Epidemiology of dementia

– With particular focus on time trends and methodology

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ABSTRACT

Dementia is a clinical syndrome characterised by deterioration in cognitive functions, which causes personal suffering and societal challenges. Studies investigating the incidence, prevalence, and mortality of dementia are needed for the understanding of the societal and economic burden of the disease. Epidemiological studies of dementia face methodological challenges. This thesis examined the time trends in dementia epidemiology among octogenarians, an age group rapidly increasing and where dementia is common. Methodological considerations, such as selection bias and the impact of the choice of diagnostic tools, were also studied. Data used in the papers was derived from the population-based Gothenburg H70 Birth Cohort Studies, and the Prospective Population Study of Women in Gothenburg, Sweden. The cohorts included were born in 1901-02, 1923-24, and 1930. Findings from **Paper I** showed that participants in general, had a lower prevalence of disorders, higher educational level, and were more often married than refusals. There were fewer differences in comparison with the target population of same-aged individuals in Gothenburg. In **Paper II**, we found that the diagnostic criteria in ICD-10 yielded the lowest prevalence of dementia and ICD-11 the highest, followed by the DSM-5. The agreement between the DSM-5 and ICD-11 was substantial. In **Paper III,** we found that the survival time increased both in those with and without dementia. Dementia was the most important predictor of death in both cohorts. Lastly, in **Paper IV,** we found a decreased prevalence of dementia at ages 85 and 88. We also found a decrease in the four-year incidence of dementia. The findings from this thesis provide insights into the time trends in the epidemiology of dementia, as well as into important aspects of methodological considerations in dementia research.

KEYWORDS

Dementia, Epidemiology, Selection Bias, Mortality, Time trends

SAMMANFATTNING PÅ SVENSKA

Demens är ett paraplybegrepp för många olika sjukdomar som har gemensamt att de försämrar den kognitiva förmågan. I takt med den ökande medellivslängden ökar antalet personer med demens, vilket kommer sätta prov på samhällets förmåga att möta dessa behov. Under det senaste decenniet har ett mönster av minskande nyinsjuknande (incidens) och förekomst (prevalens) av demens framkommit. Det är ännu oklart om den här minskningen även går att se i åldersgruppen 85–90-åringar. Därför ville vi undersöka om incidensen och prevalensen av demens har förändrats i den här åldersgruppen. Det är också oklart om ökningen i medellivslängd även omfattar personer med demens. Vi undersökte därför också om mortaliteten i relation till demens hade förändrats. Resultat från populationsbaserade studier om demens kan påverkas av selektivt bortfall, det vill säga om personer som tackar nej skiljer sig från deltagarna. Därför undersökte vi hur representativa deltagarna i våra studier var. Hur diagnosticeringen av demens görs har också betydelse för resultaten av studier på demens. De kriterier som vanligtvis används är baserade på olika upplagor av the International Classification of Diseases (ICD) och Diagnostic and Statistical Manual of Mental Disorders (DSM). Vi ville undersöka vilken påverkan valet av dessa har för beräkningen av prevalens av demens.

Data som användes i den här avhandlingen kommer från den populationsbaserade H70-studien och Kvinnostudien i Göteborg. Deltagarna som ingår i den här avhandlingen kommer från tre kohorter födda 1901-02, 1923-24 och 1930.

Vi fann att deltagarna i jämförelse med de som tackade nej hade lägre prevalens av olika sjukdomar, högre utbildningsnivå och oftare var gifta. Det var färre skillnader mellan deltagarna och den totala populationen av jämnåriga göteborgare. Vi såg också att det diagnostiska kriteriet ICD-10 resulterade i lägst prevalens av demens, medan ICD-11 och DSM-5 gav de högsta. Överensstämmelsen mellan de två nyaste kriterierna ICD-11 och DSM-5 var hög. Överlevnadstiden från 85-års ålder ökade både hos dem med och utan demens, och demens var den viktigaste faktorn kopplad till död i båda kohorterna. Prevalensen av demens vid 85- och 88-års ålder och incidensen mellan 85-89 år minskade.

Sammanfattningsvis bidrar den här avhandlingen med ökad kunskap om tidstrender i demensepidemiologi och metodfrågor gällande detta, så som selektivt bortfall och vikten av val av diagnostiska kriterier.

LIST OF PAPERS

This thesis is based on the following papers, referred to in the text by their Roman numerals.

I. **Wetterberg H***, **Rydén L*,** Ahlner F, Falk Erhag H, Gudmundsson P, Guo X, Joas E, Johansson L, Kern S, Mellqvist Fässberg M, Najar J, Ribbe M, Rydberg Sterner T, Samuelsson J, Sacuiu S, Sigström R, Skoog J, Waern M, Zettergren A, Skoog I.

Representativeness in population-based studies of older adults: five waves of cross-sectional examinations in the Gothenburg H70 Birth Cohort Study.

BMJ Open 2022;12:e068165. *HW and LR are joint first authors

II. **Wetterberg H**, Najar J, Rydberg Sterner T, Skoog I.

The effect of diagnostic criteria on dementia prevalence – A population-based study from Gothenburg, Sweden.

Submitted.

III. **Wetterberg H**, Najar J, Rydén L, Ribbe M, Rydberg Sterner T, Zettergren A, Guo X, Falk Erhag H, Sacuiu S, Kern S, Skoog I.

Dementia remains the major predictor of death among octogenarians. A study of two population cohorts of 85-year-olds examined 22 years apart.

European Journal of Epidemiology. 2021;36(5):507-17.

IV. **Wetterberg H,** Najar J, Rydberg Sterner T, Rydén L, Falk Erhag H, Sacuiu S, Kern S, Zettergren A, Skoog I.

Decreasing incidence and prevalence of dementia among octogenarians. A population-based study on three cohorts born 30 years apart.

The Journals of Gerontology: Series A, 2023; glad071.

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ABBREVIATIONS

AD	Alzheimer's disease
VaD	Vascular dementia
DLB	Lewy bodies
DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD	International Classification of Diseases
WHO	World Health Organization
OR	Odds Ratio
IRR	Incidence Rate Ratio
HR	Hazard Ratio
SD	Standard Deviation
CI	Confidence Interval
MMT	Mini Mental Test
ADL	Activities of daily living
iADL	Instrumental activities of daily living
ECG	Electrocardiogram
PAR	Population Attributable Risk
IPR	National Inpatient Register
CDREG	Cause of death register

Study names

H70	The Gothenburg H70 Birth Cohort Study
PPSW	The Prospective Population Study of Women
MRC CFAS	the Cognitive Function and ageing study
PAQUID	French Personnes Agées Quid
MoVIES	Monongahela Valley Independent Elders Survey
MYHAT	Monongahela-Youghiogheny Healthy Ageing Team
HRS	Health and Retirement study
KP	The Swedish study Kungsholmen Project
SNAC-K	Swedish National Study on Aging and Care in Kungsholmen

DEFINITIONS IN SHORT

Cognitive domains	
Aphasia	Inability to comprehend or formulate language due to damage to specific regions of the brain[1]
Apraxia	Inability to plan and perform previously learned skills of common motorial movements[1]
Agnosia	Inability to process sensory information, such as recognising people, objects, sounds, shapes or smells[1]
Executive function	Cognitive functions that control complex, goal-directed thought and behaviour, such as working memory, flexible thinking, and planning[1]
Episodic memory	Declarative memory consist of personal memory, in contrast to general knowledge[1]
Complex attention	Ability to focus on multiple things at once and deliberately choose what to pay attention to[2]
Learning and memory	Ability to record new information and then retrieve it[2]
Perceptual-motor function	Ability to coordinate the bodies' movement in response to what is happening[2]
Social cognition	Ability to process and use information in social contexts, such as control impulses, express empathy, and recognize social cues and facial expressions[2]
Epidemiology	
Time trend	A change that occurred over time, often slowly and observable only after a certain amount of time
Birth cohort	Persons classified by a particular year of birth[1]
Incidence	The number of new cases of disease during a given period in a specified population[1]
Prevalence	The total number of cases of a disease in a specified population at a designated time[1]
Mortality	All deaths reported in a given population[1]
Representativeness	The degree to which the characteristics of participants in a study are similar to the target population[3]

01

INTRODUCTION

01 INTRODUCTION

Dementia

The focus of this thesis is dementia, a syndrome currently affecting 57 million people worldwide[3] and is globally the seventh leading cause of death.[4] As a result of growing populations and increasing survival into high ages, the number of dementia cases is expected to increase to 153 million worldwide by the year 2050. Today in Sweden, around 130 to 150 000 people are estimated to have dementia.[5] The prevalence increases with age and almost doubles every five years,[6,7] from around 1.0-1.5% in 60-64-year-olds to 25-39% in those older than 90.[4,8-11]

Dementia is considered one of the major causes of disability and dependency among older adults[12] and has a major impact on the affected individuals and their relatives. Besides this, the syndrome is associated with high societal costs and a high burden of informal care. Globally, the yearly estimated cost is $1.3 trillion.[4] Nearly 50% of the cost is accounted for by informal care provided by families. Women are disproportionally affected by dementia, with higher incidence, especially in populations older than 85,[11,13,14] as well as more often providing informal care.[13]

In recent years, epidemiological studies of dementia have indicated a decline in dementia incidence in Western countries,[15-20] and more and more manageable risk factors are being identified. A recent Lancet report showed that as much as 40% of dementia cases might be preventable.[21] Being a major societal challenge for the future but also offering hopeful prospects of preventive strategies, the research of dementia distribution and determinants is crucial.

Dementia is an umbrella term for a range of diseases that affect the brain with loss of vital cognitive functions, influencing mood and behaviour, resulting in impaired function in activities of daily living (ADL) and instrumental activities of daily living (IADL) (Figure 1). Memory is commonly affected, as well as the ability to plan and perform everyday activities, language, judgment, orientation, and perception of time. The symptoms, course of the disease, and underlying pathology vary depending on the type of dementia. The most common type of dementia is Alzheimer's disease (AD), accounting for

around 60-80% of all dementia cases, the second most common is vascular dementia (VaD), and the third most common is dementia with Lewy bodies (DLB).[22] The different diseases causing dementia are grouped into primary and secondary dementia.

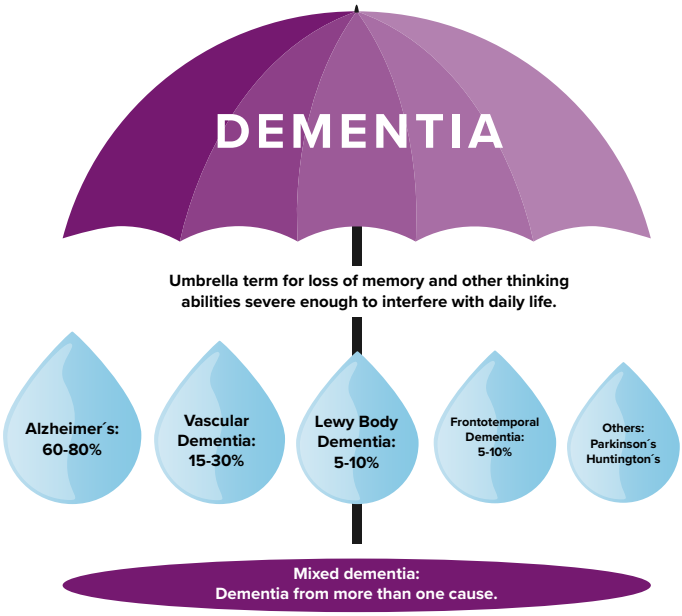


Figure 1 Disorders included in the umbrella term dementia
Dementia is an umbrella term covering a range of disorders. The most common type of dementia is AD, the second most common VaD, and the third most common DLB. In addition to these types, there is a range of less common disorders. It is also common with mixed dementia, with more than one condition causing dementia simultaneously.

Primary dementias are most often caused by progressive and degenerative neuronal loss. Symptoms of these diseases have, in general, a slow onset with a gradual worsening of cognitive function. Most cases of dementia are primary and include, for example, AD, DLB, frontotemporal dementia, Huntington's disease, and Creutzfeldt-Jakob's disease. Although VaD is a vascular disease, not a neurodegenerative condition, it is usually grouped together with primary dementias.

Secondary dementia can occur as a result of a disease or injury. They are generally progressive, however, sometimes chronic or even reversible. Examples of conditions that can cause secondary dementia or symptoms resembling dementia are normal-pressure hydrocephalus, multiple sclerosis,

depression, metabolic disorders (such as vitamin B12 deficiency), head injuries, brain tumours, and chronic alcohol abuse.[23,24]

Alzheimer's disease

AD typically has a slow onset of symptoms, usually starting with a progressive loss of episodic memory and difficulties in learning new information. AD patients commonly repeat questions and conversations.[25] Other signs of AD include apraxia, agnosia, and aphasia, as well as impaired judgment and decision-making, and orientation.[26]

AD was first described by Dr. Alois Alzheimer in 1907, who had identified the combination of cognitive symptoms with senile plaques and neurofibrillary tangles.[27] After over 115 years, this is still considered to be the hallmark of the disease.[28] The senile plaques are deposits of the protein amyloid beta (Aβ), which accumulates outside and between the neurons. The neurofibrillary tangles are hyperphosphorylated tau protein that aggregates and accumulates within the neurons. This spread progressively, ultimately leading to synaptic and neuronal loss, causing the brain to shrink.[26] This pathology starts many years, even decades, prior to the clinical symptoms appear (Figure 2).[29] What causes the disease is still not known, and there are several suggested theories, such as the amyloid cascade hypothesis, the cholinergic hypothesis, genetic susceptibility, accelerated ageing, neuroinflammation and immune dysregulation, synaptic dysfunction, neurovascular dysfunction, the mitochondrial cascade hypothesis, and environmental risk factors.[30]

One of the most dominant theories today is the amyloid cascade hypothesis.[31] The amyloid cascade hypothesis suggests that abnormal deposition of Aβ initiates a sequence of events. When the production and clearance of Aβ are imbalanced, the protein aggregates in the brain, and the formation of oligomers affects neuronal and synaptic functions in the brain.[26] Aβ forms plaques gradually, which activate microglia and astrocytes, causing an inflammatory response. The toxic accumulation of Aβ also induces the hyperphosphorylation and aggregation of tau.[26] However, as AD has a large heterogeneity in regard to clinical manifestation, pathology, and disease progression, there might be multiple pathways that cause the disease.[32] AD is often classified by the age of symptom onset as either early-onset AD (<65 years) or late-onset AD (≥65 years). The disease is often more aggressive in

early-onset AD, with a faster progression and more severe pathology. Among those with late-onset AD, the severity varies, and sometimes the level of pathology in AD patients can even be the same as in cognitively unimpaired controls.[33]

