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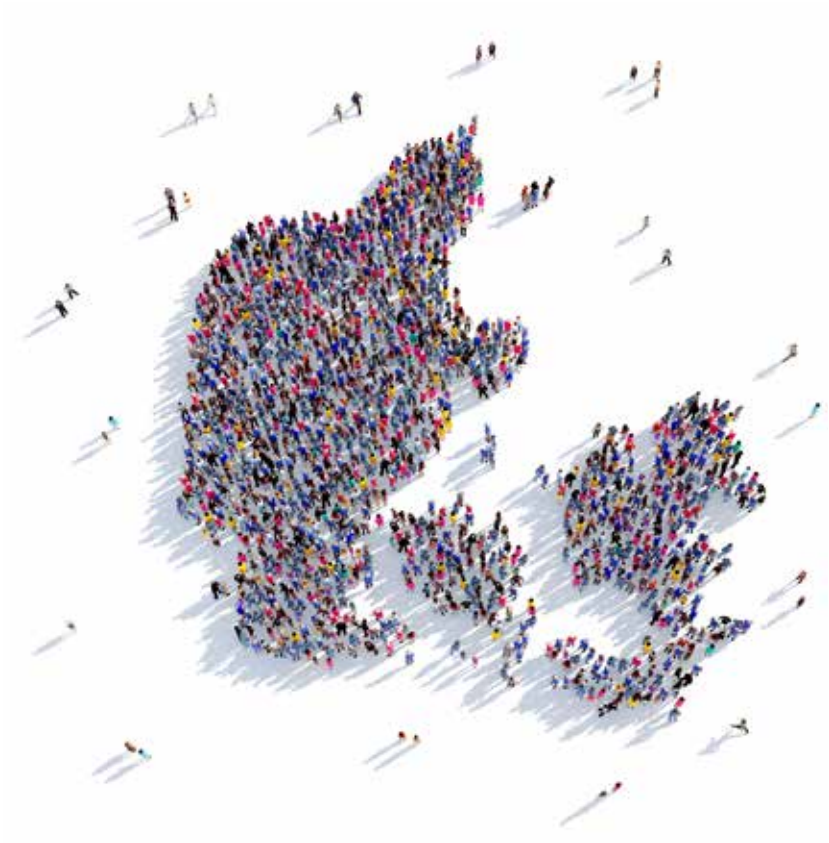
Epidemiology of Infections in Dementia

Nationwide registry-based studies on hospitalizations and adverse outcomes in Denmark



PhD thesis – Janet Janbek

DANISH DEMENTIA RESEARCH CENTRE

REGION Rigshospitalet

This thesis was submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen, June 30th 2021

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Preface and acknowledgements

This PhD thesis has taken place at the Danish Dementia Research Centre (DDRC), Rigshospitalet in Copenhagen, Denmark. The project is part of a larger epidemiological project that investigates comorbidities, health determinants, and mortality in people with dementia and their caregivers. The DDRC is supported financially by the Danish Ministry of Health, to whom gratitude is due.

I started in 2018 as a research assistant where I was given the chance to develop –together with the research team – my own topic within the larger project. I realize my privileged position of having my interests and passion define what I would be pouring energy into over the coming years. Gunhild Waldemar, my principal supervisor, I am grateful for your support, your acknowledgment and appreciation, your guidance, the space you created for me to find my research passion, and your tremendous knowledge in this field that I knew little about when I first started. Thank you for guiding me in my research career and for the tremendous support you have given and continue to give me for building myself and my identity as a researcher. I look forward to continuing our work together.

My co-supervisor Thomas Munk Laursen, I am thankful to have gotten the chance to work with you and be guided by you. I often find myself saying to others starting out on their research journey things you taught me, both in the world of statistics, but also how to approach research. To my co-authors Niels Frimodt-Møller, Lærke Taudorf, and Christian Sandøe Musaeus: I'm both honored and proud to have had the chance to work with you and learn from you, thank you for the input and expertise you brought. To all my colleagues at DDRC, administrative staff, press and education experts, thank you for the help and support throughout this journey. For almost half of the journey, we spent in lockdown, and yet, your support and help have carried on. Special thanks to Tine Olsen, Marie Ejlersen and Mette Kjær for their support in different aspects of my journey.

My background is in public health and epidemiology. My research interest before this work was in early disease programming (the research into prenatal origins of disease) with focus on neurodevelopmental outcomes at the Research Unit for General Practice, and the Section of General Practice at the University of Copenhagen, and at the Parker Institute. I am grateful to Berit Heitmann, Niels de Fine Olivarius, and Research Unit and Parker Institute family. Berit, you have started me off on my research career and I couldn't have wished for anyone better to have that role. Thank you for your guidance, trust and belief in me, and your continuous help with my scientific persona.

The brain, and factors impacting the brain have always fascinated me and so has research into origins of disease. When I first started at DDRC, I came across what is referred to as the infection hypothesis

of Alzheimer's disease (AD). This hypothesis that an infection may be the cause of AD inspired the start of this PhD project. If infections play a role in causing or accelerating dementia, together with them being very common and preventable, then this needs in-depth investigation. It has translated into what this thesis is about: people with dementia and the impact of infections on them. This is one side of the story, the other side – not in this thesis – is the role of infections for developing dementia, that I plan on getting into after this thesis.

