UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCES

Dementia and Mortality

A Nationwide Registry-Based Study

PhD thesis

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This thesis was submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen, November 25, 2020

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Tilegnet min familie

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Preface and acknowledgements

This PhD project was carried out during my employment at the Danish Dementia Research Centre, Department of Neurology, Rigshospitalet (2016 to 2020).

I would like to thank all my supervisors for guiding me through this challenging and rewarding process. Gunhild Waldemar, thank you for giving me the opportunity of conducting this PhD study. Throughout this process I have been filled with admiration of your patient centered approach and your sense of accuracy and precision. Thank you for sharing your knowledge and showing a broader perspective when I have been caught up in details. Thomas Munk Laursen, I have appreciated your problem-solving and talent of coming up with simple, elegant solutions. Thank you for your positive approach, patience and readiness to answer questions. Thanks to you and your department for hosting me. I have always enjoyed our very productive meetings in Aarhus. Ane Nørgaard, thank you for your guidance in this project. I have valued your help with structuring my work, your flair for problem solving, and talent for simplifying and cutting to the point. Thank you for sharing your thoughts on the constant balance between career and personal life. I look forward to becoming your colleague.

Thanks to my collaborators Sabrina Islamoska, Henry Brodaty, and Kasper Jørgensen for your valuable contributions.

I had the honor and privilege to spend three months as a visiting junior researcher at the Dementia Centre for Research Collaboration at the University of New South Wales in Sydney. A warm thanks to Professor Henry Brodaty for giving me the opportunity to visit his group. Your genuine, humble, and kind approach towards every person you meet is truly admirable, and you have become a role model of mine. On a personal level, I would also like to express my gratitude for you always being considerate and kind, when I was far away from home at a difficult time. Furthermore, I would like to thank the wonderful and skillful researchers and staff at the Dementia Centre for Research Collaboration in Sydney for making me feel welcomed. A special thanks to Tiffany Chau for answering whatever strange question I have posed.

Thanks to Gangstedfonden, The Graduate School at Health and Medicines, and The Graduate Programme of Public Health and Epidemiology (both at University of Copenhagen) for their travel grants making the stay possible. In addition, I would like to thank Tine Olsen for all her help with solving the practical challenges related to organizing my stay abroad.

Thanks to Lægefonden for their grant to cover expenditures related to statistical support for my projects. Research at the Danish Dementia Research Centre is supported financially by the Danish Ministry of Health.

During my time as a PhD student, I have had the privilege to work in a warm, kind, and highly professional environment where people with dementia and their relatives are always in focus. Thank you, all colleagues, at the Danish Dementia Research Centre and the Memory Clinic for creating such an atmosphere.

A warm thanks to all my fellow young research colleagues, past and present, in the premises previously known as the “Rockerfeller Basement”. Thank you all for providing a great work environment, sharing knowledge and ideas, sorrows and laughs, and huge loads of cake.

Thanks to my friends and family for your support and bearing with me these past years. Signe, thank you for always having my back, pulling me up when I need a hand, and pushing me forward, when I need that extra encouragement. Maja, Bertram, Liva, Elisabeth, and Aske, thank you for giving me a second home. Thank you for inspiring me and keeping me playful. Charlie, thank you for being exactly who you are and helping me remember to treasure all the small moments in everyday life. Let us continue playing together throughout this life (and eat lots of ice cream). My parents, I am filled with gratitude to you both. Thank you for your support, patience, confidence in me, and endless love. I am spoiled in the very best meaning of the word.

Finally, Kave, thank you for being my love, my joy, and my rock during the past years. Thank you for supporting me in my ambitions, keeping me grounded, making the best lunch boxes in the world, putting a smile on my face, and making me happy. I love you.

Lærke Taudorf, November 2020

Manuscripts

This thesis is based on four original manuscripts.

I Taudorf L, Nørgaard A, Islamoska S, Jørgensen K, Laursen TM, Waldemar G.

Declining incidence of dementia: A national registry-based study over 20 years

Alzheimer's & Dementia. 2019;15:1383–1391.

II Taudorf L, Nørgaard A, Waldemar G, Laursen TM.

Mortality in dementia from 1996 to 2015: A national registry-based cohort study

In press, Journal of Alzheimer's Disease

III Taudorf L, Nørgaard A, Brodaty H, Laursen TM, Waldemar G.

Dementia increases mortality beyond effects of co-morbid conditions: A national registry-based cohort study

Submitted

IV Taudorf L, Nørgaard A, Islamoska S, Laursen TM, Waldemar G.

Causes of death in people with dementia: A national registry-based study over 14 years

Submitted

Summary

Globally, the number of people living with dementia is expected to increase rapidly during the next decades. Age is the most predominant risk factor for developing dementia, and the number of people with dementia is predicted to grow due to increasing life expectancy. The number of people living with dementia is affected by the incidence and mortality of dementia as well as the development in demographic structure. If people with dementia live longer, or the number of elderly people increase, it will result in a rising number of people living dementia. Nevertheless, population-based studies have reported declining incidence during the past decades. Many of these studies have been based on small populations or have reported tendencies and not significant results. Consequently, it has been questioned if the observed decline in incidence was real. Moreover, if incidence is declining how is it expected to affect the prevalence of dementia. As incidence, prevalence, and mortality are interdependable parameters, providing a time trend analysis of all three parameters in a large population could be useful in assessing more correct estimate of the future prevalence of dementia. Accurate estimates are crucial when planning future health care, so the needs of a large population of people with dementia can accommodated.

Increasing age is not only associated with increasing risk of dementia, but also with increasing risk of multiple comorbidities and death. Due to longevity, the number of people with dementia and multiple chronic comorbidities is expected to grow extensively during the next decades. Mortality is know to be markedly increased in people with dementia compared to the general elderly population. However, the association of dementia and concurrent chronic diseases and how it is related to mortality, is not well described. Despite the fact that mortality is increased in people with dementia, dementia diseases may not be perceived as fatal conditions. No previous studies have investigated if causes of death in people with dementia had changed over time. Such studies could contribute with knowledge about which comorbidities are associated with mortality in dementia.

This thesis is based on four nationwide registry-based studies using the entire Danish elderly population as a cohort. Overall, the aim was to investigate aspects of mortality in people with

dementia by assessing the time trends of incidence, prevalence, mortality, and causes of death in dementia, and the effect of comorbidities on mortality in dementia.

In Study I, we found that the age- and sex-adjusted incidence rate declined by 2% annually from 2004 to 2015, while the total prevalence increased during the entire period from 1996 to 2015. In Study II, we observed that mortality declined at the same rate in people with dementia compared to the general elderly population. Nevertheless, mortality remained about 2.9 times higher in people with dementia during the entire 20-year period. Additionally, the five-year survival after a dementia diagnosis was largely similar to the five-year survival after a diagnosis of cancer or acute ischemic heart disease. In Study III, we found that when comparing people with the same load of comorbidities, the mortality was significantly higher in people with dementia compared to those without. Even after adjusting for sex, age, calendar year, and comorbidities the mortality remained 2.7 times higher in people with dementia. In Study IV, we observed that from 2002 to 2015, dementia became the leading underlying cause of death in people with dementia. At the same time, there was a marked decline in the registration of cardio- and cerebrovascular disease as underlying cause of death in people with and without dementia.

In conclusion, this thesis described the time trends of incidence, prevalence, mortality, and causes of death in people with dementia in an entire national population. It identified people with dementia as a vulnerable group emphasized by a markedly higher mortality. Moreover, it underpins that dementia conditions should be perceived as serious and fatal brain diseases, as the five-year mortality is largely similar to that in cancer and acute ischemic heart disease. Hopefully, this change in perception of dementia as a fatal disease should result in more investments in research, including continuing the search for efficacious, disease modifying drugs, and in better health care for people with dementia.

Resumé

På verdensplan forventes antallet af mennesker med demens at stige markant over de næste årtier. Da alder er den største risikofaktor for at udvikle demens, er netop tiltagende levealder den primære årsag til den forventede stigning. Befolkningsundersøgelser de seneste årtier har dog vist faldende incidens af demens. Mange af disse undersøgelser har været foretaget i mindre populationer eller har fundet tendenser snarere end signifikante resultater. Derfor har der været sået tvivl om incidensen af demens reelt er faldende og i så tilfælde, i hvilken grad det vil påvirke prævalensen af demens. Prævalensen afhænger af incidens, mortalitet samt den demografiske udvikling. Hvis antallet af nye tilfælde forøges eller mennesker lever længere tid med deres demenssygdom, vil dette afstedkomme en stigning i prævalensen af demens. For at kunne danne et mere komplet estimat af hvorledes antallet af mennesker med demens vil udvikle sig, er det derfor yderst brugbart at undersøge tidsudviklingen af incidens, prævalens og mortalitet af demens i en samlet population. Sådanne estimater vil kunne bruges i planlægningen af fremtidens samfund, således at behovene fra et voksende antal mennesker med demens kan imødekommes.

Med stigende alder øges ikke blot risikoen for at udvikle demens, men også risikoen for andre kroniske sygdomme og død. Det forventes at antallet af mennesker der kommer til at leve med demens og komorbiditeter vil tiltage pga. stigende levealder. Når man sammenligner dødeligheden blandt ældre med og uden demens, er den markant højere blandt de med demens. Tilstedeværelsen af andre kroniske sygdomme bidrager formentlig til denne overdødelighed, men dette aspekt er endnu ikke velbeskrevet. Selvom demens er forbundet med en overdødelighed, opfattes demenssygdomme ofte ikke som dødelige sygdomme. Dette er problematisk, da alvorligheden ved disse sygdomme bør understrege vigtigheden af forebyggelse og videre forskning inden for demens. Ingen tidligere studier har undersøgt om dødsårsager hos mennesker med demens har ændret sig over tid. Sådanne studier kunne bidrage med vigtig viden om hvilke komorbiditeter, der er tilgrundliggende dødsårsager hos mennesker med demens.

Denne afhandling er baseret på fire nationale registerstudier, der alle benytter den samlede danske ældrebefolkning som population. Formålet var at undersøge forskellige aspekter af mortalitet ved

demens. Det gjorde vi ved at undersøge tidsudviklingen af incidens, prævalens, mortalitet og dødsårsager hos mennesker med demens samt forholdet mellem komorbiditeter og dødeligheden.

Studie I fandt at incidensraten i gennemsnit fald 2% årligt fra 2004 til 2015, mens den totale prævalens steg fra 1996 til 2015. I Studie II observerede vi over den 20-årige periode, at dødeligheden var stabilt ca. 2,9 gange højere hos mennesker med demens end hos de uden demens. Dette var selvom dødeligheden faldt i samme tempo hos mennesker med og uden demens. Femårsoverlevelsen efter en demensdiagnose var stort den samme som ved kræftsygdom eller akut iskæmisk hjertesygdom. I Studie III sammenlignede vi mennesker, der havde den samme mængde komorbiditeter. De med demens havde en signifikant højere dødelighed i forhold til den generelle ældrebefolkning uden demens. Når vi justerede for køn, alder, kalenderår og komorbiditeter, forblev dødeligheden 2,7 gange højere for mennesker med demens. I Studie IV observerede vi, at fra 2002 til 2015 blev demens den hyppigste registrerede tilgrundliggende dødsårsag blandt mennesker med demens. Samtidig var der et markant fald i registreringen af kardio- og cerebrovaskulære sygdomme som tilgrundliggende dødsårsag hos mennesker med og uden demens.

Denne afhandling beskriver tidsudviklingen af incidens, prævalens, mortalitet og dødsårsager hos mennesker med demens. De faldende incidensrater efterlader håb om at det måske er muligt at forebygge nogle demenstilfælde. Selvom mortaliteten faldt blandt mennesker med demens, var overdødeligheden gennem hele den 20-årige periode ca. 2,9 gange højere end ældrebefolkningen uden demens. Herved identificerede vi mennesker med demens som en sårbar gruppe. Vores resultater understreger at demens bør opfattes som alvorlige og dødelige hjernesygdomme. Dette fremhæves af at femårsoverlevelsen ved demens er på samme niveau som for kræftsygdom og akut iskæmisk hjertesygdom. Demens blev hyppigere registreret som en tilgrundliggende fremfor en medvirkende dødsårsag og er nu den hyppigste registrerede dødsårsag blandt mennesker med demens. Dette afspejler muligvis en øget bevidsthed om demens som en dødelig sygdom. Det er håbet at en ændring i opfattelsen af demens som dødelig sygdom vil føre til flere investeringer i demensforskning med henblik på udvikling af effektive sygdomsmodificerende lægemidler og bedre pleje af mennesker med demens.

Abbreviations

ACME	Automated Classification of Medical
AD	Alzheimer's Dementia
ATC	Anatomical Therapeutically Chemical
CCI	Charlson Comorbidity Index
CI	Confidence Interval
ICD-8	International Classification of Diseases 8th revision
ICD-10	International Classification of Diseases 10th revision
IHD	Ischemic Heart Disease
HR	Hazard Ratio
MR	Mortality Rate
MRR	Mortality Rate Ratio
VaD	Vascular Dementia
WHO	World Health Organization

Introduction

Dementia - a growing challenge

The world's population is ageing.[1] Globally, there were 703 million people aged 65 years or older in 2019, and this number is expected to double to 1.5 billion in 2050.[1] In 2015, there were 46.8 million people living with dementia worldwide.[2] With age being the strongest risk determinant for developing dementia, the number of people with dementia is expected to increase to 131.5 million by 2050.[2] In 2005, Ferri et al. estimated that the global prevalence of dementia was 24.3 million, expecting it to double every 20 years.[3] Nonetheless, just ten years later, in 2015, the prevalence of dementia had almost doubled, emphasizing the speed of the increasing prevalence.[2] This was primarily driven by an increase in life expectancy and thereby ageing populations.[2]

As the prevalence of dementia is increasing, so are the expenses related to this group of conditions. In 2015, the worldwide cost of dementia was estimated USD 818 billion and expected to increase to one trillion dollars by 2018.[2] Besides the huge economic costs, dementia has enormous human impact on both the lives of patients with dementia and their caregivers. Losing autonomy and the ability of controlling ones' life, physical dependency in performing activities of daily living, and impaired physical health leads to reduced quality of life.[4] Impaired cognition has a strong impact on the ability of self-care management.[5] It can cause reduced medical compliance leading to decreased physical health.[6] Moreover, up to 90% of patients with dementia experience behavioral and psychological symptoms which are known to reduce quality of life in patients and their caregivers.[7] Consequently, dementia also affects the health of caregivers. Having a partner with dementia is associated with impaired mental health and reduced life satisfaction.[8]

To this day, there is no cure for dementia. The existing pharmaceutical treatments for dementia are symptomatic.[9,10] Thus, it is essential to provide the best treatment, care, preservation of activities of daily living, and support for each person with dementia and her or his caregivers.

A historical perspective

Defined by the World Health Organization (WHO), *"Dementia is a syndrome, usually of a chronic or progressive nature, caused by a variety of brain illnesses that affect memory, thinking, behaviour, and ability to perform everyday activities".* [11]

The most frequent cause of dementia is Alzheimer's disease (AD), first described by Alois Alzheimer's in 1907.[12,13] He reported the case of a 51-year-old woman, Auguste Deter, who at this relatively young age showed symptoms (e.g. paranoia, cognitive impairment, hallucinations) that was known in senile dementia.[13] Until the late 1970s, senile dementia was viewed as a normal process of ageing, and the term AD was reserved for younger cases.[14] However, large population studies subsequently described that the majority of people actually preserved their intellectual capacity despite getting older.[15] In the mid-1980s, beta amyloid and tau were identified as the proteins causing plaques and tangles, in the pathogenesis of AD.[16,17] Autopsy studies also showed that the pathological brain changes in presenile AD and in elderly people who had died from senile dementia were similar.[18] Accordingly, AD was recognized as the most common cause of dementia in elderly as well as younger people. Better biological understanding of the disease led to the ability of earlier diagnostics. In the USA, Germany, and Sweden the first clinics for people with dementia opened around 1985.[15] They provided assessments, counselling, and follow-up. The first pharmaceutical treatment against Alzheimer's disease was introduced in USA that same year.[15] Alzheimer's associations and organizations had already been established to support patients and their families while bringing awareness of the need of a specialized dementia intervention. In Denmark, the first memory clinic was established in 1995, and the first pharmacological treatment against AD was licensed in 1997.[15] Since then, more advanced diagnostic tools have been introduced in the aim of making more precise diagnoses. National clinical and evidence-based guidelines for diagnostic evaluation of dementia have been available in Denmark since 1998 when a national multidisciplinary reference program was published by the Danish Neurological Society.[19]

Incidence, prevalence, and mortality

The prevalence of people living with dementia is highly related to incidence and mortality of dementia. With no cure for dementia, the only ways the prevalence can change is if incidence, mortality, or the development in demographic structure alter. In a paper by Wu et al., the authors use an example with a water tank to illustrate the association between incidence, prevalence, and mortality (Figure 1).[20] The prevalence is visualized as the water level in the tank. The prevalence can change either by adjusting flow rate of new dementia cases into the tank (incidence) or the flow rate of cases leaving the tank (mortality). This way of visualizing the relationship between incidence, prevalence, and mortality can be useful in illustrating how changes in each of the parameters could affect the future prevalence of dementia.

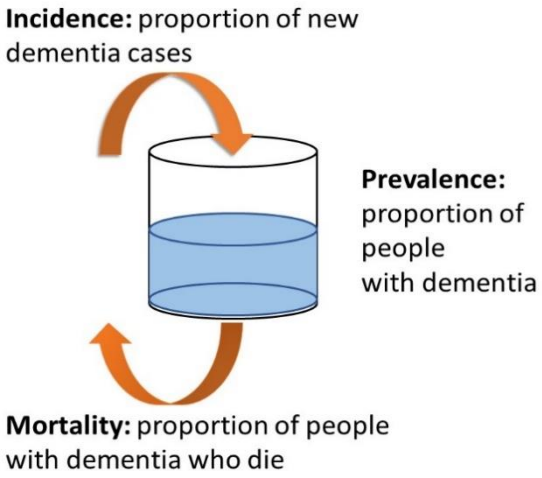


Figure 1. Relation between incidence, prevalence, and mortality. Modified from Wu et al.[20]

A recent Lancet commission report quantified individual risk factors' impact on developing dementia (Figure 2).[21] It concluded that 40% of the risk of developing dementia is potentially modifiable (with most of the exposure happening in mid- or later life), whereas 60% of the risk attribution is unknown.

Likewise, a study based on existing meta-analyses concluded that approximately one third of cases of AD might be attributable to potentially modifiable risk factors.[22]

A Finnish study investigated a multidomain lifestyle intervention in at-risk elderly people. They found results suggesting that intervention in life style factors could maintain or improve cognitive functions.[23] Since then, multiple studies have been initiated worldwide, investigating a multiple domain life style intervention in order to reduce cognitive decline and dementia.[24] In high-income countries there has been an increased focus on healthier lifestyle and improvement and on reduction of cardiovascular risk factors during the last decades. Thus, it is possible that with general improvement of health and reductions of risk factors, dementia may to some extent be preventable.

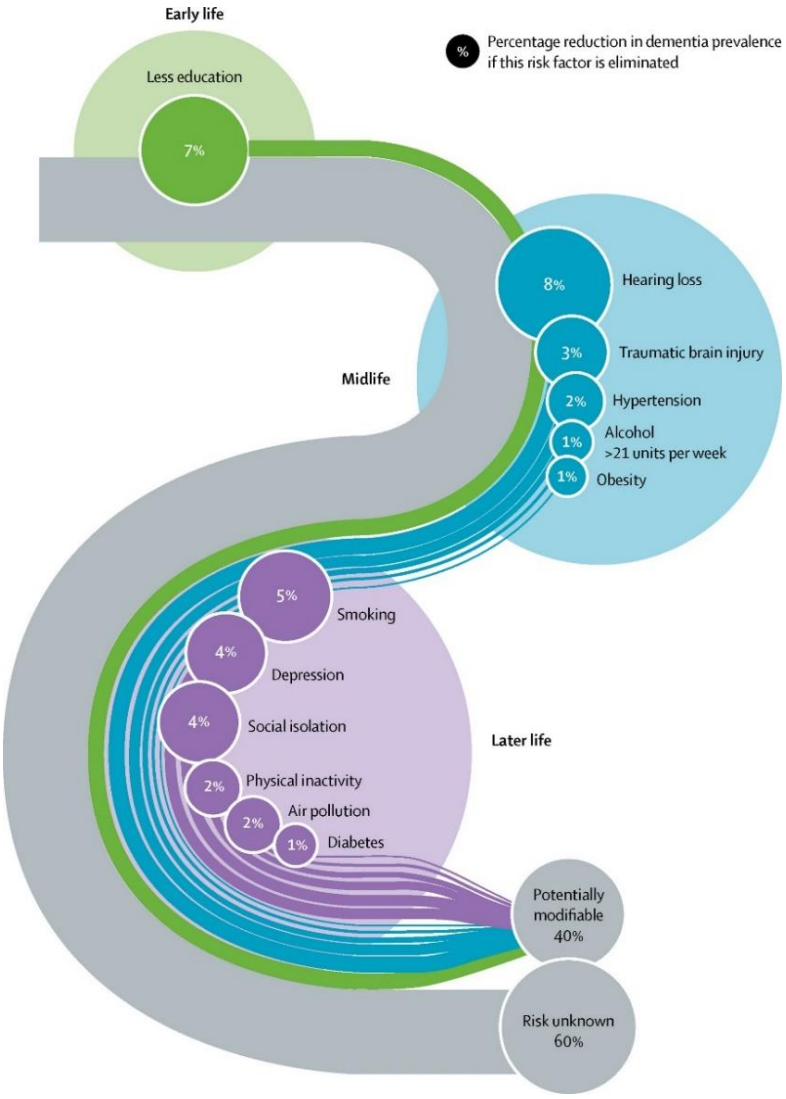


Figure 2. Population attributable fraction of potentially modifiable risk factors for dementia. Reprinted from Livingston et al.[21] with permission from Elsevier.

Accordingly, population-based studies investigating time trends of incidence of dementia in high-income countries during the past decades have indicated tendencies of declining incidence of dementia in elderly people.[25–32] However, one study from Japan indicated an increase.[33] Findings from registry-based studies on incidence of dementia are not consistent.[34–38]

Population-based studies investigating time trends of prevalence show no clear trend. One American, one Spanish, and three Swedish studies reported stable prevalence[39–43], one American and one British study observed declining prevalence[44,45], one study from Japan found an increase in prevalence[33], whereas one American and one French study found more inconclusive results[46,47].

Fewer studies have investigated time trends of mortality in people with dementia. Four population-based studies, one from Sweden, two from the Netherlands, and one from Japan observed a declining mortality [26,33,43,48] , contradicting results from one German and one American study indicating increasing mortality[34,49].

Even though the time trend of incidence, prevalence, and mortality in dementia has been investigated in previous studies, only two of the study cohorts have investigated all three parameters, and none of

these studies used continuous data.[32,33,43] As incidence, prevalence, and mortality are interdependent parameters, assessing all three of them in the same population is important to obtain a more detailed picture of the development over time. This knowledge is important in making projections and planning future health care services and costs.

Mortality in dementia

Mortality is known to be markedly increased in people with dementia.[50,51] The increased mortality seems to be complex and influenced by a range of multiple factors. Research is quite consistent when establishing an association between level of severity and subtype and increased mortality in dementia.[51–56] Increased mortality in dementia has been linked to age[57–63], male sex[61–64], reduction in activities of daily living[57,59,65,66], and institutionalization[58]. Furthermore, studies have suggested that mortality in people with dementia is related to low cognitive performance[56–58,64,67,68], antipsychotics[57,69], and polypharmacy[70,71].

The presence of concurrent chronic comorbidities have also been associated with increased mortality in people with dementia.[50,52,56,72,73] In addition, specific comorbidities have been found to increase mortality in dementia. These include cerebrovascular disease[52], diabetes[72], and hypertension[72]. Other studies compared mortality in people with and without dementia, and even after adjusting for comorbidities and other relevant variables, an excess mortality persisted in people with dementia.[74–76] In a study based on the world's largest dementia cohort, the Swedish SweDem database, Haaksma et al. introduced a tool to predict three-year survival in patients diagnosed with dementia.[56] They found that when they included comorbidity load as defined by the Charlson Comorbidity Index (CCI), it resulted in more accurate estimates. Overall, by using five variables (sex, age, cognitive function, CCI score, and dementia subtype), they were able to predict survival probability within a three-year period correctly in 71-72% of the cohort.[56] In line with the Swedish study, a Canadian study reported an increased mortality related to the numbers of comorbidities in people with dementia.[73]

Mortality is substantially increased in people with dementia and caused by multiple factors. However, studies investigating the association between load of comorbidities and mortality in people with

dementia compared with people without dementia are scarce.[56,73] As the risk of developing dementia increases with age, so does the prevalence of chronic comorbidities. Therefore, it becomes essential to gain more knowledge about the association between comorbidities and mortality in the growing population of people with dementia. Additionally, many people may not perceive dementia as a fatal disease. To create a context for emphasizing the severity of a dementia diagnosis it may be helpful to compare mortality and survival in dementia with the most frequent causes of death in high income countries; cancer and heart disease.[77,78]

Dementia - a leading cause of death

With the number of people living with dementia rapidly growing[2], the registration of dementia as a cause of death is also increasing. From 2005 to 2015, the Global Burden of Disease study reported a 38% increase in dementia disorders as cause of deaths.[79] WHO estimated that in the year 2016, AD and other dementias were the fifth leading cause of death globally.[77] In high-income countries, dementia was the third leading cause of death in 2016[77]. In the UK[80] and Australia[81] dementia has become the leading cause of death in women.

Thus, the proportion of people registered with dementia as cause of death has increased during the last decades. In the Norwegian population, the proportion of death certificates with dementia registered as a cause of death increased substantially from 1969 to 2010 (in women from 4% to 15% and in men from 3% to 7%).[82] The same study observed that the proportion of dementia as cause of death was highest in the oldest age groups.[82] Likewise, a report from the UK described that the percentage of dementia registered as a cause of death in people ≥20 years increased from 6.6% in 2001 to 15.8% in 2014.[83]

Death certificates can include multiple causes of death. This includes one underlying, one immediate, and multiple contributing causes of death. According to WHO, death certificates must state the underlying cause of death, whereas listing immediate and contributing causes of death are optional.[84] The underlying cause of death is defined as the disease or condition that started the process leading to death.[84] The immediate cause of death is defined as the immediate disease or injury that causes

death.[85] Contributing causes of death can either be diseases or conditions describing the path from underlying to immediate cause of death as a chain of events.[85] Otherwise, contributing causes of death can be diseases or conditions that increase susceptibility to the conditions causing death.[85]

A Canadian report found that in the period from 2004 to 2011, AD was registered as cause of death in 4.3% of all deaths during that period, and it was more frequently reported as an underlying (2.6%) compared to a contributing cause of death (1.7%).[86] The previously mentioned Norwegian study also investigated the registration of dementia as underlying versus contributing cause of death.[82] The proportion where dementia was registered as underlying cause of death as opposed to a contributing cause of death increased from 6.2% in 1972 to 50.6 % in 2009.[82]

Thus, the registration of dementia as a cause of death is increasing. Additionally, the Norwegian study suggests an increase in the registration of dementia as an underlying as opposed to a contributing cause of death. These changes may reflect a paradigm shift towards perceiving dementia as fatal diseases.

No studies have assessed if causes of death in people with dementia have changed over time. Mortality risk and risk of dementia increase with age. Thus, when investigating changes in dementia as a registered cause of death over time, it is essential to perform analyses stratified by sex and age-groups. Additionally, a potential change in the registration of dementia as an underlying cause of death as opposed to a contributing cause of death may provide an insight about an altered perception of the fatality of dementia among medical doctors.

Causes of death in people with dementia

While the registration of dementia as a cause of death is increasing, dementia may still be underreported as cause of death in people diagnosed with a dementia disorder.[87] A systematic review based on seven population-based studies concluded that only 7%–42% of the people diagnosed with dementia also had a dementia diagnosis registered on their death certificate.[87] The review also found that people diagnosed with AD were more likely to be registered with a dementia diagnosis on their

death certificate compared to people diagnosed with unspecific dementia or vascular dementia (VaD).[87] It also concluded that the probability of having a dementia diagnosis registered on death certificates was higher if the dementia disease was severe.

Studies based on death certificates report that besides dementia the leading causes of death in people with dementia are cardiovascular disease or pneumonia/respiratory diseases.[88–91] These findings are in line with observations from autopsy studies reporting pneumonia as the leading cause of death in people with dementia followed by cardiovascular disease or ischemic heart disease (IHD).[92–96] Additionally, a meta-analysis concluded that people with dementia had a higher risk of dying from pneumonia compared with people without dementia (odds ratio = 2.2)[97], while they were less likely to be registered with cancer as a cause of death.[88,91,98]

It is yet to be explored if there has been a change in registered causes of deaths in people with dementia over time. Fluctuations over time could identify some causes of death as less frequent in people with dementia. This could be a sign that they may be underdiagnosed. If people with dementia are more likely to die of some disease groups, this knowledge should lead to increased awareness and potential interventions. Furthermore, if causes of death in people with dementia have changed over time, this knowledge may inform us about alterations in comorbidities and their association to death over time.

Dementia and mortality - the importance of more knowledge

The prevalence of dementia is expected to increase substantially during the next decades due to increasing life expectancy. Incidence, prevalence and mortality are interdependent parameters. Although studies from high income countries have suggested trends of declining incidence of dementia during the last decades,[25–32] studies assessing prevalence[28,33,39–44,46,47] and mortality[26,33,34,43,48,49] show no clear trends. Furthermore, only findings from two population-based cohorts have described all three parameters in the same populations, and these found different results.[32,33,43] Most time trend studies have been performed in smaller population and without access to continuous follow up, which can result in less accurate results. Though observational studies

cannot be used to establish causal pathway, but only associations, they can still provide valuable knowledge and help establish associations and time trends.

With growing elderly populations, the number of people living with one or multiple chronic comorbid diseases is expected to increase as is the number of people living with dementia. Dementia is associated with excess mortality, and some of this excess mortality might be associated to other chronic conditions. However, the association between comorbidities and mortality in dementia is not well described.

In investigating dementia as a fatal disease, an aspect that has previously not been investigated is whether causes of death have changed over time in people with dementia. This knowledge may help identify some diseases that are potentially underdiagnosed. Furthermore, it may provide an insight in the use of dementia as a registered cause of death and how it has changed over time. This could potentially be used as a marker of awareness about the fatality of dementia.

The Danish national registries enable the use of an entire population as a cohort. Combined with access to continuous data over decades, it is possible to assess sex and age-stratified time trends of incidence, prevalence, mortality and causes of death in dementia. To be able to plan the future health care system meeting the specific requirements for a large population of people with dementia, more knowledge is needed about the time trends incidence, prevalence, mortality, and causes of death in people with dementia.

Aim and hypothesis

The overall aim of this PhD thesis was to investigate aspects of mortality in people with dementia. We wished to do so by assessing the time trends of incidence, prevalence, mortality, and causes of death in dementia, as well as the effect of comorbidities on mortality in dementia.

Study I
Aim: to investigate the time trend of incidence and prevalence of dementia from 1996 to 2016.
Hypothesis: the incidence of dementia may have declined in recent years, despite increasing prevalence, due to healthier lifestyle.

Study II
Aim: to investigate survival and the time trend of mortality in people with dementia compared to the general elderly population and to people diagnosed with acute IHD or cancer from 1996 to 2015.
Hypothesis: mortality is higher in people with dementia but have declined more rapidly than in the general population due to higher awareness and provision of appropriate care.

Study III
Aim: to assess the contribution of concurring psychiatric and chronic somatic conditions on mortality in people with dementia compared to the general elderly population.
Hypothesis: the presence of other somatic and psychiatric conditions is associated with increased mortality in people with dementia. After adjusting for comorbidities, people with dementia will have higher a mortality than people without dementia.

Study IV
Aim: to assess causes of death, including annual changes, in people with dementia compared to the general elderly population in the time period from 2002 to 2015.
Hypothesis: the proportion of people who were registered with a diagnosis of dementia on their death certificates increased from 2002 to 2015. Furthermore, we hypothesized that the leading underlying causes of death in people with dementia were pneumonia, cardiovascular, and cerebrovascular disease.

Methods

The Danish health care system and the Danish national registries

Denmark has a long tradition of public welfare. This includes tax-financed universal health care.[99] All contacts to hospitals, general practitioners, and specialist are free for residents in Denmark.[99] At the same time the private health care sector is very limited.[99] Since 1968, all residents in Denmark have been assigned a unique personal identification number.[100] This makes it possible to link information from a range of different registries, including health data, at an individual level.[101]

This study used data from the following Danish national registries:

1) The Civil Registration System

The system was established in 1968 when all people alive and living in Denmark were assigned a personal identification number, known as a CPR number.[100] Since then, all live born babies and immigrants have been assigned CPR numbers.[100] The registry is run by Statistics Denmark, and data is continuously updated, including information on sex, civil status, residence, and date of birth, emigration, immigration, and death.

2) The Danish National Patient Registry

Since 1977, the registry has included data on all hospital inpatient admissions.[101] Since 1995, additional information on outpatient and emergency contacts has been included.[101] From 1977 to 1994, diagnosis codes were registered according to the International Classification of Diseases 8th revision (ICD-8), and from 1995 and onwards, registration has been recorded according to the International Classification of Diseases 10th revision (ICD-10).[101]

3) The Danish Central Psychiatric Research Register

This registry was established in 1969 and contains information on every psychiatric admission since then.[102] From 1995, the registry has also included data on outpatient and emergency contacts.[102] That same year, the Danish Central Psychiatric Research Register was integrated in the Danish National

Patient Registry.[102] Like the Danish National Patient Registry, the ICD-8 codes were used in the period from 1970 to 1994, and the ICD-10 codes have been used since 1995.[102]

4) The Danish National Prescription Registry

This registry was established in 1994 and includes data on all redeemed prescription drugs.[103] It includes information on date of completed sale, number of packages and package size, dose and WHO-defined Anatomical Therapeutically Chemical (ATC) codes.[103]

5) The Danish Register of Causes of Death

Registration of causes of death was established in 1875 by the National Board of Health.[84] Since 1970, the Register of Causes of Death has been fully computerized and holds data on all Danish residents that have died in Denmark including causes of death, manner of death, date and place of death.[84] In 2002, the Automated Classification of Medical Entities (ACME), a new international decision-making tool for coding causes of death, was introduced in Denmark.[84] The ACME software determines the underlying cause of death by examining if there can be established a causal link between the immediate, the contributing, and underlying cause of death.[104] In the rest of this thesis, the ACME code will refer to the underlying cause of death as determined by the ACME tool. About 10% of death certificate data are validated by coding specialist, who decide causes of death manually (appear as the ACME code in our datasets). In Denmark, death certificates have been electronically submitted since 2007.

This thesis used copies of datasets from the registries listed above. All datasets were updated to December 31, 2015.

Population

The study population consisted of all individuals living in Denmark who were born before 1961 and alive at least one day during the follow-up periods in the different studies. Hereby, our population comprised people who were all 65 years or older in 2015. In all studies only people aged 65 years or older were included. Due to risk of misregistration, people were excluded if aged ≥110 years.

People with dementia were identified as individuals who were either 1) registered with a dementia diagnosis in the Danish National Patient Register or the Danish Psychiatric Central Research Register or 2) individuals who had redeemed at least one prescription for an anti-dementia drug, whichever event came first. Diagnosis codes for dementia are presented in Table 1. ATC codes are presented in Table 2. Date of onset was defined as the first date where a dementia diagnosis was registered or a prescription on an anti-dementia drug was filled. We chose to use data on filled prescriptions on antidementia drugs in order to include people diagnosed by their general practitioner or in a private healthcare setting.

Table 1. ICD-8 and ICD-10 diagnosis codes for identification of dementia

Disease name	ICD-8	ICD-10
Alzheimer's disease	290.10	F00.0-00.9, G30.0-30.9
Vascular dementia	293.09-19	F01.0-01.9
Frontotemporal dementia	290.11	F02.0
Dementia without specification	290.09-19	F03.9, G31.9
Other dementias	-	G31.8

Table 2. Anatomical Therapeutic Chemical (ATC) codes for identification of pharmaceutical treatment of dementia

Drug name	ATC code
Memantine	N06DX01
Donepezil	N06DA02
Rivastigmine	N06DA03
Galantamine	N06DA04

Covariates

All analyses were performed separately for men and women. Age was used as a continuous variable or, when appropriate, in one-, five- or ten-year age groups. Data on sex and age was obtained from the Civil Registration System at Statistics Denmark. Age, sex, and calendar year were included as covariates in all four studies. Table 3 lists the additional variables included in the four studies.

Information on somatic and psychiatric comorbidities was obtained from The Danish National Patient Registry and The Danish Central Psychiatric Registry. They were defined using diagnoses codes from all hospital contacts (in- and outpatient as well as emergency room contacts).

In Study III and Study IV, we included a modified version of the CCI. In the original version of the CCI, dementia is included. Comorbidity scores assign weights from 1–6 to each comorbidity for every individual. Individuals who are then given a sum of the weights based on all present comorbidities. A CCI score of zero represents no comorbidities, and a score from 1 to ≥6 represents a gradually higher load of comorbidities.[105] In our use of the CCI, all comorbidities were defined as continuous variables based on the weighted comorbidity scores. As dementia was the exposure, we wished to examine, it was removed from the index. In the rest of this thesis this modified CCI will be referred to as the CCI.

Table 3. A list of covariates included in the four studies. Because age, sex, and calendar year were included as covariates in all four studies, these have not been listed in the table.

Study	Covariates
I	-
II	Cancer Acute ischemic heart disease
III	Charlson Comorbidity Index 19 somatic disease groups 4 psychiatric disease groups
IV	Charlson Comorbidity Index Marital status

Data analysis

In Study I-III we used Poisson's regression model for most of our analyses. The Poisson model is equivalent to a Cox regression model.[106] However, it has some advantages compared to the Cox Regression, including the possibility to include several time origins.[106] Another advantage of the Poisson Regression is that the assumption of proportional (constant) rates only has to apply to piecewise constant rates, as oppose to the Cox Regression where the assumption of proportional hazards is often difficult to fulfill.[106] Before applying the Poisson model to our data, we made sure

that the assumption of piecewise constant intensity was verified. In Study II, we included analyses on survival using the Kaplan-Meier estimator. This model was chosen over models taking competing risks into account, as mortality was the only outcome, and no competing risks were deemed relevant to adjust for.

Data management and analyses were all performed using SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina, U.S.A.). We defined statistical significance to a p-value of 0.05.

Study specific methods

All four studies were designed as observational cohort studies using the Danish elderly population (age ≥65 years) as a cohort. The study specific methods and statistical analyses are described in the following sections.

Study I

This study assessed incidence and prevalence of dementia in the period from January 1, 1996 to December 31, 2015. On January 1, 1996, all Danish residents aged ≥65 years and up to 110 years were included. During the 20-year period, people were included upon turning 65 years of age, or if they immigrated to Denmark at age ≥65 years.

Incidence study: We defined incident cases as people registered with dementia for the first time within a given calendar year. Individuals registered with a dementia diagnosis prior to the age of 65 were excluded. The following events led to censoring: 1) a dementia diagnoses (the outcome), 2) emigration, 3) loss to follow-up, 4) death, 5) turning 110 years old, or 6) the end of the study period (whichever event came first).

Prevalence study: We defined prevalent cases as people aged 65 years or older registered with dementia from 60 years of age. We chose to exclude people with dementia diagnosed prior to the age of 60 years as a previous study found that the validity of dementia diagnoses in the Danish registries given before that age is low.[107] The rest of the study population comprised the reference group. Events leading to censoring were 1) emigration, 2) loss to follow-up, 3) death, 4) turning 110 years

old, or 5) the end of the study period (whichever event came first).

We tested trends in incidence rates using Poisson regression analysis evaluating the calendar year as a time-dependent covariate. Trends in prevalence were assessed as annual period prevalence percent. For each year, we compared the number of person-years lived by people with dementia to the total number of person-years lived by the study population. Incidence rates and period prevalence percent were assessed for men and women in five-year age groups. During the rest of this thesis, period prevalence percent will be referred to as prevalence rates. Lastly, we evaluated total incidence as the total number of new dementia cases in a year, whereas total prevalence was evaluated as point prevalence on January 1 each year.

Study II

This study assessed both mortality and survival in dementia using different time periods, study populations, and statistical methods. To bring mortality and survival of dementia into perspective, we chose to compare these results with other leading causes of death in high-income countries; cancer and acute IHD.[77,78] Thus, we assessed mortality and survival in acute IHD and cancer using the same methodology as is described for dementia. Our definition of these two disease groups were based on the diagnosis codes as defined in the CCI (Table 4). People diagnosed with dementia, acute IHD, or cancer prior to the age 65 were excluded from the respective analyses.

Table 4. ICD-8 and ICD-10 diagnosis codes for identification people with cancer and acute IHD

Disease name	ICD-8	ICD-10
Myocardial infarction	410	I21; I22; I23
Cancer	140-189; 195-199; 200-207; 275.59	C00-85; C88; C90-96

Mortality: In assessing mortality, the study period was defined as January 1, 1996 to December 31, 2015. On January 1, 1996, all Danish residents aged ≥65 years were included, and until December 31, 2015 people were included the day, they turned 65. During follow-up, people were censored if they 1) died, 2) emigrated, 3) were lost to follow-up, 4) turned 110 years, or 5) at the end of the follow-up. People not registered with dementia comprised the reference group.