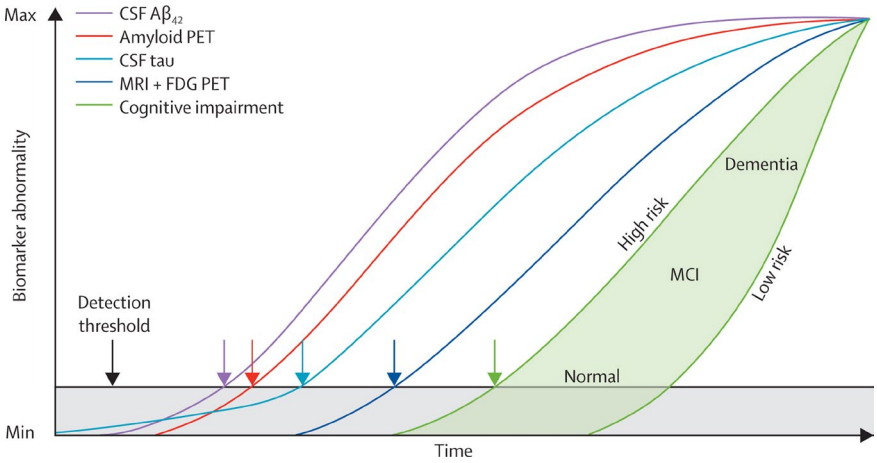


Figure 2 The Alzheimer's disease pathological cascade.
Measurable changes in biomarkers for AD, shown as the thin lines, start many years prior to the clinic appearance of cognitive impairment, shown by the light-green zone. The high and low-risk borders illustrate differentiated risks for cognitive impairment, indicating that two individuals with the same biomarker profile can present with different cognitive levels. Source: Jack et al., 2013.[29]

Vascular dementia

The main feature of VaD is cerebrovascular pathology damaging the brain and impairing cognition.[34] There are many different underlying vascular pathologies of VaD, such as large infarcts and haemorrhages, and small vessel disease.[34,35] The research field of VaD has expanded during the past decades, moving from the hypothesis that only large cortical infarcts caused dementia to the understanding that there are many potential causes.[35] In conjunction with this, vascular cognitive impairment (VCI) was suggested as a broader term since cerebrovascular effects impact the brain in more ways than previously appreciated.[35,36] It is, for example, common with related vascular pathology in AD cases, and its contribution to dementia with other pathologies is acknowledged.[36] Commonly, the prevalence of VaD is estimated to be 15-30% of all dementia cases, but if also counting dementia cases due to mixed pathology and white matter hyperintensities, the estimates would rise to 50-70% of all dementia cases.[37]

Compared to other types of dementia, the symptoms are more variable as it depends on the type and location of the underlying pathology.[37] It is, however, common with subcortical vascular pathology, which often leads to deficits in attention, executive functions, and information processing, not always with a clear impact on memory.[35] Depression and apathy are also common symptoms of VaD.[35]

Other dementia subtypes

Beyond the most common types of dementia is a range of less common types, such as Lewy body dementia, frontotemporal dementia, and disorders linked to dementia, such as Huntington's disease, traumatic brain injury (TBI), and Creutzfeldt-Jakob disease.

Lewy body dementia (dementia with Lewy bodies or Parkinson's disease dementia) is like AD progressive and with deposits of proteins α-synuclein, forming clumps called Lewy bodies within the neurons.[38] Typical symptoms of Lewy body dementias are deficits in attention, executive function, visuospatial ability, fluctuation cognition, spontaneous parkinsonism, sleep problems, and recurrent visual hallucinations. Frontotemporal dementia is a collection of neurodegenerative dementias that affect the frontal and temporal lobes, leading to deficits in behaviour, executive function, and language.[39]

Mixed dementia

Mixed dementia is the combination of more than one underlying cause of the disease co-occurring in the brain (Figure 3). It was long believed that dementia was due to one single cause, but studies have shown that there is a range of neuropathological abnormalities besides the AD neuropathological changes that are associated with changes in cognition,[40-44] and that the synergistic effect of multiple types of disease processes increases the likelihood of severe cognitive impairment or dementia.[44,45] This becomes more evident with advancing age. For example, in the Religious Orders Study and Rush Memory and Aging Project, two longitudinal cohort studies with participants with a mean age of 89 years at death, as much as 95% of those with a clinical diagnosis of probable AD had mixed pathologies at autopsy.[46] Most common to coexist was a vascular disease, which was present in 90% of cases, and other pathologies were present in 65%. In the longitudinal 90+ Study from

California, pathological evaluations found that 45% of dementia cases had mixed pathologies,[42] and results from the same cohort found microinfarcts in 51% of the participants.[47]

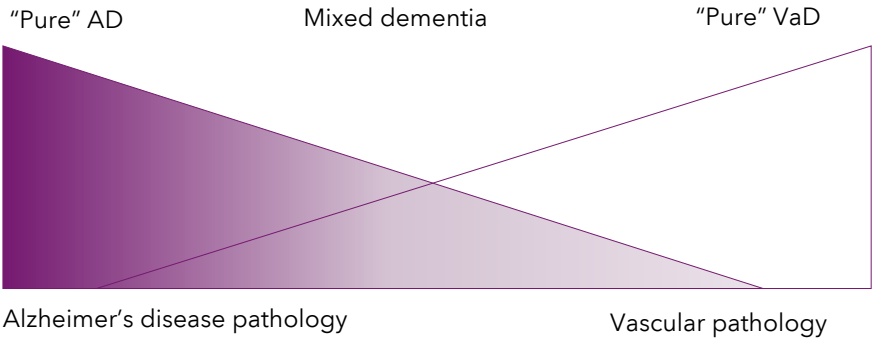


Figure 3 Conceptual diagram over the relationship between AD and VaD pathology and mixed dementia.
Other changes, such as DLB, also often coexists with AD or VaD, causing mixed dementia.[37,48]

It is, therefore, difficult to determine the type of dementia based on only clinical symptoms and medical history. To correctly diagnose the type of dementia requires sophisticated biomarkers and is sometimes impossible without a pathological examination, which, in many cases, is difficult and expensive in the research setting. It is instead common to perform analyses on all cases of dementia without stratifying by dementia subtype.[6] This is especially true for those older than 85, and this is the age group of the main population included in this thesis. In **Paper II** and **Paper IV**, we only used the umbrella term dementia. In **Paper III**, we used the umbrella term dementia as the main outcome, but we also performed subanalyses stratified by AD, VaD, and mixed dementia, to evaluate the results further.[49]

Risk factors for dementia

Throughout the life course, the accumulation of risk and protective factors affects the risk of dementia.[21,36,50] Today there are a wide range of acknowledged risk factors for dementia, both non-modifiable as well as modfiable.[6,51]

Among non-modifiable risk factors are age, genetics, and biological sex. Although dementia is not a normal part of ageing,[36] age is considered the most crucial risk factor as the prevalence increases almost exponentially with age (Figure 4).[6,7] Genetic factors are associated with the risk of dementia. However, less than five percent of all dementia cases are caused by an autosomal dominant mutation, labelled as familial AD.[30] The common type of AD is considered to be sporadic. Still, a family history of sporadic AD increases the risk of dementia, and the heritability of sporadic dementia is estimated to be 60% to 80%.[52] Genome-wide association studies have shown that the strongest genetic risk factor for sporadic AD is the ε4 allele of the apolipoprotein E (*APOE).*[53,54] The *APOE* gene codes the apolipoprotein E protein (apoE) and has three polymorphic alleles, ε2, ε3, and ε4. While the ε4 allele is a risk factor for AD, the ε2 is considered to be protective, and the ε3 neutral.[55] Having one *APOE* ε4 allele increases the risk of AD 3-4 compared to having none, and having two copies increases the risk 9-15 times.[56] In addition to *APOE* ε4, there are other genetic regions related to AD risk.[57] These are not as strong risk factors as the *APOE* ε4 and are commonly grouped together in polygenic risk scores in studies.[58]

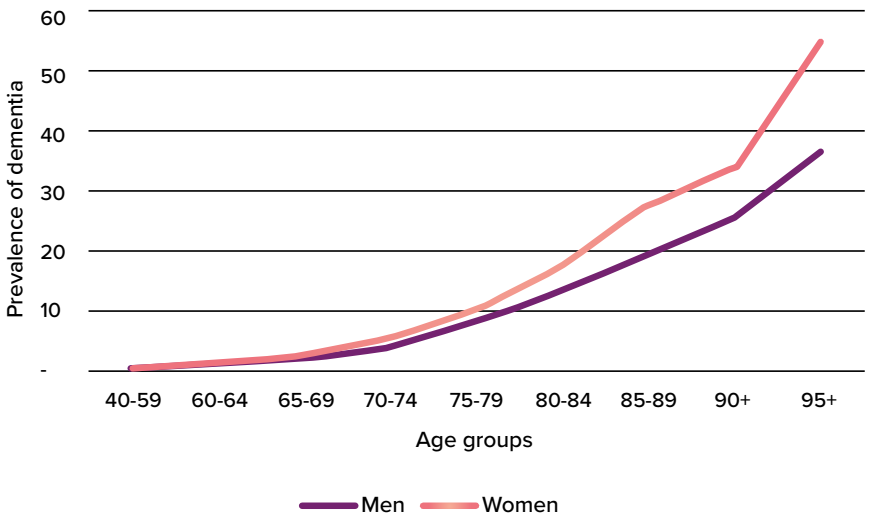


Figure 4 Prevalence of dementia in men and women by age.
Prevalence data based on data from Kodesh et.al., 2019, the World Health Organisation, 2021, Crimmins et.al., 2018, Cao et.al., 2020, and Börjesson-Hanson et.al., 2004.[4,8-11]

Biological sex is also considered a risk factor for dementia,[59] as women are affected by dementia to a greater extent than men in several ways. Approximately two-thirds of all dementia cases are women, and women have a higher lifetime risk of developing AD.[32] A part of this is explained by women living longer than men, and as age is the strongest risk factor for dementia, more women live long enough to develop the disease.[14,59,60] It is also hypothesized that due to the lower mortality in women, there is a survival effect among men reaching high ages. This survival effect would mean that the men reaching the high ages in which dementia is common, would have protective factors making them less vulnerable to dementia. There are, however, other factors explaining the sex difference. For example, a meta-analysis with data on almost 58 000 participants found that women with the APOEε3/ε4 genotype in the age group 65 to 75 years had a higher risk of developing AD than men with the same genotype.[61] Similarly, previous studies have found lower cognitive function among women with the genotype than men,[62] and a higher risk of conversion from mild cognitive impairment to AD.[63] Moreover, the sudden reduction of oestrogen due to menopause has been suggested as a factor affecting risk for AD in women. Oestrogen has, in animal and cell models shown to be neuroprotective in several ways.[13] The role of oestrogens on the risk of AD is, however, debated. Previous observational studies report a reduced risk of AD in women using exogenous estrogen (i.e., hormonal replacement therapy),[64,65] while others report an increased risk.[66,67] Further, studies examining endogenous estrogen exposure (e.g., reproductive period [age at menarche to age at menopause]) also report divergent results, with some showing that a longer reproductive period increases the risk of AD,[68,69] while others report a reduced risk among women with a shorter reproductive period.[70] In addition to the sex-specific risk factors, there are sociocultural aspects that relate to the below-described modifiable risk factors for dementia.[71]

Interacting with non-modifiable risk factors is a wide range of modifiable risk factors for dementia that have been identified in the last decades.[21,36] A meta-analysis showed that up to 40% of all dementia cases theoretically are accounted for by modifiable risk factors, meaning that a large proportion of dementia cases could be prevented or delayed.[21,72] These include twelve specified risk factors, being lower education, hearing impairment, depression, physical inactivity, infrequent social contact, head injury, hypertension, smoking, diabetes, obesity, excessive alcohol consumption, and air pollution (Figure 5). The mechanisms of how prevention or managing of these risk

factors could prevent or delay dementia are proposed to be mediated in two different paths; reduced neuropathological damage and increased and maintained cognitive reserve.

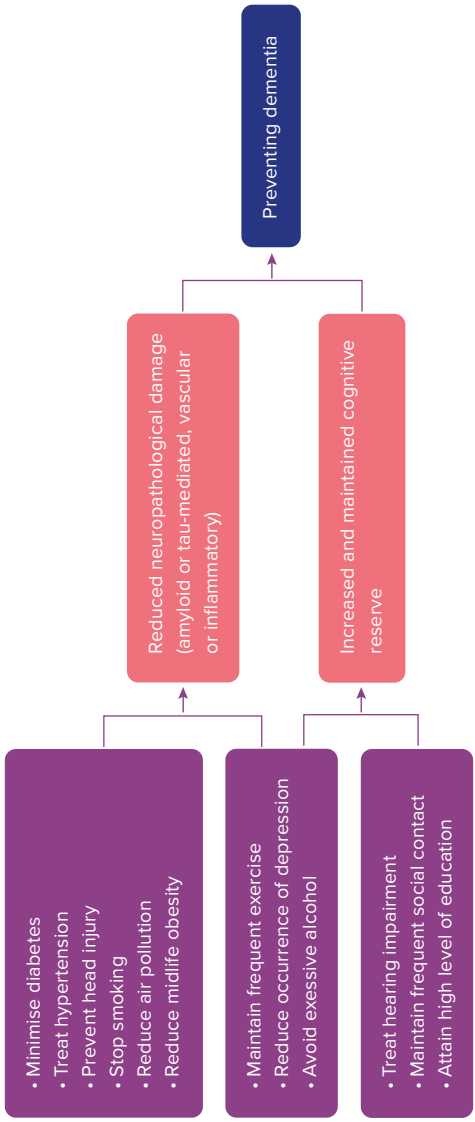


Figure 5 Suggested mechanisms for promoting cognitive reserve and risk reduction. A summary of the twelve modifiable risk factors and the suggested pathways in which they are modelled to change the risk of dementia. Source: Livingston, et.al. 2020.[21]

Neuropathological damage can be increased by diabetes, hypertension, obesity, head injury, smoking, and air pollution. Diabetes, hypertension, and obesity are all vascular risk factors that increase the risk of cognitive decline.[73] Smoking and air pollution have a vascular and toxic effect on the brain, and head injuries have recently been recognized to increase the risk of neuropathological damage. If the exposure is minimized and adequately treated, the neuropathological damage could be reduced.

The hypothesis of cognitive reserve is based on evidence of individual variability of cognitive symptoms at the same levels of neuropathological changes, indicating resilience in some individuals.[74] This resilience can both be manifested as a cognitive reserve and a brain reserve. In short, the cognitive reserve stands for the adaptability of the brain to more functional brain processes, and this adaptability can be improved by lifestyle factors. The brain reserve is the neurobiological capital, meaning the number of neurons and synapses, which can be increased or maintained through cognitive stimulation.[74] Higher education and frequent social contact are thought to increase the cognitive reserve, while untreated hearing impairment reduces the cognitive reserve, likely due to avoidance of stimulating activities.[21,72] Physical inactivity, depression, and excessive alcohol use are thought to affect the risk of dementia through both the cognitive reserve and neuropathological damage.