I was lucky to spend 3 months on a research stay, right before lockdown would have made it impossible. I went to the University of Edinburgh, where I worked in collaboration with researchers from the Division of Infection Medicine (IM), on an exciting project on antivirals and dementia. Professors Juergen Haas and Richard Lathe, Linda Williams, and Christian Schnier: I'm grateful for your guidance, extensive knowledge, and the fruitful collaborative environment we created together. Continuing this work with you is a privilege. Juergen, a special thank you for welcoming me into your unit and team and guiding my scientific journey as well. The IM family is very lucky to have you as their leader, and I'm also thankful to them for making my stay wonderful. I would also especially like to thank you Christian for all of our insightful epidemiological discussions, and for everything I have learned and continue to learn from you (including when the cows come home, and when the Swedish elk cross). Knowing you has been an absolute highlight of my journey.

Last but definitely not least, my friends and family in Denmark, Jordan, Russia, and spread around the world, thank you for your support and always being there for me. My mother Galina and brother Zawer, you have and always will be my role models, and I always hope to make you proud. My life partner, PhD buddy, and – for the past year and a half – my home office buddy Mikele, we got to do our PhD journeys simultaneously, picking each other up and giving tough love when needed. Thank you for staying (and waking) up nights to sit by my side while I "just" re-run a code because I wanted to check on a detail. I am thankful for our involvement in and motivation for each other's research.

Back to this thesis. I wanted this thesis to be read easily by everyone regardless of their background and expertise. Through my public health glasses, the story in this thesis is of people living with dementia, a disease we don't have a cure for, and who are further burdened with infections, a disease we can most definitely do something about. But one can't find solutions to unknown problems. My hope with this thesis is that through highlighting where the problem is, both I and other researchers will help move this topic even more to the forefront to reach solutions. When Neil Armstrong was asked (at least as attributed on the series The Crown): "What exactly do you hope to discover?" he replied with what continues to inspire and motivate my work: "I think even more important than the answers that we'll be able to find will be the fact that we get a whole bunch of new questions to ask".

Studies

This thesis is based on three original studies:

Study I. **Janbek, J.,** Frimodt-Møller, N., Laursen, T.M., Waldemar, G. Dementia identified as a risk factor for infection-related hospital contacts in a national, population-based and longitudinal matched-cohort study. Nat Aging 1, 226–233 (2021). https://doi.org/10.1038/s43587-020-00024-0

Study II. **Janbek, J.,** Taudorf, L., Musaeus, C.S., Frimodt-Møller, N., Laursen, T.M., Waldemar, G. (2021), Increased short- and long-term mortality following infections in dementia: a nationwide registry-based cohort study. Eur J Neurol, 28: 411-420. https://doi.org/10.1111/ene.14595

Study III. **Janbek, J.,** Frimodt-Møller, N., Laursen, T.M., Waldemar, G. Hospital readmissions following infections in dementia: a nationwide and registry-based cohort study. Eur J Neurol. 2021; 00: 000– 000. https://doi.org/10.1111/ene.14911

Note: Following publication, we have decided to update studies II and III due to an error found in the coding of the Charlson Comorbidity Index in one of the adjustment models in the two studies. The coding had resulted in a slight over-adjustment of our estimates. None of the result interpretations or conclusions were affected by this. The two article papers are in the process of correction and updating by the *European Journal of Neurology*, thus these two are included in the thesis in a manuscript form with updated estimates, and these are all updated in the thesis text.

Abbreviations

AD	Alzheimer's Disease
ApoE4	Apolipoprotein E4
ATC	Anatomical Therapeutic Chemical
CCI	Charlson Comorbidity Index
CI	Confidence Interval
COVID-19	Coronavirus Disease of 2019
DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD	International Classification of Disease
IRR	Incidence Rate Ratio
MRR	Mortality Rate Ratio
NPR	National Patient Registry
NPrR	National Prescription Registry
OR	Odds ratio
PCRR	Psychiatric Central Research Registry
PPV	Positive Predictive Value
PYs	Person Years
RR	Risk Ratio
UTI	Urinary Tract Infection

Abstract

Dementia impairs patients' ability to manage comorbidities, which puts them at risk for adverse outcomes and negatively impacts their quality of life. Infections are among the most common comorbidities that are potentially preventable. People with dementia are more susceptible to getting infections; they are more likely to have their infections underdiagnosed and mismanaged; and infections may play a role in the pathology of dementia by worsening/ accelerating the disease. However, this topic remains insufficiently explored, and evidence is needed to shape interventions.

This thesis investigates the role of infections in people with dementia aged ≥65 years in Denmark. It's based on three population and registry-based studies exploring hospitalization and mortality. These studies are the first to explore and compare such outcomes in all types of infections.

Results from our studies showed that people with dementia had a 50% higher risk for an infection-related hospital contact than those without dementia, and that infections may be an early sign of dementia. Following an infection-related hospital contact, people with dementia were 7-fold more likely to die compared with the general population, and increased mortality was both short- and long-term. Acute admissions for an infection of people with dementia were more likely to result in 7-day readmissions than of people without dementia, mostly in the youngest dementia patients. Readmissions were mostly due to infections as well.

Most frequent infections in our studies were of the respiratory and urinary systems, sepsis, infections of the digestive system, skin infections, and other uncategorized/unspecified infections. For these, there were increased rates of hospital contacts and mortality in people with dementia, as well as increased 7-day readmission risk (mainly in the youngest). Such associations were generally observed for all other infection sites, with some variations.