To assess time trends in mortality of dementia, we performed a survival analysis with dementia as exposure and death as outcome. We applied a Poisson Regression to assess mortality rate ratios (MRR). Mortality rates (MR) are similar to incidence rates, but the outcome assessed is death.[108] The MRR expresses the ratio between MR in different groups. We assessed MRR by defining the reference value of 1.00 for men and women without dementia in 1996. We then tested if there was a difference in the MR in men and women with and without dementia for each of the following years. Similarly, we evaluated if there was a difference in the time trend of MR between people with dementia, acute IHD, cancer, and the total elderly population.

Survival: In assessing survival, we calculated cumulative incidences of death. This was done by applying Kaplan-Meier analyses to calculate survival probabilities in five-year age groups. The study period was restricted to January 1, 2000 to December 31, 2015, because the period from 1996 to 1999 had a higher all-cause mortality and incidence of dementia than the subsequent period. We chose to exclude this period as Kaplan-Meier analyses could not adjust for calendar year efficiently. We only assessed incident cases. Thus, if people were registered with dementia, acute IHD, or cancer before January 1, 2000, they were excluded from the respective analyses. We constructed an age and calendar time matched cohort to represent the general population.

Study III

In this study, we assessed the effect of somatic and psychiatric diseases on mortality in people with dementia compared to the general elderly population. All Danish residents aged ≥65 years in the period from January 1, 2006 to December 31, 2015 were included. People diagnosed with dementia prior to age 65 were excluded. From January 1, 2006 to December 31, 2015 risk time was assessed until 1) emigration, 2) loss of follow-up, 2) turning 110 years, or 4) death (whichever event occurred the first).

Investigating the load of comorbidities, we used the CCI.[105] We defined our somatic disease groups as the ones listed in the CCI. Additionally, we decided to include atrial fibrillation, as it is a known risk factor for developing dementia,[109] and we believed it could potentially also have an effect on mortality. Table 5 presents the diagnosis codes used for defining the somatic disease.

Table 5. ICD-8 and ICD-10 diagnosis codes for identification somatic diseases

Disease name	ICD-8	ICD-10
Myocardial infarction	410	I21; I22; I23
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	440-445	I70; I74; I77
Cerebrovascular disease	430-438	I60-I69; G45; G46
Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09; M30-M36; D86
Ulcer disease	530.91, 530.98, 531-534	K22.1; K25-K28
Mild liver disease	571, 573.01, 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Diabetes mellitus	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09	E10.0, E10.1; E10.9 E11.0; E11.1; E11.9
Hemiplegia	344	G81; G82
Moderate/severe renal disease	403, 404, 581-584, 590.09, 593.19, 753.10-753.19, 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes mellitus with chronic complications	249.01-249.05, 249.08, 250.01-250.05; 250.08	E10.2-E10.8; E11.2-E11.8
Any tumor	140-195	C00-C75
Leukemia	204-207	C91-C95
Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96
Moderate/severe liver disease	70.00; 70.02; 70.04; 70.06; 70.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumor	195-199	C76-C80
AIDS	79.83	B21-B24
Atrial fibrillation	427.93; 427.94	I48

Information on all available hospital-based psychiatric diagnoses were obtained from 1970 to 2015, and information on all available hospital-based somatic diagnoses were obtained from 1977 to 2015. We chose to investigate four psychiatric disease groups: 1) mental and behavioral disorders due to psychoactive substance abuse, 2) schizophrenia and related disorders, 3) affective disorders, and 4) neurotic, stress-related and somatoform disorders (Table 6).

Table 6. ICD-8 and ICD-10 diagnosis codes for identification psychiatric diseases

Disease name	ICD-8	ICD-10
Mental and behavioral disorders due to psychoactive substance abuse	291.x9, 294.39, 303.x9, 303.20, 303.28, 303.90, 304.x9	F10-F19
Schizophrenia and related disorders	295.x9, 296.89, 297.x9, 298.29-298.99, 299.04, 299.05, 299.09, 301.83	F20-F29
Mood disorders	296.x9 (excluding 296.89), 298.09, 298.19, 300.49, 301.19	F30-F39
Neurotic, stress-related, and somatoform disorders	300.x9 (excluding 300.49), 305.x9, 305.68, 307.99	F40-F48

Mortality was assessed as MRR calculated using Poisson Regression as described in Study II. Four different approaches were used.

1. MRR were assessed for women and men with and without dementia stratified by CCI scores of 0 to ≥6 adjusted for age and calendar year. We defined the reference groups as women and men without dementia and a CCI score of zero (reference value=1.00).
2. Excess mortality was evaluated by assessing MRR for men and women stratified by both CCI score and five-year age groups. We defined the reference to be 1.00 for each of the age- and CCI score groups in women and men without dementia, hereby annulling the effect of an increasing CCI score on mortality. These analyses were adjusted for calendar year.
3. MRR were assessed for the selected 23 comorbidities in combination with dementia. We defined the reference as 1.00 for women and men with the specific comorbidity, but without dementia. This analysis was adjusted for age and calendar year.
4. MRR were assessed in three different adjusted models.

i. Model 1: age and calendar year
ii. Model 2: model 1 plus selected psychiatric conditions
iii. Model 3: model 2 plus atrial fibrillation and somatic diseases included in CCI

Study IV

This study assessed dementia-related deaths and causes of death in people with dementia compared to the general elderly population. The study design was purely descriptive. The cohort comprised all Danish residents ≥65 years who died in Denmark from January 1, 2002 to December 31, 2015.

The study used data from The Danish Register of Causes of Death. The data available came from death certificates filled out by medical doctors.[84] On death certificates, causes of death must be listed as a chain of events. The underlying cause of death is defined as the disease or condition leading to death. In this chain of events, two contributing causes of death can be listed and, additionally, an immediate cause of death; the immediate disease or injury causing death. Furthermore, up to four medical conditions or diseases can be listed as contributing causes of death. These are defined as conditions which may have led to reduced resistance or increased vulnerability; thereby making the person susceptible to the conditions causing death.

In this study we identified people registered with dementia while alive using the methodology previously described. People diagnosed with dementia prior to age 65 were excluded. Furthermore, we investigated dementia-related deaths using data from death certificate data in the complete Danish elderly population and in people with dementia. The same diagnostic codes as presented in Table 1 were used. We defined the underlying cause of death as the ACME code. Dementia as a contributing cause of death was defined as a dementia diagnosis registered as either immediate cause of death, any contributing causes of deaths, or underlying cause of death (if not equal to the ACME code). The term dementia-related deaths was used when dementia was listed as either underlying or contributing cause of death.

We also investigated underlying causes of death in people diagnosed with dementia compared to the general elderly population. Underlying causes of death were divided into 11 groups (Table 7). To

preserve anonymity, we combined groups of underlying causes of death if there were ≤5 observations.

Table 7. ICD-10 codes for categorizing underlying causes of death.

Disease category	ICD-10
Dementia	F00.0-9, F01.0-9, F02.0, F03.9, G30.0-9, G31.8-9
Cardiovascular disease	I00-I59, I70-I99 R00-R01, Q20-Q28
Cerebrovascular disease	I60-I69
Cancer	C00-C96
Pneumonia	J10- J22
Chronic respiratory diseases	J40-J47
Genitourinary diseases	N00-N98, R30-R39
Gastrointestinal diseases	K00-K93, R10-R19
Unnatural causes	F11-F16, F19, F55, V00-X44, X50-X99, Y00-Y39, Y85-87.1, Y88-89
Other causes of death	All remaining ICD-10 codes
Not registered	No underlying cause of death registered

To describe the population, the following variables were assessed on the date of death: 1) median age, 2) CCI score, and 3) civil status (i. Married/civil partnership/ separated; ii. Single/ divorced; iii. Widowed).

The aim of the study was descriptive, and our cohort comprised an entire national population. Because the cohort was not a sample, differences in percentages of distributions depicted an actual difference, and consequently statistical analyses were considered unnecessary. The time trend of dementia-related deaths was evaluated as the annual percentage of all deaths in our population. Analyses were performed separately for women and men in five-year age groups. In addition, the annual distribution of cases where dementia was registered as underlying versus contributing cause of death, was assessed in 10-year age groups. An identical analysis was performed for people diagnosed with dementia. The time trend of underlying causes of death was assessed as the annual distribution in percentages performed for women and men with and without dementia in the entire

groups and in 10-year age-groups. Last, we identified the number of people who received their first dementia diagnoses in the national registries on their death certificate from 2002 to 2015.

Ethical considerations and approvals

This PhD study was part of a larger epidemiological research project approved by the Danish Data Protection Agency (ID no: 2007-58-0015/30-0667), Statistics Denmark, and the Danish Health and Medicine Authority (ID no: 6-8011-907/1).

As all data was handled anonymously using the server of Statistics Denmark, and the personal identification numbers were encrypted, Danish law does not require ethics committee approval or informed patient consent.

Results

Presented in this chapter are the key findings from the four studies included in this thesis. Please see the appendices for additional results.

Populations, Study I-IV

Table 8 provides an overview of the time periods, populations, person-years and deaths in each of the four studies.

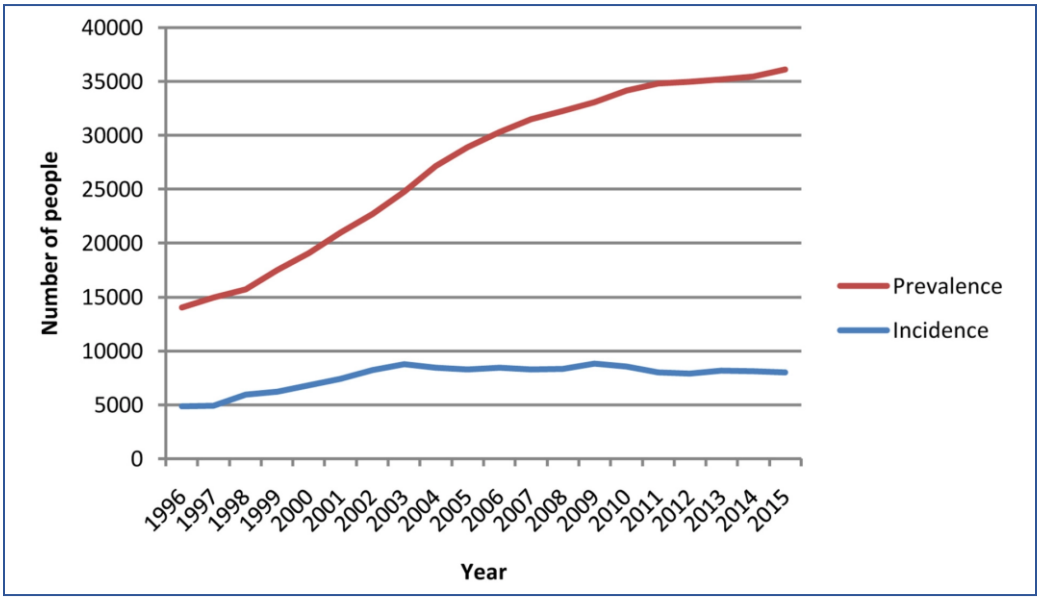
Table 8. Summary table of time periods, populations, person-years, and deaths included in Study I-IV.

	Study I	Study II	Study III	Study IV
Time period	1996-2015	1996-2015	2006-2015	2002-2015
Population, total	1,999,375	1,999,366	1,518,917	
Person-years, total	*Incidence:* 16,944,630 *Prevalence:* 17,541,315	17,541,315	9,433,208	
People with dementia	*Incidence:* 152,761 *Prevalence:* 170,478	165,716	114,109	
Person-years, dementia	*Prevalence:* 554,483	529,629	326,112	
Deaths		905,991	439,205	621,826
Deaths, people with dementia		131,321	77,409	103,785
People with acute IHD		144,380		
Person-years, acute IHD		665,640		
Deaths, acute IHD		109,154		
People with cancer		400,610		
Person-years, cancer		1,565,110		
Deaths, cancer		283,143		

Study I

The total elderly population in Denmark increased from 803,334 in 1996 to 1,055,984 in 2015, whilst the median age decreased from 74.2 years to 72.9 years. From 1996 to 2015, the total incidence as percentage of the elderly population increased from 0.58% to 0.72%. The total incidence increased from 4875 people in 1996 to 8017 people in 2015. The highest number of incidence cases was observed in 2009 (n=8832) (Figure 3). The absolute prevalence increased from 14,019 people in 1996 to 36,129 people in 2015.

Figure 3. Time trends of total incidence and prevalence of dementia in Denmark from 1996 to 2015. Reprinted from Taudorf et al.[110]



Except for men and women in the age group 65-69 years, the incidence rates of dementia were significantly higher in 2015 compared with 1996 for all women and men (Figure 4). The increase was most prevailing in the oldest age groups. The overall increasing incidence rates from 1996 to 2015 showed the pattern of a steep increase from 1996 to 2003, followed by stabilization/fluctuation until 2009 and 2010, and then a moderate decline from 2010 to 2015. This time trend was most pronounced in the oldest age groups. Adjusted for sex and age, the incidence rate increased 9% annually from 1996 to 2003, followed by an averagely annual decline of 2% from 2004 to 2015.

Prevalence rates increased from 1996 to 2015 for both sexes in all age groups (Figure 5). The older the age group, the higher the prevalence. Prevalence rates were higher in women compared to men ≥75 years. From 2010 to 2015, the prevalence rates were relatively stable in men and women.

Figure 4. Time trend of incidence rates of dementia in Danish women (A) and men (B) from 1996 to 2015. Error bars represent 95% confidence intervals. Reprinted from Taudorf et al.[110]

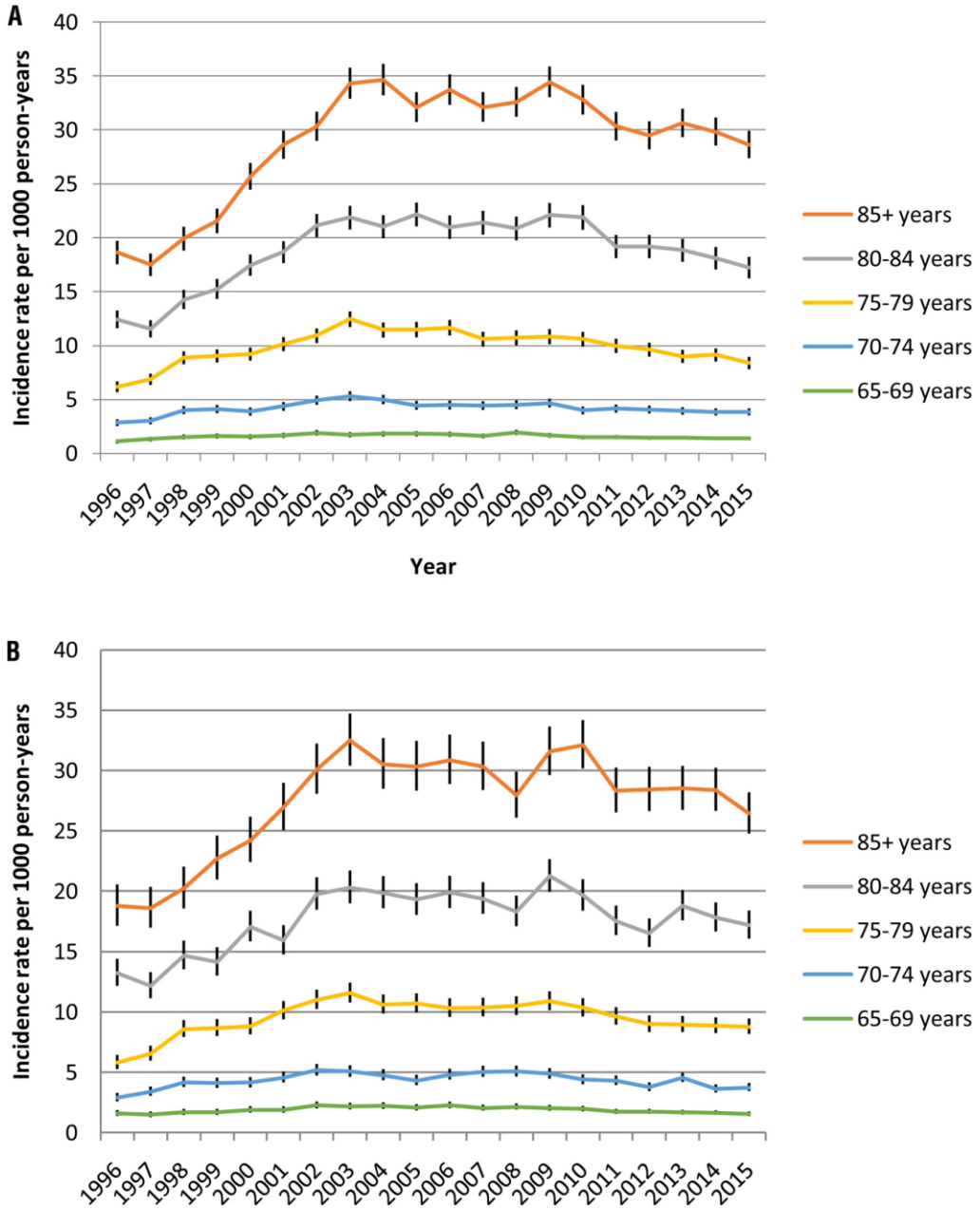
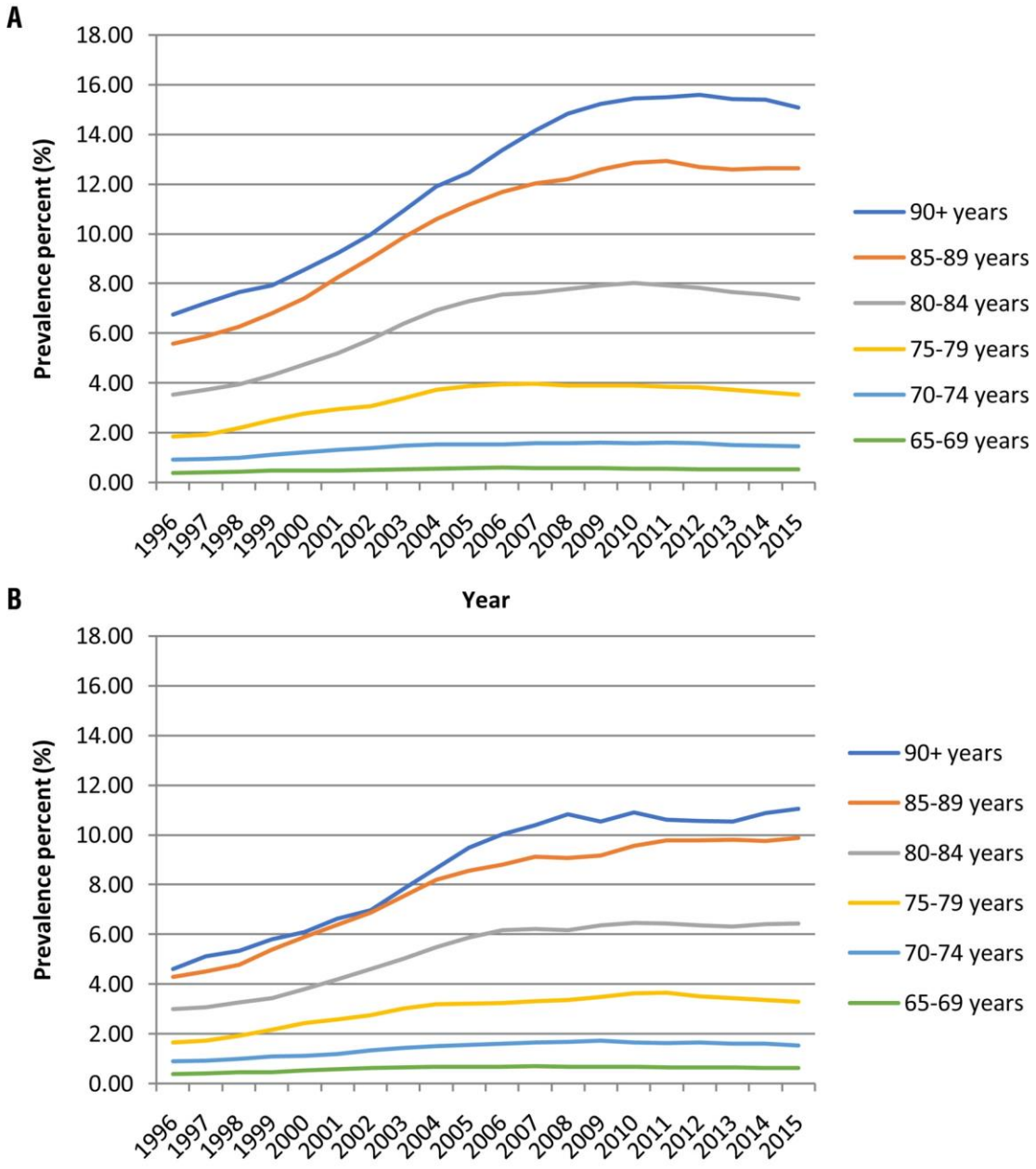


Figure 5. Time trend of dementia prevalence rates in Danish women (A) and men (B) from 1996 to 2015. Reprinted from Taudorf et al.[110]



Study II

Adjusted for age and calendar year, the MRR was 2.77 (95% CI: 2.75–2.80) for women with dementia and 3.13 (95% CI: 3.10–3.16) for men with dementia. When assessing MRR in five-year age-groups adjusted for sex and calendar year, we found that MRR varied from 5.54 (95% CI: 5.28–5.80) in people aged 65-69 years to 2.08 (2.06–2.11) in people age ≥90 years. Evaluating sex- and age-adjusted MRR in five-year calendar periods found the MRR stable.

From 1996 to 2015, the MRR was significantly higher in dementia compared with people without dementia (Figure 6). Similarly, the MRR was significantly higher in acute IHD or cancer compared to people without acute IHD or cancer. After adjusting for age, sex, and calendar year, the MRR was 2.91 (95% CI: 2.90–2.93) in people with dementia compared with the general elderly population without dementia (reference value=1.00). In women and men with dementia, the MRR declined at the same speed as in the general population from 1996 to 2015. This was in contrast to MRR for women and men with acute IHD and cancer, where mortality declined significantly faster compared with the general population during the 20-year period.

The results from the Kaplan-Meier analyses showed that the one-year survival probabilities in women and men with dementia were lower in all age groups compared to the general elderly population (Figure 7). Nonetheless, the one-year survival probability was higher for women and men with dementia compared with acute IHD and cancer. Five-year survival probabilities were lower for women and men of all age groups with dementia, acute IHD, or cancer groups when comparing to the general elderly population. However, when comparing women with dementia to women with acute IHD, the five-year survival probabilities were lower in dementia for women <80 years, while they were similar in women ≥80 years. Comparing dementia to cancer, women with dementia age <85 years had a higher five-year probability of survival compared to cancer, whereas it was lower in women with dementia age ≥85 years. When comparing five-year survival probabilities in men, they were substantially lower in dementia than in acute IHD. Comparing men with dementia to those with cancer, five-year survival probabilities were similar in the age group 65–69 years, but in all older age groups the probability of survival was lower for men with dementia than for men with cancer.

Figure 6. Time trend of all-cause mortality for women and men. Graphs showing age-adjusted MRR for women and men with dementia, acute IHD, and cancer compared to people without. The reference value was defined as 1.0 in 1996 for women and men without dementia, acute IHD, or cancer. Error bars represent 95% confidence interval. Reprinted from Taudorf et al.[111]

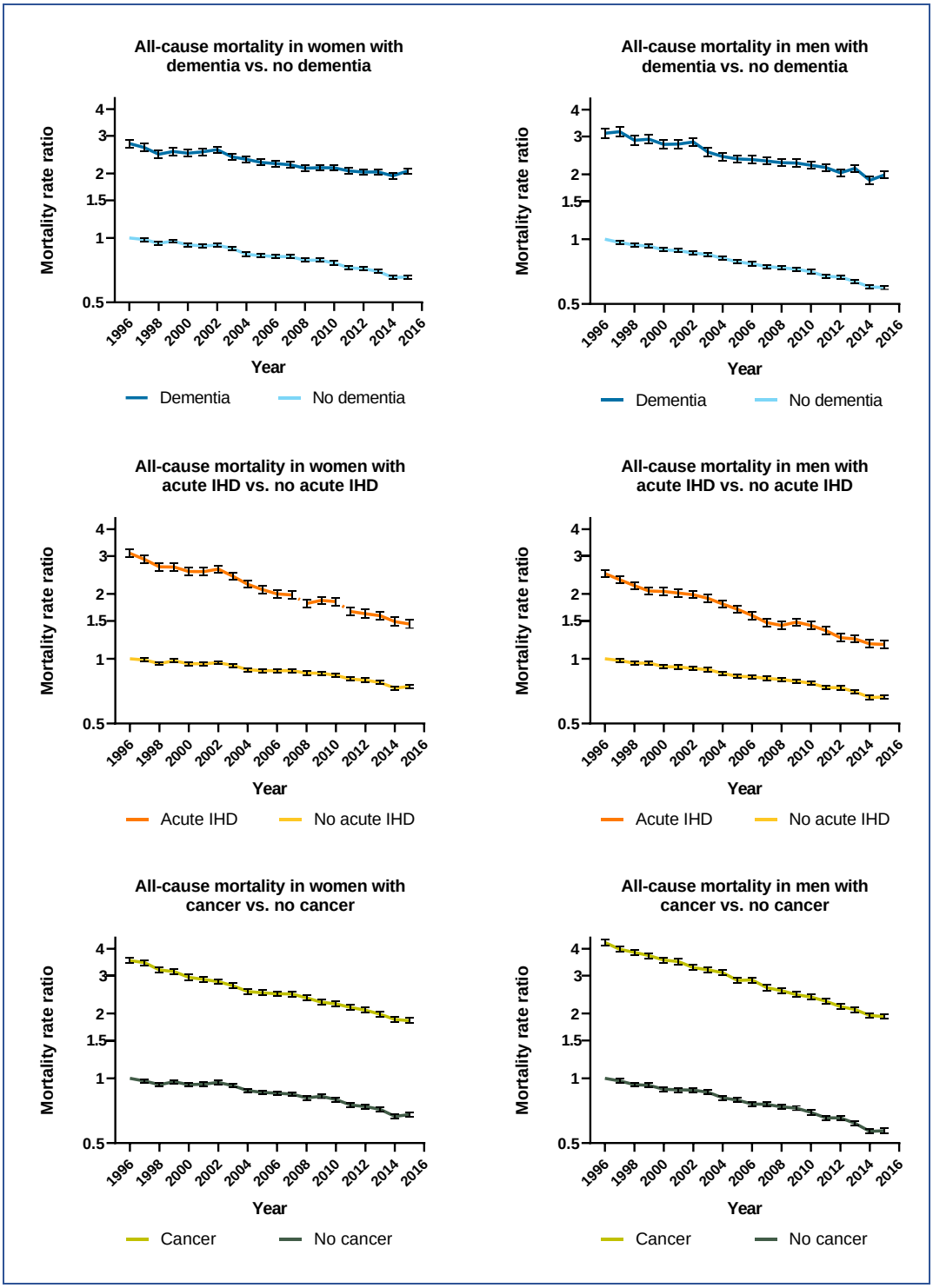
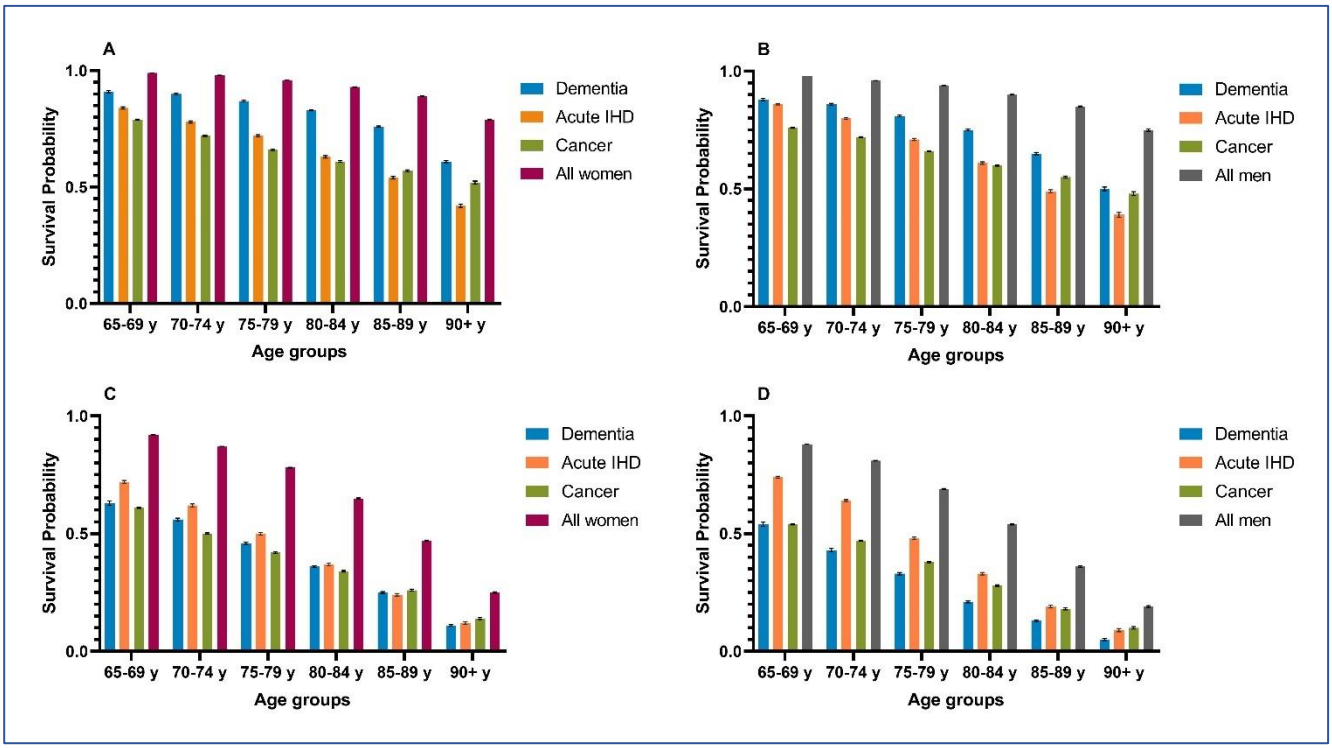


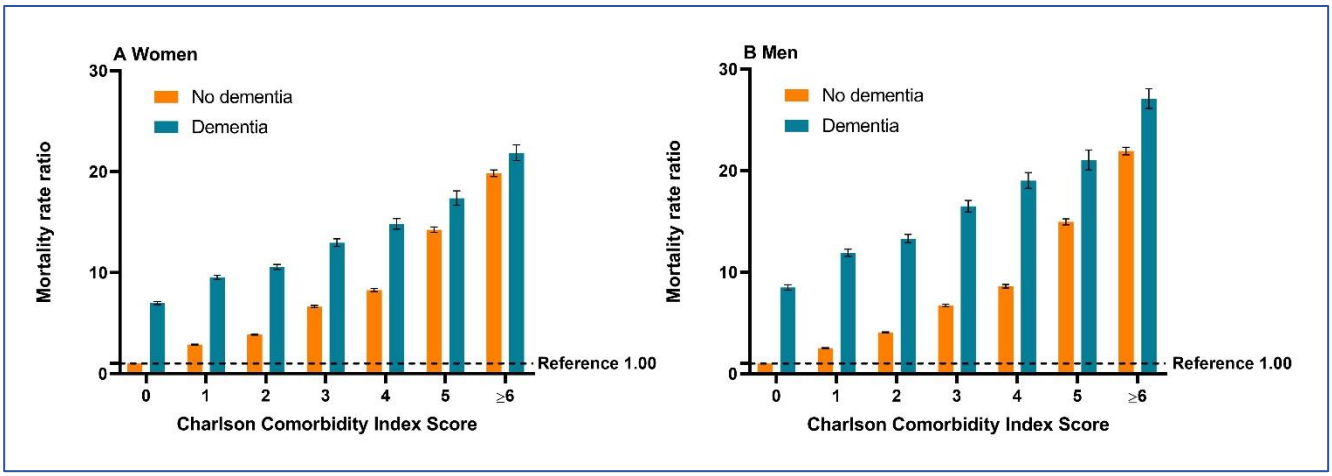
Figure 7. A) Women, one-year survival probabilities; B) Men, one-year survival probabilities; C) Women, five-year survival probabilities; D) Men, five-year survival probabilities. Reprinted from Taudorf et al.[111]



Study III

The population comprised of 1,548,917 people ≥65 years living in Denmark from 2006 to 2015. In this period there were 114,109 people registered with dementia. Comparing people <85 years, those with dementia had higher load of comorbidities compared to people without dementia. In people age ≥85 years and older, the load of comorbidities was similar in people with and without dementia. In people <85 years, the percentages of person-years lived with a low CCI scores were markedly lower in people with dementia than in those without dementia. In people ≥85 years, the distribution of person-years according to CCI score was comparable in people with and without dementia. In women and men, mortality increased with higher comorbidity load (Figure 8). However, when comparing women and men with a similar CCI score, the MRR were significantly higher in women and men with dementia than in women and men without dementia.

Figure 8. The age- and calendar year-adjusted mortality by Charlson Comorbidity Index in women (A) and men (B) with and without dementia.



Divided into five-year age groups, the excess mortality in dementia, it was most pronounced in the youngest age groups with a low CCI score. In men and women with dementia who were 65 to 79 years and had a CCI score of zero, the MR were 10.04 (95% CI: 8.16–12.35) to 17.28 (95% CI: 15.52–19.25) times higher compared to those without dementia. Furthermore, mortality was significantly higher in all CCI score- and age groups for women and men with dementia compared to those without.

This study also investigated mortality in 23 selected somatic and psychiatric disease groups in women and men with and without dementia. For all 23 conditions, also having dementia was associated with a significantly higher mortality (Figure 9).

Last, we assessed MRR in women and men with dementia applying the three models presented in Table 9. Model 1 was adjusted for age and calendar-year. The MRR was highest in the 65–69-year-old age groups (women: 5.39 (95% CI: 4.84–6.01); men: 5.41 (95% CI: 4.98–5.88)) and lowest in the ≥90 year-old age groups (women: 2.06 (95% CI: 2.03–2.10); men: 2.21 (95% CI: 2.15–2.28)). Model 3 was adjusted for age, calendar-year, and 23 psychiatric and somatic conditions. A noticeably reduction in MRR was observed for the 65–69-year-old age groups (women: 2.73 (95% CI: 2.44–3.05); men: 3.34 (95% CI: 3.07–3.63)), whereas the MRR in the ≥90-year-old age groups did not change significantly.

Figure 9. Excess mortality in dementia and concurring comorbidities. Excess mortality in women and men with dementia and selected comorbidities. The reference is defined as 1.00 for women and men without dementia but with the selected comorbidities. Error bars represent 95% confidence interval. Results for AIDS are not presented due to low sample size.

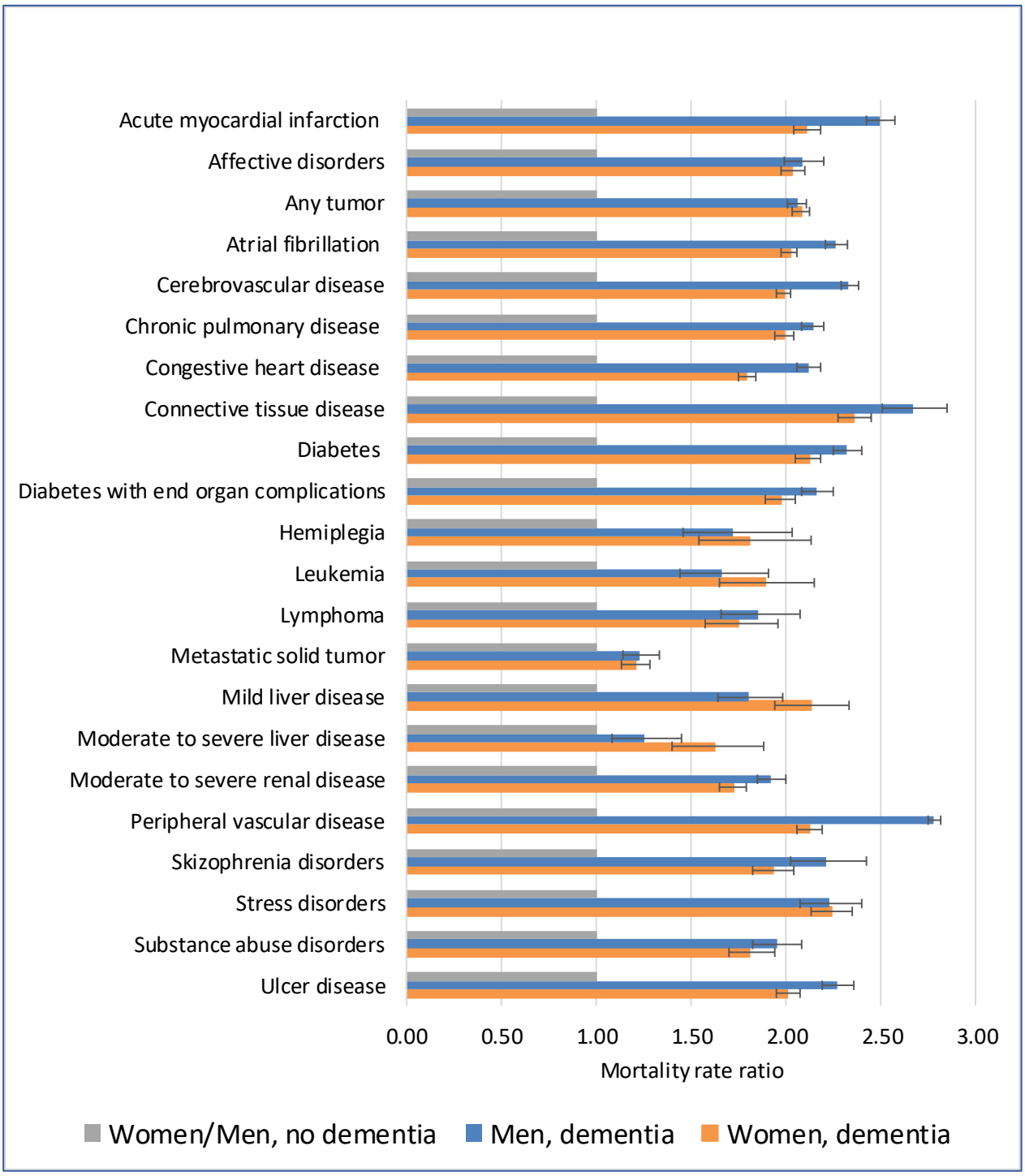


Table 9. MRR for women and men in five-year age strata and an age-adjusted average. In each of the three models presented, the reference is defined as 1.00 for women and men without dementia.

	Model 1 Adjusted for age and calendar year		Model 2 Adjusted for age, calendar year and psychiatric conditions		Model 3 Adjusted for age, calendar year, and psychiatric and chronic somatic conditions	
	Women with dementia		**Women with dementia**		**Women with dementia**	
Age	**MRR**	**95% CI**	**MRR**	**95% CI**	**MRR**	**95% CI**
Age-adjusted average	2.78	(2.75–2.81)	2.66	(2.63–2.68)	2.61	(2.59–2.64)
65–69 years	5.38	(4.82–6.00)	3.97	(3.55–4.43)	2.70[†]	(2.41–3.01)
70–74 years	5.33	(5.08–5.60)	4.51	(4.29–4.74)	3.29*	(3.12–3.46)
75–79 years	4.16	(4.04–4.29)	3.79	(3.67–3.91)	3.24*	(3.14–3.35)
80–84 years	3.46	(3.38–3.54)	3.31	(3.24–3.39)	3.12*	(3.05–3.19)
85–89 years	2.77	(2.71–2.82)	2.70	(2.65–2.76)	2.67*	(2.61–2.72)
≥90 years	2.06	(2.03–2.10)	2.04	(2.01–2.08)	2.04*	(2.00–2.08)
	Men with dementia		**Men with dementia**		**Men with dementia**	
Age	**MRR**	**95% CI**	**MRR**	**95% CI**	**MRR**	**95% CI**
Age-adjusted average	3.09	(3.05–3.13)	2.93	(2.89–2.97)	2.83	(2.79–2.87)
65–69 years	5.40	(4.97–5.87)	4.26	(3.92–4.63)	3.34*	(3.07–3.63)
70–74 years	4.69	(4.49–4.90)	4.10	(3.92–4.28)	3.39*	(3.24–3.54)
75–79 years	4.00	(3.88–4.12)	3.73	(3.61–3.84)	3.44*	(3.33–3.55)
80–84 years	3.28	(3.20–3.36)	3.18	(3.10–3.26)	3.01*	(2.93–3.09)
85–89 years	2.76	(2.69–2.83)	2.71	(2.64–2.78)	2.64*	(2.57–2.70)
≥90 years	2.21	(2.15–2.28)	2.19	(2.13–2.26)	2.17*	(2.10–2.24)

[†]Leukemia, lymphoma, and AIDS has been excluded from the model due to low sample size. *AIDS has been excluded from the model due to low sample size.

Study IV

Out of 621,846 deaths, 65,012 (10.5%) cases had a dementia diagnosis on their death certificates (underlying: 36,181; contributing: 28,831). Dementia-related deaths were more frequent in women (12.7%) than in men (7.9%).

Time trend of dementia-related deaths: In the 14-year study period, the prevalence of dementia-related deaths in the general elderly population increased for women and men ≥70 years (Figure 10). From 2002-2015, there were 14,593 persons (women: 9,964, men: 4,629) who were registered with a first-ever dementia diagnoses on their death certificate. The percentage of dementia-related deaths increased with age. From 2002 to 2015, the overall percentage of dementia-related deaths in the elderly population increased from 10.1% to 15.2 in women and from 6.3% to 9.5% in men. In people already diagnosed with dementia, the percentage of registered dementia-related death in women increased from 41.9% in 2002 to 56.2% in 2015 and in men from 39.2 % in 2002 to 53.2% in 2015 (Figure 8). The increase in dementia-related deaths was driven by an increase in the registration of dementia as an underlying cause of death, both in the general elderly population and in people already diagnosed with dementia whilst alive.