Diagnostic criteria

There are two major sets of classification systems to diagnose dementia:[36] the International Statistical Classification of Diseases and Related Health Problems (ICD) system, developed by the World Health Organization[75] (WHO), and the Diagnostic and Statistical Manual (DSM) developed by the American Psychiatric Association.[76] The ICD system is used globally within the health care system and death certificate data to code diseases and is accompanied by diagnostic guidance. The DSM is the most frequently used classification system in clinical research to categorize psychiatric diseases.[36] In the 50s, "senility and ill-defined diseases" was first introduced in the ICD-7,[77]and in the two first published editions of DSM in 1952 and 1968, chronic brain syndrome due to arteriosclerosis and senile brain disease were included. With every new edition, the description and diagnostic criteria have been updated within both systems. The current version of the ICD (ICD-11) was published in May 2019 and is being translated into Swedish but is yet to be implemented, and the DSM-5 was published in 2013.[76] As both classification systems are widely used, there have been efforts to harmonize the systems since the preparation of the ICD-10 and DSM-IV, released in the mid 90s.[78] Despite this, the criteria differ in many ways (see Box 1 and Box 2 for brief descriptions of the diagnostic criteria). The main reason for this is because of different priorities and use of the criteria between the two organizations.[78]

As the criteria differ, the choice of diagnostic criteria will affect the number of individuals diagnosed with dementia. The older versions are generally seen as more Alzheimer's oriented, as deficits in memory are mandatory for diagnosing dementia, whilst the newer versions accept deficiencies in any cognitive domain in order to capture other types of dementia.[2] There has been some research comparing the different systems, indicating that the DSM systems generally capture more cases than the ICD criteria.[79-81] To our knowledge, there are no studies comparing the latest DSM-5 and the ICD-11 criteria, which is the aim of **Paper II**.

Box 1. Diagnostic criteria in the ICD-systems

ICD-10	ICD 11
Impairment of short-term or long-term memory	Impairment in two or more cognitive domains: memory impairment, executive functioning, attention, language, social cognition and judgment, psychomotor speed, and visuoperceptual or visuospatial functioning.
Significant decline in other cognitive abilities characterized by deterioration in judgment and thinking, such as planning and organizing	Information obtained from the individual, informant, or clinical observation
Significant impairment of emotional control or motivation or change in social behaviour, presenting in at least one of the following: emotional lability, irritability, apathy, coarsening of social behaviour, representing a decline	Substantial impairment in memory performance as demonstrated by standardized neuropsychological or cognitive testing or, in its absence, another quantified clinical assessment.
	Behavioural changes (e.g., changes in personality, disinhibition, agitation, irritability) may also be present
	The symptoms result in significant impairment in personal, family, social, educational, occupational, or other important areas of functioning and represent a decline
The cognitive deficits do not occur exclusively in the context of a delirium	The symptoms are not better accounted for by disturbance of consciousness
	The symptoms are not better accounted for by altered mental status

Source: World Health Organization. International Classification of Diseases, Eleventh Revision (ICD-11). 2019/2021,[75] World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. 1993.[82]

Box 2. Diagnostic criteria in the DSM-systems

DSM-III-R	DSM-IV	DSM-5 Concern of self or informant of significant cognitive decline in one or more cognitive domains
Impairment of short-term *and* long-term memory	Impairment of short-term *or* long-term memory	Significant impairment in cognitive performance in one or more cognitive domains: learning and memory, language, executive function, complex attention, perceptual-motor, social cognition
Impairment of abstract thinking, impaired judgment, aphasia, apraxia, agnosia, constructional difficulties, and personality change	Significant impairment in at least one of the following domains: aphasia, apraxia, agnosia, and disturbance in executive functioning	
The above criteria each cause significant social/ occupational dysfunction and represent a decline	The above criteria each cause significant social/ occupational dysfunction and represent a decline	The cognitive deficits interfere with independence in everyday activity and represent a decline
The cognitive deficits do not occur exclusively in the context of a delirium	The cognitive deficits do not occur exclusively in the context of a delirium	The cognitive deficits do not occur exclusively in the context of a delirium
The cognitive deficits are not better explained by another mental disorder	The cognitive deficits are not better explained by another mental disorder	The cognitive deficits are not better explained by another mental disorder

Source: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3rd ed., revised. 1987,[83] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. 1994,[84] American Psychiatric Association. Diagnostic and statistical manual of mental disorders 5th ed. 2013.[76]

Epidemiology

Epidemiology is the study of the distribution and determinants of public health concerns in a population.[85] Descriptive epidemiology examines the distribution of diseases in regard to population, place, and time, while analytical epidemiology examines the cause or aetiology of the disease. When studying the distribution of disease, measures used include incidence, prevalence, and mortality. Incidence reflects the number of new cases within a defined population during a given time frame, while the prevalence is the proportion of individuals with the disease at a given time. These concepts interact and are often described with the "bathtub analogy" (Figure 6). The incidence, the newly diagnosed cases, is shown by the new water flowing into the bathtub. The prevalence, the proportion having the disease, is represented as the water already in the bathtub. The mortality is shown as the drain, with cases leaving the bathtub. The prevalence is influenced by the rate of new cases occurring (incidence) but also by the mortality. Changes in the incidence and prevalence of disease could move in different directions. If the incidence of the disease decreases, the prevalence could still increase if the mortality of the disease also decrease.[86] Since the aspects affect each other, it is important to study them all to understand the epidemiology of the disease. In **Paper III** and **Paper IV**, we investigate the time trends in the incidence, prevalence, and mortality of dementia among octogenarians.

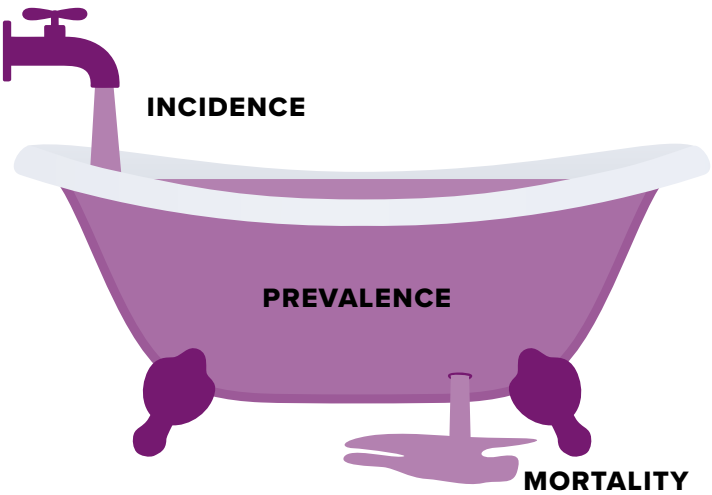


Figure 6 The bathtub analogy.
The bathtub analogy describes the relationship between incidence (newly diagnosed cases shown as water flowing into the tub), prevalence (number of cases having the disease, shown as water already in the tub), and mortality (shown as water leaving the tub).

Epidemiology of dementia

The prevalence of dementia is low among those younger than 65, ranging 1.0-1.5% in 60-64-year-olds[4,8] and is most often related to familial dementia.[87] The prevalence then increases rapidly with age, doubling every five years.[6,7] Among octogenarians, the reported prevalence has ranged between 10-35%.[8,9,88,89] Also, the incidence of dementia increases almost exponentially with age and doubles every 6 years, from 4 per 1,000 person-years at age 60-64 to 105 per 1,000 person-years at age 90+.[90] The estimated incidence of dementia among octogenarians reported from various studies also varies, from 27/1,000 up to 70/1,000.[16,18,91,92]

The wide range of estimates is likely to a great extent due to varying methods and diagnostic criteria applied,[10] however, the prevalence and incidence of dementia also vary between regions. A meta-analysis presented age-standardized prevalence among those aged ≥85 years of 24-26% in Europe, Asia, and North Africa, 33% in Latin America, and 9-16% in Sub-Saharan Africa regions.[93] In the recent decade, numerous population-based studies indicate that the prevalence and incidence of dementia vary over time and between birth cohorts, with a trend of declining rates in North America and Europe, both in prevalence[88,89,94,95] and incidence.[15-17,19,20,92] Problematically, some studies indicate an increase in East Asian and African countries, such as Japan,[96] China,[97] as well as in Nigeria.[92] These increases have been suggested to be associated with the rapid increase in cardiovascular risk factors.[86]

If the declining prevalence and incidence of dementia in North America and Europe results from the age of onset being pushed into higher ages, or if the decline remains into the high ages, such as above 85 years, is still unknown. There are some studies reporting estimates for octo- and nonagenarians, but they are scarce. In **Paper IV**, we specifically investigate the time trends of prevalence and incidence of dementia among 85-90-year-olds.

Dementia strongly influences life expectancy.[98-100] The population attributable risk (PAR) of death from dementia was 31% in men and 50% in women in a cohort of 85-year-olds born 1901-02 examined within the Gothenburg H70 studies (H70).[101] An onset of dementia at higher ages has a lower effect on survival time than an onset at younger ages, predicting shorter survival of dementia.[99,102,103] However, among those with late-onset dementia, a higher age predicts shorter survival,[100] as do more severe dementia.[102] Reported average survival time varies from three to 12 years, and a systematic

review showed that most studies find survival times of seven to ten years.[99] It is difficult to compare results from studies as it is often uncertain whether the survival time should be calculated from the onset of symptoms or the time of diagnosis.[102]

As described in a previous section, the relationship between the incidence and prevalence of a disease is related to mortality. With reported time trends in the incidence of dementia, it is interesting to study potential changes in the mortality of dementia. As the length of survival in dementia is not only related to the age of onset but also midlife sociodemographic factors, and cardiovascular risk factors (i.e., factors that are modifiable), it is likely that the length of survival in dementia is not static but can fluctuate or change over time. There are, however, few studies on time trends in mortality in dementia,[86] and even fewer among octogenarians. In **Paper III**, we aimed to examine if there were any time trends in the mortality of dementia among octogenarians, as well as the importance of dementia in relation to other common diseases to predict mortality.[49]

Potential biases in epidemiological studies of dementia

Being defined as "the study of the distribution and determinants of disease frequency," the field of epidemiology might be perceived as straightforward. However, epidemiological studies come with various methodological issues that are important to consider when interpreting results.[85] If a study result is biased, it means that the estimated association, such as the risk ratio, odds ratio, or hazards ratio, deviates from the true association in the population. When performing epidemiological studies, two major types of systematic errors can affect the validity of the study, i.e. selection bias and measurement bias.[85]

Selection bias occurs when the participants and the population of interest differ in non-random ways. This can happen if, for example, the procedure to select individuals for the study influences participation.[85] It can also occur if there are non-random differences in who accepts or refuses participation in the study. There are several characteristics that are known to be associated with the choice to participate in studies, such as being healthier (the healthy

volunteer effect),[104-107] being married,[106-109] having higher education and socioeconomic status,[104,108,109] being younger,[106,110] having lower mortality rates,[104,106] and being an immigrant.[107,109] In studies of older adults, specific factors might affect recruitment. These include sensory deficits such as hearing and visual impairment, lowering the willingness to be interviewed or tested. Cognitive slowing or dementia could make understanding the invitation information or the study procedures difficult. Multiple comorbidities, common in high age groups, often involve frequent hospitalizations making individuals difficult to contact or averse to further examinations.[111] In epidemiological studies of dementia, the risk of selection bias is prominent due to differences in study participation, attrition, or survival in individuals with and without cognitive deficits.[112] Previous studies show that cognitive decline causes attrition,[110,113] as do frailty and illness.[110] To answer questions of the distribution of disorders, or as in this thesis, time trends of dementia, it is important that the sample examined is representative of the target population.[114] In **Paper I,** we further explore the selection bias in the H70 studies.

Measurement bias is introduced into a study when the information collected within the study is wrong, or the measurement of the key study variable is inaccurate.[85] If cases are placed in the wrong category, this bias is called misclassification. In studies of dementia, this is a potential bias that could affect the validity of the dementia diagnoses. Studies have, for example, shown that the use of brief cognitive assessment commonly used within the clinical setting often leads to misclassification of dementia. For example, higher education in participants can cause false-negative misclassification, and visual impairment can cause false-positive classification.[115] As the classification often relies on reports from the key informant interview, recall bias also poses a challenge. If the key informants of those with cognitive decline report differently than those without due to a higher awareness of the symptoms, the differences between the groups could be inflated.[85] Participants in a longitudinal study could also be misclassified due to practice effects as a result of repeated administration of the same test resulting in higher performance.[112] Besides these biases, the different diagnostic criteria used within the field by default classify cases differently.[79] In **Paper II**, we compare the prevalence of dementia based on which diagnostic criteria are used, including the two most recent editions: the DSM-5 and the ICD-11.

02

AIMS

02 AIMS

The overarching aim of this thesis was to study the epidemiology of dementia, with a particular focus on time trends in the incidence, prevalence, and mortality of dementia, and methodological aspects regarding data collection and diagnostics.

Specific aims of the included papers

Paper I

Representativeness of the population being studied is essential in epidemiological studies when the aim is to describe the distribution of disease, and selection bias can affect the interpretation of results. The aim of **Paper I** was to describe the cross-sectional samples of the 1930-cohort of the H70 studies, and to examine the differences between participants, refusals, and same-aged individuals in Gothenburg (the target population) and Sweden.

Paper II

There are mainly two diagnostic systems to diagnose dementia, the ICD and the DSM, both with several editions. Previous studies have shown that these editions vary in their classifications, yielding different estimations of dementia prevalence. This makes comparisons between studies using different diagnostic systems problematic. In the last two editions of diagnostic systems, efforts have been made to reduce this problem. To our knowledge, no studies compare the newest editions in both systems: the ICD-11 and the DSM-5. The aim of **Paper II** was to compare five different editions of the ICD and DSM system, as well as the clinical consensus diagnosis based on the DSM-III-R used within the H70 studies.

Paper III

Dementia is one of the strongest predictors of mortality among older adults. Mean life expectancy has increased globally during the past decades. However, whether life expectancy has increased among those with dementia is not clear. The aim of **Paper III** was to examine if the eight-year mortality has changed between two cohorts of 85-year-olds born 22 years apart. A secondary aim was to examine if the population attributable risk of death due to dementia in relation to other common disorders has changed.

Paper IV

Previous studies have indicated a decline in dementia prevalence and incidence among older adults in North America and Europe. However, few studies have examined if this decline persists into higher ages. Moreover, among available published work, the results are inconclusive. The aim of **Paper IV** was to examine if the prevalence and incidence of dementia have changed between the cohorts of 85-year-olds born 30 years apart. A secondary aim was to examine the sensitivity and specificity of dementia diagnoses in the registers (i.e. the National Inpatient Register [IPR] and the Cause of Death Register [CDREG]), which was used for those lost to follow-up.

