Research plan- disease progression, treatment, prognosis and resource utilisation in dementia

Background

Mild cognitive impairment (MCI) is an early stage of memory loss or other cognitive ability loss. People with MCI has also an increased risk of developing dementia. Dementia is a term that covers a range of neurodegenerative conditions that lead to progressive loss of memory and other cognitive and executive functions. Alzheimer's disease (AD) is the underlying cause of approximately two-thirds of all cases of dementia. Due to aging populations, the prevalence of AD is increasing worldwide, making it one of the most important causes of disability, lost quality of life, and mortality in the elderly (1).

Currently, there are two groups of drugs that provides symptomatic relief approved for treating patients with AD: cholinesterase inhibitors and memantine. Both groups have shown to be cost-effective in more than one stage of AD (2, 3). Moreover, many patients with dementia are underdiagnosed and undertreated, especially in primary care settings. Early diagnosis and optimal care are essential for improving the prognosis and quality of life of patients and their caregivers (4). Understanding the cost-of-illness (COI), both economical and clinical, is pivotal for assessing the effects of underdiagnosis, undertreatment and the need for improvement.

Biomarkers are measurable indicators of biological processes or conditions that can be used for diagnosis, prognosis, or evaluation of treatment effects. Several biomarkers have been identified in cerebrospinal fluid (CSF) that can help distinguish AD from other causes of dementia and potentially predict the clinical course (5, 6). These include amyloid β 1-40, amyloid β 1-42, phosphorylated Tau, total Tau, neurofilament light, neurogranin, albumin ratio, and IgG/M index. These biomarkers reflect different aspects of the neuropathology of AD, such as amyloid plaques, neurofibrillary tangles, nerve cell loss, synapse loss, and blood-brain barrier damage. CSF biomarkers are routinely measured at specialised memory clinics in Sweden using the laboratory for clinical neurochemistry at Sahlgrenska University Hospital.

Another potential approach to finding new treatments for AD is to reuse existing drugs that are approved for other indications but may have beneficial effects on the brain. For example, some drugs that are used to control blood pressure or blood fats, such as calcium inhibitors, angiotensin converting enzyme inhibitors, and statins, may modulate disease processes that lead to memory impairment. Reusing old known drugs for new diseases is a cost- and time-efficient way to develop new treatments. Swedish registers cover a large proportion of the population and contain rich data on patients with dementia diseases, their medication use, cognitive status, care needs, and outcomes. These registers can be used to identify drugs for reuse and to evaluate their effect and cost-effectiveness in different patient groups with specific characteristics (e.g., comorbidity, biomarker profile). This can enable a more individualised treatment approach (precision medicine) for patients with dementia diseases.

Research questions

The research questions can be divided into three categories: Epidemiology of MCI and dementia, Diagnosis and treatment patterns and Resource utilisation and costs. All with the overall purpose to map long-term disease course, care, undertreatment and prognosis for different subgroups of patients with dementia int different stages defined by clinical diagnosis and biomarker profile.

Epidemiology of MCI and dementia

- How many patients are diagnosed with MCI and dementia in Sweden?
- Where are they (care level and setting, geography)?
- What is the natural course of disease, by patient subgroup characterised by biomarker (fluid and imaging) and clinical profile (cognitive tests, biomarkers, neuropsychiatric inventory, co-morbidities)
- What is the frequency of co-morbidity in patients with MCI and dementia compared to controls?
- How does the biomarker profile differ between patient groups with different clinical diagnoses (healthy controls, Alzheimer's disease, vascular dementia, frontotemporal dementia, Lewy body dementia, dementia in Parkinson's disease, mixed forms and other types of dementia)?
- Can biomarker profile predict the long-term natural course, care and care needs, and prognosis in dementia (progression in cognitive impairment, functional level, survival)?

Diagnosis and treatment patterns

- In which stage are patients diagnosed?
- Referral patterns: Who is referred to specialist care? When?
- Which diagnostic process and modalities are used?
- How are patients managed pharmacologically and non-pharmacologically?
- Specifically, what are the usage patterns with acetyl-cholinesterase-inhibitor (AChEI) and memantine?
- How to develop a machine learning algorithm that can classify patients based on biomarker profile and other characteristics that can predict the future disease course?

Resource utilisation and costs

- What are the resource utilisation and costs by stage of disease (assessed by cognitive status and/or biomarker/neuroimaging) and ATN classification (amyloid, tau, neurodegeneration)?
- What are the societal costs, including health care and community care?

Data

This study is based on linking existing data from several sources: Swedish dementia registry (SveDem), Swedish register for behavioural and psychological symptoms (BPSD) in dementia, National Board of Health and Welfare's health registers (patient register, drug register, cause of death register, social services registers), Longitudinal integration database for health insurance and labour market studies (LISA), regional registers (health care utilisation databases, medical records), data from the laboratory for clinical neurochemistry at Sahlgrenska University Hospital, data from the H70 study, data from the MemClin study and data from GEDOC (ethical approval 2011/1987-31 and 2022-00137-02) a clinical-based database for patients at Karolinska University Hospital memory clinic to, used for clinical-based studies to identify biomarkers for early diagnosis of AD. This

combination of data sources provides a unique opportunity to follow all patients with dementia characterised by cognitive status and biomarkers, compared with a healthy comparison group over a long follow-up time. The ambition is to receive information from regional health care utilisation database and medical records from all 21 regions, but due to time constraints or the possibility of getting data the scope may be limited.

Table 1: Included registries/data sources.