Changes in causes of death from 2002 to 2015: From 2002 to 2015, we observed a change in the registered underlying causes of death in women and men with and without dementia (Figure 11). During the 14-year period, dementia became the leading underlying cause of death in women and men already diagnosed with dementia. Meanwhile, the registration of cardio- and cerebrovascular disease as underlying cause of death declined for all women and men. This decline was more pronounced in women and men with dementia compared to those without. The proportion of cancer as underlying cause of death only increased modestly in people with dementia compared to a marked increase in people without dementia. The registration of pneumonia as an underlying cause of death declined in people with dementia, while it was stable for women without dementia, and increased in men without dementia.

Figure 10. Time trends of the distribution of dementia-related deaths in women and men in the general elderly population and women and men registered with dementia.

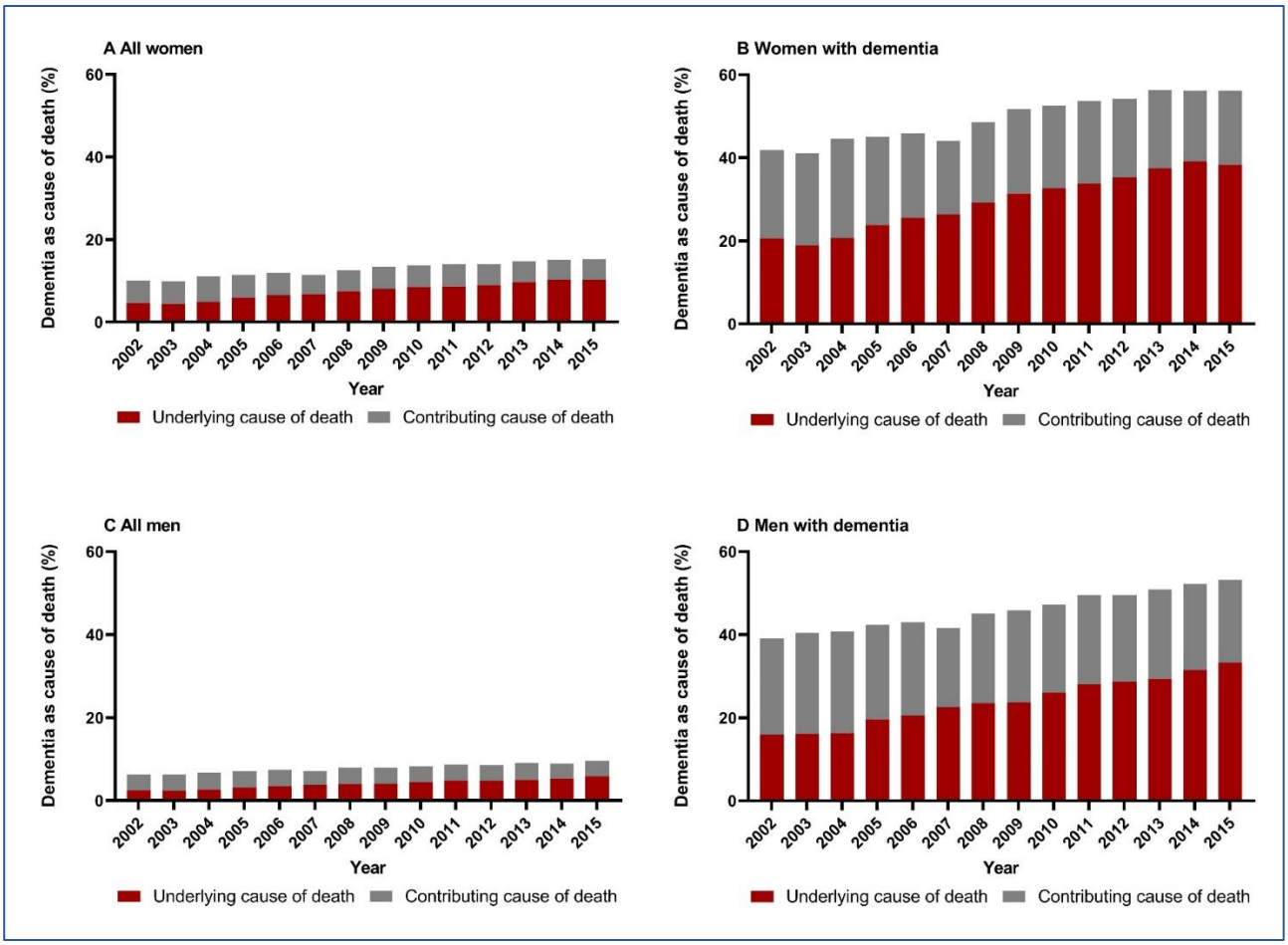
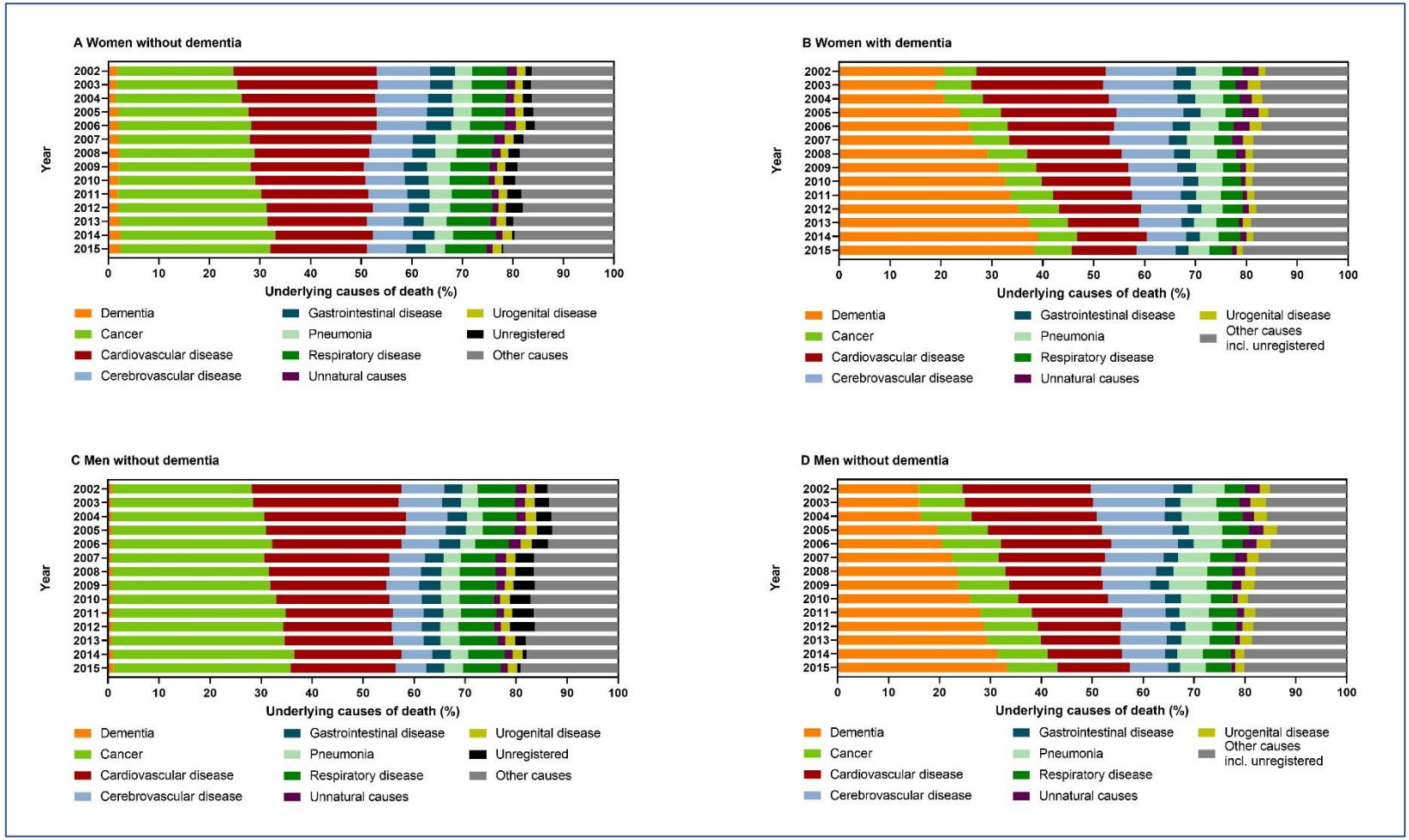


Figure 11. Time trend of the annual distribution (in percentages) of registered underlying causes of death in women and men with and without dementia, A) women without dementia, B) women with dementia, C) men without dementia, and D) men with dementia from 2002 to 2015.



Discussion

Key findings

This study included the entire population of Denmark in the time period from 1996 to 2015. We observed that incidence rates of dementia have been declining since 2010, while the total prevalence of people living with dementia is still increasing. The mortality was constantly approximately three-fold higher in people with dementia compared with people without dementia, even though mortality declined at the same rate in the two groups during the 20-year period. Dementia is a fatal disease, and the five-year survival is similar to that after a diagnosis of cancer or acute IHD. Our findings also showed that the excess mortality cannot be explained by co-morbid psychiatric and somatic conditions, as the excess mortality persisted after adjusting for 23 comorbidities. The excess mortality was most predominant in the youngest age groups with dementia, but at ≥90 years the MR was still twice as high in people with dementia compared with those without. This finding illustrates the severity of dementia, as people age 90 years in the general population already have a high age-related risk of dying. From 2002 to 2015, dementia became the leading registered underlying cause of death in people with dementia. This could reflect increased awareness that dementia is a fatal disease. However, dementia is still underreported on death certificates in people registered with dementia.

Time trends in incidence, prevalence, and mortality

Our studies assessed the time trends of incidence, prevalence, and mortality in the Danish elderly population from 1996 to 2015. We observed that age- and sex-adjusted incidence increased averagely by 9% annually from 1996 to 2003 followed by a 2% annual decline. Prevalence rates increased from 1996 to 2009 followed by a stabilization to 2015. Mortality declined in people with dementia during the 20-year period.

Incidence

We were able to identify ten population-based studies from high-income countries which had investigated time trends of incidence of dementia using multiple cohorts. Out of these, eight studies indicated trends of declining incidence rates of dementia over time[25–32] (1977-2015), while

the Chicago Health and Ageing Project (1994-2012)[112] investigating only AD reported a stable incidence rate, and the Hisayama Study (1985, 1992, 1998, 2005, and 2012)[33] reported an increase in incidence rates overall dementia and AD.

A meta-analysis based on five of these studies (the Rotterdam Study (1990 and 2000), the Indianapolis-Ibadan Dementia Project (1992 and 2001), the Bordeaux Study (1988-1989, and 1999-2000), Cognitive Function and Ageing Studies (1990-1994 and 2008-2011), and the Hisayama Study) concluded that the overall results indicated a stabilizing trend in incidence rather than a decline.[113] The Alzheimer Cohorts Consortium performed a time trend analysis based on aggregated data from the Rotterdam Study, the Bordeaux Study, the Cognitive Function and Ageing Studies, the Framingham Heart Study (1977-1983, 1986-1991, 1992-1998, and 2004-2008) plus data from four additional not previously published population-based cohorts.[114] They concluded that since 1998 there had been a decline in dementia incidence rate of 13% (95% CI: 7%–19%) per decade. For AD, this decline was 16% per decade (95% CI: 8%–24%). Both meta-analyses included only multiple-cohort studies, whereas Alzheimer Cohorts Consortium study included single cohort studies to assess a time trend of incidence based on birth cohorts.[115] The latter found a significant association between birth year and decreased incidence rates for dementia in general.[115] However, when assessing time trends for AD separately, this study found no decline in incidence rates in Western countries, while incidence increased in younger age groups in non-Western countries.[115] Even though our study observed a significant decline in incidence rate, our analyses did not show any effect of birth cohort.

Results of time trends of incidence of dementia based on registry data show inconsistent results. A German (2006-2007 and 2009-2010)[34] and a Canadian (2005-2013) study reported significant declines[35], a Dutch study (1992-2014)[37] found an increase, and a Canadian (2002-2013)[36] and Swedish (1987-2016)[38] study reported time trends with either incline or fluctuations of dementia followed by declines.

Overall, a majority of population-based studies and meta-analyses observed trends of declining incidence of dementia, which is in line with findings from our study.

Prevalence

Prevalence rates of dementia increased from 1996 to 2015 for men and women in all age-groups, although relatively stable from 2010. Multi-cohort population-based studies have observed

different time trends when examining prevalence rates. The Indianapolis-Ibadan Dementia Project (1992 and 2001)[39], a Spanish study (1988-1989 and 1994-1996)[40], and three Swedish studies (1976-2006, 1995-1998 and 2001-2003, and 1987–1994 and 2001–2008)[41–43] reported stable prevalence, whereas the Cognitive Function and Ageing Studies (1989-1994 and 2008-2011)[45], and an American study (2000 and 2012)[44] observed a decline in prevalence, while the Hisayama Study (1985, 1992, 1998, 2005, and 2012)[33] showed an increase in prevalence. Additionally, the Chicago Health And Ageing Project (1994-2012)[46] and the Bordeaux Study (1988-1989, and 1999-2000)[47] observed no clear time trends. While most studies assessing time trends of prevalence in dementia primarily have observed declining or stabilizing prevalence, our findings are in line with result from the Hisayama Study showing an increase in prevalence rates.

Mortality

In Study II, we observed that during the 20-year period the mortality declined at the same rate in people with and without dementia. However, the mortality was constantly about 2.9 times higher (age- and sex-adjusted MRR) in people with dementia compared with elderly people without dementia. A systematic review from 2011 reported a similar increase in mortality for people with dementia (odds ratio: 2.63, 95% CI: 2.17–3.21).[116] Few studies have previously examined time trends of mortality in dementia. In line with our findings, four population-based studies observed either declining mortality or increasing survival (1987-2012).[26,33,43,48] In contrast, two other studies found trends, however not significant, of increasing mortality in dementia (1993-2010).[34,49] Overall, only few studies have investigated time trends of mortality in people with dementia, and our study adds weight to the evidence that mortality in dementia has declined during the past two decades.

In Study II, we also compared the time trends of mortality in dementia to that in cancer and acute IHD. We observed that MRR declined significantly more in people with cancer and acute IHD compared with dementia. During the time period from 1996 to 2015, efficacious treatments were introduced and improvements in the organization of care were implemented for cancer and acute IHD, and both disease groups were made a priority in the Danish Health care sector.[117,118] The mortality gap between these two disease groups and the general elderly population was significantly reduced during this time period. To compare, no new medications have been approved for treating dementia diseases in Denmark since 2003.[119] Overall, we had to reject our

hypothesis that mortality in dementia had declined more rapidly than in the general population due to a higher awareness of providing appropriate care.

The one-year survival was significantly higher in people with dementia compared to cancer and acute IHD, but we found different results when assessing five-year survival. The five-year survival after diagnoses was largely similar in people with dementia compared with people with cancer and acute IHD. We believe the higher risk of dying during the first year after diagnoses is related to differences in the disease progression and time courses of the three diseases. The highest risk of mortality in acute IHD are the day of onset and the first few following days. Similarly, some cancer types have a tendency of rapid progression and are fatal early in the course of the disease, e.g. pancreas, liver, brain, lung, and esophagus cancer.[120,121] This may explain the low one-year survival in cancer diagnoses as a whole. The severity of a dementia diagnosis is emphasized by the five-year survival largely being similar when comparing with cancer and acute IHD.

Combining time trends

Combining findings from Study I and Study II produced an annual time trend of incidence, prevalence, and mortality of dementia in the Danish elderly population over a 20-year period. Previously, a Swedish and a Japanese population-based study have investigated all three parameters in the same population, albeit without access to continuous data as in our study.[32,33,43] The Swedish study observed a 30% decline in incidence (HR=0.70, 95% CI: 0.61–0.80) from follow-up in their first cohort 1987-1998 compared with follow-up in their second 2001-2003.[32] At baseline, the two different time period cohorts had similar age- and sex-standardized prevalence of dementia (17.5% vs. 17.9%). After controlling for age, sex, education, and cognitive function, the likelihood of death was reduced similarly in people with and without dementia.[43] In the Japanese study, five cross sectional surveys were performed in 1985, 1992, 1998, 2005, and 2012 when assessing incidence and prevalence.[33] The age- and sex-adjusted incidence as well as the age-standardized prevalence rates increased for all-cause dementia and AD, which was not the case for VaD.[33] Survival was assessed in two cohorts (1988 and 2002) as five-years survival rate. The five-year survival rates improved for all-cause dementia and AD from the 1988 to the 2002 cohort, whereas the 5-year survival in VaD did not change significantly.[33] Overall, the results from our time trend analyses are in agreement with findings from the Swedish study. However, neither our study nor the Swedish study investigated dementia subtypes as the Hisayama study did.

Multiple reasons have been suggested to explain a decline in incidence of dementia during the past decades. One hypothesis is that the declining incidence of dementia is related to general improvements in health, including better control of risk factors and treatments of especially cardiovascular diseases. In accordance with this hypothesis, it has been suggested that the observed decline in dementia may primarily represent a decline in VaD. This is also suggested in the meta-analysis by Gao et. al, reporting a decline in all-cause dementia, while AD remained stable.[115] The study did not assess mortality in VaD.

A second explanation of declining incidence has been linked to improvement in cognitive reserve. Both the Swedish study and the Framingham Heart study reported that their later cohorts had a higher level of education than their earliest cohorts. However, the Framingham Heart Study found that the risk reduction of dementia in the later cohorts was limited to those with at least a high school diploma, whereas the Swedish study observed the opposite result, that a decline in incidence was particularly observed in people with only elementary education.[25,43] Thus, more knowledge is needed to examine the association between time trends and incidence and cognitive reserve.

A third explanation of our observed decline in incidence could reflect a change in the use of dementia diagnoses. Over the 20-year period, there have been several improvements in neuroimaging and biomarkers related to neurodegenerative diseases. Although the same diagnostic criteria have been applied throughout the entire observation period, these improvements might have led to a more restrictive and higher precision in the use of dementia diagnoses. With the data available, we cannot exclude that the declining incidence of dementia in our cohort could be related to a decline in the diagnostic rate.

Results from Study I revealed a paradox of declining incidence rates and yet increasing total prevalence. By combining the results from Study I and Study II, we can conclude that the increase in prevalence of dementia in the Danish elderly population is driven by a decline in mortality. This is backed up by the results that the median age of incidence was similar in 1996 and 2015 (1996: 82.4 years vs. 2015: 82.3 years), while the median age at death in men and women with dementia increased from 2002 (women: 86.6; men:83.6) to 2015 (women: 88.0 years; men: 84.8 years). Thus, during the two decades observed, people lived longer after being diagnosed with dementia. This could be related to better care and improvements in health in people with dementia.

Comorbidities and mortality in dementia

Elderly people often live with one or multiple comorbidities. These comorbidities may affect mortality, and possibly differently in a person who additionally is diagnosed with dementia. Questions related to concurring comorbidity in people with dementia was investigated in Study III. We also assessed excess mortality stratified by CCI score. Comparing men and women with a CCI score of zero, men and women aged 65-79 years with dementia had MRR that were were 10.04 (95% CI: 8.16–12.35) to 17.28 (95% CI: 15.52–19.25). This emphasizes that dementia diseases are fatal progressive brain diseases. Without the presence of comorbidities, they are associated with an extensively increased mortality. Furthermore, we observed that excess mortality in people with dementia persisted after adjusting for a range of chronic comorbidities. When stratifying by age group, CCI score, and dementia status, we found that the excess mortality in people with dementia was most predominant in the youngest age groups with few comorbidities. Nonetheless, our results also showed that even in the oldest age groups with a CCI score ≥6, mortality was still significantly higher in people with dementia.

We were able to identify a single study that had investigated the effect of multiple comorbidities on mortality in dementia compared with the general elderly population.[73] In concordance with our results, this Canadian study reported that in all elderly people, mortality increased with the number of comorbidities, but was significantly higher in people with dementia.[73] Additionally, when comparing people with and without dementia, the difference in hazard ratios (HR) for mortality declined when the number of comorbidities increased. Furthermore, the HR for mortality in dementia declined with increasing age.[73] Our MRR were markedly higher compared with the Canadian study's HR. This could be related to the following; 1) the probability of having comorbidities were higher in the Canadian study, because they included more comorbidities; or 2) our comorbidities are likely to represent more severe disease or disease stages as we only included diagnoses from the secondary health sector.

In the most advanced Poisson regression model, we adjusted for age, calendar year, psychiatric and somatic comorbidities and found an MRR of 2.70 (95% CI: 2.68–2.72) for dementia. Other studies that performed analyses with models adjusting for multiple comorbidities, all reported lower estimates (HR of mortality of 1.47 (95% CI: 1.35–1.60)[74]; 2.07 (95% CI: 1.62–2.66)[75]; and a relative risk of 1.80 (95% CI: 1.46–2.21)[76]. We believe our higher estimate may be explained by

two factors. First; results from the three mentioned studies were adjusted for activities of daily living or level of care, in addition to the multiple comorbidities. Reduction in the ability to perform activities of daily living have been associated to increased mortality in dementia.[57,59,65,66] This could explain why adjusting for this parameter could result in lower estimates. Second; two of the mentioned studies assessed status of comorbidities only at time of diagnosis of dementia or baseline.[74,75] It is likely that people with dementia may have developed more comorbidities in the time period between their dementia diagnosis and death. Hereby, the association between comorbidities and mortality may have been underestimated.

Conclusively, comorbidities only explained some of the excess mortality in people with dementia. Several factors besides comorbidities and age have been linked to increased mortality in dementia including reduction in activities of daily living[57,59,65,66], institutionalization[58], low cognitive performance [57,58,61,64,67,68], antipsychotics[69], and polypharmacy[70,71]. Most dementia diseases are progressive neurodegenerative brain diseases, and it is highly likely that dementia per se contributes markedly to the persistent excess mortality. This was illustrated by quantifying the excess mortality related to dementia. In people younger than 80 years, who had no registered comorbidities (CCI score=0), the mortality rates were 10 to 17 times higher in people with dementia than those without. Additionally, it is possible that some of the excess mortality could be linked to different risk factor profiles in people with and without dementia.[122,123] As an example, a review found that falls, delirium, epilepsy, weight loss and nutritional disorders, incontinence, sleep disturbances, visual dysfunction, oral disease, and frailty were more frequent in people with dementia compared to people without dementia.[123] Furthermore, comorbidities might be underdiagnosed in people with dementia, and people with dementia might not have the same access to treatment or care.[124] People with dementia might also have a higher risk of receiving inappropriate or insufficient treatments for their comorbidities.[125,126]

What causes death in people with dementia?

The last two decades have seen numerous advances in the diagnostics, treatments, and organization of multiple disease groups, including cardio- and cerebrovascular disease and cancer. Moreover, there has been an increased awareness of improving health in the elderly population.

Globally, life expectancy is increasing. Causes of death in people with dementia as well as in the general elderly population may have changed. Therefore, we performed a time trends analysis investigating causes of death. To the best of our knowledge, this is the first study to investigate if causes of death have changed over time in people with dementia.

From 2002 to 2015, we observed an increase in the registration of dementia as cause of death in the general elderly population. This is in line with the trend that dementia globally is increasing as a cause of death.[79]

In people with dementia, we found an increase in the registration of dementia as cause of death. This incline was driven by an increased use of dementia as underlying cause of death. Findings from a UK study observed a similar increase in the registration of dementia as cause of death from 39.9% in 2006 to 63.0% in 2013.[127] Furthermore, our finding of an increase in registering dementia as an underlying cause as opposed to contributing cause of death is in line with a Norwegian study.[82] The increase in registering dementia as an underlying cause of death may reflect increased awareness of dementia as a fatal disease among doctors. Nonetheless, more than 40% of people with dementia, did not have a dementia diagnosis registered on their death certificates. Consequently, more should be done to increase awareness about dementia as a fatal disease.

Some studies use data from death certificates to assess time trends of mortality in dementia. As our results underpin that this can be problematic, such studies were not included when comparing to previous research. In Study II, we observed that the all-cause mortality in people with dementia declined from 1996 to 2015. Using results from Study IV to evaluate mortality of dementia (dementia-related deaths), we observed an increase instead. This increase represents an increase in recordings of dementia as a cause of death on death certificates, and conclusions on time trends in dementia should not be based on these data.

Previous research based on death certificates and autopsy studies has been consistent in reporting the leading causes of death in people with dementia to be cardiovascular disease or pneumonia/respiratory diseases.[88–96] In our study, we observed that the percentages of pneumonia registered as an underlying cause of death were similar in people with and without dementia. Our finding is contradictory to results from a meta-analysis concluding that people with dementia had a significantly higher risk of dying with pneumonia.[97] We believe this could be

explained by two factors: 1) The autopsy-based studies reported immediate cause of death whereas our study used the underlying cause of death, 2) Dementia was the most frequent registered underlying cause of death in our study, and increased awareness about dementia as a cause of death could have led to the preferred use of dementia as underlying cause of death instead of pneumonia.

From 2002 to 2015, we observed a marked reduction in the percentages of cardio- and cerebrovascular disease registered as underlying cause of death. This reduction was even more predominant in people with dementia compared to those without. We believe this reduction to be related to: 1) a change in the use of preferred diagnostic codes, 2) improvements in control of risk factors and treatments of cardio- and cerebrovascular disease.[25] As an example, the 90-days mortality after acute myocardial infarction was reduced from 19.6% in 1997-1998 to 11.7% 2009-2010 in Denmark likely due to improvements in the organization of treatment and pharmacotherapy.[118] This progress was reflected by our finding from Study II, observing a decline in all-cause mortality after acute IHD from 1996 to 2015. Dementia and cardio- and cerebrovascular share multiple risk factors. It is possible that a larger proportion of people with dementia have benefited from improvements of risk factor control and treatment compared to the general elderly population. This could explain why cardio- and cerebrovascular disease as underlying cause of death declined more markedly in people with dementia compared with the general elderly population. However, we cannot exclude that there may also have been a change in the preferred use of codes for underlying cause of death by medical doctors.

The registered cause of death in people with dementia could be affected by the fact that no disease modifying drugs are available. Possibly, it is more acceptable that people with severe dementia die from less severe diseases that are otherwise considered curable. Overall, this may affect what diseases are registered as causes of death.

Methodological considerations

This thesis was based on four registry-based observational studies, which used the Danish elderly population as cohort. In the following section, limitations and strengths will be discussed.

In all of our studies, we defined people with dementia by using the same diagnostic codes and ATC codes. We included the use of prescription data to be able to identify individuals diagnosed by neurologists and psychiatrists in the private health sector, or by general practitioners. In Denmark, it is only possible to receive reimbursement for dementia medication, if the medication is prescribed by either a neurologist, a geriatrician, or a psychiatrist.[128] Thus, identification by prescription data may be just as precise or even more precise than identification by diagnoses. In contrast to prescription data, dementia syndrome codes have previously been validated in the Danish registries and were found to be correct in 86% of the cases.[129] Based on extrapolations from European population-based studies, it was estimated that in 2015, there were approximately 87,000 people with dementia in Denmark.[130] However, we know that dementia is generally underreported in the Danish national registries,[130] since we only identified 36,129 people living with dementia in 2015 when using our definitions. This incoherence in dementia prevalence was supported by Study IV, identifying 14,796 people registered with a dementia diagnosis for the first time on their death certificates. People diagnosed with dementia are likely to have lived with the disease years prior to their diagnoses, and date of diagnosis does not represent onset of disease. Consequently, the number of person-years lived with dementia is likely to be underestimated in our studies. Therefore, we acknowledge that the underreporting of dementia in the Danish registries could have affected our results. Furthermore, our reference population is likely to include individuals with dementia. However, we believe that this is likely to have a limited effect, as our reference population of elderly people is large. Overall, the presence of people with dementia in our reference population is more likely to result in a dilution between the actual association between dementia and an outcome rather than an overestimation. Consequently, this will lead to results that are conservative estimates.

During the study periods, the same diagnostic criteria (ICD-10) have been used in the Danish health care system. Nonetheless, the use of the diagnoses may have changed. As we observed a decline in incidence rates starting from 2009, one could speculate that a more restrictive use in the latter years may be related to increased precision in diagnostics. We were only able to identify individuals, who were either diagnosed in the secondary health sector, or who used prescribed anti-dementia medication. We acknowledge that there are groups of people with dementia that were less likely to be included. We believe that these groups primarily represent: 1) people in the

early stages of dementia, who have not yet sought medical advice, and 2) people with late stage dementia, who are not able to participate in a diagnostic evaluation, and where a diagnosis will have no consequences. Thus, there is a risk that our population of people with dementia is less likely to represent certain clinical stages of dementia. This may affect the association between dementia and death.

In all of our studies, we chose to investigate late-onset dementia only, as previous research has shown that dementia is overdiagnosed in younger people in the Danish national registries.[107] As it is likely that incidence, prevalence, mortality, and causes of death varies with different dementia subtypes, it would have been interesting to perform analyses by subtypes specifically. Unfortunately, even though the validity of the dementia syndrome diagnoses is high, the dementia subtype diagnoses are not.[129]

We included prescription data on cholinesterase inhibitors in our definition of dementia. This group of drugs are used to treat AD, Lewy body dementia, and dementia in Parkinson's disease. However, in our definition of dementia, we did not include dementia in Parkinson's disease as a dementia outcome. Yet, we acknowledge that our dementia cohort may include some individuals with dementia in Parkinson's disease.

We chose different approaches in terms of adjustment for different variables in the statistical models that might otherwise have contributed to confounding. All our analyses addressed the effect of sex and age, using either stratification or adjustment to account for potential confounding. Furthermore, calendar year was considered a confounder, as calendar year may correlate with both the risk of a dementia diagnosis and mortality.

In Study II, we compared time trend of mortality as well as survival in people with dementia compared to people diagnosed with cancer and acute IHD. The disease groups were defined using the ICD-8 and ICD-10 codes as defined in the CCI. This way of defining cancer is heterogeneous, and mortality differs in various cancer subtypes.[117] As improvements in screening regimes, treatments, and organization of care may have differed among cancer subtypes, it is likely that the time trends of mortality have evolved differently for different cancer subtypes during the study period. Furthermore, the reduction in mortality gap observed in cancer may partly be explained by earlier diagnoses, which could be associated with increased awareness and screening regimes.

In Study III, we examined the association between comorbidities in people with and without dementia using death as the outcome. The diagnoses included in the CCI have previously been validated and the positive predictive values of the ICD-10 codes ranged between 82% and 100%.[105] To define comorbidities, we used continuous data including both ICD-8 and ICD-10 codes. As diagnoses on admissions to somatic and psychiatric hospital departments are the only ones available before 1994, there has been a change in the available diagnoses over time. Having diagnoses available only from the secondary health care sector, we acknowledge that they likely represent the most severe cases of the diseases, since these diagnoses require hospital contact to be registered. As an example, most people with diabetes are treated by their general practitioner, while people with diabetes identified in the national registries are likely to represent a group of patients with more severe diabetes needing hospitalization or treatment at an endocrinological outpatient clinic. Consequently, with only hospital diagnoses available, we are not able to adjust for the entire effect of diabetes. We acknowledge that residual confounding cannot be ruled out. This is likely the case with other comorbidities as well, if they are treatable in the primary health care sector. In some comorbidities, not only the disease, but also the treatment may contribute to increased mortality in people with dementia. For example, antipsychotics have been associated with increased mortality.[131] Additionally, people who are in contact with the hospital system may have an increased risk of being diagnosed with multiple diseases. In the case of dementia, people who are admitted with another condition may be more likely to be referred to a memory clinic.

All four studies were based on routine healthcare data from the secondary health care sector. Several variables with a possible impact on both the risk of developing dementia and mortality were unavailable. These include all of the early, midlife, and late life risk factors for developing dementia as proposed in the model by Livingston et al. (Introduction, page 17).[21] Furthermore, data including physical and cognitive performance status, whether a person lived in a nursing home, and clinical data, paraclinical evaluations and biomarkers (including Apolipoprotein E allele variant) would have been highly relevant to investigate when assessing incidence and prevalence as well as the association between dementia and mortality.

The outcome assessed in this study was either date of dementia registration, date of death, or causes of death. Date of death is for practical purposes complete with no missing data. A major limitation of Study IV is that data on causes of death have not been validated. This could have

been done in an autopsy study, but the frequency of autopsies is low in Denmark (below 10%).[84] Thus, data registered on death certificates depends on the decisions of individual medical doctors and on the coding by the National Board of Health.[84] We attempted to handle this limitation by categorizing causes of death into disease groups to ensure more robust outcomes compared with using single diagnoses.

In all our studies, our populations comprised a national cohort of the entire elderly population. Thus, there was no risk of selection bias. For practical purposes, the follow-up is complete, thereby, excluding the risk of loss to follow up. Most of the variables used in our four studies were available as continuous data. When performing time trend analyses, the access to continuous data is an advantage. It is possible to assess yearly or even monthly changes if the exposure and outcome are frequent. The power of assessing time trends using continuous data was illustrated in Study I, where we observed that the incidence rates increased markedly from 1996 to 2003 followed by a stabilization and later decline. If we had access to data from the years 1996 and 2015, we would have wrongfully concluded that the incidence of dementia had increased during the 20-year period. By the use of continuous data, time trend analyses provide a more accurate picture. Furthermore, the results from Study I and Study II showed that incidence, prevalence, and mortality varied with calendar year, illustrating that this was an important co-variate to take into account in our analyses.

Conclusions and perspective

The findings from this PhD thesis contributed with important new knowledge on incidence, prevalence, and mortality in people with dementia in a national population of elderly people.

First, our study was the first nationwide study to confirm time trends of declining incidence of dementia previously observed in primarily smaller populations. As the decline was observed during a time period with increased focus on reducing risk factors, this leads to cautious optimism that it may be possible to prevent some cases of dementia. Combined with previous studies, it also raises the question of whether the observed decline in dementia could be limited to VaD. Future research should investigate time trends of incidence classified by dementia subtypes in order to distinguish between them and to target dementia prevention action plans. Even though incidence rates have been declining since 2009, the total prevalence of people living with dementia is still increasing due to demographic changes. The increasing number of people with dementia should be considered in relation to prevention initiatives, planning future healthcare services, and creating a dementia friendly society.

Second, it is well-known that mortality is increased in people with dementia. However, our study was the first to show that the excess mortality in people with dementia has been stable during the past 20 years. The fatality of a dementia diagnosis was highlighted by our results showing that the five-year survival after a dementia diagnosis was largely similar to that of a diagnosis of cancer or acute IHD. As long as we do not have any disease modifying drugs for the underlying brain disorders, it may not be possible to fully diminish the excess mortality in dementia. However, efforts should still be made to try to reduce the excess mortality in dementia. This includes reductions of improper medication or polypharmacy, optimizing of treatment of comorbidities, maintaining of activities of daily living, and optimizing organization of support and healthcare services.

Third, this thesis emphasized the severity of dementia disorders by demonstrating the effect of comorbidities on mortality. Having any of the selected 23 somatic or psychiatric conditions in combination with dementia was associated with a significantly higher MR. When we compared people with and without dementia who had the same amounts of comorbidities, people with dementia had a significantly higher mortality. Furthermore, mortality remained high in people

with dementia after adjusting for co-morbid psychiatric and somatic condition. This indicates that dementia disorders alone contribute to excess mortality.

Last, this study was the first to assess if causes of death in people with dementia had changed over time. We observed that dementia became the leading underlying cause of death from 2002 to 2015. Furthermore, dementia was more likely to be registered as an underlying cause of death in contrast to a contributing cause of death in the later years of the study period. This could imply a change in the awareness and perception of dementia as a fatal disease. However, more than 40% of people with dementia did not have a dementia diagnoses registered as a cause of death, illustrating that dementia is still underreported on death certificates. These results call for more awareness of dementia as a fatal disease. A change in the perception of dementia as a fatal disease is important in motivating dementia research and the highly needed search for new efficacious drugs against dementia. Furthermore, awareness about dementia as a fatal disease is needed for making prioritization and investments in better health care for people with dementia.

This thesis identified people with dementia as a vulnerable group in the general elderly population with a markedly higher mortality. The severity of a dementia diagnosis was emphasized by the persistent excess mortality and by the fact that the five-years survival was similar to that in cancer and acute IHD. These findings highlight that dementia should be perceived as a fatal disease. It also emphasizes the need of reducing the negative consequences related to dementia. The thesis showed findings of declining incidence bringing hope that it may be possible to prevent some cases of dementia. Though the prevalence of dementia may not be as rapidly increasing as previously expected, measures should still be taken in order to reduce risk factors of dementia, and promote a healthy life. Furthermore, investments in dementia research are needed including development of new disease-modifying drugs and improvement of health care for people with dementia.

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Study manuscripts

Study I

Declining incidence of dementia: A national registry-based study over 20 years

Reprinted from Alzheimer's & Dementia: The Journal of the Alzheimer's Association, Vol. 15, Issue 11
Taudorf L, Nørgaard A, Islamoska S, Jørgensen K, Laursen TM, Waldemar G
Declining incidence of dementia: A national registry-based study over 20 years
Pages 1383-1391, November 2019, with permission from John Wiley and Sons.
The publication is available at Wiley through https://doi.org/10.1016/j.jalz.2019.07.006

Alzheimer's & Dementia 15 (2019) 1383-1391

Featured Article

Declining incidence of dementia: A national registry-based study over 20 years

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Abstract

Introduction: The aim of this study was to investigate the registry-based national time trends in incidence and prevalence rates of dementia from 1996 to 2015.
Methods: We assessed annual incidence and prevalence using longitudinal data from nationwide registries on dementia status and demographics on all residents ≥ 65 years old in Denmark.
Results: Our population comprised 2 million people, of whom 152,761 were diagnosed with dementia. The age- and sex-adjusted incidence rate increased, on average, by 9% annually from 1996 to 2003, followed by a 2% annual decline, while total prevalence increased during the whole period.
Discussion: This is the first study to report continuous time trends of incidence and prevalence in an entire national population. The incidence rate has declined steadily since 2003, while the total prevalence is still increasing. Future health care planning on prevention and treatment of dementia should take these findings into account.

Keywords: Dementia; Incidence; Prevalence; Time trend; Epidemiology; Registry study; Nationwide study

1. Introduction

In 2015, the World Alzheimer Report estimated that 46.8 million people worldwide were living with dementia and projected an increase to 131.5 million by 2050 [1]. The magnitude and potential consequences of the expected increase in prevalence have led to a stronger focus on the potential for prevention and on finding a cure for Alzheimer's disease (AD) and other dementia disorders.

The risk of developing dementia is influenced by a combination of lifestyle and genetic factors. In a recent Lancet Commission article, Livingston et al. presented a model for quantifying the impact of individual factors on overall risk of dementia [2]. The authors concluded that approximately 35% of the risk of developing dementia was potentially modifiable, encompassing mainly midlife and late-life risk factors such as hypertension, obesity, smoking, physical inactivity, diabetes, depression, social isolation, and hearing loss [2]. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability indicated that a multifaceted intervention program aimed at at-risk elderly people may prevent cognitive decline by focusing on cardiovascular risk factors [3]. In high-income countries, treatment of cardiovascular risk factors has improved and the focus on healthy lifestyles has increased during the last three decades [4]. Thus, it is plausible that, with general improvement in health and better control of risk factors, prevention of dementia may be possible to some extent.

Recent follow-up studies in large population-based cohorts indicated a possible decline in the incidence of dementia in the elderly during the past 10-42 years [5–11].

Conflicts of interest: G.W., K.J., A.N., and L.T. reported grants from the Danish Ministry of Health during the conduct of the study. T.M.L. and S.I. have nothing to disclose.

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https://doi.org/10.1016/j.jalz.2019.07.006

Nevertheless, study results are inconsistent and, in some studies, the declining incidence was driven mainly by certain subgroups of either men, women, or specific subtypes of dementia [5,7,8].

Although population-based cohort studies offer detailed, systematic data on the individual participants, they have limitations, such as small cohorts, discontinuous data collection with long follow-up intervals, high dropout rates, recruitment from a small geographical area, and selection bias. Denmark's unique national registries enable linkage between a wide range of registries, including, for example, demographic and continuous health care data at an individual level for every resident [12]. Consequently, it is possible to explore time trends in an entire population based on high quality health care data from the secondary sector. Investigating time trends in incidence and prevalence of dementia is vital in planning future health care services and, hence, the ability to provide the best care and treatment for people with dementia.

The aim of this study was to investigate registry-based time trends in incidence and prevalence rates of dementia in an entire national population over a 20-year period. We hypothesized that the incidence of dementia may have declined in recent years, despite increasing prevalence.

2. Methods

We linked nationwide population data from the Danish Civil Registration System to information about dementia status using data from the Danish National Patient Registry, the Danish Psychiatric Central Research Register, and the Danish National Prescription Registry [12–15]. Every individual living permanently in Denmark is given a unique personal identification number, enabling linkage of data from Danish registries [13].

2.1. Registries and data

The Danish National Patient Registry and the Danish Psychiatric Central Research Register began registering data on all hospital admissions in 1977 and 1969, respectively, and in 1995, they began collecting data from emergency departments and hospital-based outpatient clinics [12,14]. At every patient contact, date of admission and discharge, and primary and optional secondary diagnosis have been registered according to the International Classification of Diseases, 8th revision (ICD-8) from 1977 to 1993 and the 10th revision (ICD-10) from 1994 [12,14]. ICD-9 was never implemented in Denmark [12]. The Danish National Patient Registry has collected information on filled prescription medication since 1995. Data include date of dispensing, dose, strength, and the Anatomical Therapeutic Chemical code (ATC code) [15]. Because of the implementation of ICD-10 and opening of the Danish Prescription Registry, the observation period was defined as January 1, 1996 to December 31, 2015.