03

METHODS
AND MATERIALS

03 METHODS AND MATERIALS

Participants

This thesis is based on data from the population-based Gothenburg H70 birth cohort studies (H70) and the Prospective Population Study of Women (PPSW). The H70 studies are longitudinal multidisciplinary studies initiated in 1971 by Professor Alvar Svanborg to examine the general health status of 70-year-olds in Gothenburg.[116] To yield representative samples, the selection of individuals was systematic and based on pre-specified birth dates of each month. The participants were followed up continuously with examinations and medical records retrieval. New waves of 70-year-olds have been added throughout the decades to update the knowledge of health status and to facilitate cohort comparisons (Figure 7). In the autumn of 2022, the seventh and most recent wave of 70-year-olds started, examining a cohort born in 1952-53. In 2009, a cohort of 85-year-olds was added to compare the health of octogenarians of today with the previous cohort. The study procedures have been kept as similar as possible throughout the decades to ensure the study of time trends related to age-related disorders and their risk and protective factors.[117] Changes to the study protocol have mainly been restricted to adding new instruments and questionnaires. In this thesis, we used data from the cohorts born in 1901-02, 1923-24, and 1930.

The PPSW is also a population-based longitudinal multidisciplinary study, starting in 1968 under the lead of Professor Calle Bengtsson.[118] Five age groups were selected, with individuals sampled based on birth dates, similar to the H70 studies. The cohort has been followed with examinations and medical records for over 50 years, regardless of residence, and individuals have also been added throughout the decades.[68,118] One of the selected age groups was born in 1930, with selection birth dates overlapping the fifth wave of 70-year-olds in H70, examined in 2000. The two studies were therefore combined, and thus, participants from the PPSW are also included in this thesis. See Box 3 for an overview of which cohorts are included in each paper.

Birth cohort 1901-02

The birth cohort of 1901-02 was the first cohort examined within the H70 studies, and, thus also the first cohort of 85-year-olds to be examined. In 1985, all individuals born between July 1, 1901 and June 30, 1902 and registered as living in the municipality of Gothenburg were invited to a health examination (n=1502).[119] They were all given, consecutively after the date of birth, a number between 1-5 or 11-15. Those with numbers 1, 2, 11, 12, or 14 were further selected for the psychiatric examination (n=826). From these, 43 died before the examination, leaving an effective sample of 783 individuals, among which 14 (1.8%) had moved or could not be traced, 229 (29.2%) declined participation in the studies altogether, and 46 (5.9%) declined the neuropsychiatric examination. This resulted in a final sample of 494 individuals (143 men and 351 women) and a response rate of 64.4%.

In the first follow-up, 248 88-year-olds participated (response rate 70.7%, 185 women and 63 men). In addition, twelve participants (7 women and 5 men) who declined the baseline psychiatric examination participated in the follow-up examination. In the second follow-up, 155 90-year-olds participated

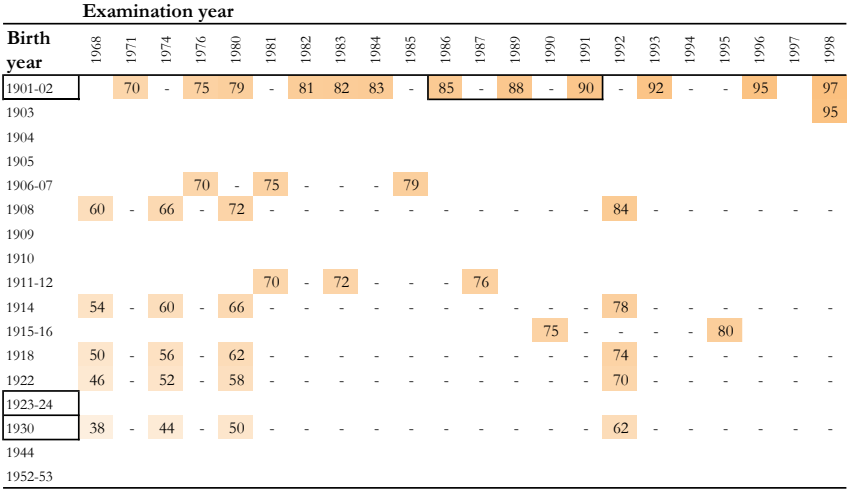
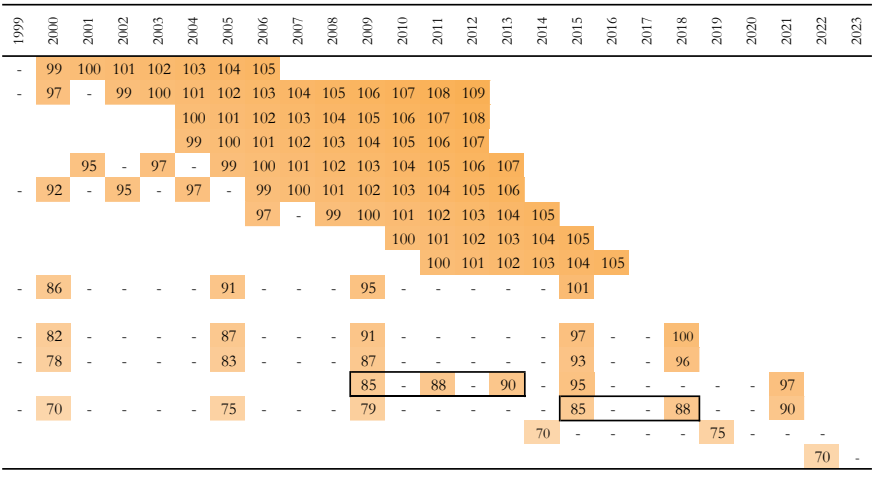


Figure 7 The Gothenburg H70 Birth cohort studies.
The figure shows the examination years on the y-axis, the birth cohort year on the x-axis, and the target age of the participants at examination within the figure. The cohorts included in this thesis are highlighted with black boxes. Source: Original picture created by Thomas Marlow, modified and published by Mellqvist Fässberg et al. 2019,[120] and further modified by author.

(response rate 61.0%, 117 women and 38 men). In addition, 45 participants who either declined or were not part of the psychiatric examination at baseline took part at the age of 90, giving a total number of 200 participants.

Birth cohort 1923-24

The birth cohort of 1923-24 was invited for the first time at the age of 85. At the baseline examination in 2008-2010, individuals born July 1, 1923, to June 29, 1924, on dates ending with 1, 3, 5, 7, or 9, and registered residents in the municipality of Gothenburg, were invited to a health examination (N=1013). Forty individuals died before the examination, 19 could not speak Swedish, four had emigrated outside Sweden, and six could not be traced, leaving an effective sample of 944 individuals, of which 571 (60.5%, 359 women and 212 men) took part in the study. In the first follow-up, 322 88-year-olds participated (response rate 73.5%, 205 women and 117 men). In the second follow-up, 250 90-year-olds participated (response rate 73.7%, 160 women, 90 men).



Birth cohort 1930

The 1930 birth cohort is more complex since it is used 1) as five cross-sectional studies with a new sampling at each wave (with one exception), 2) as two longitudinal studies (from age 70 and from age 75, where the latter included a large baseline sample), and 3) in combination with the PPSW. At all examination years, the cross-sectional inclusion criteria were based on pre-specified birth dates each month and residential addresses within the municipality of Gothenburg. The cross-sectional samples at ages 70, 75, 79, 85, and 88 are described in detail in **Paper I**.[121] The longitudinal inclusion criteria were based on individuals previously examined within the H70 studies or PPSW, even if they had moved outside of Gothenburg (applied in the H70 studies from the examination year 2009).

At the 85-year examination in 2015-2017, individuals born on dates ending with 2, 3, 5, 6, 11, 12, 16, 18, 20, 21, 24, 27, or 30, and registered residents in the municipality of Gothenburg were invited to a health examination (N=764). Forty-two individuals died before the examination, 31 could not speak Swedish, six could not be traced, and 13 were not invited due to technical issues (misclassified as not living in Gothenburg), leaving an effective sample of 672 individuals, of which 416 (61.9%, 251 women and 165 men) took part in the study. In addition, 102 individuals (effective sample n=95) previously examined within the PPSW or H70 living in other parts of Sweden were invited to a follow-up study, of which 75 (78.9%) participated.

At age 88, based on the cross-sectional inclusion criteria, of the 555 individuals invited (effective sample n=505), 258 individuals participated (51.1%, 162 women, and 96 men). In addition, 99 individuals (effective sample n=82) previously examined within the PPSW or H70, living in other parts of Sweden, were invited to the longitudinal study, of which 75 (52.4%) participated.

This cohort was planned to be examined at age 90 during 2020, but due to the Covid-19 pandemic, the wave was postponed and is thus not part of this thesis.

Box 3. Summary of the study designs in the papers

Paper	Design	Birth cohorts	Age	Outcome
I	Cross-sectional	H70: 1930	70, 75, 79, 85, and 88	Differences between participants, refusers, same-aged individuals in Gothenburg and Sweden.
II	Cross-sectional	H70 and PPSW: 1923-24, 1930	85	Number of dementia cases by different classification systems.
III	Cross-sectional, time trend	H70: 1901-02, 1923-24	85	Cohort differences in mortality of dementia.
IV	Cross-sectional, longitudinal, time trend	H70: 1901-02, 1923-24, 1930	85, 88, 90	Cohort differences in prevalence and incidence of dementia.

Study populations by paper

In **Paper I,** we used cross-sectional data from the 1930 birth cohort at five examination waves, used as cross-sectional data. As the research question was to examine the representativeness of the H70 studies, we included only the part of the sample residing in the municipality of Gothenburg.

In **Paper II,** we used data from the 1923-24 and 1930 birth cohorts at the examinations at age 85. In this paper, the research questions were focused on dementia diagnostic tools, making this sample with a high prevalence of dementia suitable. To increase the sample size, we included 75 individuals from the longitudinal sample no longer residing in Gothenburg. The same examination battery was applied in both groups.

In **Paper III,** we used data from the 1901-02 and 1923-24 birth cohorts at the age of 85. As the research question was to examine 8-year mortality, we only included the first two cohorts of 85-year olds as sufficient time since the examination had passed.

In **Paper IV,** we used data from the 1901-02, 1923-24, and 1930 cohorts at the ages 85, 88, and 90. In this paper, the research question was to examine time trends in both the incidence and prevalence of dementia among octogenarians, which is why we used a longitudinal sample from age 85 and cross-sectional samples at all ages. Due to the covid-19 pandemic, the 1930 cohort could not be examined at the age of 90.

Variables and outcome measures

After the systematic selection was made in each cohort, the potential respondents were approached with an invitation letter to participate in a health examination. A few days later, a research nurse or administrative staff member contacted them by telephone. The examination battery in the H70 studies is extensive. Although the exact included examination parts have to some extent, varied over the decades, the examination has always included semi-structured health interviews, neuropsychiatric examinations, physical examinations, and psychometric testing.[117] The semi-structured health interviews included questions regarding somatic and psychiatric disorders, social and sociodemographic factors, medications, lifestyle factors, and ADL/iADL. The physical examinations included anthropometric measures, blood pressure, blood sampling, lung function, and electrocardiogram (ECG). In addition, the participants in H70 were invited to a range of additional examinations such as ophthalmologic and hearing examinations, diet history interview, key informant interview, MRI and CT scanning, DXA scanning, and dental examination.

Although the examinations have been kept as similar as possible to ensure comparability over time, some changes have been implemented that are worth noting. In cohort 1901-02, the examination had three major parts.[119] The first part consisted of a nurse home visit to the participant to collect basic information through semi-structured interviews. The participant was then in the second part examined at an outpatient department of the Geriatric hospital, which included a physical examination by a geriatrician, neuropsychological tests administered by a psychologist, and laboratory tests such as ECG, blood tests, and chest X-ray.[116,122] In the final and third step, a psychiatrist made a home visit to perform the neuropsychiatric examination. In cohorts 1923-24 and 1930, the examination was generally performed in one step where the basic information, health examination, and neuropsychiatric examination were performed either at the outpatient clinic or in the participants' home, if requested by the participant. However, as the examination took about six hours to perform, the participants were offered to divide the examination into two or more parts to reduce the burden for those who wished.

Also, in cohort 1901-02, the same psychiatrist (Ingmar Skoog, today PI of the H70 studies) performed all neuropsychiatric examinations at the baseline examination. In the more recent cohorts, the neuropsychiatric examinations

were performed by experienced psychiatric research nurses that were trained by Ingmar Skoog. The kappa value for the agreement in rating symptoms and signs of dementia between psychiatrists and nurses in the H70 studies have been reported to be high (kappa values 0.74-1.00).[88]

Neuropsychiatric examinations and key informant interviews

The neuropsychiatric examinations included assessments of psychiatric and cognitive symptoms according to the Comprehensive Psychopathological Rating Scale (CPRS),[123] structured assessments of clinical symptoms and signs of dementia, the Gottfries-Bråne-Steen Scale (GBS),[124] and the Clinical Dementia Rating score (CDR).[125] The participants performed several tests of mental functioning, such as short and long-term memory (naming the current and former Prime minister of Sweden, remembering objects shown earlier in the interview), orientation (identifying the current place and time), abstract thinking (understanding proverbs), aphasia (naming objects), verbal functioning (Word Fluency, naming objects), apraxia (following commands, perform how one would send a letter to oneself in five steps), agnosia (naming fingers), constructional difficulties and executive abilities (copying drawings of shapes), and complex attention (mental arithmetic, correctly identifying the number of letters in a list read out with both letters and numbers). These tests are part of the Mini-Mental State Examination (MMSE)[126] and the Alzheimer's Disease Assessment Scale Cognitive Subscale – ADAS-Cog,[127] as well as a few tests specific to the H70 study protocol.

At every examination, the participants were asked to name a close relative or friend that would be able to conduct a comprehensive key informant interview. Questions during the interview included changes in memory, behaviour, personality, mood, language, psychiatric symptoms, intellectual functioning, and if the key informant reported prevalent dementia, questions regarding the age of onset and disease course were asked.[128]

A telephone interview at age 85 in cohort 1901-02 was performed with 451 key informants (91%) with a median length of the interview of 31 minutes (min 9, max 95). In the 1923-24 cohort, an interview was performed with 439 informants (77%), and the median length was 45 minutes (min 5, max 180). In cohort 1930, an interview was performed with 340 informants (82%), and the median length was 65 minutes (min 15, max 200). The key informants were often a spouse or a child (Box 4).

Box 4. Characteristics of key informant interviews

Cohort	1901-02	1923-24	1930
Number	450 (91%)	439 (77%)	340 (82%)
Median interval between examination and interview Months, (min-max)	6 (0-12)	10 (0-33)	2 (0-17)
Median length Minutes, (min-max)	31 (9-95)	45 (5-180)	70 (15-200)
Key informant			
Spouse	7%	23%	26%
Child	58%	63%	58%
Living together	12%	21%	25%
Participant MMT, median (95 % CI)			
Interview performed	27 (26-27)	27 (27-28)	28 (28-28)
No key informant interview	28 (28-29)	28 (27-28)	28 (27-29)

Dementia diagnosis

Dementia diagnoses used in the H70 studies are based on the DSM-III-R criteria,[83] using data from the neuropsychiatric examination and key informant interview. An important difference between the H70 diagnose, and the DSM-III-R criteria are that in the H70 diagnose, impairment in short-term *or* long-term memory is enough to fulfil the criteria of impairment in memory, whereas in the DSM-III-R criteria, it is mandatory with impairment in *both* short-term *and* long-term memory. The clinical expertise decided this diverging from the original criteria, finding the criteria too strict.[129] This decision was strengthened by the release of the DSM-IV, where the same change had been applied.[84] Similarities and differences between the different diagnostic tools and the clinical consensus diagnosis are further examined in **Paper II.**

The procedure for classifying dementia cases has been kept identical over the cohorts to ensure comparability (see Figure 8). First, an algorithm based on the neuropsychiatric examination and the key informant interview produced two separate diagnoses, respectively. The symptoms included in the algorithm had to attain a level causing significant difficulties in social life to generate an indication of dementia. Second, the information from both sources were combined, and at least two clinical experts separately reviewed the output of the algorithms. In cases where the algorithm output was inconclusive, the research file was reviewed in full. To classify a dementia case, four levels of ascertainment were followed:

1. Dementia, according to both the psychiatric examination and the informant interview
2. Dementia, according to either the psychiatric examination or the informant interview, supported by the other examination
3. Dementia, according to the informant interview, confirmed by MMSE
4. In cases of no informant interview, severe dementia, according to the neuropsychiatric examination

In the third and last step, the clinical experts held a consensus conference to decide on the final diagnoses.