Findings reflect pitfalls in dementia care and infection management and highlight issues of equity in healthcare. Future research is needed to test further hypotheses on the possible role of infections in dementia, and to shape interventions. I emphasize the need for focus on infection prevention and specialized care for people with dementia. This calls for strong collaborations that span disciplines of clinical care (geriatrics, neurology), research (neurology, epidemiology, sociology), and other professions e.g. social care professionals and policy makers.

Resume

Demens forringer patienters evne til selv at mestre komorbiditeter, hvilket øger risikoen for komplikationer og påvirker livskvaliteten negativt. Infektioner kan potentielt forebygges og er blandt de hyppigste komorbiditeter hos ældre med demens. Personer med demens er mere sårbare overfor infektioner; de bliver oftere udsat for mangelfuld diagnose; og infektioner spiller måske en rolle ved at forværre/accelerere demenssygdommen. Imidlertid er emnet stadig utilstrækkeligt undersøgt, og der er behov for mere evidens for at udvikle interventioner.

Denne afhandling undersøger infektioner hos mennesker med demens i alderen ≥65 år i Danmark. Den er baseret på tre befolknings- og registerbaserede studier af hospitalsbesøg og mortalitet. Disse studier er de første til at undersøge og sammenligne dette for alle typer infektioner.

Vores resultater viste, at personer med demens havde 50% højere risiko for et infektionsrelateret hospitalsbesøg end personer uden demens, og at infektioner kan være et tidligt tegn på demens. Efter et infektionsrelateret hospitalsbesøg havde personer med demens 7 gange højere risiko for at dø sammenlignet med baggrundsbefolkningen, og dødeligheden var øget på både kort og lang sigt. Akutte indlæggelser for en infektion hos personer med demens resulterede oftere i genindlæggelser indenfor 7 dage end hos personer uden demens, hovedsageligt hos de yngste demenspatienter. Genindlæggelserne var for det meste også pga. infektioner.

De hyppigste infektioner i vores undersøgelser var i luft- og urinvejene, blodforgiftning, infektioner i fordøjelsessystemet, hudinfektioner og uspecificerede infektioner. For disse var der øget hospitalsbesøg og dødelighed for personer med demens samt øget risiko for genindlæggelse indenfor 7 dage (især hos de yngste). Sådanne resultater blev generelt også observeret for andre infektionstyper, men med nogle variationer.

Resultaterne afspejler udfordringer i plejen af mennesker med demens og i forebyggelse og behandling af infektioner og fremhæver spørgsmål om ulighed i adgang til sundhed. Fremtidig forskning er nødvendig for at teste yderligere hypoteser om infektioners mulige rolle for demens og for at udvikle interventioner. Jeg påpeger behovet for fokus på infektionsforebyggelse og specialiseret pleje af personer med demens. Dette kalder på stærke samarbejder, der spænder på tværs af discipliner inden for klinisk pleje (geriatri, neurologi), forskning (neurologi, epidemiologi, sociologi) og andre erhverv, f.eks. plejepersonale og beslutningstagere.

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1. BACKGROUND

I will start out by providing a brief background on dementia and put it in the context of infections. I will highlight in this section what we already know on the topic and go through key points describing the need for research. I will then present the gaps in knowledge that led to forming the aims of this thesis.

Dementia

Dementia is not one disease, it is a syndrome (set of symptoms) that is characterized by cognitive decline and impairment to memory, behavior, reasoning, and thinking, which result from abnormal brain changes.[1] Other symptoms of disorientation, agitation, anxiety, and sometimes hallucinations are also common in people with dementia and are referred to as neuropsychiatric and behavioral symptoms.[1,2] The most common underlying brain diseases in dementia – also called dementia subtypes – include Alzheimer's Disease (AD) that accounts for 60-70% of all cases, followed by vascular dementia, dementia with Lewy bodies, and frontotemporal dementia.[1,3] More than one type may also coexist.[1,4]

In the absence of a neuropathological confirmation, dementia diagnosis relies on criteria developed to increase accuracy.[5] These are criteria developed by the World Health Organization in the International Classification of Diseases (ICD-10) in 1992 and by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) in 2013.[6,7] Although there are differences in the exact criteria between the two, both primarily require the presence of decline in memory functions and other cognitive abilities such as judgement, together with declines in social and emotional behavior (e.g. irritability).[6,7] Criteria are developed over the years based on understanding of the dementias, for example, the recent DSM-V changed the term dementia (in the earlier DSM-IV) to "Major Neurocognitive Disorder", and an updated ICD-11 is expected in 2021.[7,8]

Age is the strongest risk determinant of dementia. With advancing medicine and people living longer, far more people have dementia today than previously. It is estimated that 50 million people were living with dementia in 2018.[4] And as people continue to live longer, it is expected that

people living with dementia will also continue to grow in number, reaching an estimated sum of 152 million people in 2050.[4] That's more than the size of Russia. In Denmark, around 36,000 people were registered with dementia in 2015 (the number of people living with dementia is estimated to be at least double in reality).[9,10] A recent study has shown that the incidence has increased annually by 9% between 1996 and 2013 and decreased thereafter by 2% until 2015.[9] However, the prevalence continued to increase[9] i.e. more people are living with dementia.