2.2. Definition of dementia

A diagnosis of dementia was defined as either a registered dementia diagnosis in the Danish National Patient Registry or the Danish Psychiatric Central Research Register (Supplementary Table S1 lists the diagnostic codes), or as having filled at least one prescription for an anti-dementia drug (ATC: N06D, see Supplementary Table S2, which lists ATC codes for pharmaceutical treatment of dementia). Date of dementia onset was defined as the date of the first dementia diagnosis registered or the date of the first prescription filled, whichever came first.

2.3. Study population

People were included in the study upon turning 65 years, or if they were between 65 and 110 years old and registered as living in Denmark at some point from 1996 to 2015. Owing to the potential risk of misregistration, people older than 110 years were censored. The study population will be referred to as people aged 65 years and older.

2.3.1. Incidence study

Incident cases were defined as people diagnosed with dementia, according to the abovementioned definition, for the first time within a given calendar year. People diagnosed with dementia before the age of 65 were excluded because we wanted to investigate incident cases in people aged 65 years and older. Individuals were censored when they were diagnosed with dementia, emigrated, were lost to follow-up, died, turned 110 years old, or at the end of the study period, whichever came first.

2.3.2. Prevalence study

Prevalent cases were defined as people aged 65 years or older registered with a dementia diagnosis from 60 years of age, as a previous study showed that the validity of dementia diagnoses in the Danish registries given before the age of 60 years is low [16]. The rest of our study population served as the reference group. Individuals were censored when they emigrated, were lost to follow-up, died, turned 110 years old, or at the end of the study period, whichever came first.

2.4. Statistical analysis

Trends in incidence rates were tested with survival analysis techniques using Poisson regression analysis evaluating the calendar year as a time-dependent covariate. Incidence rates were calculated for men and women in strata of five-year age groups (65-69, 70-74, 75-79, 80-84, and 85+). Trends in prevalence were evaluated as annual period prevalence percent by comparing the number of person-years lived by people with dementia to the total number of person-years lived in the study population each year. Prevalence period percent was calculated for men and women in strata of five-year age groups (65-69, 70-74, 75-79, 80-84,

Table 1
Demographic data for all Danish residents aged 65 years and older; total number of people living with dementia; and the percentage of people living with dementia presented for the first and the last year in the 20-year observation period. The distribution is shown for men, women, age groups, median age, and interquartile range.

	1996			2015		
	All (n)	Dementia (n)	(%)	All (n)	Dementia (n)	(%)
All	803,334	14,019	1.75	1,055,984	36,129	3.42
Men	332,857	4554	1.37	481,331	13,271	2.76
Women	470,477	9465	2.01	574,653	22,858	3.98
Age (years)						
65-69	225,551	838	0.37	353,724	2036	0.58
70-74	208,162	1849	0.89	274,746	4185	1.52
75-79	163,644	2875	1.76	187,236	6492	3.47
80-84	116,090	3693	3.18	122,514	8607	7.03
85-89	63,162	3177	5.03	74,933	8744	11.67
90+	26,725	1587	5.94	42,831	6065	14.16
Median age	74.2	82.1		72.9	83.2	
IQR	69.5-80.2	76.6-86.8		68.8-79.3	77.5-88.2	

Abbreviation: IQR, Interquartile range.

85-89, and 90+). Prevalence period percent will be referred to as prevalence rates. Total incidence was evaluated as the total number of new dementia cases each year, while total prevalence was evaluated as point prevalence on January first.

Supplemental analyses of incidence by birth year were made to assess a possible birth cohort effect.

The analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC). This study was approved by the Danish Data Protection Agency, Statistics Denmark, and the Danish Health and Medicines Authority.

3. Results

Between 1996 and 2015, there were 1,999,375 people (men: 920,093; women: 1,079,282) aged 65 years and older living in Denmark. A total of 152,761 people were diagnosed with dementia (men: 57,977; women: 94,784) observed over 16,944,630 person-years (men: 7,415,232; women: 9,529,398). During the 20-year study period, 170,478 people had been living with a dementia diagnosis (men: 64,559; women: 105,919).

The population for the prevalence study was followed over 17,541,315 person-years. Of these, 16,986,832 were lived without dementia (men: 7,439,899; women: 9,546,933) and 554,483 with dementia (men: 188,936; women: 365,547).

Table 1 shows the age and sex distribution of the total elderly population and of people with dementia in 1996 and 2015. As shown, the total elderly population increased from 803,334 in 1996 to 1,055,984 in 2015, while the median age decreased from 74.2 years in 1996 to 72.9 years in 2015. The percentage of people with dementia increased over the 20-year period for all age groups, and the trend was most pronounced in the oldest age groups.

Fig. 1A and B show time trends in incidence rates in women and men, respectively. Incidence rates were significantly higher in 2015 than in 1996 in all age groups in both men and women, except for men and women aged 65-69 years. The increase in incidence rates was most dominant in the oldest age groups. However, the increased incidence rates from 1996 to 2015 reflected a steep increase from 1996 to 2003, followed by stabilization/fluctuation until 2009 and 2010, and then a moderate decline from 2010 to 2015. This time trend was most predominantly observed in the oldest age groups. When assessing trends in the incidence rate adjusted for age and sex from 1996 to 2003 and from 2004 to 2015, we found an average annual increase in incidence rate of 9% from 1996 to 2003. From 2004 to 2015, the incidence rate decreased by 2%, on average, annually. The total incidence percentage of dementia increased from 0.58% in 1996 to 0.72% in 2015. The additional analysis investigating the incidence of dementia by birth year did not show any clear effect of birth cohort on incidence (Supplementary Figs. S1-4).

Fig. 2A and B show time trends in prevalence rates (presented as percent of the total elderly population) in women and men, respectively. Prevalence rates increased from 1996 to 2015 for both sexes in all age groups. The older the age group, the higher the prevalence. The prevalence rates were higher in women than in men aged 75 years and above. For both men and women, the prevalence rates have been relatively stable since 2010.

Fig. 3 and Supplementary Figs. S5 and S6 show overall trends in total incidence and prevalence. The total incidence increased from 4875 people diagnosed in 1996 to 8017 people in 2015. The highest incidence was observed in 2009 (n = 8832). The prevalence increased from 14,019 people in 1996 to 36,129 people in 2015. The prevalence increased steadily over the total period, although with a lower rate of increase in most recent years.

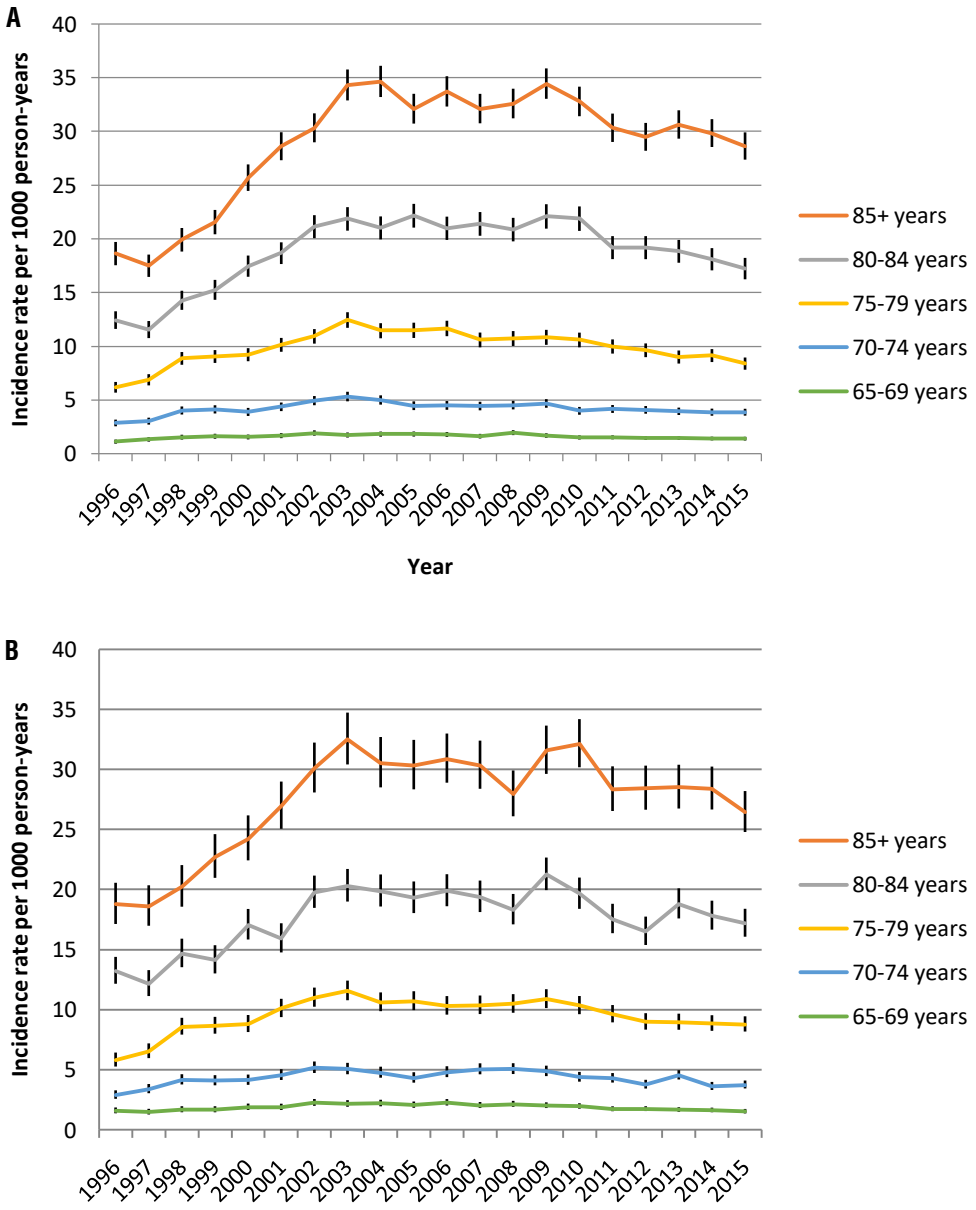

Fig. 1. (A) Time trend of incidence rates of dementia in Danish women from 1996 to 2015. Error bars represent 95% confidence intervals. (B) Time trends of incidence rates of dementia in Danish men from 1996 to 2015. Error bars represent 95% confidence intervals.

4. Discussion

To our knowledge, this is the first complete national population study based on routine health care data to confirm trends in declining incidence of dementia that have previously been described in population-based research studies. For men and women in all age groups, incidence rates reached their peak values from 2003 to 2010, followed by a decline. Adjusted for age and sex, the incidence rate of dementia in the total population increased annually by 9%, on average, until 2003, followed by a 2% annual decline. The prevalence rates increased for men and women in all age groups during the whole period from 1996 to 2015, most predominantly in the oldest age groups. Thus, while incidence rates stabilized around 2003 and have declined since 2010, the total prevalence of dementia is still increasing.

Several population-based studies have compared incidence and prevalence in two, or more, time intervals. Nine studies in high-income countries have investigated trends in dementia incidence using population-based cohort study designs: The Rotterdam Study: 1990 and 2000 (The Netherlands) [6]; The Cognitive Function and Aging Studies (CFAS): 1990-1994 and 2008-2011 (UK) [8]; The English Longitudinal Study of Aging: 2002-2013 (UK) [11]; The Indianapolis-Ibadan Dementia Project (IIDP): 1992 and 2001 (USA) [9]; The Framingham Heart Study: 1977-1983, 1986-1991, 1992-1998, and 2004-2008 (USA) [5];

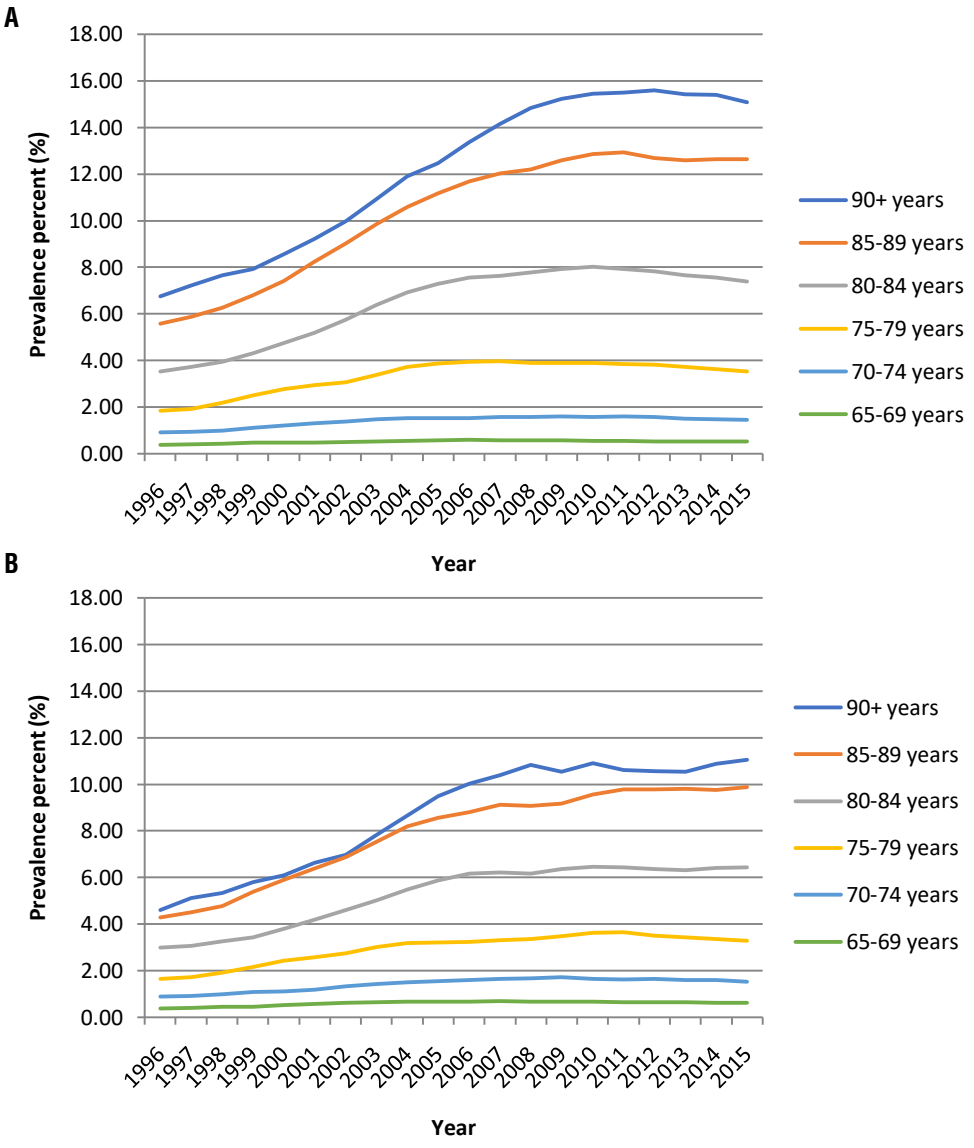

Fig. 2. (A) Time trends of dementia prevalence rates in Danish women from 1996 to 2015. (B) Time trends of dementia prevalence rates in Danish men from 1996 to 2015.

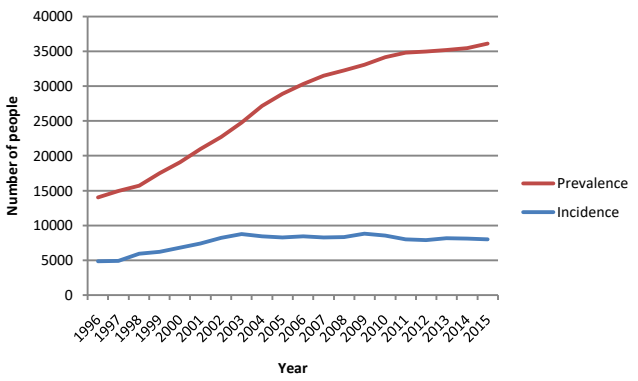

Fig. 3. Time trends of total incidence and prevalence of dementia in Denmark from 1996 to 2015.

The Chicago Health and Aging Project: 1994-1997, 1998-2000, 2001-2003, 2004-2006, 2007-2009, and 2010-2012 (USA) [17]; The Einstein Aging Study: 1993-2015 (USA) [10]; The Bordeaux Study: 1988-1989 and 1999-2000 (France) [7]; and The Hisayama Study: 1998 and 2012 (Japan) [18]. A recent meta-analysis included the Rotterdam Study, the IIDP, the Bordeaux Study, the CFAS, and the Hisayama Study [19]. Overall, the meta-analysis concluded that the results indicated a stabilizing trend in incidence of dementia rather than a decline [19]. It also found that the risk of bias for domains of external validity was high for all study populations, except for the UK and Japanese studies, indicating that the study populations could be unrepresentative of their national populations [19]. Furthermore,

they concluded that there was a risk of minimal nonresponse bias in the Rotterdam Study, the IIDP, the Bordeaux Study, and the Framingham Heart Study [19]. The quantitative synthesis suggested a nonsignificant decline of incidence of dementia; however, the heterogeneity between studies was high [19].

The declining incidence suggested in most of these studies may be related to changes over time in the risk factor profile. Thus, the Bordeaux Study found the later cohort was better educated, had a lower stroke prevalence, and used more antihypertensive and lipid-lowering drugs [7]. When adjusting for cardiovascular status and educational level, however, the association only explained some of the decrease seen in women [7]. The Framingham Heart Study found a decreasing effect of cardiovascular events and an increased effect of treatment with antihypertensive drugs on the risk of developing dementia in the later cohorts, although this benefit seemed to be more noticeable in people with at least a high school diploma [5]. When evaluating dementia subtypes, the Framingham Heart Study found a significant trend in decline only for vascular dementia, not AD, whereas the IIDP noted a decline in all-cause dementia and in AD [5,9]. The Hisayama Study reported a significant increase in incidence of AD, while incidence of vascular dementia remained stable over time [18]. This increase may partly reflect a difference in risk factor profiles and the ethnicity in high-income countries in the Western world and in East Asia.

Time trends in the incidence of dementia have also been reported in a few studies based on registry data. A German study evaluated incidence rates based on samples from health insurance data in 2006/07 and 2009/10 and reported a significant decline between the two time points [20]. Two Canadian studies assessed continuous time trends of incidence rates in the provinces of Saskatchewan (2005-2013) and Ontario (2002-2013), respectively, based on data from administrative health databases [21,22]. The Saskatchewan study reported a significant decline in incidence rates from 2005 to 2013 [21]. Findings from Ontario had a pattern similar to our study, with fluctuations from 2002 to 2008 followed by a decline, but the overall trend in declining incidence was only significant in women [22]. A Dutch registry-based study using data from primary care only reported an annual growth in incidence of 2.1% from 1992 to 2014 [23]. Registry-based data from hospitalized inpatients in Sweden on incidence rates of dementia from 1987 to 2016 demonstrated an increase until 2011, followed by a decline [24]. Thus, although there is a lack of consistency among results from registry-based studies, many have indicated stabilizing or declining trends in incidence rates of dementia during recent years, while some only observe these trends to be limited to subgroups and one study reported increasing incidence.

In our study, we also assessed time trends in prevalence rates. To sum up findings from ten population-based studies investigating time trends in the prevalence rates of dementia, the IIDP, a Spanish study, and three Swedish studies observed a stable prevalence, whereas the CFAS and an American study found a declining prevalence and the Hisayama Study found an increasing prevalence [18,25–31]. The Chicago Health And Aging Project found substantial variation over time but no secular trend from 1994 to 2012 [17]. Using two different analytical approaches, the Bordeaux study described trends moving in opposite directions [32]. Most studies investigating prevalence of dementia reported trends in declining or stabilizing prevalence, while our study observed trends similar to the Hisayama Study, with increasing prevalence in both sexes and all ages during the 20 years.

Our study demonstrates the power of access to continuous data for assessing time trends as compared with using a few discrete time points. Had we only compared incidence rates in 1996 and 2015, the decline since 2009 would have been missed. Both the initial increase and later decline in dementia incidence rates should be interpreted in the context of increased public awareness of dementia. In Denmark, the first memory clinic was established in 1995 and the first pharmaceutical drug against AD was launched in 1997. These events have potentially contributed to an increase in public awareness, and we believe that the marked increase in incidence from 1996 to 2003 reflects an increased diagnostic rate, rather than an actual increase in incidence of dementia. Likewise, there is a possibility that the later decline could be partly related to a higher precision in diagnosis resulting in a more restrictive use of the diagnosis of dementia.

Thus, when interpreting possible causes for the stabilization and later decline in incidence, one hypothesis relates to improvement in health and another to improved precision in diagnosing dementia.

First, during the last decades, we have experienced a marked improvement in living conditions and health in Western high-income countries. We believe that the general improvement in health, including better control and treatment of risk factors, may prevent vascular cognitive impairment and may contribute to the observed decline in incidence of dementia in recent years.

In the Framingham Heart Study, the declining incidence was only significant for vascular dementia, and not AD [5]. The Hisayama Study reported stabilization in the incidence of vascular dementia whereas AD increased [18]. Results from magnetic resonance imaging scans performed in the Rotterdam Study showed that people in the 2000 cohort had lesser brain atrophy and fewer white matter lesions than those in the 1990 cohort [6]. Thus, the decline in incidence rates reported in Western high-income countries may mainly represent vascular dementia.

Our analysis of dementia incidence by birth year did not demonstrate any effect of birth cohort on incidence.

Second, even though the diagnostic criteria for dementia have not changed within our study period, there have been improvements over time regarding the application of neuroimaging and biomarkers for neurodegenerative

disorders. Consequently, the precision in diagnosis may have improved, especially when diagnosing subtypes of dementia. We cannot exclude the fact that this may have led to a more restrictive use of the dementia (syndrome) diagnosis during this period contributing to a change in diagnostic rate over time and an apparent decline in incidence.

Even though incidence rates are declining, our study shows that the number of people living with a registered dementia diagnosis in Denmark (prevalence) is still increasing. There are two possible explanations for this apparent paradox. First, the number of elderly people is increasing because of increasing life expectancy and large birth cohorts from the 1940s and 1950s having reached the elderly population. As the risk of dementia increases with age, we expect that the larger elderly population will lead to an increasing number of people living with dementia over the next decades. The large birth cohorts from the 1940s also explain the fact that the median age of our total elderly population declined from 74.2 years to 72.9 years from 1996 to 2015 [33]. Second, people may live for a longer time registered with dementia because of either earlier diagnosis or decline in mortality. If our study population was registered with dementia at an earlier age later in our study period, this may have led to an increased amount of time lived with a diagnosis. However, the median age of incidence of dementia was 82.4 years in 1996 and 82.3 years in 2015. Hence, we do not believe this explanation to be very likely. As life expectancy is increasing in the general population, there is a possibility that individuals diagnosed with dementia live for a longer time with their diagnosis than previously. Population-based studies from Stockholm, Rotterdam, and Hisayama have reported declining mortality over time in people with dementia [6,18,29]. Thus, we believe it to be possible that individuals with dementia live longer after being diagnosed, which contributes to the continued increase in prevalence.

4.1. Limitations of the study

This study was based on registered diagnoses from secondary health care and prescription data identifying 36,129 people living with dementia aged 65 years or more in 2015. Based on extrapolation from European population-based studies, it is estimated that approximately 87,000 people in Denmark aged 60 years or more are living with dementia, likely leaving a large proportion of undiagnosed cases of dementia [34]. Thus, as in many other countries, the diagnostic rate may be relatively low. Our study is based on national health care data from the secondary health sector and the Danish National Prescription Registry. Thus, our data reflect diagnoses established in routine medical care and do not include information on clinical manifestations, the level of cognitive decline, or diagnostic workup leading to the diagnosis.

National clinical and evidence-based guidelines have been available in Denmark since 1998, and ICD-10 criteria were applied for the (syndrome) diagnosis of dementia throughout the entire period. Brief cognitive testing was recommended to support a diagnosis of dementia in all recommendations. Our registry-based data do not inform us to which extent these recommendations were followed when physicians were making the diagnosis. However, in a previous study, we evaluated the quality of the registered cases of dementia in the Danish health care registries and found that the diagnoses of dementia were justified in 85.8% of the cases in elderly people [35]. Unfortunately, as a large proportion of the patients were registered with a diagnosis of "unspecific dementia," our registry-based data are not sufficient for clarifying the etiology of dementia.

4.1.1. Strengths of the study

Government-funded, universal health care, combined with unique personal identification numbers, provides an excellent setting for epidemiological studies. Our study was based on data using an entire population as the cohort, which means it is large, has no dropouts, and represents trends in an entire nation. Data in the Danish registries are continuously updated and data on follow-up are, for all practical purposes, complete and registered continuously in all calendar years.

This study assessed national trends in incidence and prevalence in Denmark, and we assume that these trends can be generalizable to other Western high-income countries that have similar access to diagnostic evaluation and support.

5. Conclusions

In conclusion, our study shows that incidence rates of dementia have declined since 2010. The total incidence of dementia has also declined, while the total prevalence is still increasing, albeit less rapidly in recent years. When planning future health care services, it is crucial to take the increasing number of people living with a dementia diagnosis into account. In future models for estimating projections of prevalence and incidence, the fluctuations in incidence rates and prevalence percentage over time should be considered. The decline in total incidence and incidence rates of dementia leads to a cautious optimism that with better health and management of risk factors, it may be possible to lower the risk of dementia. However, previous studies imply that this effect may be limited to vascular dementia, highlighting the need for better prevention and treatment of AD and other neurodegenerative dementias.

Acknowledgments

The authors thank the Danish Ministry of Health for supporting the Danish Dementia Research Center. The Danish Ministry of Health played no role in designing the study, in the collection, analysis, or interpretation of data, or in writing

this report. The corresponding author has had full access to all the data used in this study and takes full responsibility for the decision to submit for publication.

Authors' contribution: A.N., G.W., and L.T. contributed to the study concept and the literature review. A.N., G.W., T.M.L., and L.T. designed the study. The statistical analyses were carried out by T.M.L., and L.T. G.W., and L.T. did the outline for the manuscript and L.T. wrote it. All authors contributed to interpreting the data and to the critical review of manuscript content.

The Danish Dementia Research Center is supported by the Danish Ministry of Health, which was not involved in the design or evaluation of the results in this study.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2019.07.006.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using a PubMed search. Even though there was evidence of declining or stabilizing incidence of dementia in Western high-income countries, the number of studies was small and the heterogeneity of findings was high.
2. Interpretation: Studying an entire national population based on high quality routine health care data from the secondary sector, we observed that the age- and sex-adjusted incidence rate increased, on average by 9% annually from 1996 to 2003, followed by a 2% annual decline from 2004 to 2015. While the total incidence and incidence rates declined, the total prevalence was still increasing.
3. Future directions: Future healthcare planning on prevention and management of dementia should take these findings into account. More studies are needed to clarify whether the decline in incidence of dementia is limited to vascular dementia. This would emphasize the great need for targeted treatment for neurodegenerative dementias.

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Study I

Declining incidence of dementia: A national registry-based study over 20 years

Supplementary material

Supplementary material

During the process of conducting this study, we created some additional figures that we believe should be accessible to our readers.

Figures S1-S4 represent the results from our analyses when investigating for the effect of birth cohort.

Figure S1 sums the effect of calendar period on incidence of dementia, as also shown in figures 1A and 1B in the manuscript. As previously described in the manuscript, we observed a strong effect of age, in that the risk of dementia increased with age.

We observed a decline in incidence in all age groups during the last period from 2010 to 2015. However, as pointed out by the reviewer, this trend could reflect a birth-cohort effect rather than a period effect.

Figure S2 reports the incidence of dementia by birth-year (five-year birth cohorts) in each of the six five-year age strata (age at diagnosis). As an example, we have highlighted the group born in the first half of the 1930s (1930-34) in yellow. As illustrated in the figure, for each birth cohort (e.g., 1920s, 1930s, 1940s), there is a clear increase in incidence by age. None of the birth cohorts showed patterns of a particularly low or high incidence. In all of the age strata, we observed a decrease in incidence for the latest birth cohorts. Hence, the declining incidence seems to be related to period rather than cohort effect.

Thus, we did not see a clear effect of birth cohorts on incidence of dementia.

To further investigate if a possible birth cohort effect could have been hidden, we investigated incidence of dementia by birth year (one-year groups) in five-year age strata for men and women (figures S3 and S4). For each of the strata, we see the exact same pattern, with low incidence when the follow-up was in the start of our study period, then high in the middle and low towards the end of our study period. Note that the end of each line should be interpreted with caution as they do not include all five years of the age group.

Figure S1. Incidence rate of dementia per 1000 person-years at risk
Calendar period (period effect) in 5-year age strata

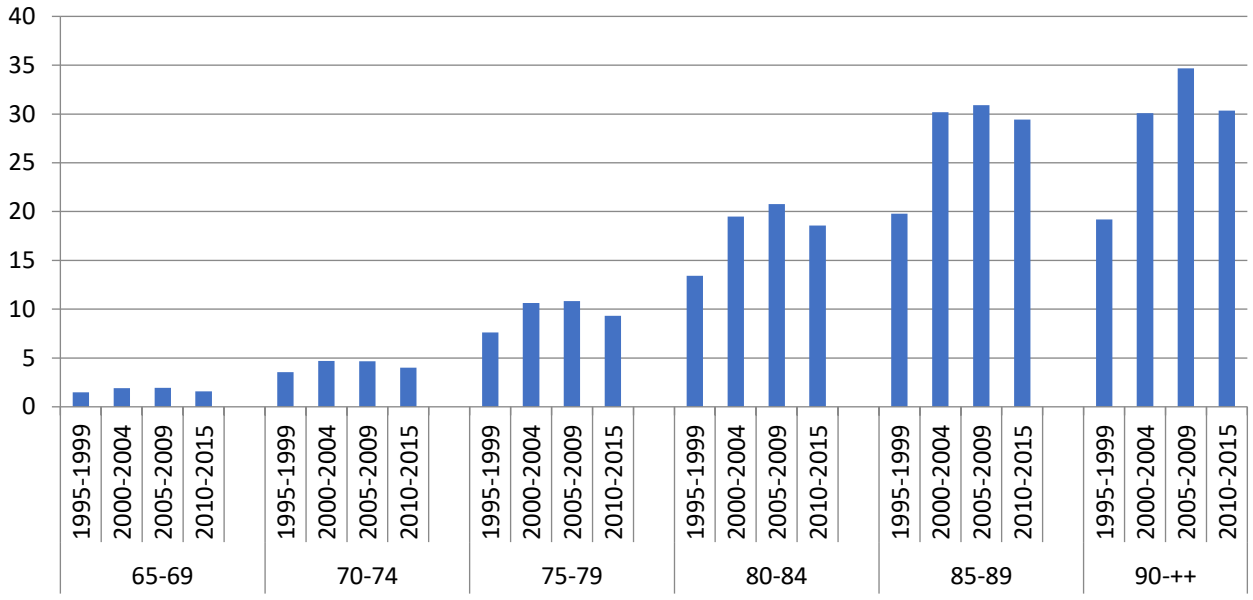


Figure S2. Incidence rate of dementia per 1000 person-years at risk
Birth years (cohort effect) in 5-year age strata

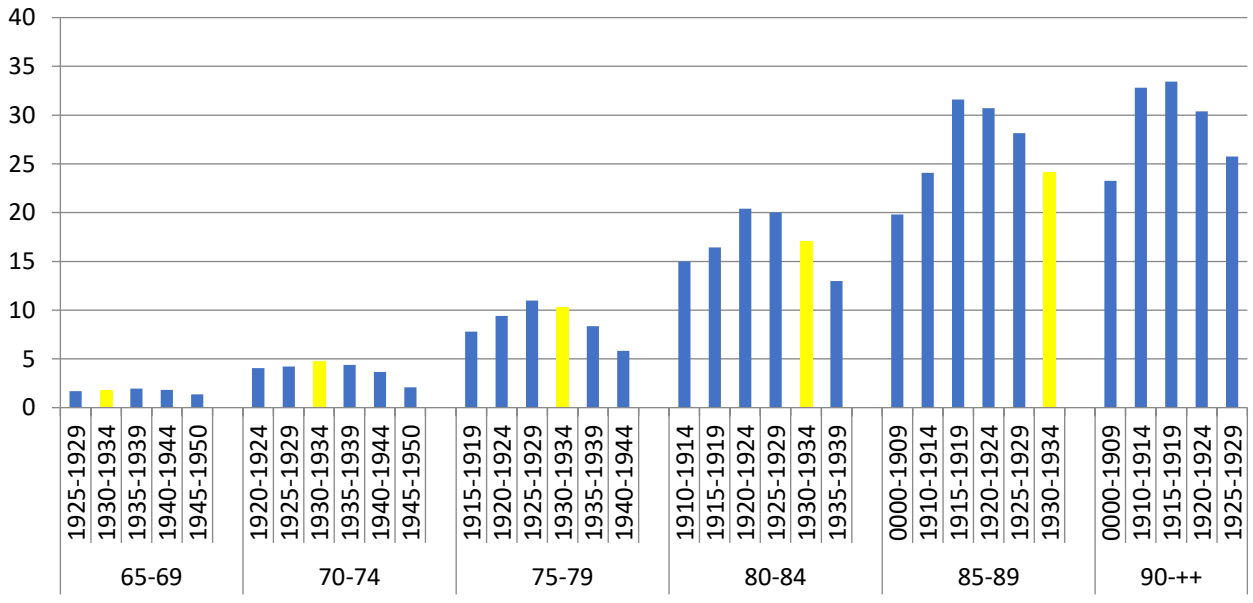


Figure S3. Incidence rate of dementia per 1000 years at risk in men by birth cohorts

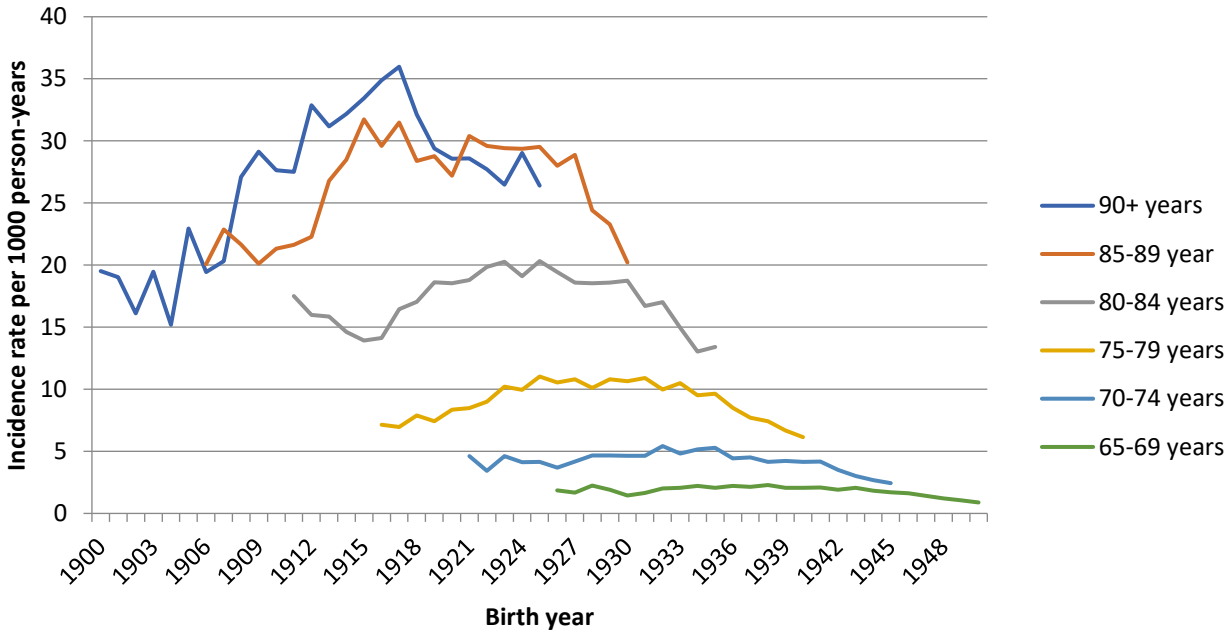
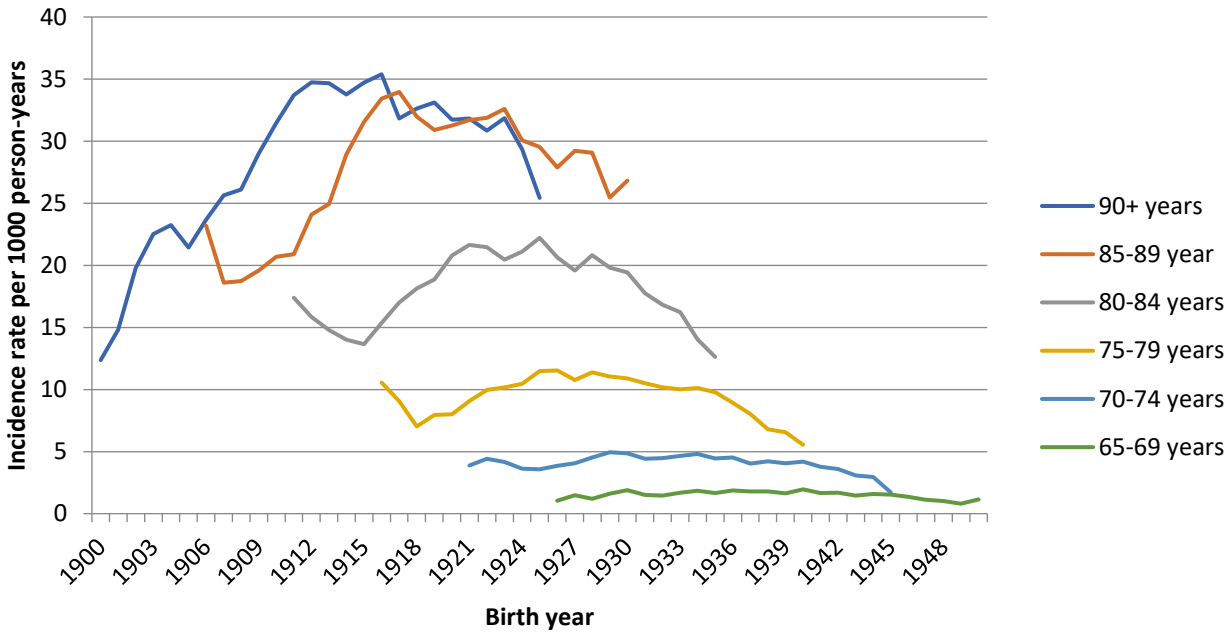


Figure S4. Incidence rate of dementia per 1000 years at risk in women by birth cohorts



Figures S5 and S6 present the incidence and prevalence of dementia by age distribution in five-year age strata. We defined the incidence age as the age at diagnosis.

Figures S5 and S6 illustrate that no specific age group accounted primarily for the increase in prevalence or the incidence of dementia. However, both graphs illustrate how incidence and prevalence of dementia have predominantly increased most in the oldest age groups.