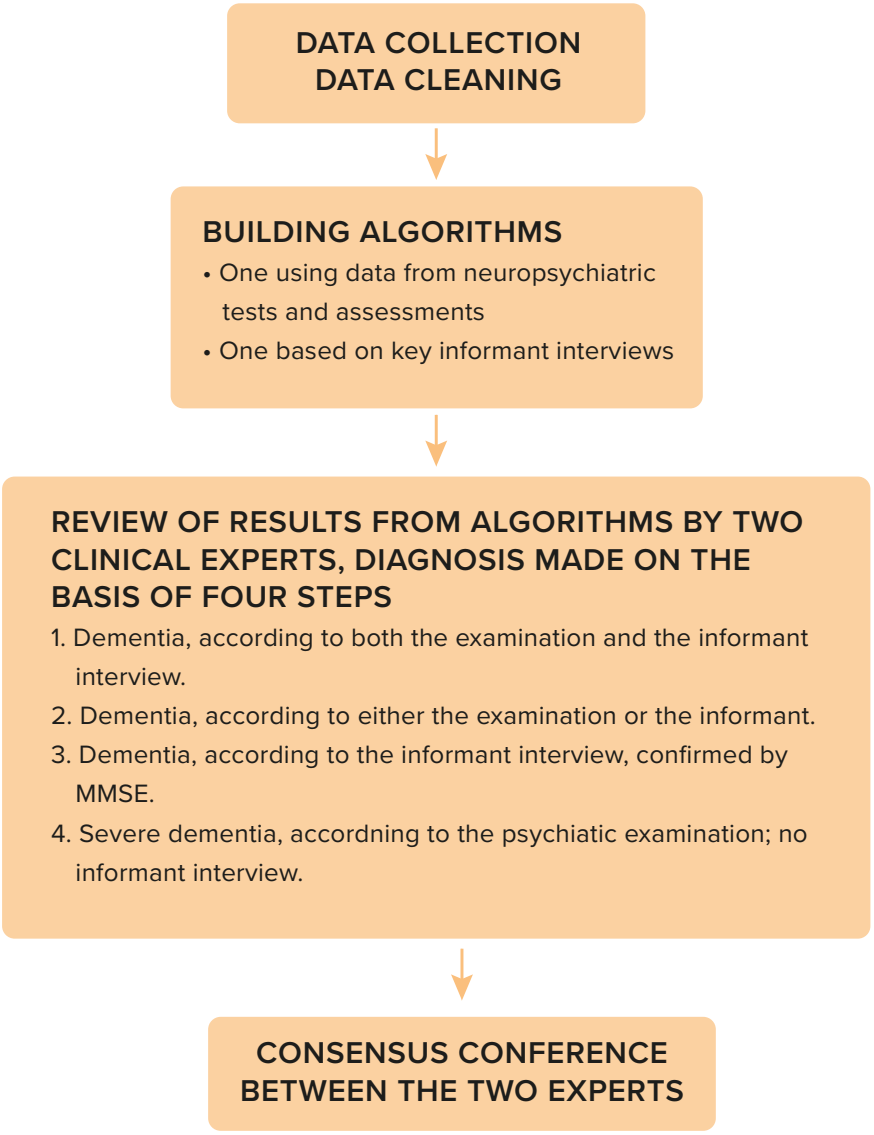


Figure 8 Workflow of setting dementia diagnoses according to the DSM-III-R.
The workflow of setting the clinical consensus diagnoses has been kept identical in all cohorts included in the H70-studies.

In 2019, to ensure comparability over the cohorts, the diagnoses for cohorts 1901-02 and 1923-24 were re-evaluated during the same time-period in which the diagnosing of cohort 1930 was initiated. The only change made was one case of dementia in the 1923-24 cohort that was re-coded to no dementia.[49]

In **Paper III**, we also classified the severity of dementia and etiological subgroups based on the likely causes of dementia. Probable or possible AD was diagnosed in accordance with the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) criteria.[130] We diagnosed vascular dementia based on the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) criteria,[131] meaning a temporal connection (within one year) between the first symptoms of dementia and a stroke or transient ischaemic attack (TIA). If there was no clear temporal connection between the onset of dementia and a stroke/TIA, we diagnosed mixed dementia. The information on stroke/TIA was based on self-report and key informant interviews and was only diagnosed when clear focal neurological symptoms (such as aphasia or hemiparesis) were reported, with a duration of symptoms of <24h for TIA and ≥24h for stroke.[88] We also used information from the IPR, which has shown to have good sensitivity and specificity of stroke.[132]

A few cases were diagnosed with other causes when other disorders in temporal connection to the dementia onset and of sufficient degree to cause dementia were identified. Other causes included NPH, alcohol dementia, Parkinson's disease, brain tumour, head injury, and unspecified dementia when no clear aetiology was identified.[88]

Severity of dementia was determined based on the criteria in the DSM-III-R.[83]

- Mild dementia: social activities were significantly impaired, but the capacity for independent living remained with adequate personal hygiene and relatively intact judgment.

- Moderate dementia: independent living would be hazardous, and some degree of supervision would be necessary

- Severe dementia: ADL would be so impaired that supervision would be continually required, such as minimal personal hygiene would be unable to maintain or the person being incoherent or mute.

The classification system for diagnosing dementia is used slightly differently in the four papers included in this thesis (see Box 5). In **Paper I**, dementia was one of the variables used for investigating selection bias. In this paper, we collected dementia diagnoses from the IPR, hence using the ICD-10 classification system. In **Paper II**, the aim was to compare the different classification systems, which is why five different editions of the systems were included (DSM-III-R, DSM-IV, DSM-5, ICD-10, and ICD-11), as well as the clinical consensus diagnosis. In **Paper III,** we only used the clinical consensus diagnosis based on the DSM-III-R (as described above). In **Paper IV,** we mainly used the clinical consensus diagnosis and added register data from the IPR and CDREG for cases lost to follow-up. As data from the first cohort was collected in the late 1980s, the register data covers three versions of the ICD: 8, 9, and 10.

Box 5. The classification systems used in the papers

Paper I	ICD 10
Paper II	Clinical consensus diagnosis (DSM-III-R) DSM-III-R DSM-IV DSM-5 ICD-10 ICD-11
Paper III	Clinical consensus diagnosis (DSM-III-R)
Paper IV	Clinical consensus diagnosis (DSM-III-R) ICD-8 ICD-9 ICD-10

Register data

In addition to the data collected during the examinations, we used register data in different ways in **Paper I**, **Paper III** and **Paper IV**.

In **Paper I**, we collected data on dates of death from the Swedish Tax Agency, demographics from Statistics Sweden, and data on discharge diagnoses from the National Board of Health and Welfare (the IPR) for participants, refusals, and same-aged individuals in Gothenburg and in Sweden. To protect the anonymity of the participants as well as the refusals, the data was received on an aggregated level.

In **Paper III**, dates of death from the Swedish Tax Agency and data on discharge diagnoses from the IPR were used for comparisons between participants and non-participants. The discharge diagnoses were also used to complement the information on diseases included in the models predicting mortality.

In **Paper IV**, we used register data to collect information on the date of death from the Swedish Tax Agency. We used the IPR and the CDREG to collect information on incident cases of dementia in those lost-to follow-up, as well as to examine the sensitivity and specificity of dementia diagnoses in the IPR and CDREG.

Data analyses

Box 6. Analyses used in Paper I

Aim: To describe the representativeness of participants in relation to three levels of representativeness; refusals, same-aged individuals in Gothenburg, and same-aged individuals in Sweden.

Variables: Sociodemographic variables included: marital status, highest attained educational level, country of birth, paid labour, and average monthly income. The hospital discharge diagnoses included: cancer, alcohol-related-, and neuropsychiatric disorders (including dementia), cardiovascular-, ischemic heart-, cerebrovascular-, and chronic obstructive pulmonary diseases, diabetes mellitus, unipolar depression, and osteoarthritis. Survival time.

Statistical methods: Persons Chi-square or Fisher's exact test, independent samples t-test, Cox proportional hazards model (using age as time-scale) presented as hazard ratios (HR), and 95% confidence intervals (CI).

Analyses:

1) The differences in response rates and the proportion excluded between the examination years.
2) Mortality in participants and refusals.
3) The difference in the prevalence of sociodemographic variables and the hospital discharge diagnoses between:
    a) Participants and refusals
    b) Participants and same-aged individuals in Gothenburg
    c) Participants and same-aged individuals in Sweden

Box 7. Analyses used in Paper II

Aim: To examine how the prevalence of dementia varies between different diagnostic tools, including the recent DSM-5 and ICD-11.

Statistical methods: Persons Chi-square test, Cohen's kappa coefficient, and McNemar's test.

Analyses:

1) Overlap between the different dementia diagnoses.
2) Agreement (Cohen's kappa) between the different dementia diagnoses.
3) Difference in proportions of dementia cases.
4) Difference in the severity of dementia in the different dementia diagnoses.
5) Sensitivity analyses:
   a) Comparison of the prevalence of dementia according to the clinical consensus diagnoses in those with and without missing data.
   b) Investigating the impact of key informant interview by performing 1), 2), and 3) after excluding this information.

Box 8. Analyses used in Paper III

Aim: To examine if the 8-year mortality in relation to dementia among 85-year-olds had changed over two cohorts born 22 years apart. We also examined the importance of dementia in relation to other diseases to predict mortality.

Statistical methods: Pearson's Chi-square, independent samples t-test, Mann–Whitney U Test, Kaplan–Meier survival analysis, and Cox proportional hazards, using time-on-study as a time-scale.

Covariates: Dementia severity, cerebrovascular disorders, congestive heart failure, diabetes mellitus, chronic bronchitis, atrial fibrillation, angina pectoris, myocardial infarction, total cholesterol, cholesterol treatment, hypertension, and hypertension treatment.

Models:

1) Age and sex
2) Age, sex, and dementia
3) Age, sex, and dementia severity
4) Age, sex, dementia, and educational level
5) Age, sex, dementia, educational level, and relevant diseases (as selected by primary analyses)

Analyses:

1) Differences in mortality between men and women within each cohort.
2) Differences in mortality between those with and without dementia within each cohort.
3) Differences in mortality between the cohorts, total group and stratified by sex, using models 1-5.
4) Interaction of sex*cohort and educational level*cohort in relation to mortality.
5) Differences in mortality between cohorts stratified by dementia status, using models 1-5.
6) The effect of each of the independent predictors for 8-year mortality was calculated as population attributable risk (PAR).

Box 9. Analyses used in Paper IV

Aim: To examine if the incidence and prevalence of dementia among 85-year-olds decreased over three cohorts born 30 years apart. We also examined the sensitivity and specificity of the IPR and CDREG.

Statistical methods: Logistic regression and Poisson regression with a natural log person-years follow-up offset term.

Models:

1) Sex
2) Sex and educational level

Analyses:

1) Comparing the prevalence of dementia at ages 85, 88 and 90 between the cohorts, using model 1-2.
2) Comparing the prevalence of dementia between men and women within the cohorts.
3) Comparing the difference in four-year incidence of dementia between the cohorts, using model 1-2.
4) Comparing the difference in four-year incidence of dementia between men and women within the cohorts.
5) Examining the sensitivity and specificity of dementia diagnoses in the IPR and CDREG.

Ethical considerations

The Regional Ethical Review Board in Gothenburg has approved all studies. Two amendments for **Paper I** regarding the use of aggregated register data were approved by the Swedish Ethical Review Authority. Informed consent was obtained before the examinations according to the Helsinki declaration, primarily by the participants, still in some cases when this was not possible (e.g. due to severe dementia), a family member or close relative consented to the participation. The participant was informed before the examination of the expected duration of the examination, that lunch and a snack would be provided, a general overview of the content of the examination, as well as data management and storage. The participants were also informed on the potential risks (i.e. no risk, but potential discomfort during blood sampling), and the potential benefits (information on current health status regarding e.g. blood pressure, cholesterol, and glucose levels, ECG, hearing, and visual status). They were also informed that withdrawal from the study would be possible (including deletion of already collected data) at any time without declaring a reason and that declining participation would not affect their contact with health care.

A medical doctor on-site reviewed the results from the examination to determine if there were potential medical implications. If no acute situation was identified, participants were referred to an appropriate clinic if previously unknown diseases or pathologies were detected.

As the examinations were extensive, participation could be demanding, especially in the high-age groups included in this thesis. To minimize this burden, participants were offered home visits and to split up the examination into more than one time point. However, most participants took part in all examination parts, and the follow-ups had high response rates.

04

MAIN **RESULTS**

04 MAIN RESULTS

A summary of the main results of the four included papers is presented in the following sections. To read the full results, please see the re-printed publications and manuscript at the end of the thesis.

Main results of Paper I

Hanna Wetterberg*, Lina Rydén* et al. *Representativeness in population-based studies of older adults – Five waves of cross-sectional examinations in the Gothenburg H70 Birth Cohort Study.* BMJ Open 2022;12:e068165.[121] * HW and LR are joint first authors.

In **Paper I**, we found that the response rate ranged from 51.1% to 69.6% and was higher at age 70 and lower at age 88 compared to all other examinations. The response rate was higher among those with higher education and those who were married, but there were no differences between men and women. Mortality was lower in participants than refusals, and the prevalence of a range of disorders in the IPR was lower, such as cardiovascular disease, neuropsychiatric-, and alcohol-related disorders. The prevalence of osteoarthritis was higher in participants, they had higher educational level, and were more often married, compared to refusals.

Compared to same-aged individuals in Gothenburg, the participants had higher educational levels and were more often born in Sweden. At age 70, they had a lower prevalence of cerebrovascular and neuropsychiatric disorders in the IPR.

In comparison to same-aged individuals in Sweden, the educational level was higher in participants, they were *less* often born in Sweden, had higher average income, were more often divorced, and had a lower prevalence of a range of disorders, such as cancer, cardiovascular-, cerebrovascular-, and ischemic heart disease.