Age and genetics are risk factors for dementia that one cannot change. However, with advancing research, we now know more and more about potentially modifiable risk factors in mid- and late life that contribute to dementia.[3,11] These include medical conditions (hypertension, diabetes, hearing loss, depression, obesity, brain injury), social factors (education, lack of social support), environment (air pollution), and lifestyle (smoking, physical inactivity, alcohol consumption).[3,11]

Dementia has serious deleterious impact on the quality of life of the person living with dementia, their caregivers, and the healthcare system and the society as a whole.[1,4,5] It is not "just another" diagnosis in a patient's medical journal. Dementia impairs the patient's ability to manage other diseases and to communicate new symptoms.[11,12] Consequently, the prognosis of dementia is impacted negatively by increased comorbidity burden that put people with dementia at higher risk for mortality, frequent hospitalizations, and further deterioration in the already afflicted cognitive and functional levels. This further decreases their overall well-being and majorly reduces their quality of life.[13,14] Understanding factors and events that contribute to this vicious cycle is a research priority – albeit a complex endeavor.

Treatment for patients with dementia have so far targeted lessening the cognitive and non-cognitive (neuropsychiatric and behavioral) symptoms.[5] Drugs that aim to put the brakes on the cognitive decline are in development, with the first drug – Aducanumab – having been approved this year for AD treatment in the United States.[15] To date, there is no cure for dementia and therefore it is of utmost importance that people living with dementia are provided with the needed optimal care, and that their comorbidities are properly managed.[3]

Living with dementia; infections

One of the most common comorbidities is infections. I will describe here the following key messages: People with dementia may be more susceptible to getting infections; they are more likely to have their infections underdiagnosed and mismanaged; these may lead more frequently to hospitalizations, readmissions, and mortality; and infections may play a role in the pathology of dementia by worsening/accelerating the disease.

It is well-known both clinically and in research that infections are common in older adults and in people with dementia. Most common infections are pneumonia, urinary tract infections (UTIs), sepsis, and skin infections.[16,17]

Susceptibility to infections in people with dementia is likely multifactorial and includes patient and social factors. Although these may be common to all older adults, dementia adds another layer. Impaired cognition in dementia and its consequences can result in changes in people's hygienic habits and can lead to difficulty in communicating needs (e.g. water intake or bathroom visit). Changes in the immune system with age makes older adults and people with dementia less capable to fight off infectious challenges,[18–21] and it has been proposed that an impaired blood brain barrier may predispose people with dementia to infections.[22,23] Other changes in the body with age may also predispose to infections such as microbiota changes,[20] swallowing difficulties,[20] reduced cough reflux, urinary/ fecal incontinence,[24] and drug-induced acquired immunodeficiency.[24] Further, reduced mobility can increase the risk for bed sores that result from prolonged periods of bed rest and can develop to skin infections.[24] Social factors include malnutrition,[25] nursing homes residence, lack of external help, and possible reduced acceptance of infection prevention measures. The relationship between patient and social factors is certainly complex and the accumulation of several factors increases susceptibility to infections.

Not only is there a question about increased susceptibility to infections, another issue is that people with dementia may be more likely to have infections mismanaged. One study showed that people with dementia are not at a higher risk for pneumonia than other older – frail – adults, but that the challenge lies in diagnosis.[26] People with dementia often present with atypical infection symptoms,[13,27] and sometimes the only clinical sign is a change in the person's mental state.[13,24] Further, cognitive decline challenges infection symptom expression and increases the risk that

infections are undiagnosed and mismanaged.[20] Mismanagement can also be due to decreased renal functions[28] and age-related changes in pharmacokinetics that affect how antibiotics are absorbed and eliminated, and hinder treatment efficacy and may even lead to toxicity.[29]

Challenges in infection diagnosis and management can lead to frequent hospitalization, readmissions, and death.

We know from previous literature that people with dementia have an increased risk for hospitalization with infections generally, and specifically with UTIs and pneumonia (and in two studies, gastroenteritis was also documented).[30–45] Hospitalization can be burdensome and destabilizing for any person, but particularly for a person with dementia, especially in older age. Frequent hospitalization comes parallel to increased comorbidity and polypharmacy, which predict readmissions and excess mortality in people living with dementia.[3,14]

Unplanned readmissions put an added strain on the well-being of a person with dementia and on the healthcare system. Previous studies have shown an increased 30-day readmission risk, recurrent hospitalization, and complications after admissions with UTIs and pneumonia in people with dementia.[33,46–51] After hospital-acquired infections, they were more likely to be readmitted and most commonly after and for *C. difficile* and UTIs (linked readmissions).[52]

Infections may also place them at an increased risk of death. Previous reviews have shown that pneumonia has been consistently reported as a common cause of death in dementia, and also more common when compared with no dementia patients.[53,54] Higher in-hospital mortality after sepsis in people with than without dementia has also been shown in one study.[55] Following respiratory infections/ pneumonia, a few studies documented increased mortality[56–58] and decreased survival[59] in people with dementia. In these studies, comparison of mortality between people with and without dementia was however scarce. There is also a growing interest in the underlying biological and pathological mechanisms involved in the interactions between infections and dementia, especially infections' role for developing/ worsening dementia. The hypothesis investigates whether infection/ inflammation contributes to cognitive decline and neurodegeneration, and is being continuously tested.[60–66] Although this thesis does not investigate such mentioned possible roles, these are of value for interpreting results of hospitalization patterns and adverse outcomes.

Public health interest- need for research

I would like to pinpoint some core considerations that motivated this PhD research project.

