (N=18 120). In December 2021, 45 clinics from all four regional health authorities in Norway participated

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