Main results of Paper II

Hanna Wetterberg, et al. *The effect of diagnostic criteria on dementia prevalence – A population-based study from Gothenburg, Sweden.* (Submitted).

As **Paper II** includes unpublished results, the summary of results is condensed. The results show that the prevalence of dementia varies depending on the choice of the edition of the classification system. The classification with the lowest prevalence was based on the ICD-10 and the highest on ICD-11, followed by the DSM-5. The kappa values of agreement between the classification systems were overall high, with the highest being between the ICD-11 and DSM-5, and DSM-IV and the clinical consensus diagnosis, which is based on the DSM-III-R criteria. Although the agreement between ICD-11 and DSM-5 was high, small differences in the criteria yielded differences in the number of dementia cases.

We also found that symptoms of cognitive decline, as well as reported concern regarding cognitive decline, were common in octogenarians. The most common symptom of cognitive decline was a "decline in other cognitive abilities characterized by deterioration in judgment and thinking" as defined by ICD-10 and "disturbance in executive functioning" as defined by DSM-IV. Less frequent were the symptoms of "impaired judgment" and "coarsening of social behaviour", as defined by the DSM-III-R and DSM-IV.

Main results of Paper III

Hanna Wetterberg, et al. *Dementia remains the major predictor of death among octogenarians. A study of two population cohorts of 85-year-olds examined 22 years apart.* European Journal of Epidemiology, 2021. 36(5): p. 507-517.[49]

We found that the median survival time among 85-year-olds increased from 4.9 (95% CI 4.4-5.5) years in cohort 1901-02 to 5.7 (95% CI 5.2-6.2) years in cohort 1923-24. Participants with dementia had higher mortality than those without in both cohorts, but the mortality decreased between cohorts among those with dementia after adjusting for dementia severity and common diseases (HR 0.7; 95% CI 0.5–0.99) (Table 1). The PAR of dementia for death was higher than the other diseases examined, such as cerebrovascular disorders, myocardial infarction, and congestive heart failure, in both cohorts, meaning that dementia was the most important predictor of death. However, the relative risk of death from dementia did not change between the cohorts.

The mortality increased with the increasing severity of dementia. For the purpose of this thesis, the effect of the interaction between cohort and dementia severity on mortality was tested with Cox proportional hazards model. After adjusting for sex and age at baseline, there was no interaction between the dementia severity and cohort (p=0.846), indicating that mortality in relation to dementia declined in all severity groups.

Table 1. Change in 8-year mortality between birth cohorts 1901–02 and 1923–24, stratified by dementia status

		Model 1	Model 5
	Deceased (%)	HR (95% CI)	HR (95% CI)
Dementia at baseline			
Cohort 1901-02	95.2	*1.0 (Ref.)*	*1.0 (Ref.)*
Cohort 1923-24	93.5	0.7 (0.5-1.0)	**0.7 (0.5-0.99)**
Dementia-free at baseline			
Cohort 1901-02	69.2	*1.0 (Ref.)*	*1.0 (Ref.)*
Cohort 1923-24	64.1	**0.7 (0.5-0.9)**	**0.7 (0.5-0.9)**

Hazards ratios derived from Cox proportional hazards model. Bolded P-values and hazard ratios have a P-value < 0.05. Model 1: adjusted for age and sex. Model 5: adjusted for age, sex, baseline dementia severity (in the dementia group), education, and relevant diseases. See reprinted paper for Models 2-4.

Source: Table 2 in Wetterberg et al. 2021.[49]

Main results of Paper IV

Hanna Wetterberg et al. *Decreasing incidence and prevalence of dementia among octogenarians. A population-based study on three cohorts born 30 years apart.* The Journals of Gerontology: Series A, 2023; glad071.[133]

When comparing 85-year-olds, the prevalence of dementia decreased from 29.8% in cohort 1901-02 to 21.5% in cohort 1923-24. The prevalence of 24.5% in cohort 1930 was not significantly different from cohort 1901-02 nor 1923-24. Among 88-year-olds, the prevalence decreased from 41.9% in cohort 1901-02 to 28.0% in cohort 1923-24 and 21.7% in cohort 1930. At age 90, the prevalence of dementia was 41.5% in cohort 1901-02 and 37.2% in cohort 1923-24, which did not represent a significant decline (cohort 1930 was not examined at age 90 due to the Covid-19 pandemic).

We also found that the four-year cumulative incidence of dementia from age 85 declined from 49/1000 person-years in cohort 1901-02 to 23/1000 person-years in cohort 1930. The 38/1000 person-years incidence rate in cohort 1923-24 did not differ from cohort 1901-02 nor 1930.

The decrease in prevalence and incidence of dementia was more accentuated among women. Women had a higher prevalence of dementia than men at age 88 in cohorts 1901-02 and 1923-24 but not in cohort 1930. The IPR and CDREG had moderate sensitivity and a high specificity, and was similar for all three cohorts.

For this thesis, additional analyses were performed to investigate potential varying attrition bias between the cohorts. The response rate at follow-up among survivors in relation to dementia status at baseline was tested with logistic regression (Table 2). The response rate was lower among those with dementia in cohort 1930 compared to cohort 1901-02, but no differences between those without dementia were found. Also, the response rate by educational level was tested in a logistic regression, showing that individuals with a lower educational level more often were lost to follow-up in cohort 1923-24 than in 1930 (Table 2).

Table 2. Potential attrition bias at follow-up

	Response rate*	Model 1	Model 2
		OR (95% CI)	OR (95% CI)
Dementia at baseline			
Cohort 1901-02	78	*1.0 (Ref.)*	**2.3 (1.1-5.0)**
Cohort 1923-24	73	0.8 (0.4-1.7)	1.8 (0.8-3.9)
Cohort 1930	60	**0.4 (0.2-0.9)**	*1.0 (Ref.)*
Dementia-free at baseline			
Cohort 1901-02	69	*1.0 (Ref.)*	0.8 (0.6-1.2)
Cohort 1923-24	74	1.3 (0.9-1.9)	1.0 (0.7-1.5)
Cohort 1930	73	1.2 (0.9-1.8)	*1.0 (Ref.)*
Elementary education			
Cohort 1901-02	70	*1.0 (Ref.)*	0.7 (0.5-1.1)
Cohort 1923-24	65	0.8 (0.5-1.2)	**0.6 (0.4-0.9)**
Cohort 1930	77	1.4 (0.9-2.2)	*1.0 (Ref.)*
More than elementary education			
Cohort 1901-02	73	*1.0 (Ref.)*	1.1 (0.6-1.9)
Cohort 1923-24	81	1.5 (0.9-2.7)	**1.6 (1.0-2.6)**
Cohort 1930	72	0.9 (0.5-1.7)	*1.0 (Ref.)*

Note. Odds ratio derived from logistic regression model, stratified first by dementia status and then by educational level. In model 1, cohort 1901-02 is used as reference. In model 2, cohort 1930 is used as reference, as this shows differences also between cohorts 1923-24 and 1930. Bolded P-values and hazard ratios have a P-value < 0.05.
*Response rates at follow-up at age 88

05

DISCUSSION

07 DISCUSSION

In this thesis, methodological aspects of epidemiological studies of dementia, as well as time trends in the epidemiology of dementia, have been studied in four separate papers. In this section, methodological considerations are discussed, as well as the strengths and limitations of the included papers. The section also includes a general discussion of the findings. In the end, suggestions for future research directions are proposed.

Methodological discussion

Selection bias

In population-based studies that aim to describe the distribution of disease, selection bias poses a threat to the external validity of the results.[85] Selection bias could cause an issue both at baseline as well as in longitudinal settings. In studies of time trends, it is especially important to consider the risk of different selection biases or attrition between the cohorts.

The choice to use birth dates to select individuals in the H70 studies increases the chance of retrieving a representative sample. In comparison, some studies of time trends in dementia have sampled individuals from electoral rolls [15,19] or patient [16,134] or insurance registers.[135] Another method applied in the H70 studies to reduce the risk of selection bias was to offer home visits. This has previously been shown to increase response rates.[136] In particular, it increased the response rate in a group with high morbidity, reluctant to visit the clinic. However, we showed in **Paper I** that there were characteristics associated with lower participation rates in the 1930 cohort, such as lower level of education, being born outside of Sweden, not being married, as well as e.g. having cardiovascular diseases, neuropsychiatric disorders, or alcohol-related disorders.[121] As these characteristics overlap with known risk factors for dementia, a lower participation rate in these groups could have caused an underestimation of the prevalence and incidence of dementia in **Papers III** and **IV**. Although this selection bias might affect the estimates, both papers aimed to investigate time trends. That is why the most important concern relates to how much the selection bias varied between the cohorts. The response rate at age 85 was consistent over the three birth cohorts included

in this thesis (65%, 61%, and 62%). However, there are some differences in selection bias. For example, the non-participants in cohorts 1923-24 and 1930 had a higher 3-year mortality rate compared to participants. This difference was not found in cohort 1901-02. This could have inflated the difference in mortality between the two cohorts (1901-02 and 1923-24) in **Paper III** if participants in the later-born cohort included a healthier sample than the first cohort. It could also have influenced the findings in **Paper IV** if the differences in mortality rate were related to dementia. Shown in this thesis as additional results, there was an interaction between cohort and dementia status in relation to attrition between ages 85 and 88. This indicated that individuals with dementia more often refused at follow-up in cohort 1930 compared to both previous cohorts. This is an important insight, not at least in regards to **Paper IV**, since it might have inflated the decline in dementia prevalence we found when comparing cohorts 1930 and 1901-02 at age 88. However, there was no difference in refusal at follow-up based on dementia status between cohorts 1923-24 and 1901-02, which strengthens the conclusion of a declining prevalence of dementia. The attrition rate between ages 85 and 88 in those without dementia did not differ between cohorts, but it is impossible to know if those with incident dementia declined participation to a greater extent than previous cohorts. However, previous studies have shown that incidence is not as sensitive to non-response as prevalence.[16,137]

Another finding presented as additional results in this thesis was that the attrition at the age 88 follow-up differed by educational level between cohort 1923-24 and 1930, with the former having a larger dropout among those with only elementary education. Knowing that the risk of dementia is larger in the group with lower educational levels, we might have underestimated the incidence more in cohort 1923-24 than in cohort 1930.

An emerging problem in population-based studies is the increasing proportion of the population that is hard to contact. It is challenging to analyse the potential selection bias from this group, as we do not know if they differ in specific ways from those we get in contact with. Previous studies have suggested that this group might have worse psychological and physical health.[110] In previous H70 examinations performed in the 1970s and 1980s, only 0.4%-1.4% were coded as "not traceable".[116,128] In **Paper I,** we showed that the proportion of those we were unable to contact in cohort 1930 ranged from 0.5% to 3.6%.[121] One reason for the increase could be the rapid decline in the use of fixed landline telephones. Even though a fixed landline is still

the most common among older Swedes, mobile phones are increasingly replacing the landline,[138] and mobile phone numbers are generally more difficult to find.[139] Another reason could be that it is now common to have a caller ID, identifying who is calling. The ID that was shown when the research team called was "unknown." This could have affected the responses, as previous research has shown that respondents are affected by the familiarity of the organisation calling.[140,141] As these changes have occurred during the decades included in the time trend analyses in **Paper III** and **Paper IV**, this also poses a threat of differences regarding the selection bias between the compared cohorts. However, the proportion who we were unable to get in contact with was low and it is therefore unlikely that this affected the results of the papers.

Measurements bias

As dementia is the primary outcome in this thesis, the diagnostic procedures must be discussed. A measurement bias in the dementia diagnostic procedure could cause misclassification, i.e. categorising participants into the wrong category. At the data collection phase of the study, measurement biases could be introduced that, in a later stage, cause misclassification. For example, there is a risk that some diverging or sliding in how the interview is performed occurs. Several of the variables included in the dementia classification are clinical assessments based on the interview and tests altogether. If the assessments of symptoms and signs of dementia have changed, the results in **Paper III** and **IV** might have been affected. To minimise this risk, the psychiatrist (Professor Ingmar Skoog) performing the interviews in the first cohort included in this thesis trained the psychiatric nurses performing the interviews in the later-born cohorts. IS continuously oversees the data collection to keep the interviews as close as possible to previous examinations. Although the inter-rater agreement between psychiatrists and psychiatric research nurses has been high within the study,[88] the agreement between waves of examination years is impossible to test. However, objective measures such as performance in cognitive tests has also improved in later-born cohorts.[142] This strengthens the conclusion that the decline in dementia prevalence and incidence we found is not an artefact due to measurement bias.

Another potential risk of misclassification arises from the choice of diagnostic tool. As the methods have been kept the same since the late 1980s, the

diagnostic criteria used at that time, the DSM-III-R, has been used throughout the studies. As we showed in **Paper II**, the choice of diagnostic criteria has major implications on the estimated prevalence of dementia. However, when diagnosing dementia in the H70 study in the 1980s, it was decided to acknowledge deficits in short- *or* long-term memory as fulfilling the requirement of memory impairment, whilst DSM-III-R requires deficits in *both*. This was decided as the requirement of deficits in both was considered as too strict.[129] This decision makes the diagnoses of dementia in the H70 study more similar to the newer versions of diagnostic criteria, such as DSM-IV. It does, however, affect the comparability of prevalence and incidence estimates with other studies.

Performing interviews with key informants provide additional information important for diagnosing dementia. Although some population-based studies do not have access to key informant interviews,[19,143] it is commonly used. However, the procedure for inclusion varies. For example, in the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) studies, a key informant interview was performed in cases when the participant was unable to answer themselves, and in cases lost to follow-up due to death.[95,144] In the Dutch Rotterdam study and the British MRC-CFAS study, key informant interviews were performed among participants below pre-specified cut-offs in dementia screening tests.[89,145] In the H70-studies, all participants were asked to name a close relative or friend to participate in the extensive semi-structured interview. This was a strength, as **Paper II** showed that the prevalence of dementia increases when including the information from key informants. However, the use of key informant interviews also poses potential issues. For example, the coverage of key informant interviews was not perfect and varied slightly between cohorts. The proportion of participants with a key informant interview varied from 77% in cohort 1923-24 to 82% in 1930 and 91% in cohort 1901-02. As the interview provides information that captures more cases of dementia, the varying proportion could have affected the estimates. The difference in dementia prevalence between cohort 1923-24 and 1901-02 was mainly seen among the mild cases of dementia,[88] in which the information provided by the key informant likely is more important to capture the subtle changes than among more severe cases. It is possible that the difference in coverage of key informant interviews led to a lower detection rate of mild cases of dementia in the newer cohorts. Another issue with key informant interviews was that the median time between the neuropsychiatric evaluation and the interview varied between and within the cohorts, potentially affecting the information given.

Use of register data

In **Papers I**, **III** and **IV**, register data from Statistics Sweden, the Swedish Tax Agency, and the National Board of Health and Welfare was used in different ways.

Dates of death, retrieved from the Swedish Tax Agency, catch virtually all deaths.[146] The exception is individuals that have emigrated from Sweden. This was the case for a few individuals in cohort 1930. As the status of these individuals was unknown, they were excluded from the mortality analyses. Since the number was low, this would not have affected the results.