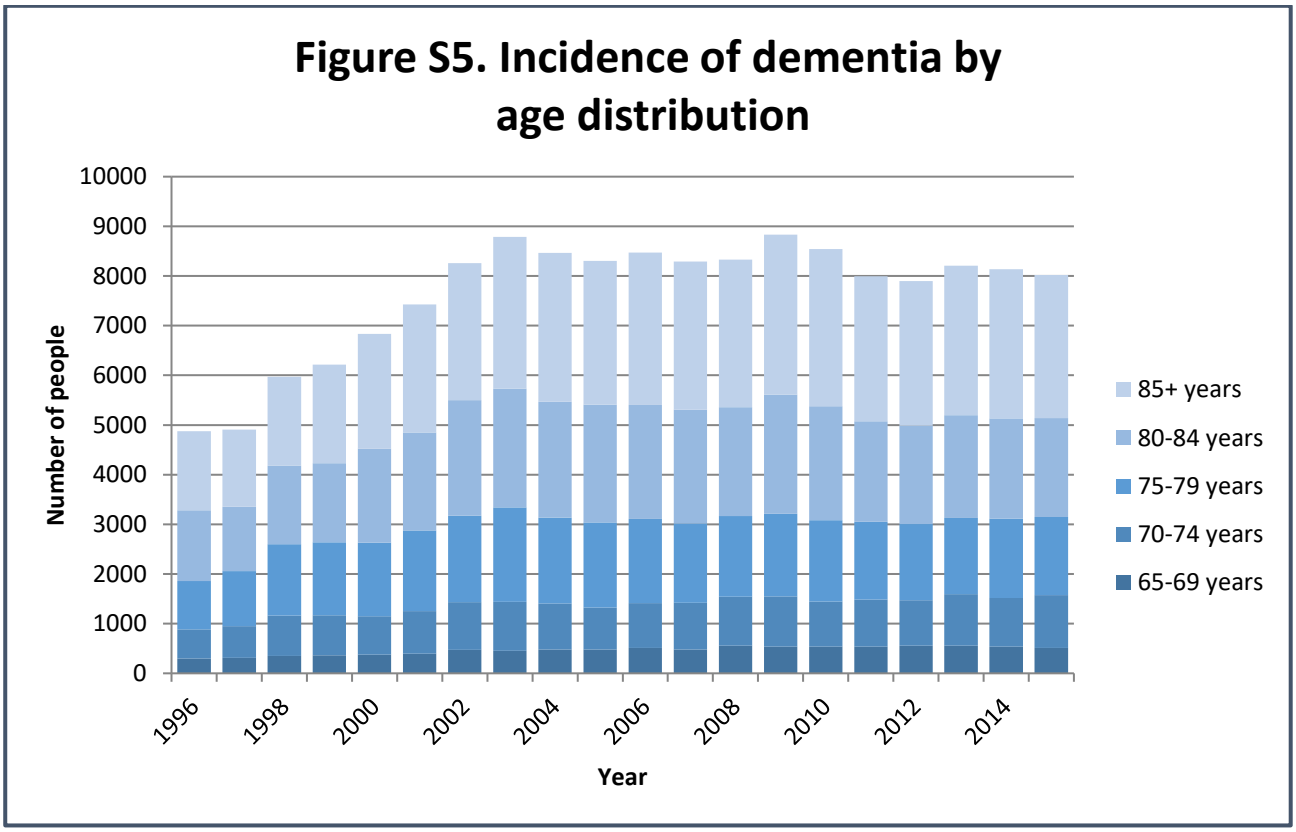


Figure S6. Prevalence of dementia by age distribution

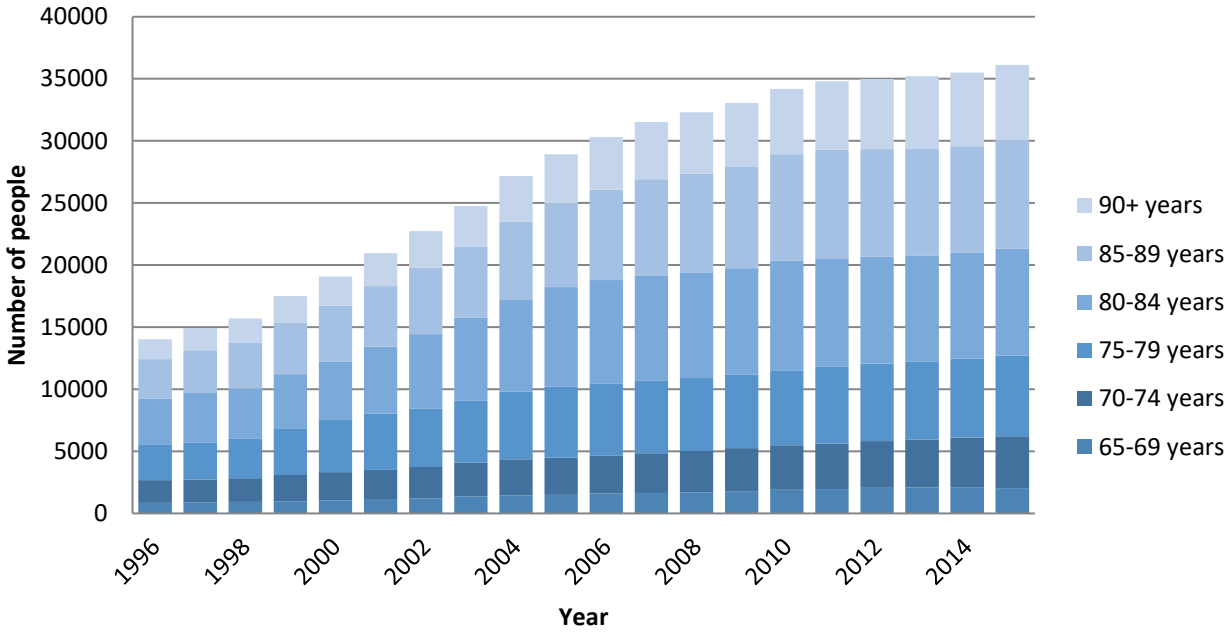


Table S1. ICD-8 and ICD-10 diagnoses codes for identification of dementia.

Disease name	ICD-8	ICD-10
Alzheimer's disease	290.10	F00.0-00.9, G30.0-30.9
Vascular dementia	293.09-19	F01.0-01.9
Frontotemporal dementia	290.11	F02.0
Dementia without specification	290.09, 290.19	F03.9, G31.9
Other dementias	290.18	G31.8

ICD = International Classification of Diseases

Table S2. Anatomical Therapeutic Chemical codes for identification of pharmaceutical treatment of dementia.

Drug name	ATC code
Memantine	N06DX01
Donepezil	N06DA02
Rivastigmine	N06DA03
Galantamine	N06DA04

Study II

Mortality in Dementia from 1996 to 2015: A National Registry-Based Cohort Study

Journal of Alzheimers Disease
Article in prepress
Taudorf L, Nørgaard A, Waldemar G, Laursen TM
Mortality in Dementia from 1996 to 2015: A National Registry-Based Cohort Study
DOI 10.3233/JAD-200823. Printed with permission from IOS Press.

Mortality in Dementia from 1996-2015: A National Registry-Based Cohort Study

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ABSTRACT

Background: It remains unclear whether the increased focus on improving healthcare and providing appropriate care for people with dementia has affected mortality.

Objective: To assess survival and to conduct a time-trend analysis of annual mortality rate ratios (MRR) of dementia based on healthcare data from an entire national population.

Methods: We assessed survival and annual MRR in all residents of Denmark ≥65 years from 1996–-2015 using longitudinal registry data on dementia status and demographics. For comparison, mortality and survival were calculated for acute ischemic heart disease (IHD) and cancer.

Results: The population comprised 1,999,366 people (17,541,315 person years). There were 165,716 people (529,629 person years) registered with dementia, 131,321 of whom died. From 1996–2015, the age-adjusted MRR for dementia declined (women: 2.76 to 2.05; men: 3.10 to 1.99) at a similar rate to elderly people without dementia. The sex-, age-, and calendar-year-adjusted MRR was 2.91 (95% CI: 2.90–2.93) for people with dementia. MRR declined significantly more for acute IHD and cancer. In people with dementia, the five-year survival for most age-groups was at a similar level or lower as that for acute IHD and cancer.

Conclusions: Although mortality rates declined over the 20-year period, MRR stayed higher for people with dementia, while the MRR gap, compared with elderly people without dementia, remained unchanged. For the comparison, during the same period, the MRR gap narrowed between people with and without acute IHD and cancer. Consequently, initiatives for improving health and decreasing mortality in dementia are still highly relevant.

INTRODUCTION

During the last two decades, there has been increased focus on improving health in the rapidly increasing elderly population [1,2]. These initiatives are important for maintaining good quality of life for the individual, for increased life expectancy, and for limiting societal economic costs. With age as the predominant risk factor for dementia, prevalence of dementia worldwide is expected to increase considerably from 46.8 million in 2015 to 131.5 million by 2040 [1].

Even though mortality is markedly increased in dementia [3], it may not be perceived of as a fatal disease in the same way as acute ischemic heart disease (IHD) and cancer are, for example.

Currently, no cure or disease-modifying treatments for dementia are available [4]. The existing antidementia drugs are only symptomatic, with documented efficacy on Alzheimer's dementia, Lewy body dementia, and Parkinson's disease with dementia. Dementia research has nonetheless seen a variety of other improvements occur in recent, including the acquisition of greater knowledge about the underlying pathophysiological changes, leading to better and more precise diagnostics and, thus, also improvements in the evaluation and management of dementia. Consequently, these changes have been accompanied by increased awareness, a change in the perception of dementia disorders as brain disorders, and greater knowledge about the need for psychosocial support, not to mention improved treatment of comorbidities. As in other high income countries, the most frequent causes of death in Denmark are heart disease and cancer [5,6]. In the general population, these are perceived as life-threatening, where as a dementia disorder may not be perceived as a fatal condition. In contrast to dementia disorders, the treatment of acute IHD and cancer, including identification of risk factors, early detection, and novel disease modifying interventions, has improved markedly in the last 20 years, leading to a significant decline in mortality. Hence, it is of interest to examine whether improvements in the management of dementia disorders have been accompanied by a decline in mortality in people with dementia and then to put results into a context, comparing with changes in mortality in people with acute IHD and cancer.

Evidence for the time trend of mortality with dementia is scarce [7–11]. Monitoring time trends is challenging as the date of dementia diagnosis must be linked to the date of death at an individual level. Of the five studies investigating changes in mortality in dementia over time, three found a declining trend in mortality rates in dementia [8,10,11]. Nevertheless, these results were based on small cohorts, covered only a few years, or included limited observation points in time. National Danish registries are uniquely poised to provide data enabling exploration of time trends of mortality in an entire population over decades [12].

We hypothesized that mortality was higher in people with dementia compared with the general population without dementia. Furthermore, we also suggested that the mortality in people with dementia had declined more rapidly than in the general population due to a higher awareness of providing appropriate care. The aim of this study was to assess time trends in all-cause mortality in people with dementia compared to the general elderly population using healthcare data from the entire population of Denmark from 1996–2015. In addition, we aimed to compare all-cause mortality in dementia with all-cause mortality in people with acute IHD and cancer. Finally, our goal was to study the current survival in people with dementia compared to both the general elderly population and people with acute IHD or cancer.

METHODS

Study setting

This cohort study was based on data from national Danish registries. Since 1968, the Danish Civil Registration System has provided all permanent residents with a unique 10-digit personal identification number that includes vital information on an individual level, such as date of birth and death [13]. This number enables individual linkage on demographic and healthcare data for the entire population [13].

Data sources

Danish Civil Registration System data was merged with data from three national registries. The first two, the Danish National Patient Registry and the Psychiatric Central Research Register, began registering data on all hospital admissions in 1977 and 1969, respectively. Since 1995, they have also collected data on contacts to emergency departments and hospital-based outpatient clinics [12]. Date of admission, date of discharge, and primary and optional secondary diagnoses have been registered according to the International Classification of Diseases (ICD), 10th Revision at every patient contact since 1994 [12]. Before then, ICD 8th Revision was in use [12]. The third registry, the Danish National Prescription Registry, has collected data on filled prescription medication since 1995 that includes date of dispensing, dose, strength, and the anatomical therapeutic chemical code [14].

Study period

The observation period was defined as January 1, 1996 to December 31, 2015. For the survival analyses calculating cumulative incidences, we restricted the study period to January 1, 2000 to December 31, 2015 as we were unable to adjust for calendar period in the cumulative incidences and because 1996–2000 had a higher all-cause mortality and incidence of dementia than the subsequent period.

Study population

All Danish residents age ≥65 years as of January 1, 1996 were included in the assessment of mortality. During follow-up, people were included the day they turned 65 and then censored if they died, left the country permanently, were lost to follow-up, or at the end of the study period. When assessing mortality in dementia, individuals registered with dementia age <65 years were excluded due to our focus on late onset dementia, while individuals not registered with dementia served as the reference group. For comparison, mortality and survival were calculated for people age ≥65 years with acute IHD and cancer using the same methodology. Thus, the analysis assessing annual mortality rate ratios (MRRs) excluded individuals diagnosed with acute IHD and cancer age <65 years.

The methodology was adjusted in three ways to calculate cumulative incidences of death. First, the study period began January 1, 2000. Second, only incidence cases were assessed, which meant that people with dementia, acute IHD, and cancer diagnosed before January 1, 2000 were excluded from their respective analyses. Lastly, we constructed a group to represent the general population (see supplementary material). Apart from these adjustments, the same criteria for inclusion, exclusion, and censoring were used when assessing MRRs and cumulative incidence of death.

Definition of dementia, acute IHD, and cancer

Dementia was defined as either a registered dementia diagnosis (primary or secondary) in the Danish National Patient Registry or the Psychiatric Central Research Register (ICD-8 codes: 290.9-11, 290.18-19, 293.09-19; ICD-10 codes: F00.0-9, F01.0-9, F02.0, F03.9, G30.0-9, G31.8-9) or having filled a prescription for an antidementia drug (ATC-codes N06DA02 (donepezil), N06DA03 (rivastigmine), N06DA04 (galantamine), and N06DX01 (memantine)). Onset date was defined as the first contact with a registered dementia diagnosis, or a prescription filled for an antidementia drug, whichever came first. Denmark has universal tax-funded healthcare and less than one percent of hospital beds are in private hospitals [15]. When people experience symptoms of dementia, they usually make an appointment with their general practitioner, who performs a preliminary examination. If the general practitioner suspects dementia, the person is referred to a hospital memory clinic, which performs diagnostic evaluation. If symptoms are obvious and additional workup safely deemed unnecessary, the general practitioner may assign the diagnosis without referring the patient to the hospital. Another factor is that some people, though a highly limited number, are seen in a private healthcare setting. In an effort to include the last two groups mentioned, we used data on prescriptions filled for antidementia drugs.

The definition of acute IHD and cancer were based on diagnosis codes as defined in the Charlson Comorbidity Index (acute IHD, ICD-8 code: 410, ICD10-codes: I21-23; cancer: ICD-8 codes: 140-189, 195-199, 200-207, 275.59, ICD-10 codes: C00-85, C88, C90-96) [16].

Statistics

Mortality: Time trends in mortality in people with dementia from 1996 to 2015 were assessed by MRRs analyzed using Poisson regression analysis, which is equivalent to a Cox regression [17]. In our first model, the exposure was dementia and the outcome was death. All analyses were stratified by sex, as mortality differs among women and men. We tested whether there was a difference in the time trend of the mortality rates in people with dementia compared to the elderly population without dementia and chose the reference value to be the mortality rate for women and men without dementia in 1996. Our second and third Poisson regression models were used to calculate MRR trends for individuals registered with acute IHD and cancer, respectively, compared to people without either disease using the same methods as described for dementia. Furthermore, we examined differences in change in mortality rates between people with dementia, acute IHD, cancer, and the total elderly population by assigning the reference value of 1.00 to all four groups in 1996. The assumption of piecewise constant intensity in the age groups was verified, as should be the case before applying a Poisson regression analysis [18].

Cumulative incidences*:* We assessed cumulative incidence rates of death in people registered with and without dementia, acute IHD, cancer, and in the general elderly population age ≥65 years from 2000–2015 using Kaplan-Meier analyses to calculate survival probabilities for women and men in strata of 5-year age groups (65–69, 70–74, 75–79, 80–84, 85–89, 90+). The Kaplan-Meier methods cannot take changes due to calendar year properly into account. In order to try and limit the effect of changes related to calendar year, we chose to exclude the years 1996-1999 because mortality was highest in this period and our previous study showed a marked increase in incidence of dementia those years as well [19]. This left us with the time period from 2000-2015 when assessing survival. To prevent any identification of individual cases, the two oldest age groups were combined into one group of people aged ≥85 for the Kaplan-Meier curves, thus maintaining anonymity. In figures, the maximum follow-up time was also limited to ten years to preserve anonymity.

A P-value was considered significant at 0.05 for all analyses, which were performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Approvals and data availability

This study was approved by the Danish Data Protection Agency (ID no.: 2007-58-0015/30-0667), Statistics Denmark, and the Danish Health and Medicines Authority (ID no.: 6-8011-907/1). As this study used anonymized data, Danish law does not require ethics committee approval or informed patient consent.

This study was based on data from nationwide public registries and, according to Danish law, sharing such datasets is not allowed. To gain access to Danish registry data, individual research projects must seek approval from the Danish Data Protection Agency. Hence, further data sharing of this project is not possible.

RESULTS

Between 1996 and 2015, there were 1,999,366 people (women: 1,079,276; men: 920,090) age ≥65 years living in Denmark. They were observed over 17,541,315 person years (women: 9,912,480; men: 7,628,835), resulting in an average of 8.77 years at risk per person. There were 165,716 people living with a dementia diagnosis (women: 103,683; men: 62,033), observed over 529,629 person years (women: 353,211; men: 176,418). A total of 15,300 people with dementia
was solely identified using prescription data.
In the same period, there were 144,380 people living with an acute IHD diagnosis (women: 65,622; men: 78,758), observed over 665,640 person years (women: 290,760; men: 374,880), and 400,610 people living with a cancer (women: 195,483; men: 205,127), observed over 1,565,110 person years (women: 841,299; men: 723,811).
The number of people with dementia who died was 131,321 (women: 81,855; men: 49,466). In the acute IHD group, the number of deaths was 109,154 (women: 51,172; men: 57,982), and in the cancer group, it was 283,143 (women: 137,834; men: 145,309).
Table 1 presents mortality rates and MRRs stratified by sex, age, and 5-year calendar periods for people with dementia compared with the general population without dementia. Age and calendar year adjusted MRRs were higher for both women and men with dementia. MRRs in dementia decreased with age from 5.54 (95% CI: 5.28–5.80) in people age 65-69 years to 2.08 (2.06–2.11) in people age ≥90 years. Sex- and age-adjusted MRRs were similar in 1996–2000, 2001–2005, 2006–2010, and 2011–2015.

Table 1. Distribution of number of deaths, person years, mortality rates, and mortality rate ratios in people with and without dementia who died from 1996–2015 for women and men, for age-standardized 5-year age groups, and age- and sex-adjusted five-year calendar periods.

Variable	Dementia			No dementia			MRR[a] (95% CI)
	n	PY	MR	n	PY	MR	
Women	81,855	353,211	231.7	405,048	9,529,139	42.5	2.77 (2.75, 2.80)*
Men	49,466	176,418	280.4	369,622	7,415,073	49.8	3.13 (3.10, 3.16)*
Age groups							
65–69	1767	17,127	103.2	92,770	5,390,626	17.2	5.54 (5.28, 5.80)*
70–74	7289	54,893	132.8	115,363	4,222,806	27.3	4.81 (4.70, 4.93)*
75–79	17,564	102,533	171.3	140,657	3,230,175	43.5	3.99 (3.92, 4.05)*
80–84	31,426	140,918	223.0	152,891	2,220,656	68.8	3.34 (3.30, 3.38)*
85–90	38,638	132,920	290.7	139,527	1,259,591	110.8	2.72 (2.69, 2.75)*
90+	34,637	81,239	426.4	133,462	620,357	215.1	2.08 (2.06, 2.11)*
Time periods							
1996–2000	21,909	79,664	275.0	215,235	3,908,805	55.1	2.91 (2.87, 2.95)*
2001–2005	32,003	123,854	258.4	197,639	3,928,311	50.3	2.89 (2.86, 2.93)*
2006–2010	38,276	157,020	243.8	184,273	4,214,293	43.7	2.85 (2.82, 2.88)*
2011–2015	39,133	169,092	231.4	177,523	4,892,802	36.3	2.95 (2.91, 2.98)*

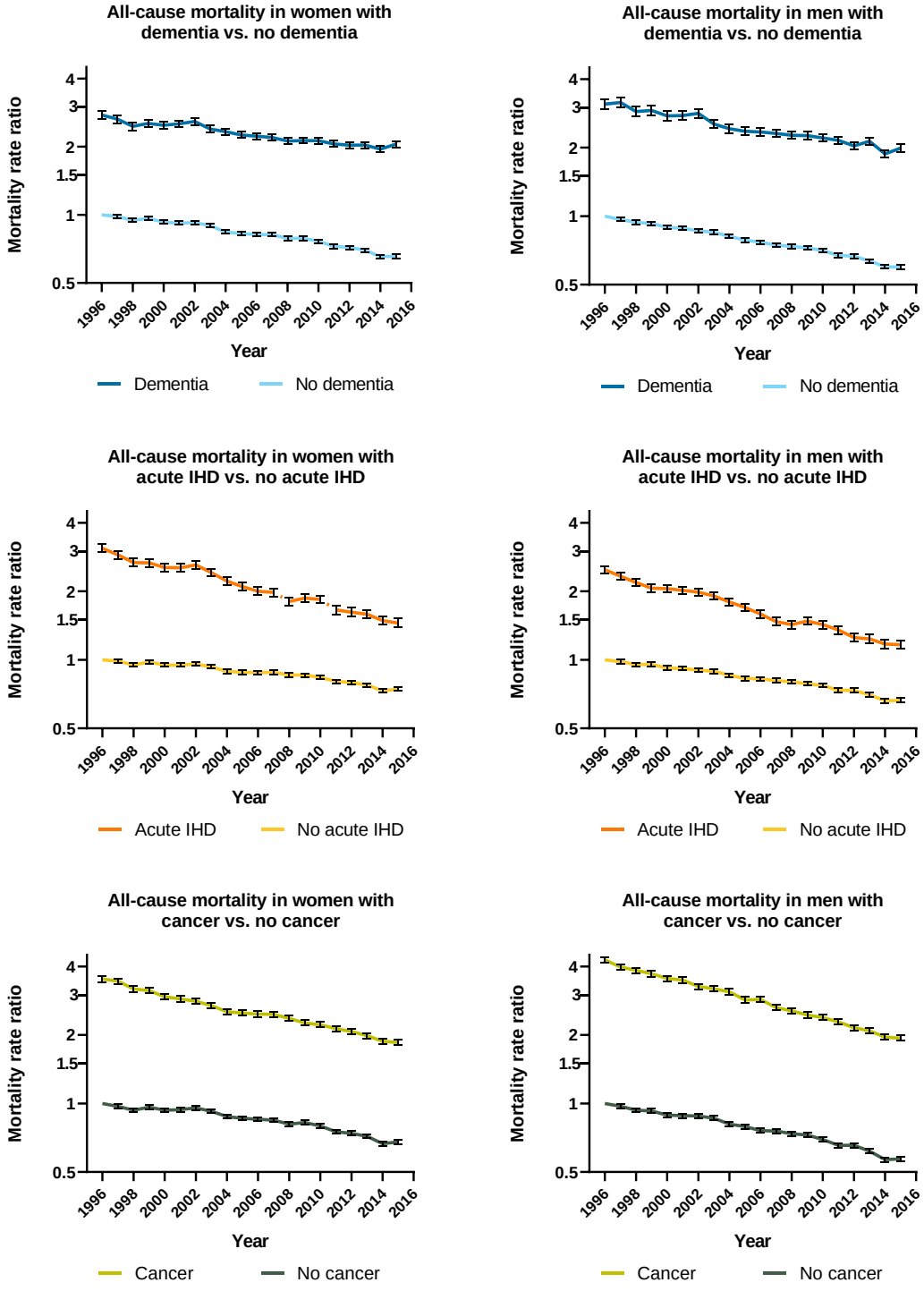
Mortality rates are listed in 1000 person years. MRR, mortality rate ratio; CI, confidence interval; N, number of deaths; PY, person years, MR, mortality rates; [a], adjusted/stratified for age, calendar year, and sex; *, *P* value <.00001;

Figure 1 presents the MRR time trends for women and men with and without dementia, acute IHD, and cancer. MRRs was significantly higher in dementia compared with people without dementia throughout the 20-year period. Similar trends were observed for acute IHD and cancer. Adjusted for age, sex, and calendar year, the MRR was 2.91 (95% CI: 2.90–2.93) in people with dementia compared with the general elderly population without dementia.

Figure 2 presents MRR time trends using the reference value of 1.00 in 1996 for dementia, acute IHD, cancer, and the total elderly population. For both women and men with dementia, the MRRs declined at the same speed as in the general population, just as a similar decline was observed in MRRs for both groups when comparing each year from 1997–2015 to the index year 1996. The MRRs, in contrast, declined significantly faster in acute IHD and cancer compared with the general population.
Figure 3 shows Kaplan-Meier curves for women and men with dementia, acute IHD, cancer, and the general elderly population. A steeper decline in survival was observed in the first months after onset of acute IHD and cancer compared with dementia.

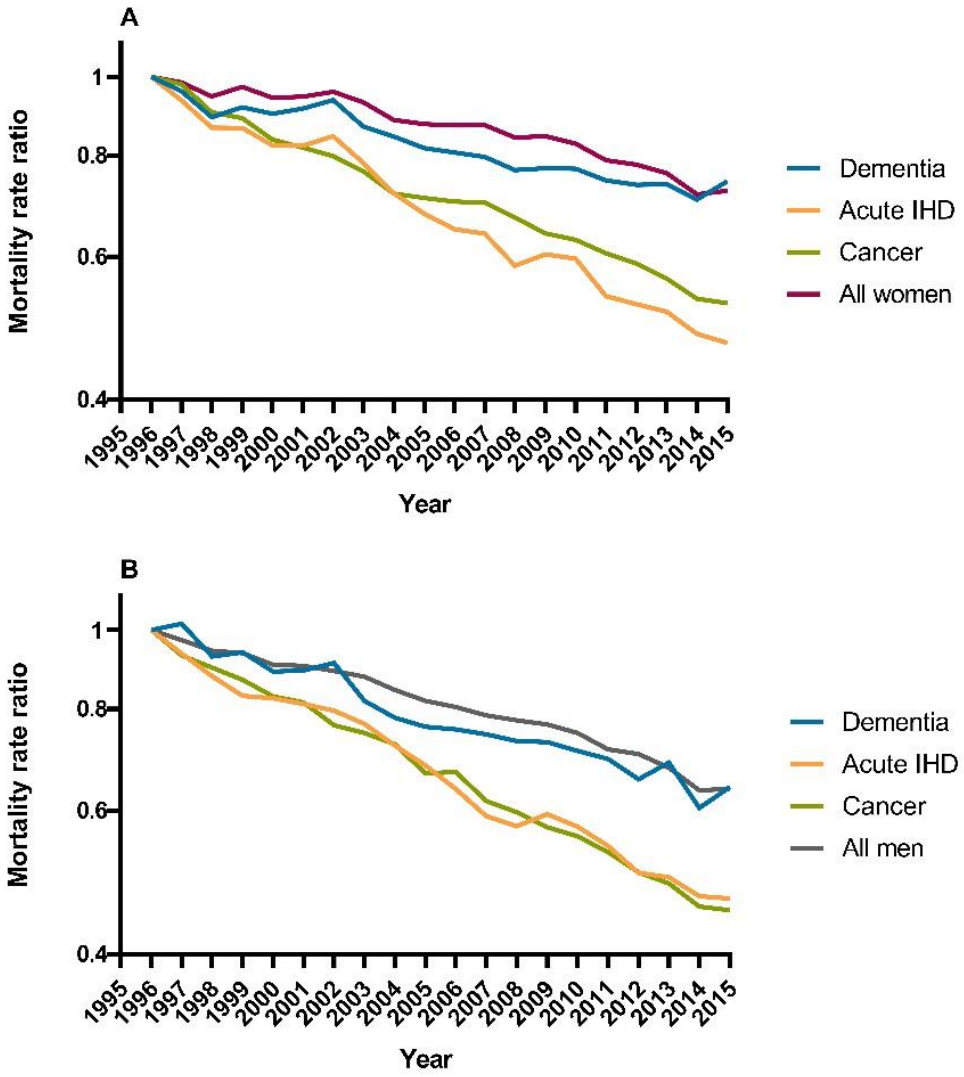
Figure 4 presents 1- and 5-year probabilities of survival in the same groups. In women and men with dementia, the 1-year survival probabilities were lower compared with the whole elderly population in all age groups. However, they were higher in women and men with dementia compared with acute IHD and cancer. The 5-year probability of survival was lower for the dementia, acute IHD, and cancer groups compared with the general elderly population in both sexes for all age strata. In women, the 5-year survival probability was lower in dementia than in acute IHD in women age <80 years, whereas in age ≥80 years, they were comparable. Women with dementia age <85 years had a higher 5-year probability of survival compared with cancer, whereas it was lower in women with dementia age ≥85 years.
When comparing 5-year survival probabilities in men, they were substantially lower in dementia than in acute IHD. Comparing men with dementia to those with cancer, 5-year survival probabilities were similar in the age group 65–69 years, but in all older age groups, the probability of survival was lower for men with dementia than for men with cancer.
Lastly, we calculated the 50% fractiles of the survival curves, i.e. how many years have passed before half of the population in each subgroup has died (Supplementary Material, Table S1 and S2). In women and men with dementia ≤ 75years, the 50% fractiles were comparable to or lower than for those with acute IHD, cancer, and the general elderly population.

Fig. 1 Time trend of all-cause mortality for women and men



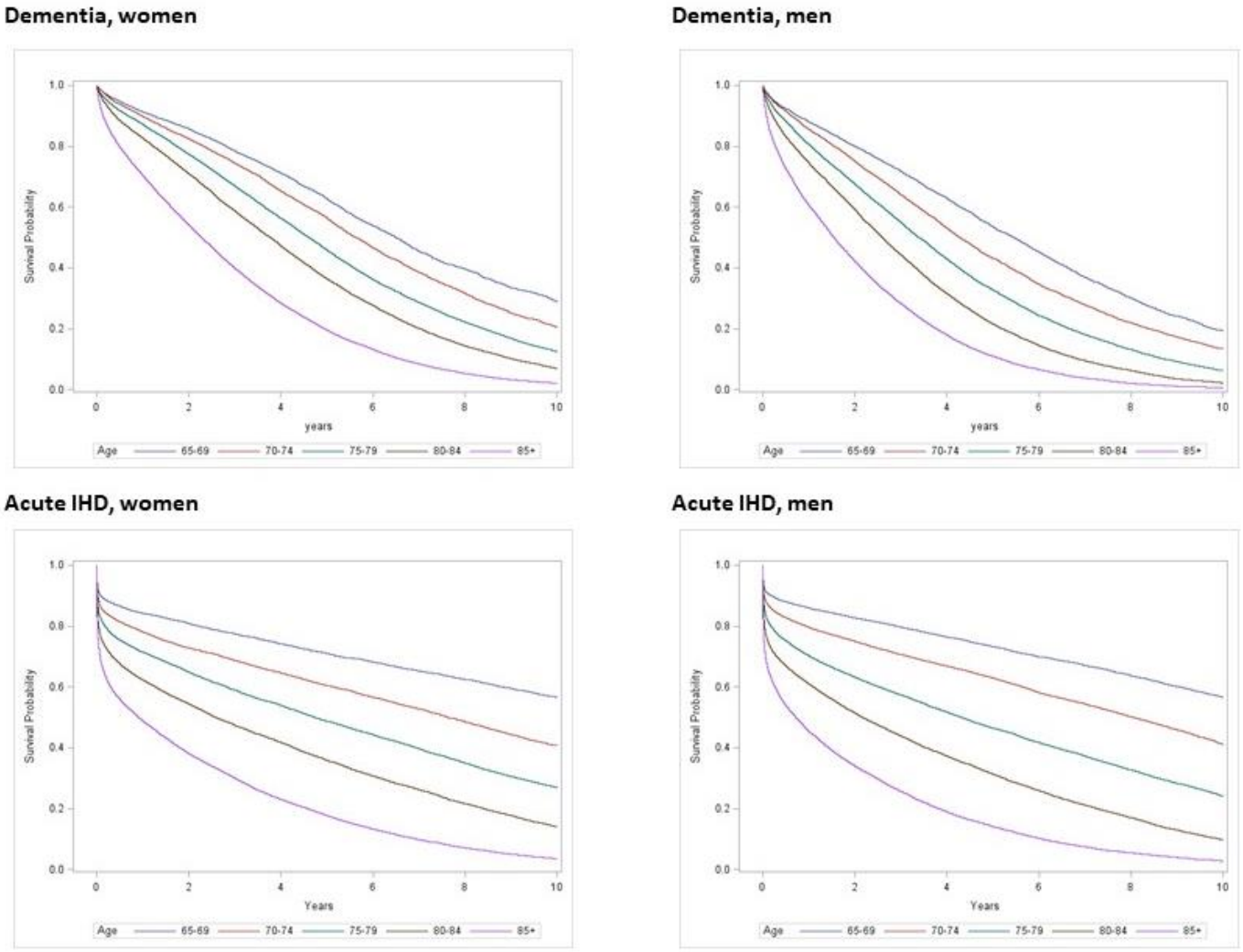
Graphs showing age-adjusted mortality rate ratios for women and men with dementia, acute ischemic heart disease (IHD), and cancer compared to people without. The reference value was defined as 1.0 in 1996 for women and men without dementia, acute IHD, and cancer. Error bars represent 95% confidence interval.

Fig. 2 Time trend of all-cause mortality for women and men



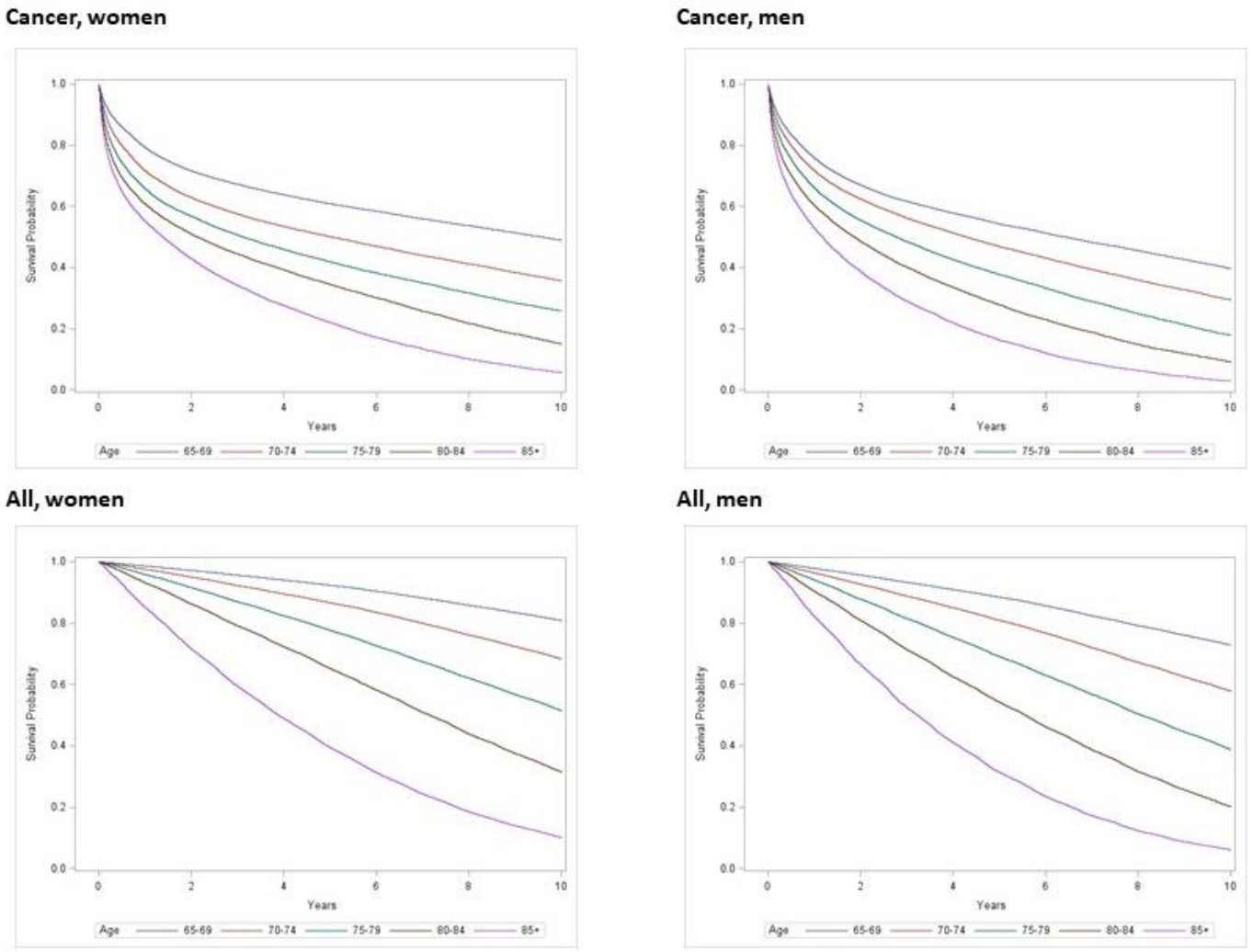
Age-adjusted mortality rate ratios for women and men with dementia, acute ischemic heart disease (IHD), cancer, and the general elderly population. The reference value was defined as 1.0 in 1996. A) All-cause mortality in women, B) All-cause mortality in men.

Fig. 3 Survival for women and men



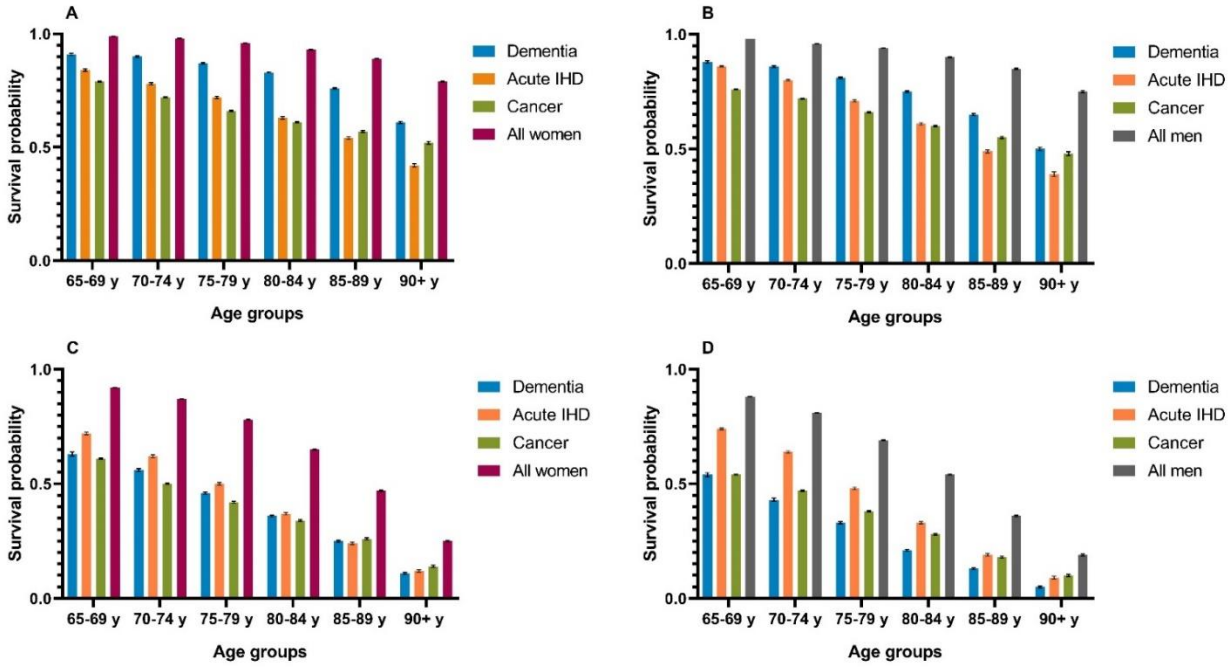
Age-stratified Kaplan-Meier survival curves for women and men with dementia, acute ischemic heart disease (IHD), cancer, and the general elderly population, 2000–2015.

Fig. 3 Survival for women and men



Age-stratified Kaplan-Meier survival curves for women and men with dementia, acute ischemic heart disease (IHD), cancer, and the general elderly population, 2000–2015.

Fig. 4 1-year and 5-year survival for women and men



Survival probabilities presented as 1-year and 5-year for women and men with dementia, acute ischemic heart disease (IHD), cancer, and the general elderly population from 2000-2015. A) Women, 1-year survival probabilities, B) Men, 1-year survival probabilities, C) Women, 5-year survival probabilities, and D) Men, 5-year survival probabilities. Error bars represent standard errors.

DISCUSSION

To our knowledge, this is the first study of time trends in mortality for dementia in an entire national population. In accordance with previous findings, our study confirmed that all-cause mortality rates in dementia were higher than in people without dementia [3]. Although MRRs in dementia declined over the 20-year period, it occurred at the same rate as in those without dementia, leaving the excess mortality in people with dementia unchanged. In contrast, the excess mortality from acute IHD and cancer was significantly reduced during the same period.

Our results highlight the fact that dementia is associated with increased mortality at all ages. Even though the MRRs were higher in the youngest of the elderly when comparing people with and without dementia, a dementia diagnosis was associated with significantly higher MRRs in women and men in all age groups. Furthermore, the 5-year probability of survival after a dementia diagnosis was largely comparable to the 5-year probability of survival after acute IHD or a cancer diagnosis. We believe this age-related difference in MRRs is associated to the fact that the risk of mortality increases with age, which means that it is generally high in people age >90 years. The risk of mortality is also affected by comorbidities, which are more frequent in the most elderly. Thus, when comparing the people in the youngest dementia groups with the general elderly population in the same age group, the latter will have fewer comorbidities and are at a lower risk of dying. However, in the oldest age groups mortality rates are generally higher and the frequency of comorbidities are similar in people with and without dementia. Thus, in the youngest there is a greater difference in MRR between people with and without dementia because the background mortality is low and, compared to their peers, people with dementia have more comorbidities.

We found that, over a 20-year period, the age- and sex-adjusted MRR was about 2.9 times higher in people with dementia compared with people without dementia. In their meta-analysis, Dewey and Saz estimated a similarly increased mortality risk for people with dementia (odds ratio: 2.63, 95% CI: 2.17–3.21) [20]. However, only few studies have investigated time trends of mortality. Our findings of declining mortality are in line with findings from four population-based studies, one from Sweden, two from the Netherlands, and one from Japan [8,10,11,21]. In contrast, two other studies found a tendency of increasing mortality in dementia. A German study based on health claims registry data from 2006–2007 to 2009–-2010 found that mortality with dementia tended to be lower in the first period, although this was only significant in women [9]. This study observed mortality in dementia over a relatively short period. Similarly, a U.S. study based on data from a population-based longitudinal survey observed that the 2-year mortality was higher in individuals with moderate and severe cognitive impairment in 2002–2004 compared with 1993–1995 [7]. However, these results were not significant. To conclude, there is limited evidence of an increase in

mortality in dementia, and our study results, based on data from an entire national elderly population over a 20-year period, add weight to the scientific evidence that mortality in dementia is declining.

From 1996–2015, the mortality rates declined more in men compared with women in the groups with dementia, cancer, and the general elderly population. For men and women with acute IHD, the mortality rates declined at a similar rate. Interestingly, life expectancy is higher in women than in men. From 2000–2015, this sex gap in Denmark narrowed by nearly one year [22]. Thus, we believe that the steeper decline in mortality rates seen in most groups of men may be explained by an increased life expectancy in men in general.