1) **Global burden.** Dementia and infections are among the top 10 leading causes of death worldwide, highlighting their impact globally.[67] The interaction of the two may contribute to an even bigger disease burden.
2) **Infections are common and preventable**. Such avoidable causes for hospitalization and consequent adverse events should thus be a research priority.
3) **Dementia care and equity.** Outcomes of hospitalizations, readmissions, and mortality are important to investigate because these provide evidence for dementia care. They show disease trajectories, can be markers for the quality of healthcare, and are important for healthcare service planning and policy making. These outcomes can also reflect equity issues in the healthcare services received. If there are differences in these outcomes between people with and without dementia, then there is a problem. Indeed, previous findings point out this equity gap in the provision of services.[11] The gap is only expected to grow in importance in the coming years as the number of people living with dementia increases, especially if the gap is present for such common events as infections. Consequences of such a gap burdens the patients, their families, and the healthcare system in terms of both the quality of life and the societal expenses.
4) **Possible underlying biological mechanisms in interactions between infections and dementia.** Large observational studies cannot provide evidence on such mechanisms, but they are valuable to guide novel hypotheses on infections' possible role in dementia. These may include mechanisms involved in increased susceptibility to infections, an altered reaction to an infection, and infections' role for developing/ accelerating dementia.
5) **A focus on all types of infections**. A comprehensive investigation of all infections is needed to provide important avenues for intervention. Research on pneumonia (mainly), UTIs, and sepsis has allowed for development of targeted interventions and generation of hypotheses on e.g. hospitalization and treatment decisions.[57,68,69] The research loop thus continues with these infections, and it is of value to compare with and include other infections. Further, patient-social factor interactions and possible biological mechanisms may vary by infection type. Thus, all types need to be investigated together and in comparison, to develop interventions for appropriate dementia care and to further knowledge on dementia through possible biological and pathological mechanisms underlying interactions with several infection types.

Knowledge gaps

Previous studies that investigated hospitalizations, readmissions, and mortality in the context of infections in dementia are few. Studies only assessed outcomes for pneumonia (mainly), followed by UTIs and sepsis and in a few studies also infectious diseases generally. However, no studies have investigated such outcomes with focus on all types of infections or comparing infection types. Further, studies that were based on entire populations are few[31,35,44,48,49,55] and previous work is generally limited by smaller, single-site, or selected study samples such as a single hospital, patients on a specific insurance scheme, recruited cohorts, selected nursing home facilities, persons with advanced dementia or terminally ill persons with dementia (end of life care). Majority of the already few population-based studies assessed all-cause hospitalization rates where the mentioned selected infections were included. Only three assessed mortality or readmission and these were focused on pneumonia and sepsis only.[48,49,55] Together with short follow-up periods in most studies, findings from previous work may face issues in generalizability and bias.

In addition to these common pitfalls, there is also a need for more comprehensive knowledge on the mentioned outcomes. For example, research on hospitalization patterns from the time of dementia diagnosis is needed to assess its impact on the rates of infection-related hospital contacts; knowledge on readmission reasons after infections in people with dementia is needed to inform targeted interventions; and the short- and long-term mortality following infections is valuable knowledge for investigating the consequences of infections in dementia. Regarding the latter, the impact of infections may extend beyond the period right after the infection[70] as shown in several studies in sepsis survivors (without focus on dementia).[70–72] Such studies highlight the value for investigating the long-term consequences of infections.

Finally, there is a lack of evidence to date on which types of infections are behind increased hospital contacts, and which infections show an increase in adverse outcomes of readmissions and mortality in people with dementia.

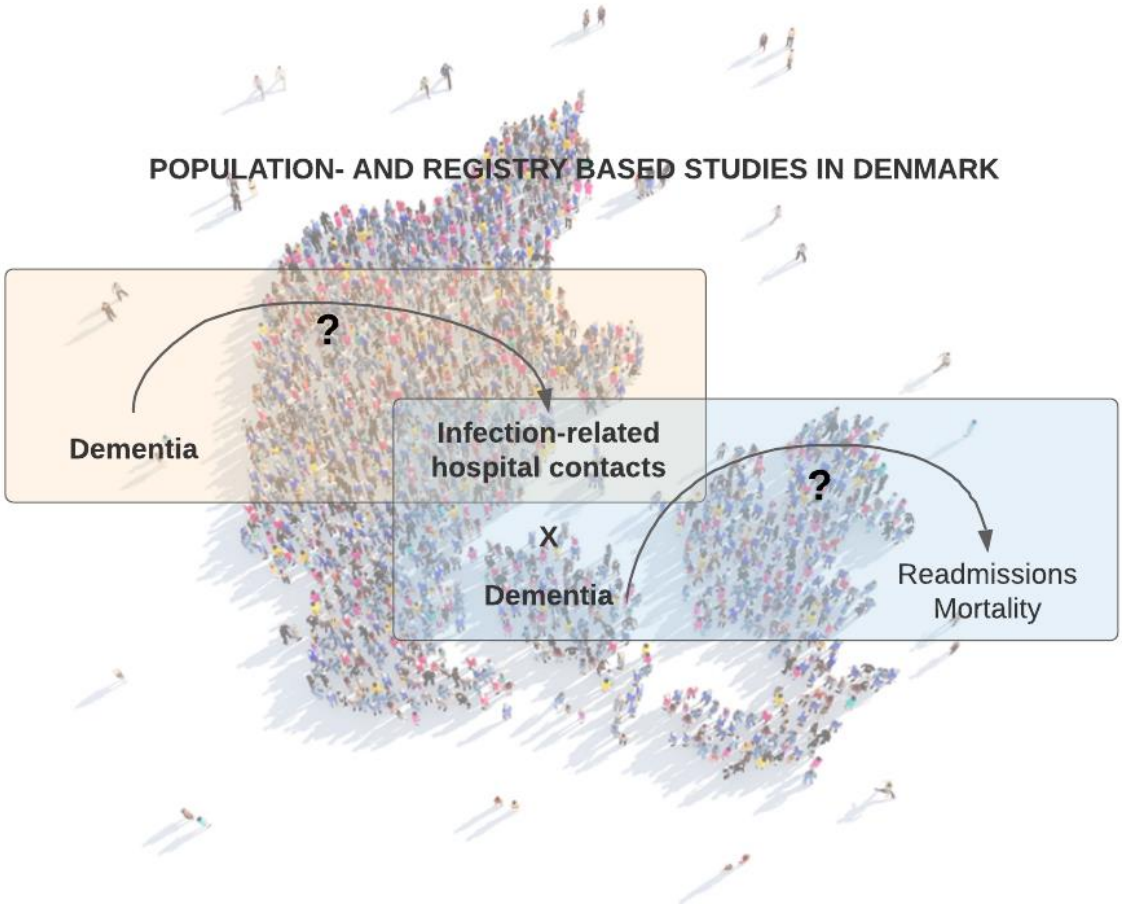
Thus, the role of infections for hospitalizations and mortality in people living with dementia remains insufficiently explored and such gaps in knowledge hinder public health and clinical efforts that aim to target these outcomes in people with dementia.