In **Paper I**, sociodemographic characteristics and discharge diagnoses were retrieved from Statistics Sweden and the National Board of Health and Welfare. A strength of using register data was that the same data was used for all groups and collected during the same period. As it is mandatory for all physicians to report data to the IPR, the coverage of hospital visits has been almost 100% since 1987.[147] However, data on this level might be crude and not sensitive enough to reveal actual differences.[104] A Danish study investigating the selection bias in a population-based cohort study compared the use of register data with previously collected clinical data. They found that the more detailed data, collected 20 years prior to the follow-up, confirmed more differences between participants and refusals compared to the use of register-based data.[104] Another limitation with register-based data is that hospital discharge diagnose codes only are proxies for disease, with varying sensitivity and specificity.[148] These considerations are also valid for **Paper III**, where register data, to some extent, was used for the data collection of diseases included as covariates in the models. Another concern in **Paper III** and **IV** was that we compared two cohorts examined 20 years apart. The diagnosing of some of the included diseases might have been influenced by time trends in awareness and diagnostic procedures. The diagnoses based on registers from the hospitals are also linked to changes in policies in the hospitals. However, in **Paper IV,** we found that the sensitivity of dementia in the IPR and CDREG did not differ between the three cohorts. Another limitation regarding registers is that the sensitivity for dementia is low or moderate, particularly in this high age group.[133,149] This directly affects the incidence estimates of **Paper IV**, as the source of information on dementia among those lost to follow-up only was based on register data.

Paper I

Paper I was based on a series of cross-sectional examinations, and we used aggregated data to compare the characteristics of participants in the H70 studies with refusals and same-aged individuals in Gothenburg and Sweden.[121] The sociodemographic variables included in the paper were selected based on previously known characteristics associated with declining participation. The hospital discharge diagnoses were chosen based on both disorders that are common in this age group, such as cardiovascular disease, and disorders associated with participation, such as neuropsychiatric or alcohol-related diseases.

The nature of the data makes adjustment of confounders impossible, which limits the interpretation of the individual characteristics. Instead, we used chi-square tests to analyse differences between participants, refusals, and same-aged individuals in Gothenburg and Sweden, for each sample characteristic. This ended up with many tests, which increased the risk of type I errors (false positives). One might argue that correction for multiple testing, such as Bonferroni correction, would lower this risk. This is true, but such corrections are also known to be very conservative and increase the risk of type II errors (false negatives).[150]

Another limitation in Paper I was that the comparison groups of same-aged individuals in Gothenburg and Sweden include the sampled population. This was considered necessary as the participants represent 15-25% of the population in its age group in Gothenburg, so excluding them might skew the comparison group.[121]

Paper II

In Paper II, we used cross-sectional data from two cohorts of 85-year-olds, an age group where dementia is common, to investigate the impact of the choice of diagnostic criteria on the prevalence of dementia.

Although the different algorithms were constructed to correspond to different editions of the DSM and ICD-systems, we could not validate the algorithms against a gold-standard clinical diagnosis corresponding to the correct criteria. The usefulness of the algorithms would have increased if their sensitivity and specificity had been analysed.

Another issue with algorithmic diagnoses is the difficulty of handling missing data. Previous studies have shown that those with too much missing data for the algorithm to classify, often have severe dementia, making them unable to answer questions or perform tests.[151]

We did not standardise the cognitive tests included in the algorithms based on educational level, which previously have been shown to increase the accuracy of algorithmic diagnoses.[152] This could potentially have led to a higher prevalence of dementia in the group with lower education. However, as many of the variables included in the algorithm are based on clinical assessments, where the clinician takes all information into consideration, it is unlikely that this would be a major issue.

Paper III

Paper III is a prospective cohort study of two cohorts of 85-year-olds where time trends in mortality among those with and without dementia were examined. We also examined the PAR of dementia and other common diseases on death.

The choice of diagnoses included was based on previous knowledge about common diseases in this age group. However, using a validated index score of diseases, such as the Charlson Comorbidity Index, would have increased the comparability with other studies. This was, however, not feasible in this project, as the collected data in the two cohorts limits the application of standardised indexes. This was because we had to prioritise variables that were as similar as possible to ensure comparability over the two cohorts,

which ended up with variables not matching a standardised index. Another limitation was that as the included diseases represent diseases prevalent at age 85, we cannot evaluate the effect on mortality of incident diseases that occurred after the examination.

To obtain the diagnoses of diseases included, data from self-report, laboratory results, medication lists, and register data were triangulated. This increased the potential to capture diseases.

Paper IV

Paper IV was a cross-sectional study to examine time trends in the prevalence of dementia at ages 85, 88, and 90, and a longitudinal study to investigate the four-year incidence of dementia.

As the participants were of advanced age, the risk of biased results due to selective survival and competing risk of death are prominent. However, as the mortality was higher in the first cohort, more cases were likely to be missed due to the competing risk of death in this cohort. This would underestimate the decline in dementia incidence and prevalence that we found rather than inflating it.

As the number of participants in each cohort was not very high, the analyses had low power to detect true differences in the prevalence and incidence of dementia between the cohorts. This could explain why we did not find a difference in dementia prevalence at age 85 between cohorts 1901-02 and 1930. In a posthoc power analysis, we found that with the number of 910 included in the analysis, there was a power of 0.56, at alpha 0.05, to detect an OR of 0.75.

General discussion

The main findings of **Paper I** were that participants had higher educational levels and mean income, and lower prevalence of disorders in the IPR, in comparison to refusals, and that the response rate declined with age. The participants were, however, more similar to the target population of same-aged individuals in Gothenburg and to same-aged individuals in Sweden, where they mainly differed in that participants had higher educational levels. The main findings of **Paper II** were that the ICD-11 and DSM-5

classification systems for dementia generated higher prevalence compared to older editions of both ICD and DSM, and that dementia classification has become more similar between the two as a result of intentional work to harmonise the systems. **Papers I** and **II** provide important insights on methodological considerations in studies of older adults, such as how the representativeness is affected by selection bias, and further emphasise the importance of comparing dementia prevalence utilising the same or similar criteria. In **Paper III**, we showed that 85-year-olds with dementia survived longer in a cohort born 1923-24, compared to a cohort born 1901-02, after adjusting for dementia severity, but that dementia still remains the most important factor of death. In **Paper IV**, we showed that the prevalence and four-year incidence of dementia decreased among the examined 85-88-year-olds over the past 30 years. A secondary finding was that the sensitivity of dementia in the IPR and CDREG was moderate, but the specificity was high. Interestingly, the sensitivity and specificity did not differ between the cohorts.

Representativeness

The results from **Paper I** align with previous studies indicating that those choosing to participate in health examination studies generally have higher education, fewer diseases, and higher income, compared to refusals.[107-109] Response rates in health examination studies have in general, decreased over the past decades.[153,154] This trend is worrying, as it might decrease the representativeness in epidemiological studies. For example, a Finnish study examining the representativeness in a health examination survey conducted over 25 years showed that even though the participation rate declined in all socioeconomic groups studied, the decline was larger in the group with lower occupational class and educational level.[153] Suggested reasons for the declining rates include participation exhaustion due to the increasing number of examinations and surveys performed and lower volunteerism overall.[155]

The response rate in the H70-studies among 70-year-olds was 85% in the early 1970s,[116] a high response rate which declined to 81% in the mid 1970s, to 77% in the early 1980s, and to 70% in 2000. This trend of declining response rate was broken in the most recent cohort of 70-year-olds in 2014–16, with a response rate of 72%.[117] In **Paper I,** we did see a decline in response rate over the years in cohort 1930, but we interpreted this mainly as an age effect.[121] Despite the declining response rate, the refusals had a higher

prevalence in more disorders than participants at age 70 than at age 85 or 88. This highlights the notion that response rate is not necessarily the best indication of study quality. It is more important to understand the non-response bias. In addition, it has been suggested that these two concepts are only weakly associated.[156] This relates to the finding that the participants were more similar to the target population, in line with results shown in previous studies.[104] However, the non-response bias is generally difficult to assess, as the bias is a result of the unknown response probability in interaction with the response rate of the study.[156]

Having a representative study sample is important in studies where the purpose is to describe the target population. It is also important in studies where the outcome of interest might vary between different subgroups. For example, the risk of dementia is suggested to vary by a number of characteristics, such as educational level, ethnicity, sex, and marital status.[13,157,158] These characteristics also coincide with factors associated with refusing participation. As shown in supplementary figure S1 in **Paper I**, the group with the lowest response rate at all examinations was unmarried men with lower educational levels. This could have affected the estimates of mortality, incidence, and prevalence of dementia found in **Papers III** and **IV**. In **Paper I**, we also found in that those refusing to participate at age 70 more often had dementia according to the IPR. However, as shown in **Paper IV,** the sensitivity of the IPR and CDREG was only 43%, making it difficult to interpret this finding. It is also worth noting that the higher frequency of dementia diagnoses among refusals might be a result of this group being in less health, having more hospital visits, and thus a higher chance of receiving a dementia diagnose in the registers.

Choice and use of diagnostic criteria

We found in **Paper II** that the choice of diagnostic criteria for dementia has an important effect on the prevalence of cases identified. This is not only supported by previous studies,[79,159,160] but also, to some extent, expected. During the past three to four decades, the research of dementia has made major progress in understanding the disorder, and the diagnostic systems have been updated accordingly. The criteria that yielded the highest prevalence were the latest ICD-11 and DSM-5 criteria, which corresponds well to the attempts to make the criteria more inclusive towards other dementias than primarily AD.[2] The differences in criteria emphasise the need

for harmonisation and awareness when comparing results. For example, a French study reported an increase in clinical consensus-diagnosed dementia over a ten-year period.[15] However, the two cohorts that were compared had been diagnosed based on the DSM-III-R in the first cohort and DSM-5 in the second cohort. As we found in **Paper II,** DSM-5 yields a considerably higher prevalence than DSM-III-R. The finding in the French study of an increasing incidence of dementia could, therefore, rather be a result of the differences in two editions of the DSM. The French study also reported that when diagnosing dementia with the same algorithmic approach in both cohorts, the incidence decreased. This additionally highlights the impact choice of diagnostic criteria has on the results.

In **Paper IV**, those lost to follow-up were followed by register data, where the first cohort was coded in accordance with the ICD-9 and the second with ICD-10. As ICD-10 has been found to yield a higher prevalence than the ICD-9,[79] there might be a risk that more cases were detected in the latter cohort. However, in **Paper IV,** we found that the sensitivity of register data was similar in all three cohorts.

Many large population-based cohort studies on older adults were initiated in the late 1980s or early 1990s, which is why the DSM-III-R criteria for dementia is commonly used.[15,16,18,92,144] The next edition, the DSM-IV, contained important differences, such as the change to allow for short-term *or* long-term memory deficits, as opposed to the requirement of deficits in both. In the most recent DSM-5, the differences compared to previous editions are even larger, as memory impairment is no longer required. These large differences put into question how future diagnosing of dementia in population-based studies from the 1980-1990s should be applied. Keeping the DSM-III-R diagnostic procedures enables cohort comparisons but reduces the possibility of estimating dementia prevalence that corresponds to modern criteria. One option would be to create two diagnoses, one based on modern criteria and one corresponding to the historically used criteria. This process is however, labour intensive and might not be possible in large population-based studies. Instead, algorithmic diagnoses based on different diagnostic criteria might be more feasible.

There have been several attempts to produce algorithms with varying results.[152,161,162] When comparing the overall accuracy of five different algorithms produced within the context of the Health and Retirement Study

in the US, the researchers concluded that it was high enough to justify the use of algorithms.[161] However, the performance varied across subgroups such as minorities, educational groups, and age groups. A recent Australian study found that their algorithms for dementia according to DSM-5 and DSM-IV had high accuracy compared to clinical consensus diagnoses.[162] Interestingly, in this paper, a subset of cases was diagnosed by two clinicians to test the inter-rater reliability ($\varkappa$ = 0.79, 95% CI; 0.54–1.0) which was found to be only slightly higher than the agreement between the clinician and the algorithm ($\varkappa$ =0.72, 95% CI 0.62–0.80). This is in line with a study from the 1980s, reporting that the agreement between the clinical consensus diagnosis and an algorithmic diagnosis was on the same level as between clinical raters.[163] This together with the notion that the algorithm holds high reliability as it is not affected by secular trends or intrapersonal changes as might happen in an assessor, forms arguments toward using an algorithmic approach in population-based studies.[151,163] There are also hybrid designs available, where a smaller subset of the participants is randomized to be examined with an extensive clinical protocol, and from this creating models, to predict dementia among the other participants.[164]

Among the disadvantages of using algorithms are that the validity could be lowered as not all information can be taken into account.[163] In comparison, in clinical consensus diagnoses, the research file has often been reviewed in full. In addition, a concern raised against algorithmic diagnoses is that they might have good sensitivity and specificity for prevalent cases of dementia but lower among incident dementia cases.[162,165] It was argued that the prevalent cases are easier to detect by algorithms, as they tend to be more severe compared to incident dementia cases. Although the aim in **Paper II** was to identify prevalent cases, it questions how high the sensitivity of the algorithms was for milder cases of dementia.

Mortality, incidence, and prevalence of dementia

In **Paper III** and **Paper IV**, we investigate the time trends in the mortality, incidence, and prevalence of dementia among octogenarians. We found that the mortality among those with prevalent dementia at age 85 was lower in cohort 1923-24 compared to cohort 1901-02.[49] Previous studies investigating time trends in survival time with dementia has shown varying results. Results from the Swedish study KP and SNAC-K showed that the mortality among those with dementia decreased between the late 1980s and the 2000s,[144] as did the French PAQUID comparing cohorts during the same time period.[166]

There are also studies showing the opposite, with higher mortality after dementia onset, such as the Health and Retirement study (HRS) comparing cohorts examined in 2000 and 2010,[167] the Cognitive Function and ageing study (MRC CFAS) comparing cohorts examined between the early 1990s and 2010s,[168], and the Framingham study comparing cohorts examined between the late 1970s and mid-2000s.[169] The results from the Framingham study also showed an increased age of onset of dementia. The shorter survival time in these studies has been interpreted as a compression of morbidity, i.e. shorter periods of disease. It has been suggested that compression of morbidity in dementia could be a result of an increasing cognitive reserve, making the brain withstand a greater pathological load before clinical symptoms become detectable.[74] However, once the onset of clinical symptoms occurs, the dementia is more severe and the disease course will progress more rapidly. In **Paper III**, we adjusted the mortality analyses for dementia severity as we previously have shown that the severity at age 85 decreased between the two cohorts.[88] However, we did not specifically examine if there had been different changes in survival rate by dementia severity. Additional analyses performed for the purpose of this thesis shows that there was no interaction between the dementia severity and cohort in relation to mortality, indicating that the mortality decreased evenly in mild, moderate, and severe dementia.