Most dementias are progressive, fatal brain diseases, which means that dementia alone contributes to an increased risk of death [23]. It is also well-established that increased mortality in dementia is related to the level of severity and subtype of dementia [24–28]. We did not investigate the potential contributors of other possible causes for the excess mortality in people with dementia found in our study. Previous studies suggest that increased mortality in dementia may also be related to polypharmacy [23,29], antipsychotics [30], frailty [29,31], co-occurring chronic conditions [24], and functional impairment [32]. Furthermore, it is possible that insufficient treatment of other health conditions, unhealthy lifestyle, and compromised access to healthcare due to a dementia diagnosis may contribute to the excess mortality.

We observed a decline in mortality rates in elderly people with and without dementia. There are several possible explanations for this finding. First, the health of the entire elderly population with and without dementia has generally improved. Second, increased awareness about dementia and improved dementia care during our study period may have also contributed to the decline in mortality. Third, an artificial decline in mortality rates of dementia unrelated to improved health may be due to earlier age at diagnosis. If there had been a shift towards earlier diagnosis while overall life expectancy remained unchanged, this would, somewhat misleadingly, result in increased survival after dementia diagnosis. Even though, our previous study on declining incidence of dementia in Denmark showed that median age at diagnosis did not change significantly from 1996 to 2015 [19], it is still possible that diagnoses towards the end of the study were registered at an earlier stage of the disease process.

The mortality gap between people with acute IHD or cancer and the general elderly population was reduced during the same 20-year period. The period covered by the present study saw the development of better and more efficacious treatments, just as the diseases we examined were and are a priority in the Danish healthcare sector, with full government support [33,34]. For example, the treatment and organization of healthcare for acute IHD improved. From 1997–1998 to 2009–2010, the practice of

revascularization (percutaneous coronary intervention) after onset of acute myocardial infarction increased from 2.5% to 38.2%, while the use of statins and clopidogrel also increased even more markedly [34].

Although multiple disease-modifying drugs against Alzheimer's disease are in the pipeline, no new medications have been approved since 2003, and numerous attempts to find more effective drugs have failed [35]. Nonetheless, several actions can be taken to possibly reduce mortality in dementia, for instance, better treatment of comorbidities, a reduction in polypharmacy and inappropriate medications, and improved access to healthcare to reduce functional impairment and frailty in people with dementia.

This study also assessed survival after first diagnoses. For 1- and 5-year survival probabilities, we observed that survival was higher in the general elderly population, as compared to people with dementia, acute IHD, or cancer. Nonetheless, 1-year survival for women and men with dementia was significantly higher than for those with acute IHD and cancer. We believe this reflects the difference in the disease development and time course of the three conditions examined. Acute IHD has the highest mortality on the day of onset and closely after, which is why the general standard for reporting mortality is 30-day survival [36]. Our definition of cancer covers a broad range of cancer diseases with very large differences in disease progression patterns. The reason why the 1-year survival in cancer was lower than for dementia is related to the fact that some cancer types are fatal very early in the course of the disease, e.g. pancreas, liver, brain, lung, and esophagus cancer [37].

In terms of the 5-year survival probabilities, we observed different patterns for women and men when comparing dementia with cancer and acute IHD. In general, the 5-year survival probability for the three disease groups ranged from 0.72–0.11 in women and 0.74–0.04 in men, according to age groups. In women age <80 years, the 5-year survival was lowest in cancer, higher in dementia, and highest in acute IHD, whereas in women age ≥80 years, the three diseases are largely comparable.
Overall, being diagnosed with dementia was more dangerous in men than a diagnosis of acute IHD and cancer. We believe that one of the reasons why survival in men with acute IHD was relatively high may be related to our selection of the group. From 1997–2010, the median age of first acute myocardial infarction in men was 64–66 years and 73–75 years in women [34]. The fact that we excluded people with a previous history of acute IHD prior to the age of 65 may have led to selection bias, possibly favoring men who were healthier than the average male with acute IHD.

This study, which is based on routine healthcare data from the secondary sector, has limitations. Hence, for dementia, one of the limitations is that we do not have access to data on, e.g., cognitive status or physical performance status, that may affect mortality in dementia. Studies have shown that mortality differs according to the various subtypes of dementia [24–26]. We would be interested in performing additional

analyses investigating subtypes but, even though the dementia syndrome diagnosis has high validity in Danish national registries, the validity of dementia subtype diagnoses is limited [38]. Our definition of cancer is heterogeneous. As mortality varies with cancer subtypes [33], the time trend of mortality may have changed differently for the various subtypes during our study period. Furthermore, the steep decrease in cancer mortality may partly be mediated by earlier time of diagnosis due to screening regimes for some cancer subtypes. In addition, not everyone with dementia is registered in our secondary healthcare registries. Our previous study showed that there were 36,129 people age ≥65 years registered with dementia in Denmark in 2015 [19]. Nevertheless, extrapolations from population-based studies estimate the prevalence of dementia in Denmark to be around 87,000 [39]. Thus, a considerable number of people with dementia are either undiagnosed or diagnosed in primary care only. We hypothesize that possibly unregistered individuals with dementia may represent those with the mildest and the most severe symptoms. The inability to include these groups may have influenced our results. However, having the entire Danish elderly population as our reference group we believe the contamination of the comparison group is limited. Thus, the underreporting of dementia in the registries may only lead to a limited underestimate of the association between dementia and excess mortality.

Among the strengths of our study is the use of data from an entire large, unselected national cohort with minimal dropout, no missing data, and a large sample size. Second, our data is continuous in terms of time, enabling us to assess time trends at yearly intervals. This strengthens our time-trend analysis as compared to only comparing two or a few points in time.

The validity of dementia syndrome diagnoses in the Danish registries used in this study has been assessed and found to be correct in 85.8% of cases [38].

We believe our results are generalizable to high-income Western countries with similar improvements in health in the elderly population over the last 20 years and with equal access to healthcare.

CONCLUSION

This study demonstrated that dementia is associated to a considerably increased mortality in women and men of all age groups. The mortality rates declined for dementia over the 20-year period under study. However, contrary to our hypothesis, we found that the mortality gap between people with dementia and the general elderly population was not reduced, despite a stronger focus on appropriate care for people with dementia during the study period. In the future, the discovery of more efficacious disease-modifying treatments may hopefully contribute to lower mortality. In the meantime, initiatives for improving health

and decreasing mortality in people with dementia are still highly relevant and can include improving the treatment of comorbidities and the organization of support and healthcare services for people with dementia.

ACKNOWLEDGEMENTS

The authors would like to thank the Danish Ministry of Health for supporting the Danish Dementia Research Centre. Additionally, the authors thank Kasper Jørgensen, Danish Dementia Research Centre, for his thorough review of this paper.

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Study II

Mortality in Dementia from 1996 to 2015: A National Registry-Based Cohort Study

Supplementary material

Supplementary Material (Appendix)

Cumulative Incidence: Composition of Cohort Representing the General Elderly Population

We calculated cumulative incidence rates of death for dementia, acute IHD, and cancer. To put these results into perspective, we wanted to be able to compare our results to the Danish elderly population. However, cumulative incidence rates depend on a defined time of onset. For dementia, acute IHD, and cancer, this is the date the disease was first registered. As the general population did not have a date of onset, we had to construct a reference group representing the entire Danish elderly population from 2000–2015.

We evaluated point prevalence on June 1 in 2000, 2005, and 2010, stratified by 5-year age groups.

On June 1, in each of the three years selected, we created a cohort representing the population for each of the six age groups (65–69, 70–74, 75–79, 80–84, 85–89, 90+).

This meant that people could occur in more than one group. If someone appeared in more than one group, it was indicated as separate lines of data. To prevent this, we assigned everyone a random number and sorted them based on that number. If someone was represented by more than one line of data, the first line was used and the rest deleted.

Table S1. The table shows 50% fractiles in years for women with dementia. acute ischemic heart disease (IHD), cancer, and all women aged ≥65 years.

	Dementia		Acute IHD		Cancer		All ≥65 years	
	Women		Women		Women		Women	
Age	50% fractile	95% CI	50% fractile	95% CI	50% fractile	95% CI	50% fractile	95% CI
65-69	6.5	(6.3- 6.7)	12.2	(11.5- 12.6)	9.6	(9.3- 9.8)	>15*	- -
70-74	5.6	(5.5- 5.8)	7.6	(7.4- 8.0)	5.0	(4.8- 5.2)	14.1	(14.0- 14.2)
75-79	4.6	(4.5- 4.7)	4.7	(4.5- 5.0)	3.1	(3.0- 3.2)	10.3	(10.2- 10.4)
80-84	3.8	(3.7- 3.8)	2.6	(2.5- 2.8)	2.1	(2.0- 2.2)	7.1	(7.1- 7.2)
85-89	2.7	(2.7- 2.8)	1.3	(1.2- 1.4)	1.6	(1.5- 1.7)	4.7	(4.7- 4.8)
90+	1.6	(1.5- 1.6)	0.5	(0.4- 0.7)	1.1	(1.0- 1.2)	2.7	(2.7- 2.8)

*The maximum follow-up time was 15 years. Thus, the 50% fractile was not reached for this age group during the 15 years.

Table S2. The table shows 50% fractiles in years for men with dementia. acute ischemic heart disease (IHD), cancer, and all men aged ≥65 years.

	Dementia		Acute IHD		Cancer		All ≥65 years	
	Men		Men		Men		Men	
Age	50% fractile	95% CI	50% fractile	95% CI	50% fractile	95% CI	50% fractile	95% CI
65-69	5.5	(5.2- 5.6)	11.8	(11.5- 12.2)	6.4	(6.2- 6.6)	>15*	- -
70-74	4.3	(4.2- 4.4)	8.0	(7.8- 8.3)	4.3	(4.2- 4.4)	11.6	(11.5- 11.7)
75-79	3.4	(3.3- 3.5)	4.3	(4.1- 4.5)	2.8	(2.7- 2.8)	8.1	(8.0- 8.1)
80-84	2.6	(2.5- 2.7)	2.2	(2.0- 2.3)	1.9	(1.8- 1.9)	5.6	(5.5- 5.6)
85-89	1.8	(1.7- 1.9)	0.9	(0.8- 1.0)	1.3	(1.2- 1.3)	3.6	(3.6- 3.7)
90+	1.0	(0.9- 1.1)	0.4	(0.3- 0.5)	0.9	(0.8- 1.0)	2.4	(2.3- 2.4)

*The maximum follow-up time was 15 years. Thus, the 50% fractile was not reached for this age group during the 15 years.

Study III

Dementia increases mortality beyond effects of co-morbid conditions:

A national registry-based cohort study

Dementia increases mortality beyond effects of co-morbid conditions: A national registry-based cohort study

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Abstract

Background: Mortality is known to be markedly increased in people with dementia. However, the association between multiple chronic conditions and mortality in dementia is not well clarified. The aim of this study was to investigate the impact of somatic and psychiatric diseases on mortality in dementia compared with the general elderly population.

Methods: Using a cohort study design, nationwide registry data from 2006–2015 on dementia and psychiatric and somatic comorbidities defined by the Charlson Comorbidity Index (CCI) were linked. Impact of chronic conditions was assessed by mortality rate ratios (MRR) in all Danish residents ≥65 years with and without dementia.

Results: Our population comprised 1,518,917 people, of whom 114,109 people were registered with dementia. MRR was 2.70 (95% CI 2.68, 2.72) in people with dementia after adjusting for sex, age, calendar year, and comorbidities. MRR increased with higher CCI score, and when comparing people with a similar comorbidity load, MRRs were significantly higher for people with dementia.

Conclusions: The comorbidity load was associated with increased mortality in both people with and without dementia. Mortality in dementia remained increased, even after adjusting for psychiatric and chronic somatic comorbidities. Our findings suggest that dementia disorders alone contribute to excess mortality, which may be further increased by comorbidities.

Introduction

Mortality is markedly increased in people with dementia (1). This excess mortality is complex and associated with multiple factors, such as age (2–8), being male (6–9), dementia subtype and severity (10), reduction in activities of daily living (2,4,11,12), institutionalization (3), and possibly low cognitive performance (2,3,6,9,13,14). Concurrent chronic comorbidities have also been linked to increased mortality in people with dementia (1,15,16), just as specific comorbidities have been found to increase mortality in dementia, including cerebrovascular disease (15), diabetes (16), and hypertension (16). It is possible that insufficient treatment of comorbidities could attribute to excess mortality in dementia. However, studies investigating the association between the load of chronic comorbidities and mortality in people with and without dementia are scarce (17,18).

Globally, the number of people living with dementia is increasing, and due to higher life expectancy, it is expected to increase more rapidly during the next decades (19). The prevalence of comorbidities also increases with age. Therefore, in understanding the association between comorbidities and mortality in the growing population of people with dementia more knowledge is needed.

Our study comprised three hypotheses: 1) the presence of other somatic diseases and psychiatric conditions is associated with increased mortality in people with dementia; 2) even after adjusting for comorbidities, people with dementia will have higher mortality compared with people without dementia; and 3) people with chronic somatic or psychiatric conditions and dementia have excess mortality compared with people with the same chronic somatic or psychiatric conditions and without dementia.

Denmark's longstanding practice of assigning all residents an individual personal identification number means that Danish national registries represented unique data sources for investigating the three hypotheses in an entire national population. The aim of this study was to investigate the impact of psychiatric and somatic conditions on mortality in people with dementia compared to people without dementia.

Methods

Study design and data sources

The study was designed as a registry-based cohort study using data from Danish national registries: the Danish Civil Registration System, the Danish National Patient Registry, the Psychiatric Central Register, the National Prescription Registry, and Statistics Denmark (20–23). Denmark has universal free access to health

care. The second and third registries just listed include information on all contacts to the secondary health care system since 1995. The registries have previously been described (24).

We obtained data on all hospital-based psychiatric diagnoses from 1970 to 2015 and on all somatic diagnoses from 1977 to 2015, and dementia medications from 1995 to 2015. Data were made available through Statistics Denmark, which also provided data on immigration and date of death. Data were linked using anonymized personal identification numbers.

Study period and study population

The study period was defined as January 1, 2006 to December 31, 2015. Within this ten-year period all Danish residents and immigrants to Denmark aged ≥65 years were included. Each person was considered at risk of death from time of inclusion until death, emigration, loss to follow-up, the day they turned 110 years old, or until the study period ended, whichever occurred first. People were censored at the age of 110 as the risk of accidental misregistration at this age was considered high (although rare).

Definition of dementia

Dementia was defined as either being registered with a dementia diagnosis in the Danish National Patient Registry or the Psychiatric Central Register or as having filled a prescription for an anti-dementia medication. Tables S1 and S2 in the Supplementary Material present the diagnosis codes and Anatomical Therapeutic Chemical codes for this identification. Date of dementia onset was defined as either the date of the first hospital contact (in- or outpatient) where a dementia diagnosis was registered, or the date an anti-dementia drug prescription was fill for the first time, whichever occurred first. Dementia is usually diagnosed in a hospital setting in Denmark. As we wanted to examine late-onset dementia, we excluded people registered with dementia prior to age 65.

Definition of comorbidities

Comorbidities were defined as continuous variables, and risk time was delineated as the disease being absent or present. We included information on 19 somatic diseases and four categories of psychiatric conditions.

Somatic conditions

In accordance with the Charlson Comorbidity Index (CCI) method, all comorbidities were defined as continuous variables based on weighted comorbidity scores. Comorbidity scores assign weights, from 1–6, to each comorbidity for every individual, who are then given a sum of the weights based on all present

comorbidities. A CCI score of zero represents no comorbidities, and a score from 1 to ≥6 represents a gradually higher load of comorbidities (25).

To examine the load of comorbidities, we used a modified version of CCI in which dementia was excluded, leaving 18 chronic somatic conditions: 1) myocardial infarction, 2) congestive heart disease, 3) peripheral vascular disease, 4) cerebrovascular disease, 5) chronic pulmonary disease, 6) connective tissue disease, 7) ulcer disease, 8) mild liver disease, 9) diabetes mellitus, 10) hemiplegia, 11) moderate/severe renal disease, 12) diabetes mellitus with chronic complications, 13) any tumor, 14) leukemia, 15) lymphoma, 16) moderate/severe liver disease, 17) metastatic solid tumor, and 18) AIDS.

As atrial fibrillation is a known risk factor for developing dementia and could have an impact on mortality in dementia, we added it to the list of investigated somatic diseases without including it in the CCI. In this study, the modified CCI will be referred to as the CCI. Table S3 presents the diagnostic codes.

Psychiatric conditions

A recent study investigating psychiatric diseases and mortality found that all classes of psychiatric diseases were related to excess mortality, even single episodes of depression (26). Thus, we believe that the psychiatric diseases listed can have a potential effect on mortality, even after being declared cured.

We included data on four groups of psychiatric conditions: 1) mental and behavioral disorders due to psychoactive substance abuse; 2) schizophrenia and related disorders; 3) affective disorders; and 4) neurotic, stress-related and somatoform disorders. Table S4 presents the diagnosis codes.

Statistics

We used Poisson regression to calculate mortality rate ratios (MRR) with SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina, U.S.A.). First, we assessed MRR comparing women and men, respectively, with and without dementia stratified by CCI scores of 0 to ≥6. The reference group was defined as people without dementia with a CCI score of zero (reference value was 1.00). Second, we quantified the excess mortality by assessing MRR for men and women by CCI score stratified into five-year age groups (65–69, 70–74, 75–79, 80–84, 85–89, and ≥90 years). For each age- and CCI score-stratified groups, the reference groups were defined as 1.00 in the same age- and CCI score group without dementia. Thus, in these analyses, the effect of an increasing CCI score on mortality was annulled. Third, we assessed MRR for the selected 23 comorbidities in combination with dementia by defining the reference as 1.00 for women and men who had the specific comorbidity but not dementia. Fourth, we assessed MRR using three different models adjusting for the listed covariates: model 1: age and calendar year; model 2: model 1 plus selected

psychiatric conditions (substance abuse disorders, schizophrenia, affective disorders, and neurotic, stress-related, and somatoform disorders); model 3: model 2 plus atrial fibrillation and somatic diseases included in CCI. Additionally, we performed a sensitivity analysis equivalent to Model 1–3, including only incident cases diagnosed with dementia at age ≥65 years during the period from January 1, 2006 to December 31, 2015.

Statistical significance was defined according to a 5% significance level.

Data approvals

This study was approved by the Danish Data Protection Agency, Statistics Denmark, and the Danish Health and Medicines Authority. Using anonymized registry data, no ethics committee approval was required by Danish law.

Results

Our population comprised 1,518,917 people ≥65 years of age (women: 820,758; men: 698,159) observed over 9,433,208 person years (women: 5,008,459; men: 4,209,921). There were 114,109 people (women: 71,528; men: 42,581) registered with dementia, accounting for 326,112 person years (women: 214,828; men: 111,284). Mean follow-up time for people without dementia was 6.48 years and 2.86 years for people with dementia. During the ten-year period, 439,205 people died (women: 234,517; men: 204,688) of whom 77,409 were registered with dementia (women: 48,295; men: 29,114). Table 1A and 1B show descriptive data of the population. Additionally, we calculated the distribution of person years for the five-year age groups by CCI score (Tables S5 and S6). In people with dementia ≤85 years, the percentage of years lived with a low CCI scores was markedly lower than those without dementia, whereas in people ≥85 years, the distribution was similar in people with and without dementia.

TABLE 1A Demographic data for the Danish elderly population, 2006 to 2015, stratified by sex and dementia status; number of persons, number of deaths, person years, crude mortality rates, mean age in 2006 and 2015, and the average mean age at death. Number of deaths, person years, and crude mortality rates are presented in five-year age strata.

		Women		Men	
Variables		**Dementia**	**No dementia**	**Dementia**	**No dementia**
	N, persons	71,528	749,230	42,581	655,578
	N, deaths	48,295	186,222	29,114	175,574
	Person years	214,828	5,008,459	111,284	4,098,637
	Mortality rate, per 100 person years	22.5	3.7	26.2	4.3
	Mean age, January 1, 2006 (SD)	83.8 (6.5)	75.9 (7.7)	81.1 (6.5)	74.1 (6.8)
	Mean age, January 1, 2015 (SD)	84.3 (6.9)	75.0 (7.6)	81.4 (6.7)	73.7 (6.6)
	Average mean age at death (SD)	87.1 (6.5)	83.1 (9.0)	84.1 (6.5)	79.6 (8.3)
Age groups					
65–69 years	N, deaths	331	18422	576	27,506
	Person years	4902	1,590,642	5477	1,526,855
	Mortality rate, per 100 person years	6.8	1.2	10.5	1.8
70–74 years	N, deaths	1758	22145	2198	30497
	Person years	17,026	1,198,014	15,918	1,076,665

	Mortality rate, per 100 person years	10.3	1.8	13.8	2.8
75–79 years	N, deaths	4717	28035	4795	33,492
	Person years	34.827	896,874	25,295	727,928
	Mortality rate, per 100 person years	13.5	3.1	19.0	4.6
80–84 years	N, deaths	10,032	33,916	7775	34,441
	Person years	54,791	656,181	30,535	452,816
	Mortality rate, per 100 person years	18.3	5.2	25.5	7.6
85–89 years	N, deaths	14,710	36,770	8334	28,582
	Person years	59,912	420,858	23,640	226,193
	Mortality rate, per 100 person years	24.6	8.7	35.3	12.6
≥90 years	N, deaths	16,747	46,934	5436	21,056
	Person years	43,370	245,889	10,419	88,180
	Mortality rate, per 100 person years	38.6	19.1	52.2	23.9

TABLE 1B Descriptive data for the Danish elderly population, 2006 to 2015, stratified by sex and dementia status; number of persons, number of deaths, person years, crude mortality rates stratified by the Charlson Comorbidity Index score and by the occurrence of psychiatric comorbidity.

		Women		Men	
Charlson Comorbidity Index		**Dementia**	**No dementia**	**Dementia**	**No dementia**
0	N, deaths	13,056	27,597	5698	20677
	Person years	83,297	2,775,629	34,631	2,089,297
	Mortality rate, per 100 person years	15.7	1.0	16.5	1.0
1	N, deaths	10,935	29,733	5967	21,420
	Person years	48,683	803,780	25,524	709,212
	Mortality rate, per 100 person years	22.5	3.7	23.4	3.0
2	N, deaths	9154	36,495	5362	30477
	Person years	37,838	768,855	19,704	614,165
	Mortality rate, per 100 person years	24.2	4.7	27.2	5.0
3	N, deaths	5886	26,957	4020	24,729
	Person years	19,573	282,883	11,939	270,484
	Mortality rate, per 100 person years	30.1	9.5	33.7	9.1
4	N, deaths	3421	17,640	2600	18,748

	Person years	10,453	156,391	7160	165,885
	Mortality rate, per 100 person years	32.7	11.3	36.3	11.3
5	N, deaths	2438	19,761	1984	21,015
	Person years	6917	111,188	4919	110,479
	Mortality rate, per 100 person years	35.2	17.8	40.3	19.0
≥6	N, deaths	3405	28,039	3483	38,508
	Person years	8067	109,732	7407	139,115
	Mortality rate, per 100 person years	42.2	25.6	47.0	27.7
Psychiatric comorbidity					
No	N, deaths	39,494	165,189	24,916	161,592
	Person years	172,784	4,631,956	94,412	3,895,119
	Mortality rate, per 100 person years	22.9	3.6	26.4	4.1
Yes	N, deaths	8801	21,033	4198	13,982
	Person years	42,044	376,503	16,873	203,517
	Mortality rate, per 100 person years	20.9	5.6	24.9	6.9

Figure 1 presents the age- and calendar-year adjusted MRR stratified by CCI score for men and women. The MRR increased with higher CCI scores and was significantly higher for men and women with dementia for all CCI scores compared to those without dementia. Additionally, the highest difference in MRR between people with and without dementia was observed in the groups with zero or few comorbidities.

Figure 1A and 1B Mortality by Charlson Comorbidity Index
Mortality rate ratios adjusted for age and calendar year for women (Figure 1A) and men (Figure 1B) stratified by Charlson Comorbidity Index. The reference is defined as 1.00 for women and men without dementia with a CCI score of zero. Error bars represent 95% confidence intervals.

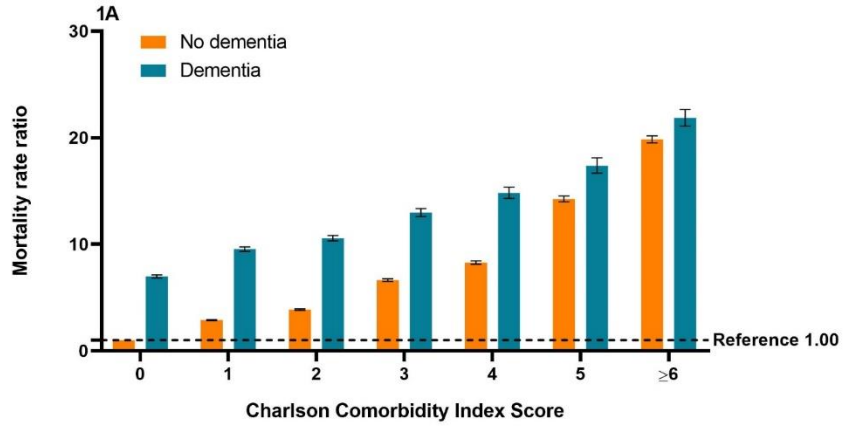

Figure 1A Age- and calendar year-adjusted mortality by Charlson Comorbidity Index in women

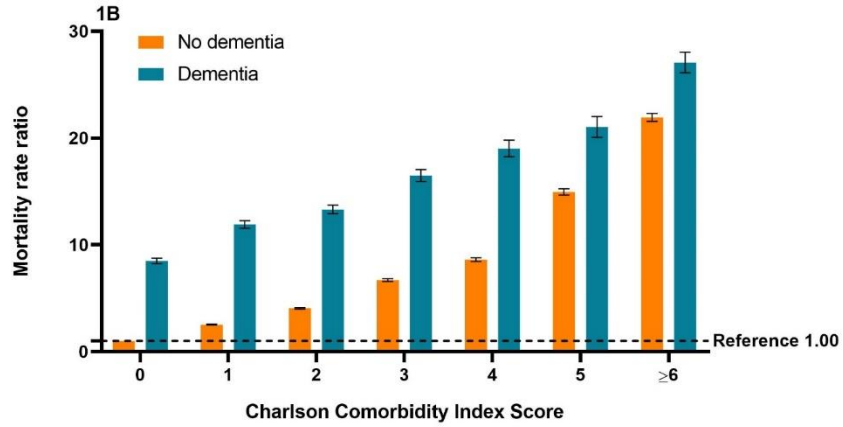

Figure 1B Age- and calendar year-adjusted mortality by Charlson Comorbidity Index in men

Figure 2 presents the excess mortality related to women and men with dementia stratified by age and CCI score. Excess mortality was most predominant in the youngest age groups with a low CCI score. The mortality was significantly higher for women and men in all age- and CCI score groups when compared with women and men without dementia. Furthermore, we observed a higher excess mortality in women than in men.

Figure 3 illustrates the excess mortality when comparing mortality in women and men with selected chronic conditions to those with the chronic conditions and dementia. For all individuals with any of the chronic somatic and psychiatric conditions, also having dementia was associated with a significantly higher mortality.

Table 2 presents three models of MRR for women and men with dementia adjusted for age divided into five-year age groups. The reference groups were women and men, respectively, in the same age groups without dementia. Model 1 was adjusted for age and calendar year. The results showed that the MRR was highest in the 65–69-year-old age groups (women: 5.39 (95% CI: 4.84, 6.01); men: 5.41 (95% CI: 4.98, 5.88)) and lowest in the ≥90 year-old age groups (women: 2.06 (95% CI: 2.03, 2.10); men: 2.21 (95%CI: 2.15, 2.28)). In model 3, we adjusted for chronic psychiatric and somatic diseases and observed a decline in MRR for the 65–69-year-old age groups (women: 2.73 (95%CI: 2.44, 3.05); men: 3.34 (95%CI: 3.07, 3.63)), whereas the MRR in the ≥90-year-old age groups was stable (women: 2.04 (95%CI: 2.00, 2.08); men 2.17 (95% CI: 2.10, 2.24)). The sensitivity analysis on incident cases did not change the results (Table S7).

Figure 2A and 2B Excess mortality by Charlson Comorbidity Index
The age and calendar year-adjusted mortality rate ratios (MRR) are presented for women (Figure 2A) and men (Figure 2B) with dementia in five-year age groups stratified by Charlson Comorbidity Index (CCI). For each of the age groups and CCI scores, the reference is defined as 1.00 for women and men without dementia in the same age group and with the same CCI score. Thus, MRR becomes a measure of the excess mortality stratified by CCI score. Error bars represent 95% confidence intervals.

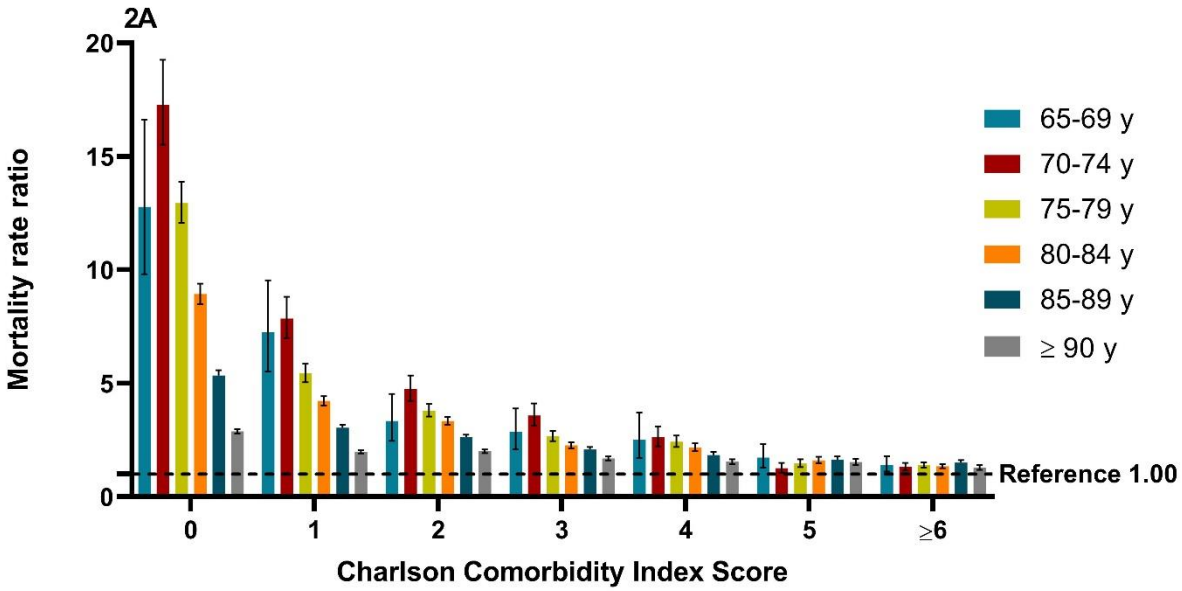

Figure 2A Excess mortality in women with dementia by Charlson Comorbidity Index

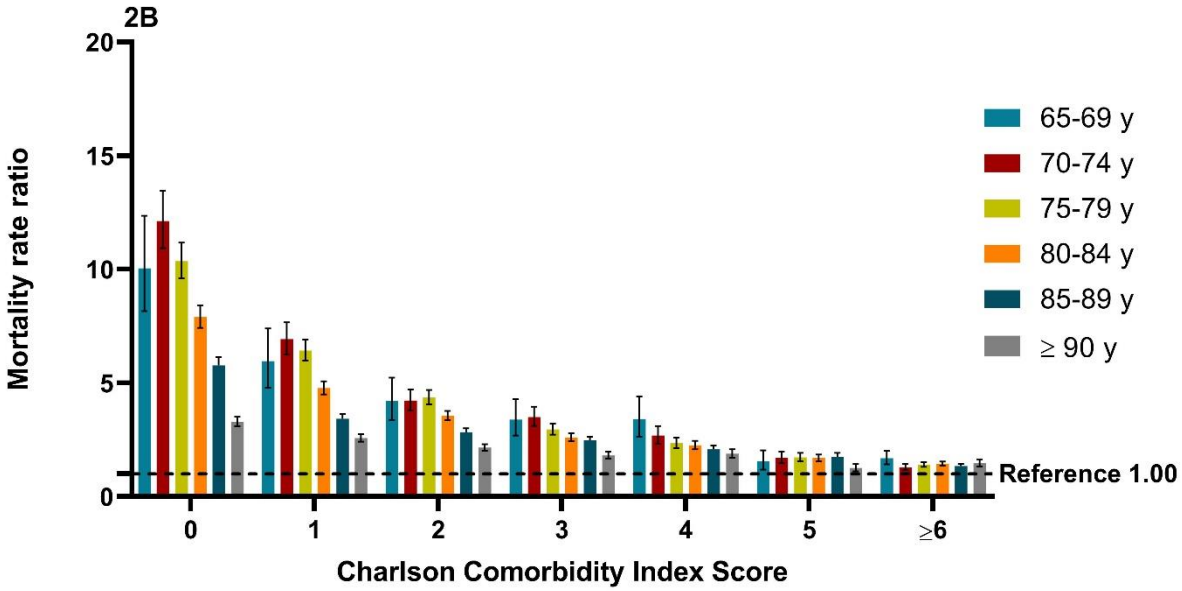

Figure 2B Excess mortality in men with dementia by Charlson Comorbidity Index

Figure 3 Excess mortality in dementia and concurring comorbidities

Excess mortality in women and men with dementia and selected comorbidities. The reference is defined as 1.00 for women and men without dementia but with the selected comorbidities. Error bars represent 95% confidence interval. Results for AIDS are not presented due to low sample size.

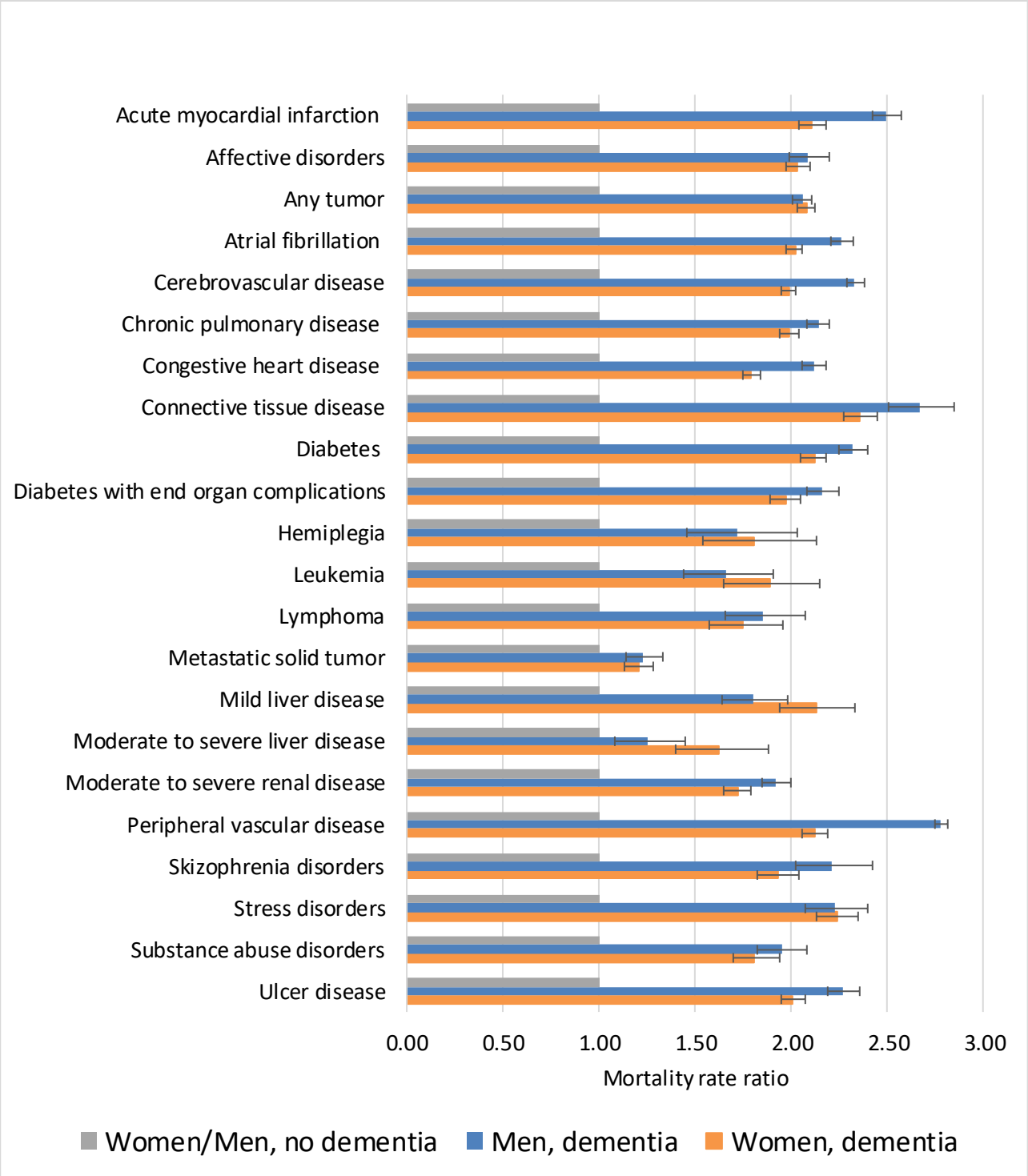

TABLE 2 Mortality rate ratios are presented for women and men in five-year age strata and an age-adjusted average. In each of the three models presented, the reference is defined as 1.00 for women and men without dementia in each of the five-year age stratum.

	Model 1		**Model 2**		**Model 3**	
	Adjusted for age and calendar year		**Adjusted for age, calendar year and psychiatric conditions**		**Adjusted for age, calendar year, and psychiatric and chronic somatic conditions**	
	Women with dementia		**Women with dementia**		**Women with dementia**	
Age	**MRR**	**95% CI**	**MRR**	**95% CI**	**MRR**	**95% CI**
Age-adjusted average	2.78	(2.75, 2.81)	2.66	(2.63, 2.68)	2.61	(2.59, 2.64)
65–69 years	5.38	(4.82, 6.00)	3.97	(3.55, 4.43)	2.70†	(2.41, 3.01)
70–74 years	5.33	(5.08, 5.60)	4.51	(4.29, 4.74)	3.29‡	(3.12, 3.46)
75–79 years	4.16	(4.04, 4.29)	3.79	(3.67, 3.91)	3.24‡	(3.14, 3.35)
80–84 years	3.46	(3.38, 3.54)	3.31	(3.24, 3.39)	3.12‡	(3.05, 3.19)
85–89 years	2.77	(2.71, 2.82)	2.70	(2.65, 2.76)	2.67‡	(2.61, 2.72)
≥90 years	2.06	(2.03, 2.10)	2.04	(2.01, 2.08)	2.04‡	(2.00, 2.08)

	Men with dementia		Men with dementia		Men with dementia	
Age	**MRR**	**95% CI**	**MRR**	**95% CI**	**MRR**	**95% CI**
Age-adjusted average	3.09	(3.05, 3.13)	2.93	(2.89, 2.97)	2.83‡	(2.79, 2.87)
65–69 years	5.40	(4.97, 5.87)	4.26	(3.92, 4.63)	3.34‡	(3.07, 3.63)
70–74 years	4.69	(4.49, 4.90)	4.10	(3.92, 4.28)	3.39‡	(3.24, 3.54)
75–79 years	4.00	(3.88, 4.12)	3.73	(3.61, 3.84)	3.44‡	(3.33, 3.55)
80–84 years	3.28	(3.20, 3.36)	3.18	(3.10, 3.26)	3.01‡	(2.93, 3.09)
85–89 years	2.76	(2.69, 2.83)	2.71	(2.64, 2.78)	2.64‡	(2.57, 2.70)
≥90 years	2.21	(2.15, 2.28)	2.19	(2.13, 2.26)	2.17‡	(2.10, 2.24)

†Leukemia, lymphoma, and AIDS has been excluded from the model due to low sample size. ‡AIDS has been excluded from the model due to low sample size. Abbreviations: MRR, mortality rate ratio

Discussion

This is the first nationwide study to investigate the impact of comorbid psychiatric and somatic conditions on mortality in dementia compared with the general elderly population. We found that a higher load of somatic comorbidities, captured by the CCI, was associated with a higher mortality. Although the excess mortality in people with dementia was most pronounced in groups with no or few comorbidities compared with the general elderly population, it was, nonetheless, significantly higher for all CCI score groups.

In our fully adjusted model where we adjusted for calendar year, age, and psychiatric and somatic comorbidities, mortality remained more than double that in people with dementia compared with the general elderly population. Thus, our data suggest that the excess mortality in dementia cannot solely be explained by the load of comorbidities. Finally, for each of the investigated somatic and psychiatric conditions, having a coexisting dementia disease was associated with a significantly higher mortality, even in terms of metastatic cancer.