2. AIMS

I present here the overall aims and specific aims per study (Figure 1). The overall aim was to investigate the role of infections in dementia in 65+ year old persons in Denmark.

In study I, the aim was to investigate the association between incident dementia and rates of hospital contacts with infection, and to investigate which infections are behind such rates. In study II, the aim was to investigate the impact of infection in people with dementia on the short- and long-term mortality, and to investigate this impact in the different infection sites. In study III, the aim was to investigate the impact of dementia on readmission in a population with at least one acute inpatient admission for an infection. We further aimed to investigate readmission risks in the different infection sites, and to explore reasons for readmissions. In all studies, we hypothesized that people with dementia have increased risk for the listed outcomes.

Figure 1. Graphical presentation of the main aims of this thesis



3. MATERIALS AND METHODS

Since all three studies of this thesis use the same source population and data on infections and dementia, I will first present an overview of these as used in all studies and will later go into study specific methods. All methods are described in detail in each of the study manuscripts and their supplementary materials. Here I will give an overview of key methods that serve in understanding the studies and findings.

Setting and data source

This thesis takes place in the Danish healthcare system. Most healthcare services are provided by the state free of charge (tax-financed) for everyone with a residency in Denmark.[73,74] All contacts, procedures, and redeemed pharmaceutical prescriptions are registered in the national registries digitally using the person's unique 10-digit civil registration number. This number allows for accurate individual-level linkage between all registries. The Civil Registration System (CRS) is the main administrative registry in Denmark. It was established in 1968 and contains individual-level data such as date of birth, kinship, and status (e.g. emigration).[75] Sources of health data in this thesis are: the National Patient Registry (NPR), the Psychiatric Central Research Registry (PCRR), and the National Prescription Registry (NPrR), each described briefly in the following.

The NPR was established in 1977 and originally covered inpatient admissions in somatic wards and in 1995, outpatient and emergency contacts were included. The PCRR was established in 1969 and has included all inpatient admissions in psychiatric wards,[76] and in 1995, the register also included outpatient and emergency contacts. Here, the PCRR also became integrated in the NPR.[77]

Several records may be recorded for each hospital contact in the NPR if there were e.g. transfers between hospital departments. In our studies, such records were combined into one merged record if they occurred on the same date (or +1 day), and we grouped outpatient clinic and emergency contacts into "outpatient contacts", resulting in records divided into inpatient and outpatient contacts. All diagnoses given by the physician during a hospital contact are recorded upon discharge (hereafter referred to as discharge diagnoses) using the ICD codes (version 8 until 1993 and version 10 from 1994 and onwards).[77] These diagnoses are categorized into primary and secondary based on the diagnosis seen as the primary reason for the hospital contact. In our studies,

each hospital contact may – as a result of the merged records described – contain several primary and/or secondary diagnoses. The data management of this for each study is detailed in their supplementary material.

The NPrR contains individual-level information on all drugs prescribed in the primary and secondary sectors and dispensed at Danish pharmacies from 1995.[78] All medication is registered with an Anatomical Therapeutic Chemical Classification (ATC) code.

Identifying people with dementia

In all studies of this thesis, (registered) dementia was defined as a recorded dementia diagnosis at age ≥65 years, using the ICD-8 and ICD-10 codes from the NPR and PCRR (secondary care setting), or a redeemed prescription for an anti-dementia medication (ATC code) from age 65 years from the NPrR (outside of the secondary care setting) (Table 1). A recorded dementia diagnosis (using ICD codes) included all primary and secondary discharge diagnoses recorded during in- or outpatient contacts. Dementia cases before age 65 years were excluded in all studies, because dementia was found to be over-diagnosed in younger patients.[79] The date of (registered) dementia was the first of either a recorded dementia diagnosis or the redeemed anti-dementia prescription.

Table 1. Algorithm for defining a registered dementia

Dementia type	**ICD-8 code**	**ICD-10 code**
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
Medication	**ATC code**	
Cholinesterase inhibitors		
Donepezil	N06DA02	
Rivastigmine	N06DA03	
Galantamine	N06DA04	
Glutamate-receptor antagonists		
Memantine	N06DX01	

Identifying people with infections

In all studies of this thesis, data on infections were those diagnosed in the public secondary care hospital setting. Data were extracted from the NPR where primary and secondary diagnoses recorded as ICD-10 codes upon a hospital in- and out-patient contact were used as a surrogate marker for the presence or absence of infection during a hospital contact.