Registers	**Main variables**
Longitudinal integration database for health insurance and labour market studies (LISA)	Demographic and socioeconomic information (labour market outcomes)
Pharmaceutical register	Pharmaceutical use and costs
National Patient Register	Diagnoses, co-morbidity, and health care utilisation
Cause of Death Register	Cause and time of death
Municipality health care register	Health care by the municipalities (HSL)
Register of social care for elderly and persons with functional disability	Social care interventions by the municipalities (SOL)
Register of interventions according to the law regulating support and service to persons with certain functional disabilities	Social care interventions by the municipalities (LSS)
Swedish Dementia Registry (SweDem)	Interventions and treatments
Swedish register for behavioural and psychological symptoms (BPSD) in dementia	Presence and severity of BPSD, residential care, non-pharmacological interventions
Regional Health Care Utilisation Database (all regions)	Primary care diagnoses. Health care utilisation and cost.
Data from regional medical records (all regions)	Cognitive test results for disease stage at diagnosis/follow-up, CT-scan, MRI
MemClin database	Diagnoses, cognitive test results, results from biomarker testing CT-scan, MRI
Sahlgrenska hospital	Results from biomarker testing
H70-study	Results from biomarker testing, cognitive test results
GEDOC	Clinical data from memory clinic Karolinska hospital in Stockholm

See attached variable lists for a complete list for the more extensive registries.

Research subjects, Inclusion, and exclusion criteria

The following research subjects will be included in the project (from first available date in each register and to the latest available data):

- All persons diagnosed with dementia or mild cognitive impairment* in primary care from regional registries.
- All persons diagnosed with dementia or mild cognitive impairment* in the National Patient Register.
- All persons registered in the Swedish dementia registry diagnosed with dementia or mild cognitive impairment*.
- All persons registered in the BPSD registry diagnosed with dementia or mild cognitive impairment*.
- All persons who have been analysed for biomarkers related to dementia at clinical neurochemistry, Salhgrenska hospital.
- All participants diagnosed with dementia or mild cognitive impairment* in the H70 project.
- All participants diagnosed with dementia or mild cognitive impairment* in the MemClin project.
- All persons that have collected at least one prescription of AChEI or memantine (ATC N06DA or N06DX01) from the National Patient Register.

*Dementia and mild cognitive impairment includes the following ICD-10-codes: F00, F01, F02, F03, F06, G30, G31, G32, R41.8A

Procedure for compiling an integrated research database

The research group has, based on a previously approved ethical application (diary no. 2021-03304), compiled a database consisting of data from all participants in SveDem, combined with the patient register, the drug register, the cause of death register, H70 study, the laboratory database at clinical neurochemistry Sahlgrenska Hospital, SOL-registry. For the current study, it is required that this existing database is updated and combined with data from additional registries and databases. This is intended to take place in several steps, but can be modified 1) SweDem, BPSD and Sahlegrenska sends key with personal numbers for inclusion to regional data holders. 2) Regional data holders identify study population based on their registers and key from quality registers and draws two controls from the public 3) SveDem and Sahlgrenska Hospital, Regional registry holders (inclusive controls), the H70-stud, MemClin, GEDOC and BPSD sends new or updated files containing personal identification numbers of the research subjects and current variables to the National Board of Health and Welfare. 4) The National Board of Health and Welfare sends personal numbers of individuals in study population to SCB that extracts demographic and socioeconomic information from LISA. SCB also draws two controls from the public and sends the file back to the National Board of Health and Welfare. 5) The National Board of Health and Welfare combines the new files with the existing research database using a previously saved code key and creates a new research database where personal identification numbers are replaced with serial numbers. This is supplemented with updated data from the National Board of Health and Welfare's own registers (the patient register, the drug register, the cause of death register and the social services registers [SOL, HSL and LSS]) and then handed over to the research group.

Analysis

The methods of analysis will depend on the research questions presented above and include descriptive statistics and hypothesis testing to test differences between groups and stages of the disease, decision modelling to describe treatment pathways and disease progression, treatment optimisation analysis to evaluate undertreatment and Cox-regression to analyse the effect stage of disease and treatment on disease specific outcomes. Biomarkers, information from cognitive test and computed tomography (CT) scans will be used to classify the stage of the disease. This information is collected as a part of the basic medical evaluation of patients with dementia recommended by The National Board of Health and Welfare (7). Based on clinical experience in Region Stockholm the basic dementia investigation requires radiological test. Usually with CT scans, in about 90% of patients in primary care. Also, some MRI can be done in primary care, however MRI will be done in about 40% of patients in specialty care. Around 50% of patients are only diagnosed in primary care. Based on the results incidence, prevalence treatment pathways depending on the stage of AD will be studied.

The treatments paths of patients with MCI and AD will also be examined using registry data to conduct a cost-of-illness analysis. The analysis will include calculating incidence and prevalence and estimating the total costs of care for patients with MCI and AD and the costs associated with specific types of care and stages of the disease. Regional differences in diagnosis and treatment and expected incidence and prevalence derived from literature will be used to assess underdiagnosis and undertreatment (8, 9).

Significance

The aim is for the study to better understand the effect of suboptimal treatment and contribute to an individualised care and treatment of people with dementia, by mapping differences in disease course, prognosis, and care needs/resource utilisation between different subgroups. This information can form the basis for development of individualised programs for diagnosis and treatment and for more detailed and accurate information to patients and relatives about prognosis disease progression. The results can also form the basis for evaluation of new strategies for diagnosis and treatment, as well as for planning of resource needs.

References

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