We examined survival time from the examination, meaning that we cannot know if the survival time from the onset of the disease also changed. As depicted in Figure 9, there are a number of potential scenarios of changes in mortality in relation to dementia severity. The different scenarios depend on potential cohort changes occurring prior to the baseline examination at age 85. On the x-axis in Figure 9 are years prior to and after the baseline examination shown. The bars represent the median survival time from dementia onset, stratified by dementia severity and cohort. In **a)** shows that the median survival from the baseline examination was shorter by dementia severity in both cohorts, but was longer in cohort 1923-24 compared to 1901-02. We do however not know if this represents a compression of morbidity or longer survival with dementia, since we don't know when the disease onset occurred. In **b)**, it is assumed that the onset of dementia has not changed between the cohorts. If this was the case, the number of years lived with dementia would have increased. In **c)**, the dementia onset is assumed to be postponed for the same time as the survival after age 85. This would mean that the survival time with dementia remained the same. In **d)**, it is assumed that the onset of dementia has been postponed closer to the examination point. If this was the case, the survival with dementia would be shorter, and the number of years lived with the disease lower, i.e., the morbidity would be compressed.

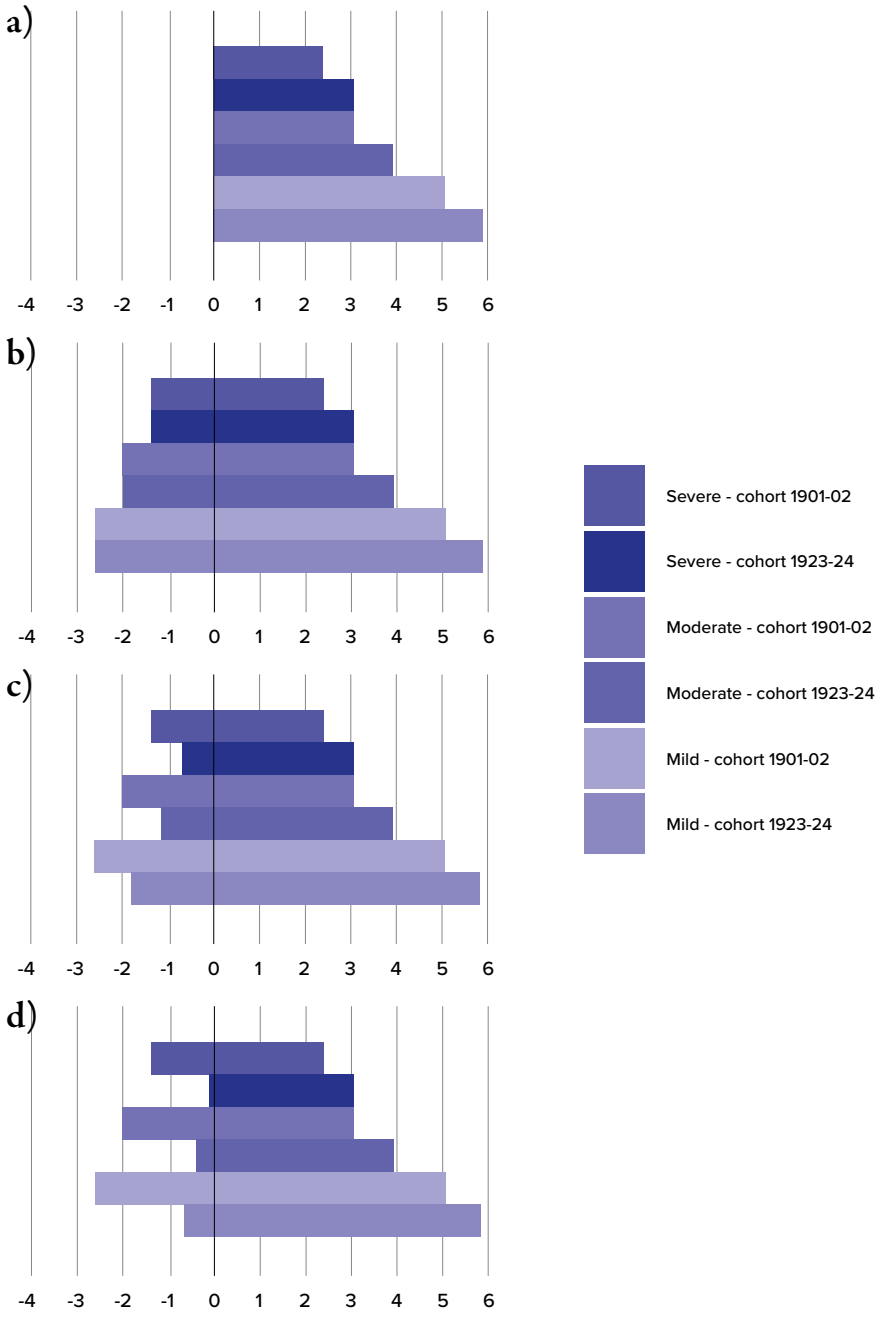


Figure 9 Figures over potential changes in survival with dementia
Results from **Paper III** shows a lower mortality in both those with and without dementia from the baseline examination at age 85. Depicted in this figure are three potential scenarios of what happened with the timing of dementia onset prior to the examination.

A potential effect of a lower mortality rate in individuals with dementia could be an increasing prevalence. However, in **Paper IV,** we show that the prevalence of dementia was decreasing between ages 85 and 88 in these two cohorts. We also show that the incidence declined between cohorts 1930 and 1901-02. However, the prevalence at age 85 between cohorts 1930 and 1901-02, and the incidence between cohorts 1923-24 and 1901-02, did not change statistically, although the estimates were lower in the more recent cohorts. As the sample sizes were relatively small, it is difficult to evaluate whether there was no change or if it was a result of low power.

In some studies where information on incidence of dementia was not available, changes in incidence was inferred based on mortality and prevalence data only.[95,144] One of these studies compared populations of 78+ examined in 1995-97 and 2001-03. The results showed a decline in prevalence of dementia among men, who also had a lower mortality. Another study compared populations of 75+ examined in 1987-89 and 2001-2004. They did not find a difference in prevalence of dementia, but they found that the survival time with dementia increased.[144] In both studies, this led to the conclusion that a decline in the incidence of dementia explained the lower and stable prevalence.

The prevalence of dementia reported in **Paper IV** decreased from 30% to 25% at age 85, from 42% to 22% at age 88, and 42% to 37% at age 90. The prevalences we report are in line with previous studies; however, ours are somewhat higher. For example, in the Swedish SNAC-K study, the prevalence at ages 85-89 was reported to be around 18% in both the late 1980s and 2010s'.[144] In the Spanish ZARADEMP-projects, the prevalence among participants $\geq$85 years was 16% and 18% in the late 1980s and mid-1990s.[170] In the British MRC-CFAS study the prevalence in the late 1980s was 24%, and in the 2010's 16%, in participants aged 85-89.[89] In this study, the identification of dementia cases was based on an algorithmic approach, which might be one explanation for the lower estimates. Another explanation for the lower rates in previous studies, compared to **Paper IV,** is that all studies, including previous studies from our research team, based the dementia diagnosis on the DSM-III-R criteria. However, as we found in **Paper II**, the H70 clinical consensus diagnosis has a higher agreement with the DSM-IV criteria, likely due to the change in memory requirement of accepting deficits in short-term *or* long-term memory. We also show that the prevalence of dementia presents higher prevalence when applying the DSM-IV compared

to the DSM-III-R. This highlights the importance of the choice of diagnostic criteria in epidemiological studies on dementia.

In **Paper IV,** we also found a decline in four-year dementia incidence between ages 85-89, from IR 49/1,000 person-years to 23/1,000 person-years. The incidence rates we report are similar to findings in the Rotterdam study, where the five-year incidence rate in the age group 85-89 years was 31/1,000 person-years in the early 90s, and 26/1,000 person-years in year 2000.[18] Other studies show higher incidence numbers in this age group. For example, the SNAC-K study presented rates of ten-year incidence in this age group from 108/1,000 person-years to 70/1,000 person years.[91] The MRC-CFAS presented two-year incidence rates of 62/1,000 person-years to 49/1,000 person-years, in the age group 85+.[16] Comparing incidence rates is not only difficult due to the point made above regarding how dementia is diagnosed. Previous studies also vary largely in the time of follow-up, including age groups in the age bands presented, and in methods of follow-up. For example, in the MRC CFAS study, a likelihood model to calculate the incidence of dementia among dropouts at follow-up was used.[16] In PAQUID, information about refusals and deaths was collected from close informants and medical practitioners.[15] The Rotterdam study had a similar approach, but only in persons with low cognition at baseline, and used information from the regional institute for outpatient mental health care for the total group.[18] In the SNAC-K study, a similar approach as us ours were used, where information was collected from medical records and key informants in those who died between waves.[91] Whether these different approaches explain the different results between studies is not clear.

Potential explanations for time trends in dementia epidemiology

In the papers published during the past years indicating a decline in dementia prevalence and incidence, the most common explanatory models for the declining trend include better control of vascular risk factors, higher and better quality of education, and higher living standards.[16,17,19,20,171] These protective factors also overlap with factors associated with overall better health and lower mortality. However, the decline is yet to be fully understood, as studies have not been able to identify causal mechanisms to fully account for the decline.[20] For example, The Framingham Heart study showed a decrease of 44% in the incidence of dementia between 1975 and early 2010,

simultaneously with a decrease of vascular risk factors.[17] However, the reduction in vascular risk factors did not fully explain the decreased incidence of dementia. Similarly, pooled data from the MoVIES and the MYHAT showed that the decreasing incidence of 77%, when comparing a cohort born in 1932-41 with a cohort born in 1902-1911, could not be explained by an increasing educational level.[19] The PAQUID and Three-city studies compared populations examined in the 1990s and 2000s and showed that education and vascular factors explained only a small part of the 35% decrease in dementia incidence.[15] The KP and SNAC-K showed a 30% decline in dementia incidence, comparing cohorts examined in the 2010s to the 1980s, and improvement in lifestyle factors, vascular disorders, education, and work conditions, only in part explained this decline.[91]

Simultaneously as the trends of declining dementia incidence and prevalence have occurred, large societal and medical events and developments have happened.[171,172] In Figure 10, the widely different life courses lived by the cohorts included in the H70 studies are shown in relation to examples of important events and developments that have occurred during the past century.[173] Individuals in the cohort born 1901-02 were born in a time of widespread poverty, and survived the Flu pandemic in their 20s. They were in their 40's when penicillin became available, and treatment of hypertension was not available until they were in their 60s. The individuals in the latest cohort were born in 1930 during the Great depression and they were young during the World War II. However, governmental funding for maternal and perinatal care had been initiated, public food service in schools was developed during their childhood, and they were in their 30s when the working week was changed from six to five days. Moreover, during the past century, large changes have occurred in food availability and diet, working conditions, access to information, and access and quality of education and care.[171,174] The differences in the birth cohorts' life courses have affected risk and protective factors in diverse ways, which in turn could have influenced the risk of dementia.[172]

Figure 10 Different birth cohorts' life courses in the view of important societal events. The risk of dementia should be considered in the broader historical and geographical context in which the cohort was born and lived their life. Source: Skoog et.al.,[173] Statistics Sweden.[175]

06

CONCLUSION

06 CONCLUSION

Epidemiological studies investigating the incidence, prevalence, and mortality of dementia are needed for the understanding of the societal and economic burden of the disease, as well as for policy makers to plan for the consequences of dementia on the public health and welfare system. Several studies published during the last decade have shown an overall trend toward a decline in the incidence and prevalence of dementia.[15-17,19,91] Results from **Paper IV** showed that this trend might be continued also among octogenarians, an age group few studies have reported on. This age group is rapidly increasing, and a decline in the incidence and prevalence of dementia could slow down the alarming projected increase in the burden of dementia.

In **Paper III**, we found that the survival time from age 85 has increased both in those with and without dementia. However, the relative risk of dementia on mortality remained similar between the cohorts. These findings indicate that individuals live with dementia to higher ages than in previous cohorts. Results from **Paper III** and **IV** can be used to further understand the time trends of dementia incidence, prevalence, and mortality. Moreover, to adequately plan for health care and welfare, it is imperative for policy makers to have up-to-date data to base the forecasting of the future epidemiology of dementia on.

In **Paper II,** we found that the diagnostic criteria that have been used during the past decades differ, resulting in varying prevalences of dementia. The newest editions, ICD-11 and DSM-5, generated the highest prevalence of dementia compared to the ICD-10, DSM-III-R, DSM-IV, and the clinical consensus diagnosis. This finding highlights the importance of the choice of diagnostic tools, as it has a direct effect on the estimates. We also found that the agreement between the ICD-11 and DSM-5 was high, suggesting that the work to harmonize the two systems has to some extent been successful.

Finally, in **Paper I,** we showed that participants in the H70-study cohort born in 1930 to some degree, differed from refusals, as they had higher educational levels and mean income, and lower prevalence of several disorders. The participants were more similar to the target population of same-aged individuals in Gothenburg than to refusals. The selection bias might have resulted in lower estimates of dementia prevalence and incidence, as the refusals had more illness and lower educational levels than the participants.

Future perspective

Few studies have examined time trends in dementia incidence and prevalence among octogenarians. It is unclear whether the increasing life expectancy is associated with a compression of morbidity, or if the time spent in disease will expand. It is difficult to achieve a high enough number of participants in this age group to ensure the power to detect smaller changes in time trends in dementia epidemiology. Future studies combining data from several longitudinal population-based studies could have the potential to validate the trends in incidence, prevalence, and mortality of dementia found in this thesis.

To further the understanding of how selection bias affects the estimates of dementia will be important for retrieving accurate estimates of dementia incidence and prevalence. In addition, future population-based studies might benefit from applying methods to increase the representativeness in groups known to refuse participation to a greater extent. One such approach could be weighted sampling.

Several long-running population-based studies diagnose dementia based on the DSM-III-R, published in 1987. As the newer editions are more widely defined to cover symptoms associated with other dementias than AD, future studies would benefit from applying these criteria. However, performing clinical consensus diagnoses is time-consuming and labour intensive. An alternative would be to apply algorithmic diagnoses and machine learning methods. We do, however, need more knowledge about the advantages and trade-offs of using these methods for diagnosing dementia in population-based studies.

The evolution of dementia epidemiology should be followed closely, as the decline in prevalence and incidence is not necessarily a stable downward trend. For example, better treatment of vascular disorders is believed to have had a suppressing effect on the risk of dementia. The frequency of obesity and diabetes type II is, however, increasing,[19] and this could, in turn, have a negative effect on the declining trend in dementia incidence and prevalence. Therefore, it is important to continuously examine new cohorts of older adults to update estimates of dementia incidence and prevalence.

It is estimated that 40% of all dementia cases could be prevented,[21] but despite this, no study has been able to fully explain the decline in dementia prevalence and incidence. Future studies examining the mechanisms of known risk factors for dementia, as well as studies searching for additional risk factors, are needed. In addition, studies on interventions aiming at reducing the risk of dementia at a population level are needed, as such interventions have the potential to, in a cost-effective way, promote brain-healthy lifestyles.[176]

07

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07 ACKNOWLEDGEMENT

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