ICD-10 codes for infections were selected after a thorough process described in detail in the Supplementary material of study I and study II.[80,81] Briefly, the ICD-10 manual was reviewed through its sections (disease system categories). All codes were screened by three of the authors independently and agreed on subsequently with one authors' guidance as an infectious disease expert. We further relied on previous literature that used ICD-10 codes of infections from the NPR.[82–85] Conditions that occur due to an infection but that are not an infection were not extracted, and conditions that may have mixed etiologies including an infection were carefully judged where some conditions were deemed unspecific (further handled in sensitivity analyses in our studies). All chosen ICD-10 codes were categorized according to the system in which the infection was found (following the ICD-10 manual disease system categories), referred to as the "infection site". Infection sites were: Respiratory, urinary, digestive, circulatory, genital, musculoskeletal, nervous, surgical, skin, eye, ear, sepsis, herpes, hepatitis, uncategorized/ unspecified, and less occurring. The latter five sites were put in separate categories instead of the disease system categorization in the ICD-10 manual. Detailed rationale for this is in supplementary material of studies I and II. A list of ICD-10 codes included in each of the studies are in the supplementary tables of each study. In all studies, HIV infections were not included in our list of infections, and instead were counted as one of the diseases included in the Charlson Comorbidity Index (CCI) described below.

Overview of variables used in the studies to refer to infections

In studies I and II, identified hospital contacts with an infection included all in- and out-patient contacts with either primary or secondary diagnoses. In study I, this was referred to as **infection-related hospital contacts.** In study II**,** only the first such contact was counted and thus is referred to as **infection** or **first infection**. In study III, to focus on unplanned hospital stays that were due to infection, only the acute inpatient hospital contacts with a primary diagnosis of infections were counted and are thus referred to as **infection index admissions**.

Covariates

Covariates were chosen as factors judged to be associated with exposures and are risk factors for the outcomes in each study, as indicated by previous literature. All covariates were obtained from the national registries and included: socio-demographic information on age, sex, civil status, and highest educational level attained; comorbidity information; calendar year; and in study III, information on the length of hospital stay (LOS) was also included.

Civil status was defined as married, unmarried, divorced, or widowed. Highest educational level attained was defined as low (primary school), medium (upper secondary, business high school, vocational internship), and high (short-term further education, middle-range education, bachelor's degree, extended education and research degree). Information on comorbidities was obtained using the CCI, which was first developed in 1987 and includes 19 comorbidities.[86] For each comorbidity, a person is given a score between one and six depending on the disease severity and the associated mortality risk. Scores are summed to give an index per person. Dementia was taken out of the CCI algorithm, keeping 18 comorbidities using the ICD-8 and 10 codes. The CCI has been shown to be an appropriate measure of disease burden in health care research that is based on administrative data.[87] Finally, LOS was defined as the number of days from the admission date of an acute inpatient admission until the discharge date.