It is difficult to compare our results with other studies because, to the best of our knowledge, there are no studies available investigating the impact of multiple comorbidities in people with dementia in a complete nationwide population. However, a Canadian study based on data from physicians, hospital admissions, ambulatory care utilization, and clinical laboratory results included the entire elderly population of Alberta (N = 610,457) for practical purposes (17). The study investigated the impact of 29 comorbidities, as well as occurrence of multiple comorbidities on the risk of mortality in people with dementia compared with people without (17). In line with our results, they reported that 1) mortality increased with the number of comorbidities for all elderly people but was significantly higher in people with dementia, and that 2) differences in hazard ratios for mortality comparing people with and without dementia were reduced with an increasing number of comorbidities and were attenuated with increasing age (17). When comparing the hazard ratios from the Canadian study with our MRR, our values were markedly higher, especially in the youngest age groups with few comorbidities. These differences could be explained by 1) the Canadian study included more comorbidities, thus increasing the risk of having comorbidities; 2) our study only included data on comorbidities diagnoses from the secondary health sector, hereby possibly reflecting more severe diseases or disease stage; and 3) our study adjusted for calendar year. Thus, overall, our findings give weight to the existing knowledge that mortality in people with dementia increases with the number of comorbidities. The importance of including information about comorbidities when assessing risk of mortality was also emphasized by Haaksma et al. (18). They introduced a survival prediction table, estimating three-year survival probability after dementia diagnoses (18). The four strongest predictors of

mortality were included in the model (age, sex, comorbidities, and global cognition). Hereby, the model predicted three-year survival probability accurately 70-71% of the time in a primary care setting (18).

In this study, we also assessed mortality in people with dementia compared with the general elderly population. In our fully adjusted model (age, calendar year, psychiatric and somatic comorbidities), the MRR was 2.70 (95% CI: 2.68, 2.72). Other studies have assessed mortality in smaller populations comparing people and without dementia, adjusted for multiple comorbidities (27–29). They found hazard ratios of mortality of 1.47 (95% CI: 1.35, 1.60) (27); 2.07 (95% CI: 1.62, 2.66) (28); and a relative risk of 1.80 (95% CI: 1.46, 2.21) (29). However, these results all included adjustments for activities of daily living or level of care. Furthermore, two of these studies assessed comorbidities at time of diagnosis of dementia or baseline only (27,28), whereas our comorbidities were continuous variables, allowing the number of comorbidities to increase throughout the study period. These two factors may explain why we found a higher MRR.

Our data suggest that the excess mortality in dementia cannot solely be explained by the load of comorbidities. We believe that the excess mortality is caused by the dementia disorder per se, as most dementia disorders are progressive, fatal brain diseases. There are several possible explanations for the excess mortality in dementia. First, there may be an association between frailty, dementia, and mortality. Frailty, identified as a risk factor for developing dementia (30), has also been associated to increased risk of mortality in people with dementia (31,32). Furthermore, an autopsy study by Wallace et. al. reported that people with less frailty were less likely to develop Alzheimer's dementia clinically, despite similar neuropathological Alzheimer's pathology in their brains, whereas people who were more frail were more likely to express both neuropathological changes and clinical dementia symptoms (33). Frailty may be a moderator of the Alzheimer's disease pathology and a risk factor of Alzheimer's dementia. In our study, we did not investigate the impact of frailty in people with dementia. However, we believe that increased frailty could lead to increased risk of dementia, further increasing mortality. As a result, frailty could potentially explain some of the observed excess mortality in dementia in our study.

Second, people with dementia have a different risk factor profile than people without dementia. A review identified nine comorbidities to be more frequent in people with dementia (falls, delirium, epilepsy, weight loss and nutritional disorders, incontinence, sleep disturbances, visual dysfunction, oral disease, and frailty) (30) whereas a population-based study found that other comorbidities were less frequent (hypertension, type 2 diabetes mellitus, ischemic heart disease, angina, and myocardial infarction) (34). There is also the issue of whether comorbidities were actually less prevalent or just underdiagnosed (34).

Third, we believe that there might be higher risk of inappropriate or insufficient treatment of other diseases in people with dementia and that this could increase mortality. For example, a review by Bunn et

al. found some evidence that people with dementia and diabetes or visual impairment did not have the same access to care as people with diabetes or visual impairment without dementia (35). We believe that a difference in management of comorbidities could attribute to the excess mortality in dementia.

We found that in the youngest age groups, MRR was reduced significantly when adjusting for comorbidities, whereas the adjustments did not change much in the oldest age groups. Younger age was associated with higher MRR after adjusting for comorbidities. We believe that there are three possible explanations for this. First, the mortality for people ≥85 years of age is already high, which is why concurring conditions do not increase the mortality as much proportionally. Second, since comorbidities were more frequent in the oldest age groups and the distribution of comorbidities was similar in people ≥85 years of age with and without dementia, our results suggest that comorbidities represent an equally great risk of mortality for people with and without dementia. In other words, the effect of dementia becomes diluted by having more comorbidities. Third, there may be a difference in the distribution of dementia subtypes in the various age groups, and this could affect mortality. Onset of frontotemporal dementia and Lewy body dementia usually occurs earlier compared with Alzheimer's disease and vascular dementia. These two first-mentioned dementia subtypes have been reported to have significantly higher mortality than in Alzheimer's disease (3). Thus, an unequal distribution of dementia subtypes favoring the ones with the highest mortality rate in the youngest age groups may partially explain the persistent excess mortality in our fully adjusted model.

Limitations

This study has limitations. First, different comorbidities may increase the risk of dying from the various dementia subtypes. However, even though the validity of dementia diagnoses in the Danish national registries is high, the specific dementia subtypes are not useful, as a large proportion of people have an unspecific dementia diagnosis (36). Second, the study aims of providing an overview of how a range of multiple different conditions is associated to mortality in dementia led to broadly defining disease groups. One example of this is cancer comorbidity since different cancer types and additional subtypes are associated with different mortality risks (37). Thus, when interpreting our results, the differential mortality risks for each disease group should be considered. Third, in Denmark, as in many other countries, the estimated number of people living with dementia is substantially higher than the number of people that are registered with a diagnosis. A study based on findings from population-based studies estimated that Denmark would have approximately 87,000 people living with dementia in Denmark in 2015 (38). However, in our previous study, only 36,000 people were registered with dementia in 2015 (39). Thus, our study may underestimate the prevalence of dementia. Fourth, we included all diagnoses on comorbidities registered

from the 1970s to 2015, and it is possible that the use of diagnoses changed during this period, also in terms of the use of dementia diagnoses in the study period. Fifth, treatments for comorbid conditions may have had an effect, for example antipsychotics have been associated with increased mortality in older people (40).

Strengths

A strength of this study is the use of data from an entire, unselected national cohort. The population is large and represents many person years at risk. The dates of diagnoses and deaths are continuous variables, where the time intervals are days, which means that the risk time that each person in this study contribute with is quite accurate. Furthermore, due to follow-up in national registries, this large cohort has minimal dropouts and no missing data. Our information on comorbidities covered continuous variables over a long period from the 1970s to 2015, allowing us to track changes in comorbidities until time of death, instead of assessing a comorbidity status at baseline only. Finally, the registered dementia diagnoses and somatic conditions have a high validity in the national registries, making them beneficial for use in epidemiological studies (25,41).

Implications and generalizability

This study identifies people with dementia as a vulnerable group with increased mortality, especially, those who have concurring chronic comorbidities. Without any disease-modifying treatments for dementia disorders, attempts to moderate their course through better access to care and treatment of comorbidities should be strengthened. We believe that the findings from our study are generalizable to other high-income Western countries with similar access to health care.

Conclusion

The findings of this study emphasize the severity of dementia disorders. Having an additional dementia disease associated with any of a wide range of somatic or psychiatric conditions was associated with a significantly higher mortality rate. Mortality in dementia remained high, even after adjusting for psychiatric and somatic comorbidities, which indicates that dementia disorders alone contribute to excess mortality.

Acknowledgements

The authors thank the Danish Ministry of Health for supporting the Danish Dementia Research Centre.

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Study III

Dementia increases mortality beyond effects of co-morbid conditions:

A national registry-based cohort study

Supplementary Material

Supplementary Material

TABLE S1. ICD-8 and ICD-10 diagnosis codes for identification of dementia

Disease name	ICD-8	ICD-10
Alzheimer's disease	290.10	F00.0-00.9; G30.0-30.9
Vascular dementia	293.09-19	F01.0-01.9
Frontotemporal dementia	290.11	F02.0
Dementia without specification	290.09; 290.19	F03.9; G31.9
Other dementias	290.18	G31.8

Abbreviations: ICD, International Classification of Diseases.

TABLE S2. Anatomical Therapeutic Chemical (ATC) codes for identification of pharmaceutical treatment of dementia

Drug name	ATC code
Memantine	N06DX01
Donepezil	N06DA02
Rivastigmine	N06DA03
Galantamine	N06DA04

TABLE S3. ICD-8 and ICD-10 diagnosis codes for identification somatic diseases

Disease name	ICD-8	ICD-10
Myocardial infarction	410	I21; I22; I23
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	440-445	I70; I74; I77
Cerebrovascular disease	430-438	I60-I69; G45; G46
Chronic pulmonary disease	490-493; 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09; M30-M36; D86
Ulcer disease	530.91, 530.98, 531-534	K22.1; K25-K28
Mild liver disease	571, 573.01, 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Diabetes mellitus	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09	E10.0, E10.1; E10.9 E11.0; E11.1; E11.9
Hemiplegia	344	G81; G82
Moderate/severe renal disease	403, 404, 581-584, 590.09, 593.19, 753.10-753.19, 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes mellitus with chronic complications	249.01-249.05, 249.08, 250.01-250.05; 250.08	E10.2-E10.8; E11.2-E11.8
Any tumor	140-195	C00-C75
Leukemia	204-207	C91-C95
Lymphoma	200-203; 275.59	C81-C85; C88; C90; C96
Moderate/severe liver disease	70.00; 70.02; 70.04; 70.06; 70.08; 573.00; 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumor	195-199	C76-C80
AIDS	79.83	B21-B24
Atrial fibrillation	427.93; 427.94	I48

Abbreviations: ICD, International Classification of Diseases

TABLE S4. ICD-8 and ICD-10 diagnosis codes for identification psychiatric diseases

Disease name	ICD-8	ICD-10
Mental and behavioral disorders due to psychoactive substance abuse	291.x9, 294.39, 303.x9, 303.20, 303.28, 303.90, 304.x9	F10-F19
Schizophrenia and related disorders	295.x9, 296.89, 297.x9, 298.29-298.99, 299.04, 299.05, 299.09, 301.83	F20-F29
Mood disorders	296.x9 (excluding 296.89), 298.09, 298.19, 300.49, 301.19	F30-F39
Neurotic, stress-related, and somatoform disorders	300.x9 (excluding 300.49), 305.x9, 305.68, 307.99	F40-F48

Abbreviations: ICD, International Classification of Diseases

TABLE S5. The distribution of person-years in women with and without dementia by age-group and Charlson Comorbidity Index score

	Dementia											
	65–69 years		70–74 years		75–79 years		80–84 years		85–89 years		≥90 years	
CCI	Person-years	%	Person-years	%	Person-years	%	Person-years	%	Person-years	%	Person-years	%
0	2226	45.41	7434	43.66	13,877	39.85	20,650	37.69	22,384	37.36	16,725	38.56
1	866	17.67	3204	18.82	7379	21.19	12,612	23.02	14,168	23.65	10,453	24.10
2	764	15.59	2771	16.28	5968	17.14	9663	17.64	10,894	18.18	7776	17.93
3	377	7.69	1277	7.50	2999	8.61	5130	9.36	5666	9.46	4124	9.51
4	227	4.63	806	4.73	1737	4.99	2680	4.89	2976	4.97	2028	4.68
5	190	3.88	697	4.09	1257	3.61	1846	3.37	1799	3.00	1129	2.60
≥6	252	5.14	837	4.92	1609	4.62	2210	4.03	2024	3.38	1135	2.62
Total	4902	100	17,026	100	34,826	100	54,791	100	59,911	100	43,370	100
	No dementia											
	65–69 years		70–74 years		75–79 years		80–84 years		85–89 years		≥90 years	
CCI	Person-years	%	Person-years	%	Person-years	%	Person-years	%	Person-years	%	Person-years	%
0	1,030,827	64.81	696,717	58.16	463,391	51.67	305,154	46.50	179,019	42.54	100,520	40.88
1	209,179	13.15	18,553	15.15	153,841	17.15	122,216	18.63	83,969	19.95	53,022	21.56
2	210,075	13.21	178,423	14.89	144,978	16.16	113,540	17.30	76,190	18.10	45,648	18.56
3	57,325	3.60	58,956	4.92	56,857	6.34	49,792	7.59	36,935	8.78	23,018	9.36
4	33,870	2.13	33,251	2.78	31,591	3.52	27,120	4.13	19,339	4.60	11,220	4.56
5	27,090	1.70	25,309	2.11	22,227	2.48	18,234	2.78	12,124	2.88	6205	2.52
≥6	22,276	1.40	23,805	1.99	23,988	2.67	20,126	3.07	13,281	3.16	6256	2.54
Total	1,590,642	100	1,198,014	100	896,873	100	656,182	100	420,857	100	245,889	100

Abbreviations: CCI, Charlson Comorbidity Index

TABLE S6. The distribution of person-years in men with and without dementia by age-group and Charlson comorbidity index (CCI) score

	Dementia											
	65–69 years		70–74 years		75–79 years		80–84 years		85–89 years		≥90 years	
CCI	Person-years	%	Person-years	%	Person-years	%	Person-years	%	Person-years	%	Person-years	%
0	2103	38.40	5335	33.52	7842	31.00	9086	29.76	6954	29.42	3311	31.78
1	1179	21.53	3691	23.19	5834	23.06	6936	22.72	5564	23.54	2318	22.25
2	791	14.44	2564	16.11	4345	17.18	5539	18.14	4394	18.59	2071	19.88
3	455	8.31	1397	8.78	2575	10.18	3496	11.45	2789	11.80	1227	11.78
4	323	5.90	965	6.06	1654	6.54	2025	6.63	1564	6.62	629	6.04
5	252	4.60	715	4.49	1105	4.37	1408	4.61	1016	4.30	423	4.06
≥6	373	6.81	1251	7.86	1940	7.67	2044	6.69	1359	5.75	439	4.21
Total	476	100	15,918	100	25,295	100	30,534	100	23,640	100	10,418	100
	No dementia											
	65–69 years		70–74 years		75–79 years		80–84 years		85–89 years		≥90 years	
CCI	Person-years	%	Person-years	%	Person-years	%	Person-years	%	Person-years	%	Person-years	%
0	932,519	61.07	560,491	52.06	318,154	43.71	170,709	37.70	77,557	34.29	29,867	33.87
1	233,844	15.32	186,072	17.28	136,490	18.75	89,063	19.67	45,303	20.03	18,440	20.91
2	185,545	12.15	160,091	14.87	124,636	17.12	83,265	18.39	43,342	19.16	17,286	19.60
3	65,664	4.30	65,754	6.11	58,865	8.09	44,833	9.90	25,314	11.19	10,054	11.40
4	44,203	2.90	40,752	3.79	34,553	4.75	26,062	5.76	14,601	6.46	5715	6.48
5	30,012	1.97	27,921	2.59	23,537	3.23	16,988	3.75	8829	3.90	3192	3.62
≥6	35,069	2.30	35,583	3.30	31,693	4.35	21,895	4.84	11,246	4.97	3628	4.11
Total	1,526,856	100	1,076,664	100	727,928	100	452,815	100	226,192	100	88,182	100

TABLE S7. Sensitivity analysis including only incident cases of dementia from January 1, 2006 to December 31, 2015. Mortality rate ratios are presented for women and men in five-year age strata and an age-adjusted average. In each of the three models presented, the reference is defined as 1.00 for women and men without dementia in each of the five-year age stratum.

	Model 1 **Adjusted for age and calendar year**		**Model 2** **Adjusted for age, calendar year and psychiatric conditions**		**Model 3** **Adjusted for age, calendar year, and psychiatric and chronic somatic conditions**	
	Women with dementia		**Women with dementia**		**Women with dementia**	
Age	**MRR**	**95% CI**	**MRR**	**95% CI**	**MRR**	**95% CI**
Age-adjusted average	2.75	(2.71, 2.78)	2.64	(2.60, 2.67)	2.54	(2.50, 2.57)
65–69 years	5.47	(4.87, 6.15)	4.04	(3.59, 4.55)	2.79†	(2.48, 3.14)
70–74 years	5.25	(4.96, 5.56)	4.44	(4.19, 4.70)	3.08‡	(2.91, 3.27)
75–79 years	4.05	(3.90, 4.20)	3.70	(3.56, 3.84)	3.06‡	(2.95, 3.19)
80–84 years	3.27	(3.18, 3.37)	3.14	(3.05, 3.23)	2.90‡	(2.82, 2.98)
85–89 years	2.67	(2.61, 2.73)	2.61	(2.55, 2.67)	2.53‡	(2.47, 2.59)
≥90 years	2.11	(2.07, 2.16)	2.09	(2.04, 2.14)	2.06‡	(2.01, 2.10)
	Men with dementia		**Men with dementia**		**Men with dementia**	
Age	**MRR**	**95% CI**	**MRR**	**95% CI**	**MRR**	**95% CI**
Age-adjusted average	3.11	(3.06, 3.16)	2.97	(2.92, 3.01)	2.83	(2.79, 2.88)
65–69 years	5.42	(4.96, 5.93)	4.29	(3.92, 4.69)	3.30‡	(3.02, 3.61)
70–74 years	4.59	(4.36, 4.83)	4.01	(3.81, 4.23)	3.34‡	(3.18, 3.52)
75–79 years	3.98	(3.84, 4.12)	3.73	(3.60, 3.87)	3.41‡	(3.29, 3.54)
80–84 years	3.26	(3.17, 3.36)	3.16	(3.07, 3.26)	2.96‡	(2.87, 3.05)
85–89 years	2.77	(2.69, 2.85)	2.72	(2.64, 2.80)	2.64‡	(2.56, 2.72)
≥90 years	2.27	(2.19, 2.35)	2.25	(2.17, 2.33)	2.22‡	(2.15, 2.30)

†Leukemia, lymphoma, and AIDS has been excluded from the model due to low sample size. ‡AIDS has been excluded from the model due to low sample size. Abbreviations: MRR, mortality rate ratio.

Study IV

Causes of death in people with dementia:

A national registry-based study over 14 year

Causes of death in people with dementia from 2002 to 2015: A nationwide study

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ABSTRACT

Background: Dementia is associated with increased mortality. However, it is not clear whether causes of death in people with dementia have changed over time.

Objective: To investigate if causes of death changed over time in people with dementia compared to the general elderly population.

Methods: We included longitudinal data from nationwide registries on all Danish residents aged ≥65 years to 110 years who died between 2002 to 2015. We assessed the annual frequency of dementia-related deaths (defined as a dementia diagnosis registered as a cause of death) and of underlying causes of death in people registered with dementia compared to the general elderly population.

Results: From 2002 to 2015, 621,826 people died, of whom 103,785 were diagnosed with dementia. During this period, the percentage of dementia-related deaths increased from 10.1% to 15.2% in women, and from 6.3% to 9.5% in men in the general elderly population. From 2002 to 2015, dementia became the leading, registered underlying cause of death in people with dementia. Simultaneously, a marked decline in cardiovascular and cerebrovascular deaths was observed in people with and without dementia.

Conclusion: This is the first study to investigate if the causes of death change over time in people with dementia compared with the general elderly population. The increase in the registration of dementia as an underlying cause of death could reflect increasing awareness of dementia as a fatal condition.

INTRODUCTION

Dementia was the third leading cause of death in high-income countries in 2016 [1]. From 2000–2015, the number of estimated deaths from dementia more than doubled, making dementia the seventh leading cause of death globally in 2015 [2]. In the United Kingdom and Australia, dementia has become the leading cause of death in women [3,4]. Thus, dementia as a registered cause of death is increasing globally, while the number of people living with dementia is rapidly increasing [5]. However, only few studies have reported nationwide age-specific time trends for dementia-related deaths [6]. Since mortality and dementia risk increase with age, performing an age-specific time trend analysis of dementia-related deaths is important to identify which age groups contribute to the observed increase in dementia-related deaths.

While the number of dementia-related deaths is increasing, dementia may be underreported as cause of death in people with a known dementia disorder [7]. A review based on seven population-based studies included people with dementia and concluded that only 7.2%–41.8% had a dementia diagnosis registered on their death certificates [7]. It also found that people with Alzheimer's disease were more likely to have a dementia diagnosis registered on their death certificates than people with unspecific dementia or vascular dementia [7].

The literature is quite consistent when investigating registered causes of death in people with dementia. Studies based on data from death certificates list, besides dementia, the most frequent causes of death as either cardiovascular disease or pneumonia/respiratory diseases [8–11]. Even though the literature is quite consistent when reporting causes of death in people with dementia, no previous studies have investigated if a change has occurred over time.

Thus, the objective of this study was to perform a thorough descriptive time trend analysis assessing population-based data on dementia-related causes of death in the general elderly population as well as in people with dementia using national registry data on the entire Danish population.

METHODS

Study design, study period and study population

The study used a cohort design. We defined the study period from January 1, 2002 to December 31, 2015. We chose the first year to be 2002, as new procedures for coding causes of death was introduced this year. All Danish residents aged ≥65 years to 110 years who died within the 14-year period were included.

Data sources

Data was provided by the: 1) the Danish Civil Registration System [12]; 2) National Patient Registry [13]; 3) Central Psychiatric Register [14]; 4) National Prescription Registry [15]; 5) Danish Register of Causes of Death [16]; and 6) Statistics Denmark. Since 1968, all Danish residents have been assigned a unique, personal identification number that enables linkage of personal data from different registries [17].

The Danish Register of Causes of Death includes data on all deaths among Danish residents occurring in Denmark since 1970 [16]. Medical doctors fill out the death certificates and, since 1994, causes of death have been registered according to the International Classification of Diseases, 10th Revision (ICD-10) [16]. The causes of death are listed as a chain of events: 1) the immediate cause of death, 2) up to two (optional) contributing causes of death, and 3) the underlying cause defined as the disease or condition leading to death. Furthermore, up to four contributing conditions or diseases can be listed as contributing causes of death. These are defined as conditions that may have led to reduced resistance or increased vulnerability, putting the person at higher risk due to the conditions causing death. In solely 2002 and 2005, five additional contributing causes of death could be listed on death certificates. In 2002, the Danish National Board of Health introduced a new international decision-making tool, the Automated Classification of Medical Entities (ACME), for coding causes of death [16]. Using decision-making tables based on an international standard, ACME determines the underlying cause of death by deciding if a causal link can be established between the immediate, contributing, and underlying cause of death [18]. In cases where ACME has been shown to be imprecise, coding specialists manually evaluated selected groups of causes of death. Since 2007, death certificates have been electronically submitted in Denmark.

The other above-mentioned registries have been described previously elsewhere [19]. All data were made available through Statistics Denmark, which also provided data on immigration, civil status, and date of death.

Identification of people with dementia

Dementia was defined as either a registered dementia diagnosis (primary or secondary) in the Danish National Patient Registry or the Psychiatric Central Research Register (Appendix, Table 1A presents the diagnostic codes) or based on filling an antidementia drug prescription while alive (Appendix, Table 2A presents the Anatomical Therapeutic Chemical codes). As we wished to investigate death in late-onset dementia, dementia was defined as being registered in people ≥65 years, while people registered with a dementia diagnosis <65 years were excluded.

Causes of death

When investigating dementia-related deaths using death certificate data, we applied the list of ICD-10 codes as used when diagnosing dementia in people while still alive (Appendix, Table 1A). The underlying cause of death was defined as the ACME code. Contributing causes of death were defined as any of the ICD-10 codes listed as either immediate cause of death, any contributing causes of deaths, or underlying cause of death if it was different from the ACME code.

When investigating the underlying causes of death in people diagnosed with dementia compared with the general elderly population, the underlying cause of death was defined as the ACME code. Causes of death were divided into nine categories of natural causes: 1) dementia; 2) cardiovascular disease; 3) cerebrovascular disease; 4) cancer; 5) pneumonia; 6) chronic respiratory diseases; 7) genitourinary diseases; 8) gastrointestinal diseases; and 9) other causes of death and unnatural causes of death. Furthermore, we made a category for people without a registered cause of death.

Demographic variables

Age at death was defined as a continuous variable. Calendar year was defined as the year of death and as a continuous variable. Civil status at time of death was defined as: 1) married/civil partnership/separated; 2) single/ divorced; or 3) widowed. Load of comorbidity was assessed using the Charlson Comorbidity Index (CCI) score on the day of death, where dementia was excluded from the standard CCI version [20].

Statistical analysis

Since our data comprises an entire population as opposed to a sample, a difference in, e.g., percentage of a distribution in two different groups, describes an actual difference.

We assessed the time trend of dementia-related deaths as the annual percentage of all deaths in the population. These analyses were carried out for women and men in five-year age strata (65-69 years, 70-74 years, 75-79 years, 80-84 years, 85-89 years, and ≥90 years). The stratification in five-year age groups ensured that different calendar trends in age at death in the general population and among persons with dementia did not affect the results. Additionally, we assessed the annual distribution of dementia registered as underlying versus contributing cause of death in women and men in ten-year age groups (65-74 years, 75-84 years, and ≥85 years). The same analyses were performed in people diagnosed with dementia.

Furthermore, we assessed the annual distribution as percentages of underlying causes of death in ten-year age groups (65-74 years, 75-84 years, and ≥85 years) in women and men registered with dementia compared with women and men in the general elderly population from 2002 to 2015. If a cause of death had ≤5 observations a year, we combined the cause of death categories to preserve anonymity. Finally, we

assessed the total number of people whose first dementia diagnoses was given on their death certificates during the study period.

All analyses were carried out using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Data approvals

This study was approved by the Danish Data Protection Agency, Statistics Denmark, and the Danish Health and Medicines Authority. As all data comprised anonymized registry data, no ethical approval was needed, according to Danish law.

RESULTS

During the study period, 621,826 people died (women: 333,857; men: 287,969), of whom 103,785 were registered with dementia diagnoses prior to death (women: 64,879; men: 38,906).

In the total population, 65,012 (10.5%) people were registered with dementia as a cause of death (underlying: 36,181; contributing: 28,831). Dementia-related deaths were more frequent in women (12.7%) compared with men (7.9%). On average, from 2002 to 2015, the median age at death was 87.4 years (95% CI: 82.8; 91.5) in women with dementia, and 84.4 (95% CI: 79.6; 88.6) in men with dementia. From 2002 to 2015, median age at death increased more in the dementia groups compared with women and men without dementia (Supplementary Table 1). At time of death, 15.5% of women with dementia and 50.9% of men with dementia were married, while 69.7% of women with dementia were widowed and only 16.6% of men with dementia were widowed.

Dementia-related deaths in the general elderly population

From 2002 to 2015, the percentage of dementia-related deaths increased for women and men ≥70 years (Figure 1). The percentage of dementia-related deaths increased with age; however, this seemed to stabilize at age ≥85 as the time trend graphs were similar for men and women for the age groups 85-89 and ≥90 years. In people ≥75 years, the percentage of dementia-related deaths was higher in women compared with men.

During the study period, there was an increase in the registration of dementia as an underlying cause of death as opposed to a contributing cause of death (Figure 2). From 2002 to 2015, the percentage of dementia-related deaths increased from 10.1% (underlying: 4.6%) to 15.2% (underlying: 10.2%) in women, and from 6.3% (underlying: 2.5%) to 9.5% (underlying: 5.8%) in men. For women and men of all age groups,

the percentage of contributing cause of death was quite stabile, while the increase in percentage of underlying cause of death primarily explained the overall increase in dementia-related deaths. The percentage of dementia-related deaths increased with age in both men and women (Supplementary Figures 1 and 2).

Table 1. Descriptive distribution of demographics in complete population, and women and men with dementia

	Complete population	**Women with dementia**	**Men with dementia**
Number (%)	621,826	64,879 (62.5%)	38,906 (37.5%)
Median age at death (interquartile range)	82.5 (75.5– 88.6)	87.4 (82.8–91.5)	84.4 (79.6–88.6)
Marital status			
married (%)	214,352 (34.5%)	9,431 (14.5%)	19,799 (50.9%)
divorced/ single (%)	111,311 (17.9%)	10,218 (15.8%)	6101 (15.7%)
widowed (%)	285,434 (45.9%)	45,199 (69.7%)	12,969 (33.3%)
missing (%)	10,729 (2.1%)	31 (0.1%)	37 (0.1%)
Median CCI score at time of death (interquartile range)	2 (1–5)	1 (0–3)	2 (1–4)

Abbreviation: CCI, Charlson Comorbidity Index

FIGURE 1. Time trend of dementia-related deaths, 2002–2015

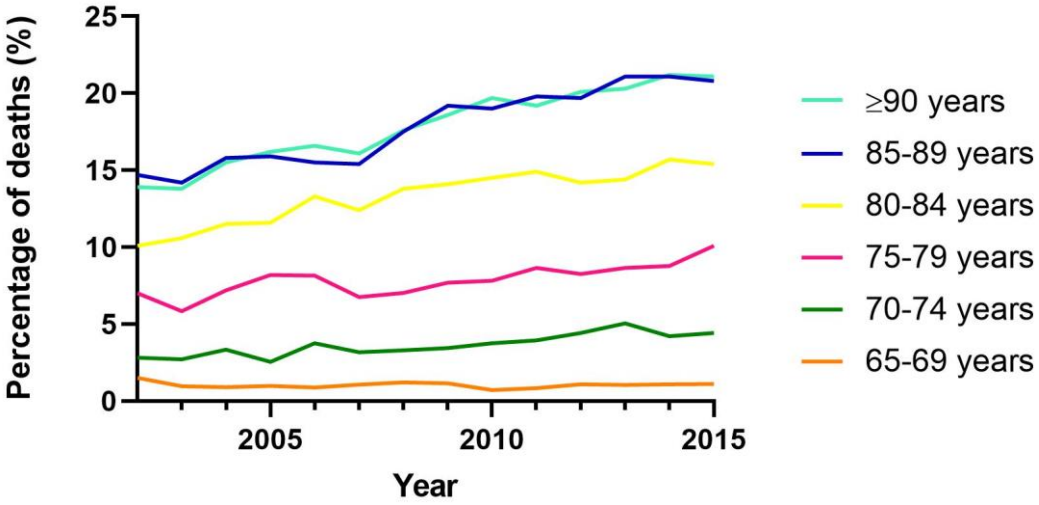


Figure 1A. Time trend of dementia-related deaths as a percentage of all deaths in women divided into five-year age groups

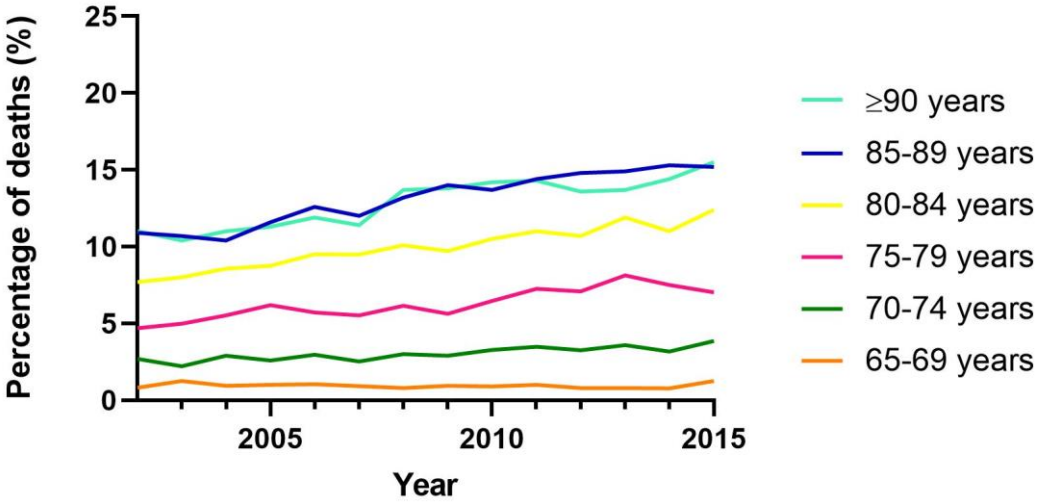


Figure 1B. Time trend of dementia-related deaths as a percentage of all deaths in men divided into five-year age groups

Dementia-related deaths in people registered with dementia

In people diagnosed with dementia, the percentage of registered dementia-related deaths increased from 41.9% (underlying: 20.6%) to 56.2% (underlying: 38.4%) in women, and from 39.2% (underlying: 15.9%) to 53.2% (underlying: 33.3%) in men from 2002 to 2015 (Figure 3). The percentage of causes of death registered as dementia increased with age in both women and men (Supplementary Figures 3 and 4)

Causes of death in people with and without dementia

The leading underlying causes of death in women with dementia were dementia (29.9%), cardiovascular disease (18.7%), and cerebrovascular disease (10.6%), whereas in women without dementia, the leading causes were cancer (26.8%), cardiovascular disease (23.3%), and cerebrovascular disease (8.7%). In men with dementia, the leading underlying causes of death were dementia (24.3%), cardiovascular disease (19.2%), and cerebrovascular disease (11.1%), while in men without dementia, the leading underlying causes of death were cancer (31.5%), cardiovascular disease (24.1%), and respiratory disease (7%).

From 2002 to 2015, there was a change in the distribution of registered causes of death both in people with and without dementia (Figure 4). During the period, dementia became the leading underlying cause of death in women and men diagnosed with dementia. The proportions of cardio- and cerebrovascular disease as underlying cause of death declined for all women and men, though more markedly in women and men with dementia. The registration of cancer as underlying cause of death increased markedly in women and men without dementia, whereas in women and men with dementia, there was only a modest increase.

In women and men with dementia, the percentage of pneumonia as the underlying cause of death declined, but was quite stable in women without dementia, though it increased in men without dementia. However, in 2015, pneumonia as the underlying cause of death was still more frequent in men with dementia (5.1%) compared with men without dementia (3.7%), while in women the frequency was similar (dementia: 4.1%; no dementia: 3.9%).

There were 12,650 people (2%) without a registered underlying cause of death, and this was more frequent in people without dementia (n=12,537) compared with people with dementia (n=113).

The Supplemental material presents the time trend of underlying causes of death in men and women with and without dementia in ten-year age groups (Supplementary Figures 5 and 6).

During the 14-year study period, 14,593 people (women: 9,964, men: 4,629) were registered with their first-ever dementia diagnosis on their death certificates (Supplementary Tables 2 and 3), which is equivalent to 24.3% of all registered dementia-related deaths.

FIGURE 2. Time trend of the distribution of dementia-related deaths in the general elderly population

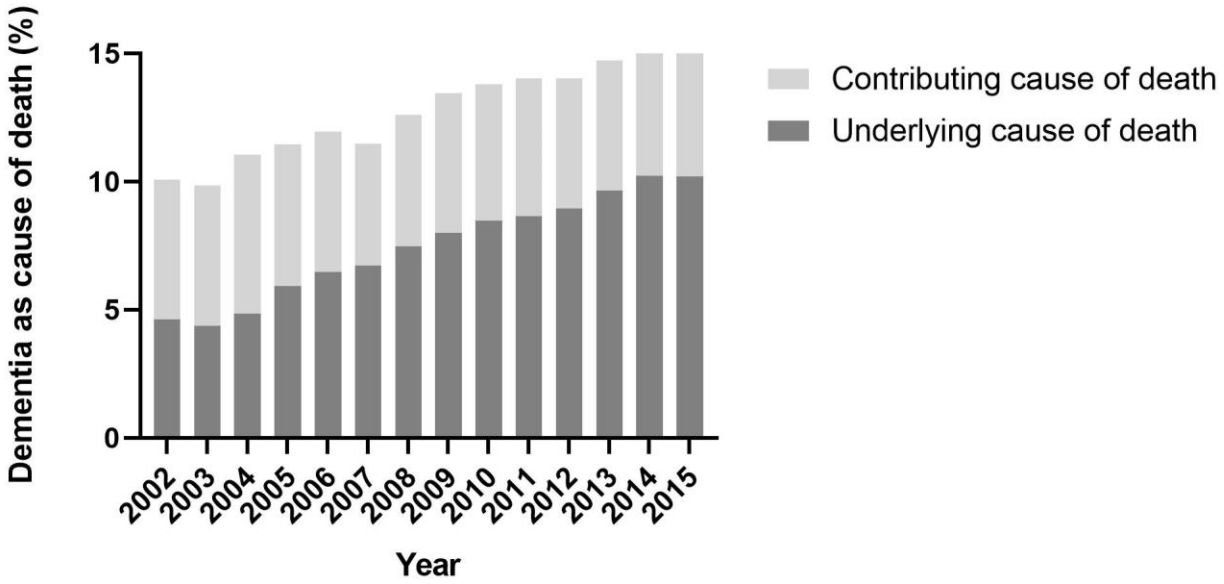


Figure 2A. Time trend of the distribution of dementia-related deaths registered as contributing or underlying in women in the general elderly population

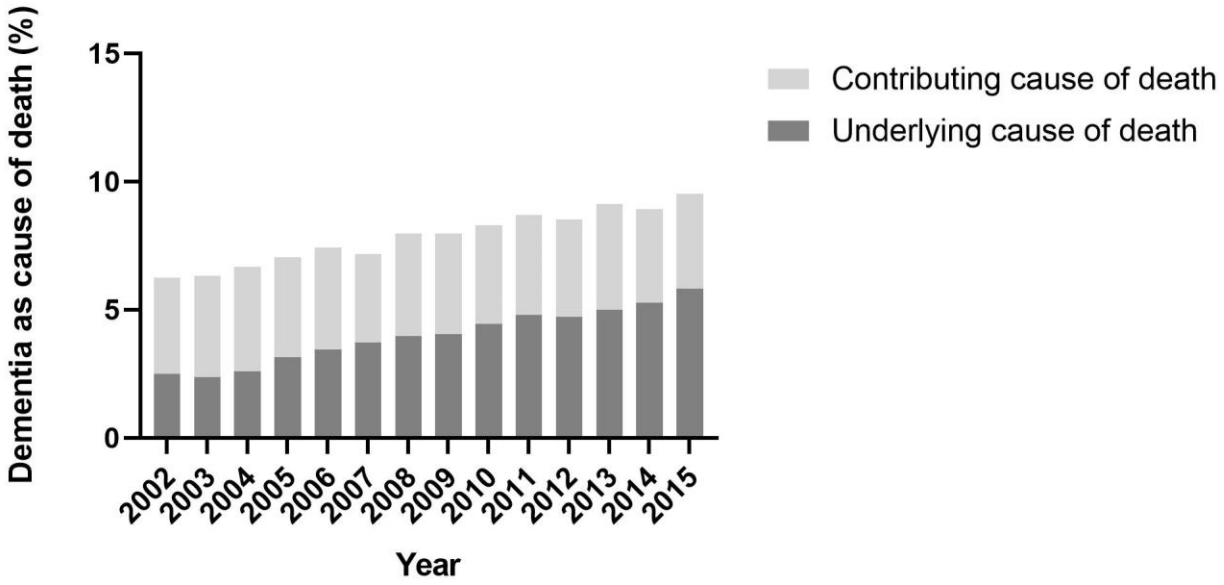


Figure 2B. Time trend of the distribution of dementia-related deaths registered as contributing or underlying in men in the general elderly population

FIGURE 3. Time trend of the distribution of dementia-related deaths in women and men with dementia

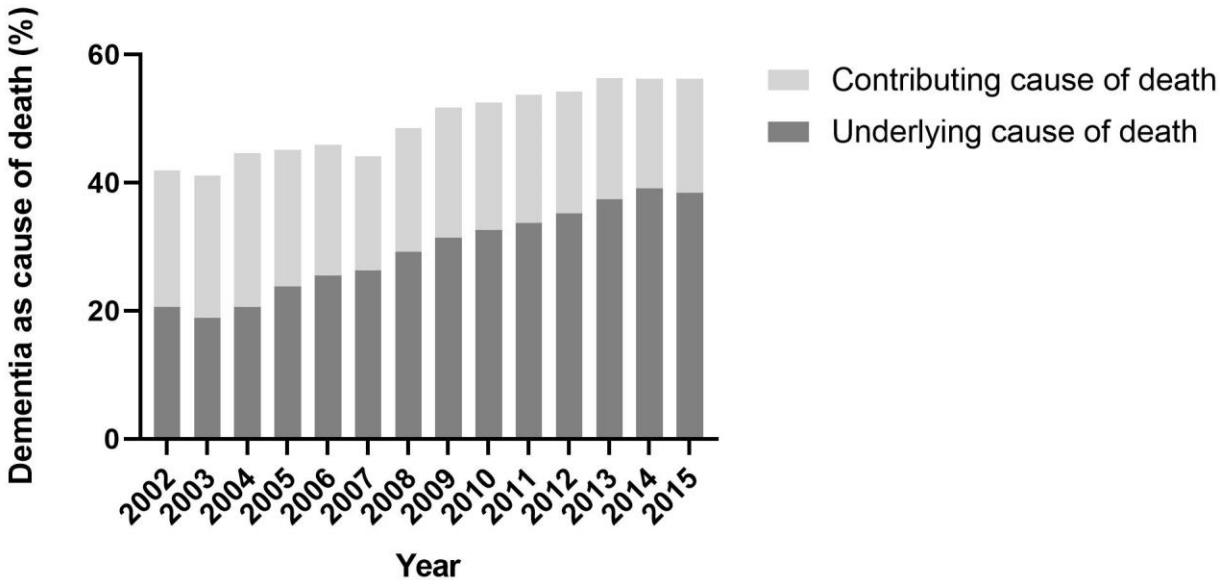


Figure 3A. Time trend of the distribution of dementia-related deaths registered as contributing or underlying in women with dementia

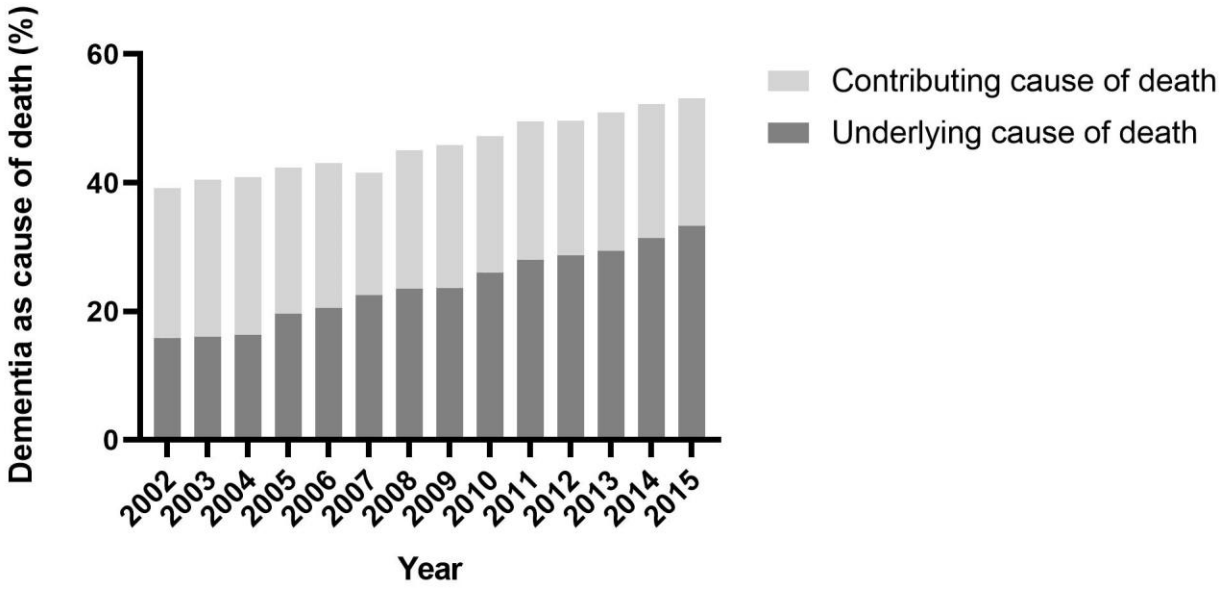
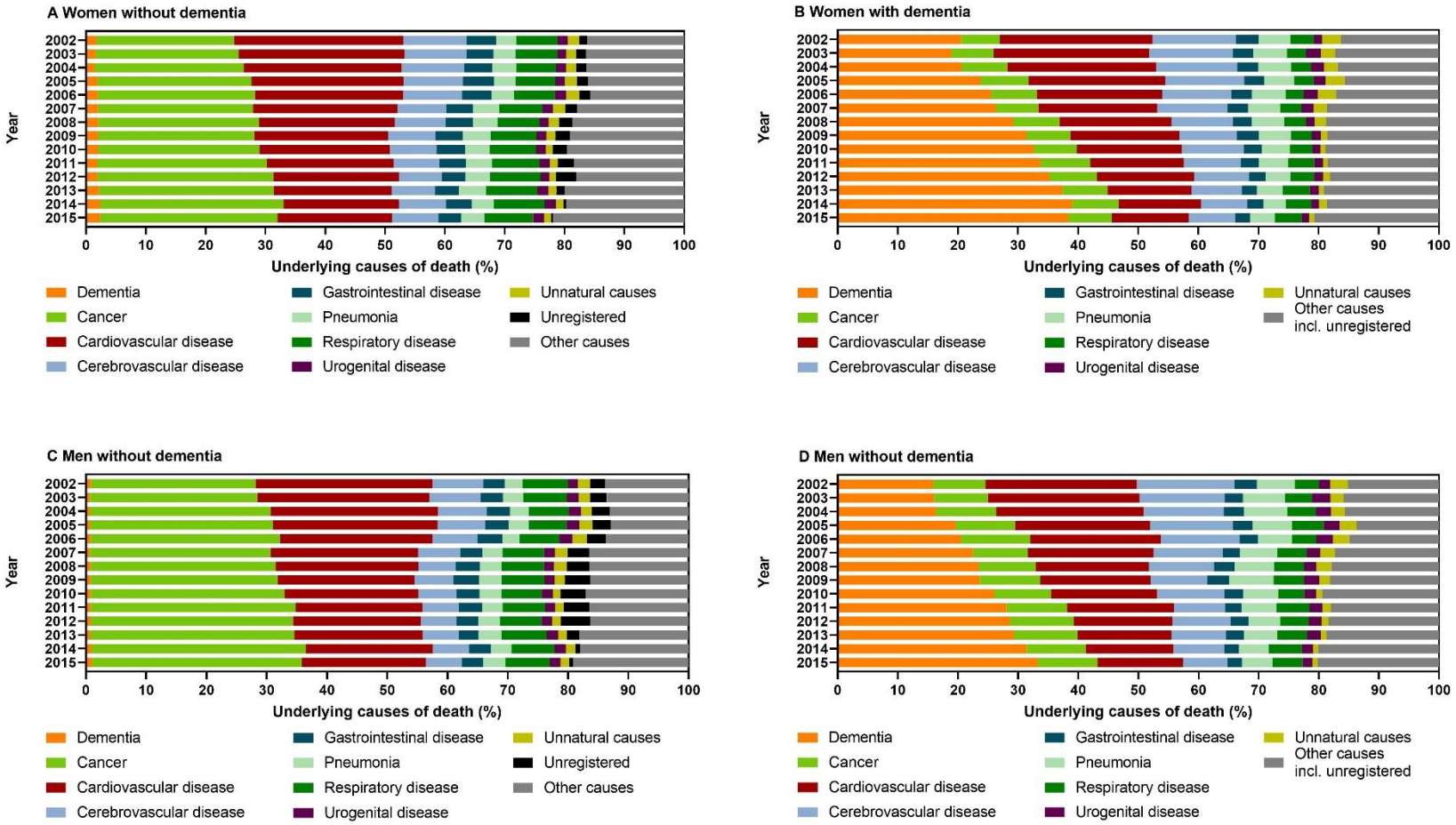


Figure 3B. Time trend of the distribution of dementia-related deaths registered as contributing or underlying in men with dementia

Table 2. The distribution of causes of death (dementia-related versus other causes) in women and men not diagnosed with dementia, diagnosed with dementia, and all women and men

	Women			**Men**		
	Not diagnosed with dementia	Diagnosed with dementia	All women	Not diagnosed with dementia	Diagnosed with dementia	All men
Dementia-related causes of death (%)	10,131	32,277	42,408	4665	17,939	22,604
	(3.03%)	(9.67%)	(12.7%)	(1.62%)	(6.23%)	(7.85%)
Other causes of death (%)	258,847	32,602	291,449	244,398	20,967	265,365
	(77.53%)	(9.77%)	(87.3%)	(84.87%)	(7.28%)	(92.15%)
Total (%)	268,978	64,879	333,857	249,063	38,906	287,969
	(80.57%)	(19.43%)	(100%)	(86.49%)	(13.51%)	(100%)

FIGURE 4. Time trend of the distribution of registered underlying causes of death in women and men with and without dementia



DISCUSSION

This is the first study to investigate the time trends of a range of underlying causes of death in people with dementia. During the study period, dementia became the leading underlying cause of death in people with dementia. From 2012 to 2015, cardio- and cerebrovascular disease as an underlying cause of death declined even more markedly in women and men with dementia compared to those without. Cancer was registered less frequently as the underlying cause of death in people with dementia compared with the general elderly population, and only increased very modestly in people with dementia compared with elderly people without dementia. In the general elderly population, the proportion of dementia-related deaths increased markedly from 2002 to 2015. This was primarily driven by an increase in the registration of dementia as an underlying cause of death. In people diagnosed with dementia, we observed the same pattern of an increase in registering dementia as an underlying cause of death.

To the best of our knowledge, since no previous studies have investigated if the causes of death change over time in people with dementia, our findings cannot be compared with other studies. Since ischemic heart disease and dementia share common risk factors, we believe that the reduction in cardio- and cerebrovascular disease as the underlying cause of death in people with dementia observed in our study could be related to a reduction in risk factors and an improvement in the treatment of cardiovascular risk factors [21]. This assumption is supported by the fact that the Framingham Heart Study, which reported a decline in the incidence of dementia, also reported a decline in vascular risk factors from the late 1970s to the early 2010s [21]. It also found that the risk of dementia associated with stroke, atrial fibrillation, and heart failure decreased over time [21]. In Denmark, there was a marked improvement in the organization of treatment and an increase in the use of pharmacotherapy after myocardial infarction from 1997–1998 to 2009–2010, and the 90-day mortality decreased from 19.6% to 11.7% [22].

Autopsy studies are consistent in reporting pneumonia as the leading immediate cause of death (38%-66%) in people with dementia [23–27]. Also, studies based on death certificates identified pneumonia as a leading underlying cause of death in people with dementia [8,10,11,28]. A meta-analysis found that people with dementia had higher odds (OR = 2.2; 95% CI: 1.44; 3.42) of dying from pneumonia compared with people without dementia [29]. Thus, we hypothesized that our study would confirm these findings. However, in our study, pneumonia was only registered as an underlying cause of death in 4.1% of women and 5.1% of men with dementia in 2015, making it comparable in women with and without dementia. Autopsy studies may show a clear difference in results because they primarily list the immediate cause of death. Studies based on death certificates, in contrast, either registered the underlying cause of death or multiple causes of death. Such studies show markedly lower prevalence of pneumonia as a cause of death,

compared to autopsy studies. In our study, the percentage of people with dementia as the underlying cause of death was markedly lower compared to other studies, perhaps because of increased awareness of dementia as a cause of death.

In our study, cancer was less likely to be registered as the underlying cause of death in people with dementia compared to the general elderly population, which is in line with findings from other studies [8,10,30]. The question can be asked whether people with dementia less frequently die from cancer, or whether there is a reluctance to diagnose cancer in people with dementia. One autopsy study reported that cancer was less frequent in people with dementia [24], while another found that 7% of the deceased with dementia had unregistered clinically undiagnosed neoplasms [27]. Thus, it is unclear whether cancer is underdiagnosed in dementia.

This study observed an increase in the registration of dementia as a cause of death, which is in line with findings from other studies [6,31]. A UK study reported that in people with clinically diagnosed dementias, the percentage of dementia registered as cause of death increased from 39.9% in 2006 to 63.0% in 2013, but the study did not report other causes of death [31]. We also observed that during the study period, dementia was more likely to be registered as an underlying cause of death as opposed to a contributing cause, which is in line with findings from a national Norwegian study [6]. We find this change interesting, as it may reflect a changing medical view on dementia, and a paradigm shift towards perceiving that dementia is fatal. We believe our study emphasizes that dementia is underreported as a cause of death, and this calls for further improvements.

In our previous study involving a time-trend analysis of all-cause mortality in dementia, we found that the mortality rate, assessed as mortality rate ratios, declined at the same rate as in the general elderly population from 1996 to 2015 [32]. Some studies, however, base time trends in mortality on data from death certificates. This study underpins why this can be problematic. If we used the results from this study to evaluate dementia mortality rates, we would observe an increase primarily related to the increase in recordings of dementia as a cause of death on death certificates.

Limitations

The most critical limitation of this study is that the data available from the Danish Register of Causes of Death has not been validated in autopsy studies. The most accurate way to establish causes of death is by performing autopsies, and the autopsy rate in Denmark is below 10% [16]. Thus, the data from death certificates depends on the individual doctor and on changes in recommendations about which diagnostic

codes should be prioritized [16]. We handled this limitation by dividing causes of death into more broadly defined disease groups instead of using single diagnostic codes as outcomes.

Because dementia is a syndrome with many different etiologies, causes of death have been shown to vary with different dementia subtypes, both in studies based on death certificates [8,33] and autopsies [23,24]. Thus, optimally, it would have been best to assess causes of death by dementia subtypes. Unfortunately, though the validity of diagnoses for dementia syndrome is high, the subtype diagnoses are not accurate enough [34].

Dementia is underreported in the Danish health registries. A study estimated that in 2015, there were approximately 87,000 people in Denmark with dementia [35]. In our previous study, we were nevertheless only able to identify 36,129 people with dementia in 2015 using the same methodology as in this study [19]. Thus, we know that dementia is underreported in the national registries, which was emphasized by the fact 14,593 people were identified by registration with a first-time dementia diagnosis in the national registries on their death certificates from 2002 to 2015. We believe some patients are diagnosed by their general practitioner but diagnoses from the primary health care sector are not included in Danish national registries.

Strengths

This study comprised a large nationwide cohort, which made it possible to assess if the causes of death changed over time. Using the national healthcare registries, we were able to identify people with dementia and make comparisons with the entire general elderly population without dementia. This was possible because the use of diagnoses for dementia syndrome in the Danish registries have been validated and found to be correct 85.6% of the time [34]. Last, the number of deceased without a registered underlying cause of death was low (2%).

Conclusion

This is the first study to investigate if causes of death change over time in people with dementia. From 2002 to 2015, dementia became the most frequently registered underlying cause of death in people with dementia. Additionally, dementia was more likely to appear as an underlying cause of death as opposed to a contributing cause in the latter years of the study period. We believe that this shift may reflect a positive change in diagnostic procedures and in perceiving dementia not only as a disease that contributes to mortality but as a disease that is actually fatal. Even though we observed an increase in the use of dementia as cause of death, we believe that dementia is still underreported on death certificates and that more can be done to increase awareness that dementia is fatal.

ACKNOWLEDGEMENTS

The authors thank the Danish Ministry of Health for supporting the Danish Dementia Research Centre.

CONFLICTS OF INTEREST

The authors have nothing to declare.

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Appendix

TABLE A1. ICD-8 and ICD-10 diagnosis codes for identification of dementia

Disease name	**ICD-8**	**ICD-10**
Alzheimer's disease	290.10	F00.0-00.9; G30.0-30.9
Vascular dementia	293.09-19	F01.0-01.9
Frontotemporal dementia	290.11	F02.0
Dementia without specification	290.09; 290.19	F03.9; G31.9
Other dementias	290.18	G31.8

Abbreviation: ICD, International Classification of Diseases

TABLE A2. Anatomical Therapeutic Chemical (ATC) codes for identification of pharmaceutical treatment of dementia

Drug name	**ATC code**
Memantine	N06DX01
Donepezil	N06DA02
Rivastigmine	N06DA03
Galantamine	N06DA04

TABLE A3. ICD-10 codes for categorizing causes of death. For these analyses only the underlying cause of death, defined here as the Automated Classification of Medical Entities generated code, was used.

Disease category	ICD-10 codes
Dementia	F00.0-9, F01.0-9, F02.0, F03.9, G30.0-9, G31.8-9
Cardiovascular disease	I00-I59, I70-I99 R00-R01, Q20-Q28
Cerebrovascular disease	I60-I69
Cancer	C00-C96
Pneumonia	J10- J22
Chronic respiratory diseases	J40-J47
Genitourinary diseases	N00-N98, R30-R39
Gastrointestinal diseases	K00-K93, R10-R19
Unnatural causes	F11-F16, F19, F55, V00-X44, X50-X99, Y00-Y39, Y85-87.1, Y88-89
Other causes of death	All remaining codes

Abbreviation: ICD, International Classification of Diseases

Study IV

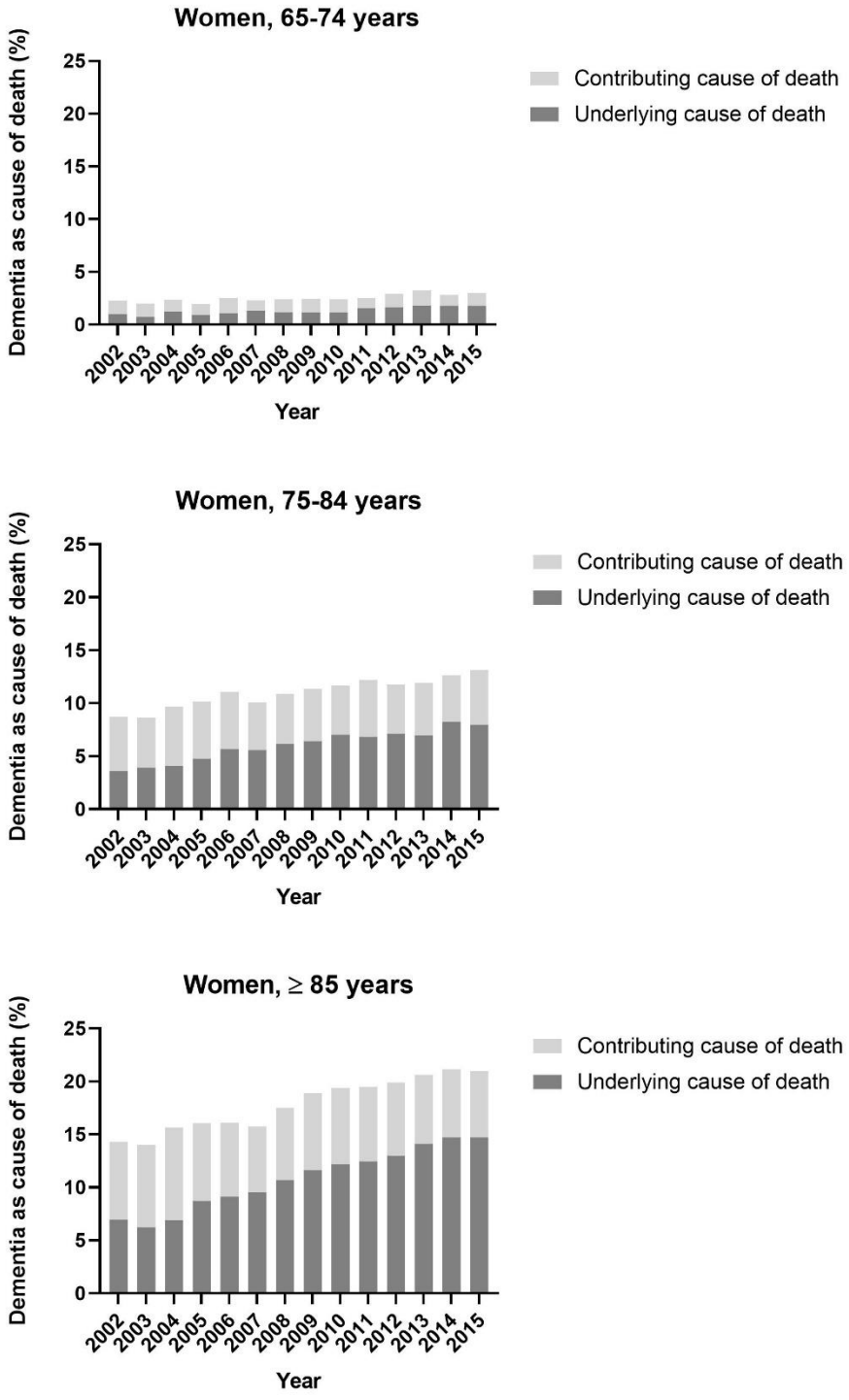
Causes of death in people with dementia:

A national registry-based study over 14 years

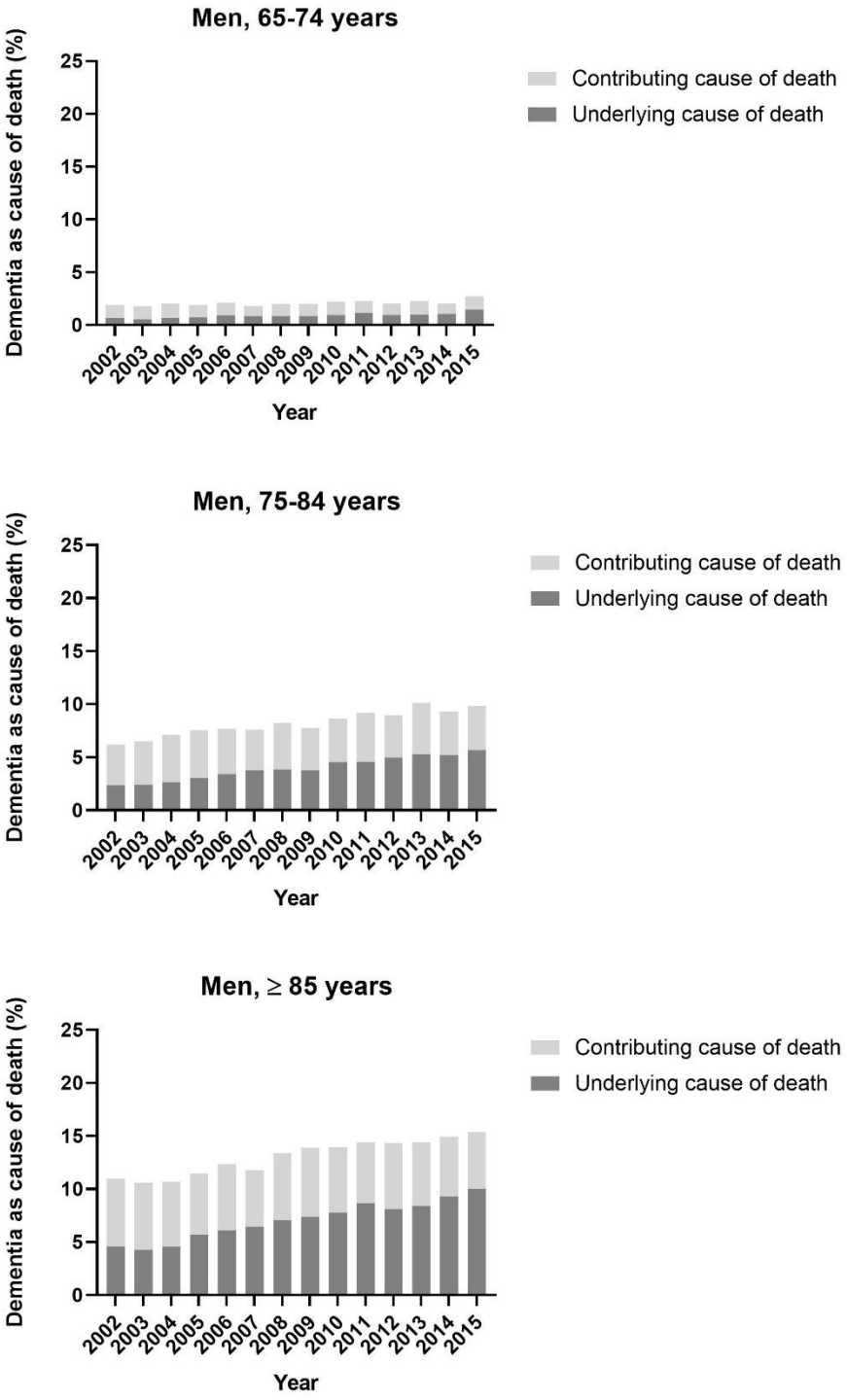
Supplementary Material

Supplementary material

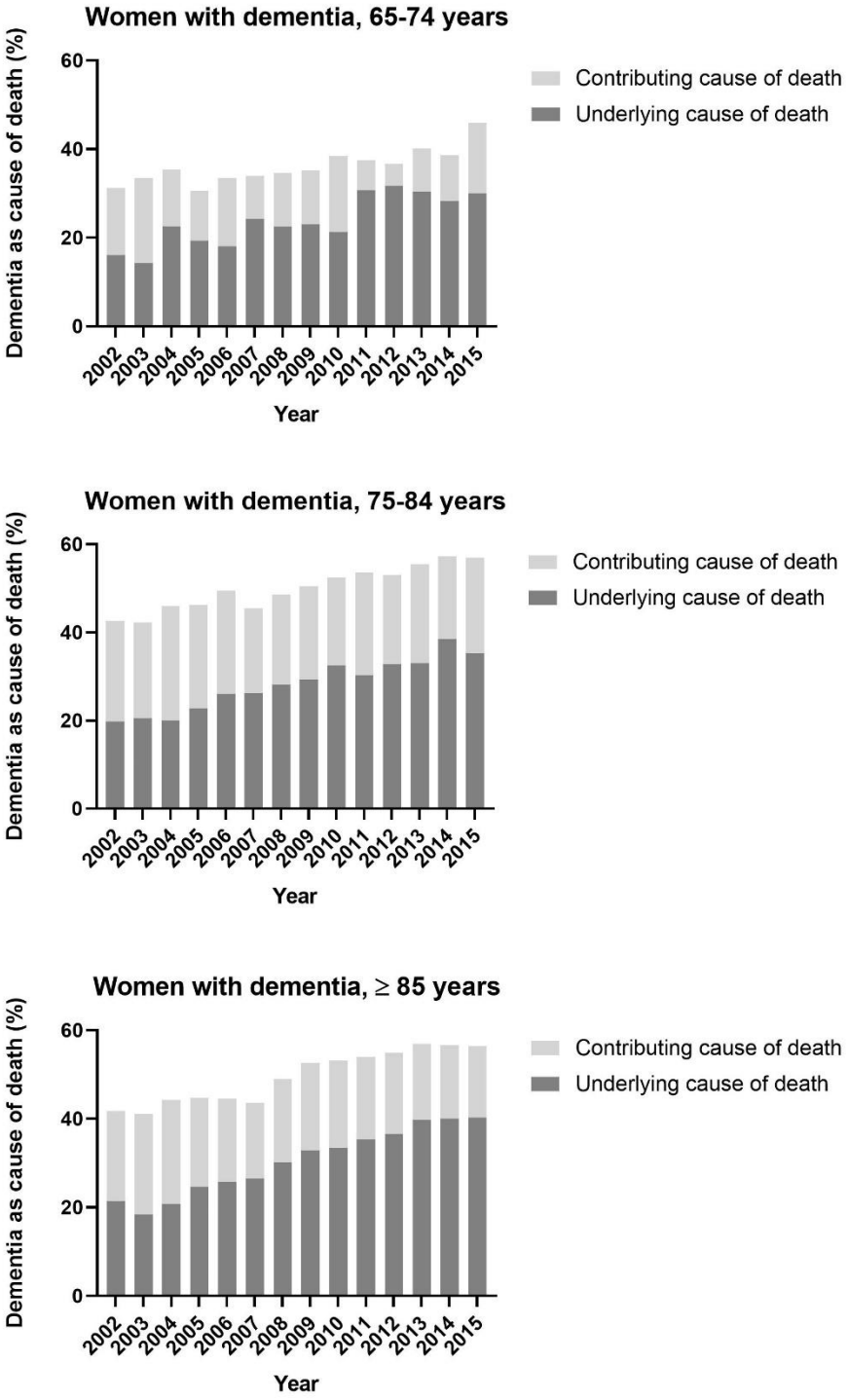
Supplementary Figure 1. Time trend of the distribution of dementia-related deaths registered as contributing or underlying cause of all deaths in women in the general elderly population divided into three age groups



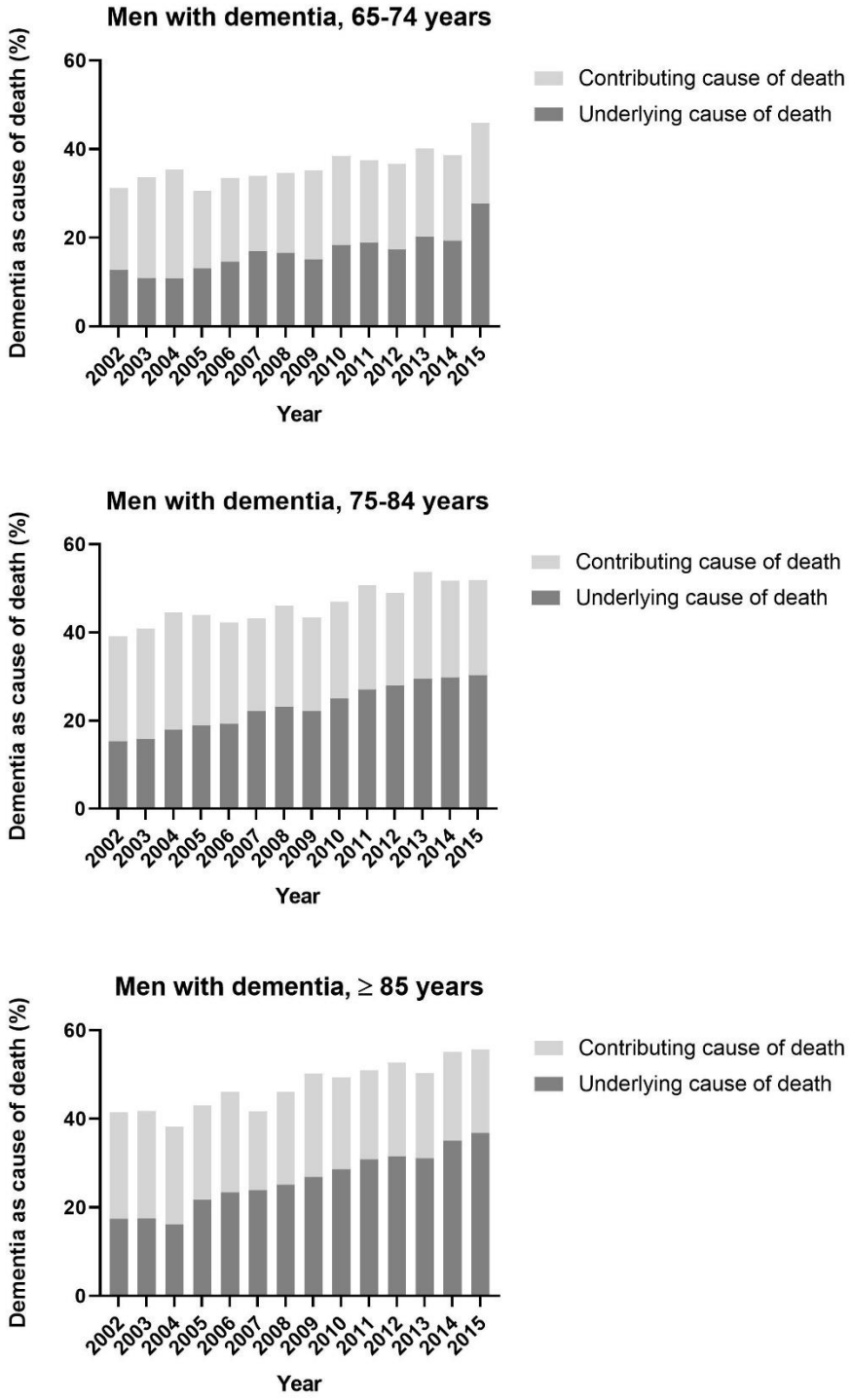
Supplementary Figure 2. Time trend of the distribution of dementia-related deaths registered as contributing or underlying causes of all deaths in men in the general elderly population divided into three age groups



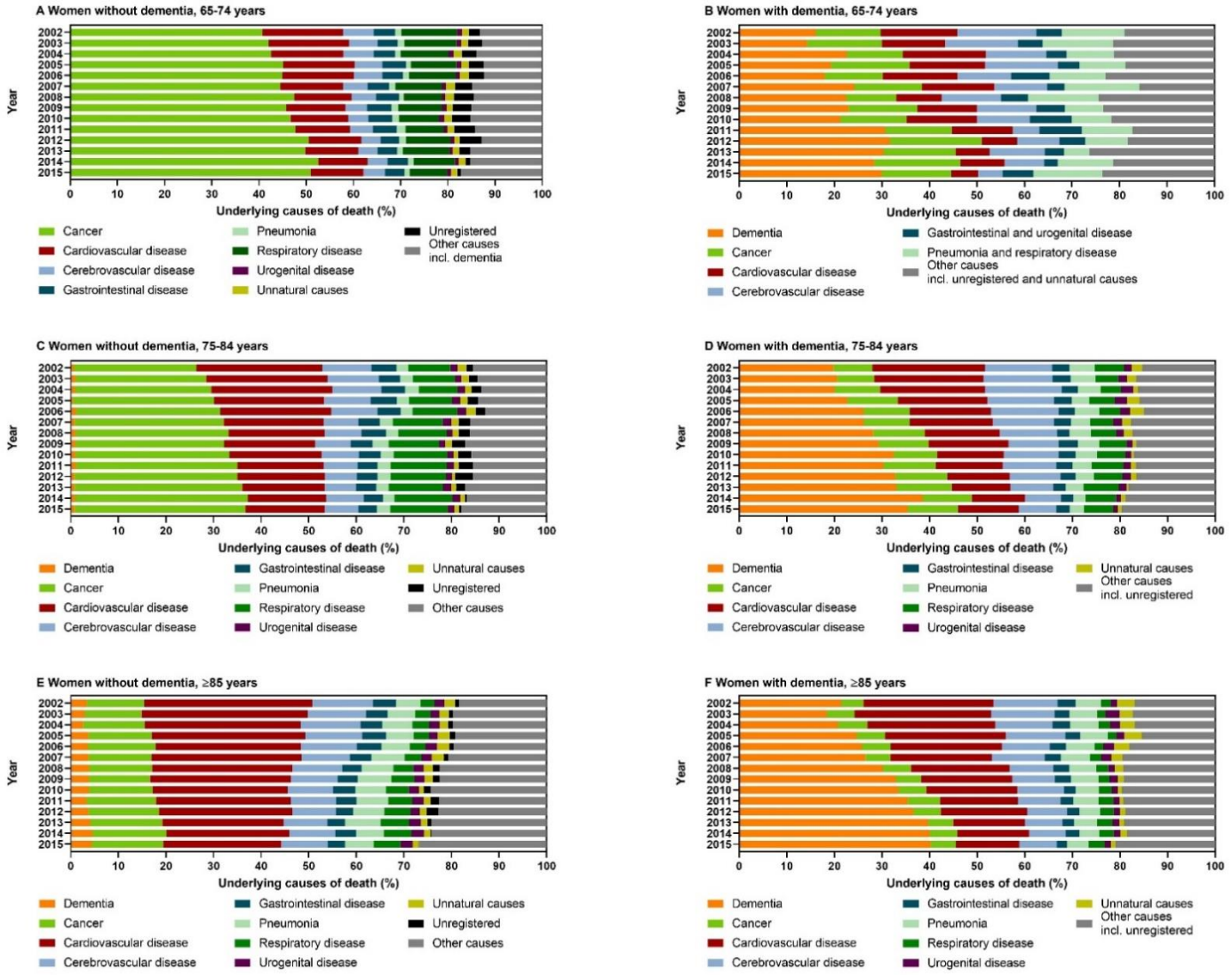
Supplementary Figure 3. Time trend of the distribution of dementia-related deaths registered as contributing or underlying causes of all deaths in women with dementia divided into three age groups



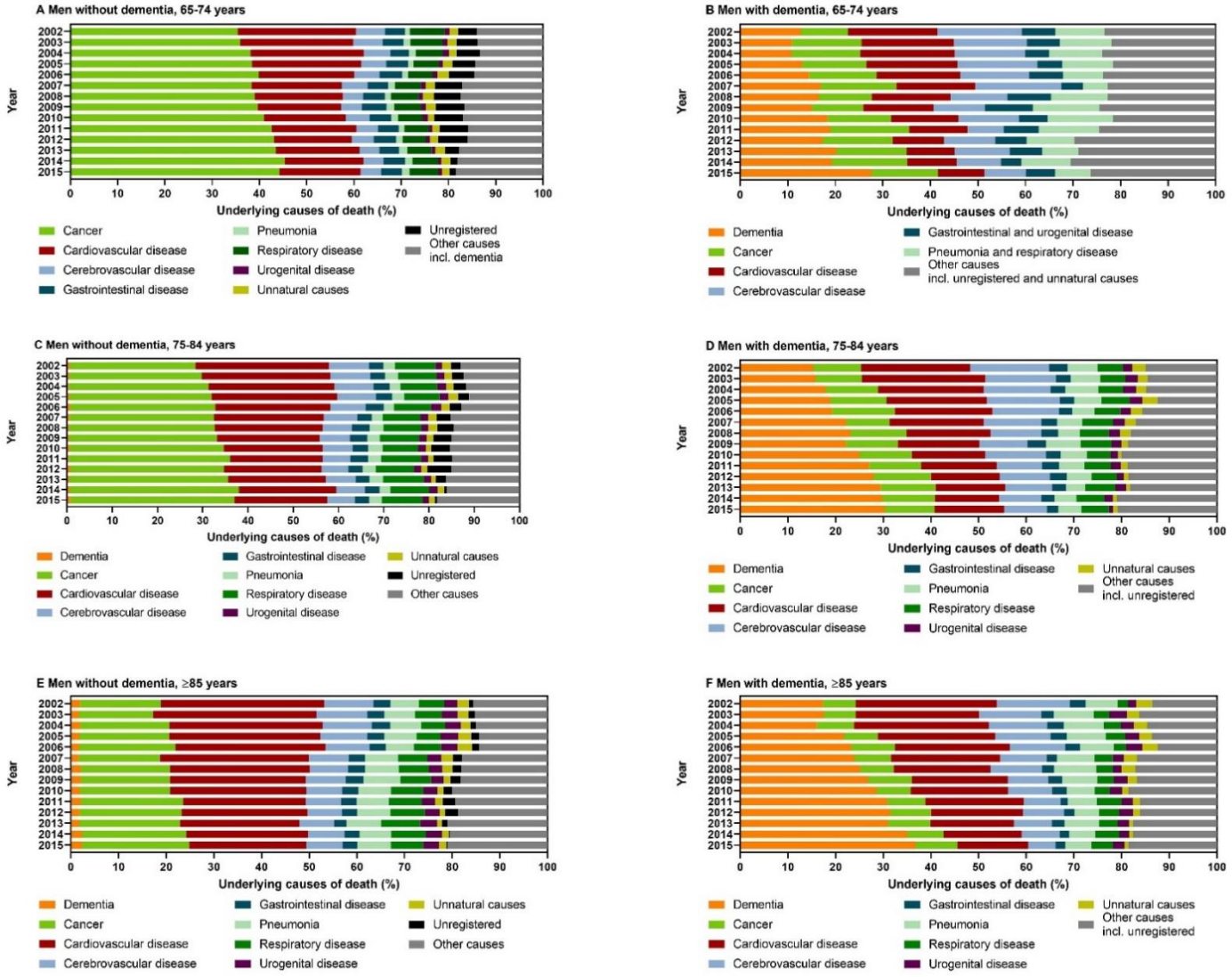
Supplementary Figure 4. Time trend of the distribution of dementia-related deaths registered as contributing or underlying causes of all deaths in men with dementia divided into three age groups



Supplementary Figure 5. Time trend of the distribution (in percentages) of registered underlying causes of death in women with and without dementia divided into three age groups from 2002 to 2015



Supplementary Figure 6. Time trend of the distribution (in percentages) of registered underlying causes of death in men with and without dementia divided into three age groups from 2002 to 2015



Supplementary Table 1. The annual median age at time of death in women and men not registered and registered with dementia while alive

	Women, no dementia		Women, dementia		Men, no dementia		Men, dementia	
	Median age	**IQR**	**Median age**	**IQR**	**Median age**	**IQR**	**Median age**	**IQR**
2002	83.2	(76.4–89.4)	86.6	(81.7–90.6)	79.3	(73.3–85.2)	83.6	(78.9–87.9)
2003	83.2	(76.4–89.5)	86.9	(82.2–90.7)	79.4	(73.4–85.4)	83.5	(79.1–88.0)
2004	83.2	(76.3–89.5)	87.0	(82.4–91.1)	79.6	(73.4–85.3)	83.7	(79.1–88.2)
2005	83.5	(76.4–89.7)	87.0	(82.4–91.2)	79.6	(73.4–85.4)	84.1	(79.4–88.4)
2006	83.5	(76.4–89.7)	86.8	(82.3–91.1)	79.4	(73.2–85.5)	83.9	(79.1–88.2)
2007	83.6	(76.5–89.6)	87.0	(82.7–91.2)	79.5	(73.1–85.6)	84.4	(79.9–88.4)
2008	83.7	(76.3–89.9)	87.3	(82.7–91.4)	79.5	(72.8–85.7)	84.6	(79.8–88.7)
2009	83.7	(76.4–89.8)	87.4	(83.0–91.4)	79.7	(73.0–85.8)	84.5	(79.5–88.5)
2010	83.6	(76.2–89.8)	87.6	(83.0–91.7)	79.4	(72.7–85.7)	84.5	(79.9–88.7)
2011	83.7	(76.0–90.2)	87.7	(83.2–91.7)	79.2	(72.6–85.8)	84.7	(79.7–88.8)
2012	83.5	(75.9–90.1)	87.9	(83.0–91.8)	79.3	(72.5–85.9)	84.5	(79.8–88.7)
2013	83.9	(76.2–90.4)	88.1	(83.3–92.0)	79.5	(72.4–86.0)	84.8	(80.0–88.9)
2014	83.7	(75.8–90.5)	88.1	(83.4–92.0)	79.5	(72.4–86.3)	84.9	(79.8–89.2)
2015	83.9	(76.0–90.8)	88.0	(83.1–92.3)	79.6	(72.7–86.4)	84.8	(80.1–89.2)

Abbreviation: IQR, inter quartile range

Supplementary Table 2. Number of first-ever dementia diagnoses on death certificates in women by calendar year

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
65-74 years	32	24	21	13	24	22	18	13	14	23	22	20	23	18	287
75-84 years	224	210	172	157	167	131	131	136	123	123	100	106	104	102	1986
≥85 years	711	607	573	609	580	547	555	560	525	456	490	532	553	560	7858
Total	**967**	**841**	**766**	**779**	**771**	**700**	**704**	**709**	**662**	**602**	**612**	**658**	**680**	**680**	**10,131**

Supplementary Table 3. Number of first-ever dementia diagnoses on death certificates in men by calendar year

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
65-74 years	29	26	23	34	26	16	30	21	27	28	35	28	25	33	381
75-84 years	147	128	128	123	129	97	106	95	87	94	102	96	86	93	1511
≥85 years	226	224	217	179	183	167	210	193	192	173	205	194	204	206	2773
Total	**402**	**378**	**368**	**336**	**338**	**280**	**346**	**309**	**306**	**295**	**342**	**318**	**315**	**332**	**4665**

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