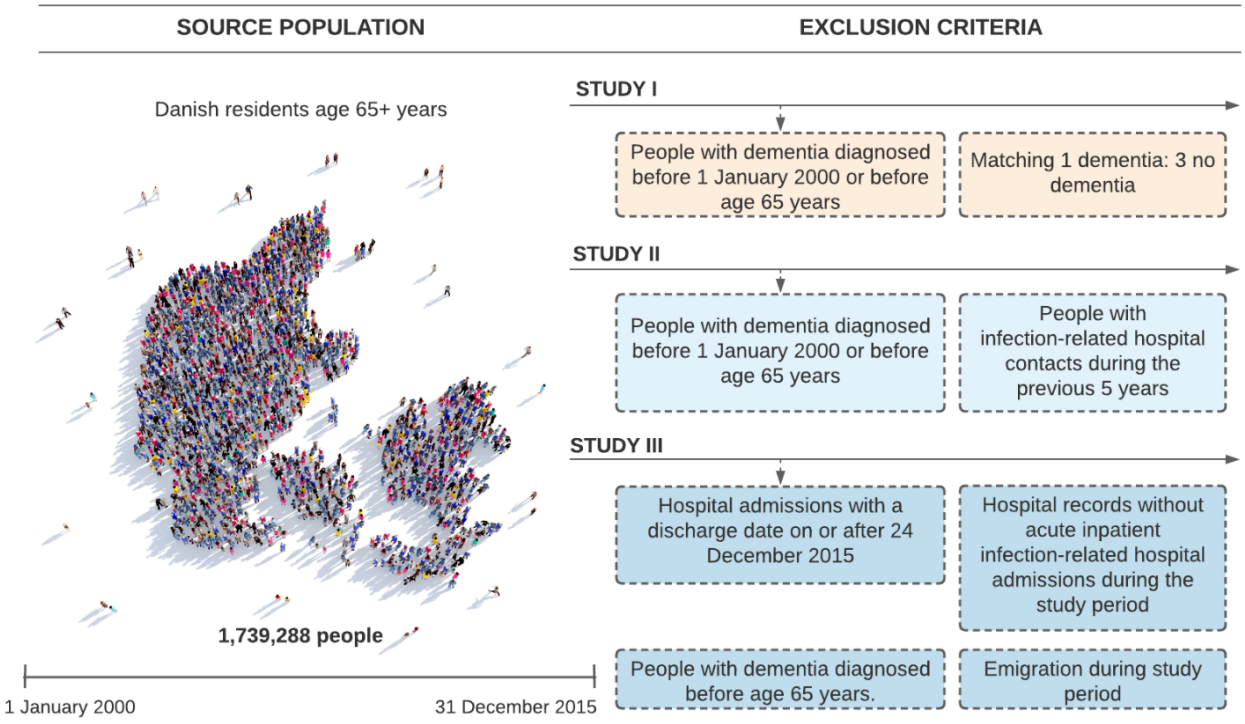
Ethics and approvals

This PhD was conducted as part of a larger epidemiological research project approved by Statistics Denmark, the Region's Data Protection Agency (ID no: 2007-58-0015/30-0667), and the Danish Health Data Authority. Ethics committee approval and patient consent are not required for registry-based studies.[88] Data were handled in an anonymized form (using encrypted personal numbers) on the platform of Statistics Denmark following all regulations.

Source population and study design (all studies)

The three studies in this thesis were observational cohort studies using prospectively collected administrative and health data from the Danish national registries. The source population for all studies was all Danish residents born in or before 1950 included in the population from 1 January 2000 if they were at least 65 years of age, or from their 65th birthdate between 1 January 2000 and 31 December 2015 (all studies' period). People were alive and residing in Denmark at the start of the studies. Figure 2 presents each study's population and exclusion criteria. Table 2 presents methods that are further detailed in the following section.

Figure 2. Source population and exclusion criteria for each of the three studies



In all studies in this thesis, analyses and data management have been conducted using SAS 9.4. (SAS Institute inc.). A two-sided type I error of 5% was considered as statistically significant.

Study specific methods

Table 2. Overview of methods in all three studies of this thesis

	Study I	Study II	Study III
Study unit	Individuals	Individuals	Admissions
Exposure	Incident dementia	Incident dementia and first infection	Dementia
Exposure groups	People with dementia People without dementia (reference)	Dementia/Infection Dementia/No infection No dementia/Infection No Dementia/No infection (reference)	Infection index admissions of people with dementia Infection index admissions of people without dementia (reference)
Primary outcome	Infection-related hospital contacts	All-cause mortality	All-cause 7-day readmissions
Covariates	Sex, age, calendar year, highest attained educational level, civil status, and CCI	Sex, age, calendar year, highest attained educational level, civil status, and CCI	Sex, age, calendar year, highest attained educational level, civil status, CCI, and LOS
Statistical analysis	Poisson regression	Poisson regression	Generalized estimating equation
Measure	Incidence rate ratio (IRR)	Mortality rate ratio (MRR)	Risk ratio (RR)

Study I

The aim was to investigate the association between incident dementia (exposure) and rates of infection-related hospital contacts (outcome). After excluding people with dementia before the start of the study period (Figure 2), we identified everyone with an incident dementia (defined as the date of a first registered dementia diagnosis or the date of first redeemed anti-dementia drug). On the date of incident dementia (index date), people were matched on sex and birthdate (±90 days) with three randomly chosen people without dementia.

To avoid counting rehospitalizations for the same infection, we chose a period of 90 days between each counted infection-related hospital contact (or one year for specific infections with longer treatment). Hepatitis and herpes were counted as one-time events per person. People were followed from index date until date of death, emigration, or 31 December 2015, whichever came first. Matched people without dementia also ended follow-up on the date of a registered dementia. They were then censored and further matched as people with dementia.

Incidence rate ratios (IRRs) were calculated in people with dementia compared with those without dementia (reference group), with 95% confidence intervals (CI). Poisson regression with the logarithm of the person years (PYs) at risk as an offset variable was used to calculate the IRRs (a model equivalent to a Cox regression model).[89,90] Dementia was a time-dependent variables. IRRs were calculated for any infection-related hospital contact, and by infection site, sex, and age. If one contact included diagnosis codes of several infection sites, then that contact was represented in several infection sites. Additionally, we calculated the percentage

of people with infection-related hospital contacts during the five years prior to index date. Finally, three adjustment models were used, and multiple sensitivity analysis models were conducted to test whether any arbitrarily made decisions influenced the results.

Study II

The aim was to investigate the association between incident dementia and first infection (exposure) and all-cause mortality (outcome). Four exposure groups were thus analyzed: Dementia/infection, Dementia/No infection, No dementia/infection, and No dementia/no infection (reference groups). For people with a first infection prior to dementia, it was judged incorrect to categorize them in the Dementia/No infection group or in the Dementia/infection group, so they were put in their own sub-category. People were followed from start of study period (age 65 years, or 1 January 2000) until the date of death, emigration, or 31 December 2015, whichever came first.

IRRs (here called Mortality Rate Ratios- MRRs) were estimated as described above using Poisson regression, in the four exposure groups for any infection, and stratified by sex, infection site (from first infection in each site), and time since infection (for short- and long-term mortality, and also stratified by sex). For each infection site, MRRs were estimated for infections of each site and no other infections compared with the reference group.

We further quantified the additive interaction between infections and dementia for any infection and in each infection site. This is often referred to as biological interaction and is widely used in clinical epidemiology research.[91–94] We used the Synergy Index as described in Andresson et al.[94] that quantifies the excess risk of the outcome (here, death) for two interacting exposures (here, dementia and infection). In this thesis, the term "excess" mortality will refer to results of the Synergy Index.

Finally, three adjustment models were used (same as study I), and similarly, multiple sensitivity analyses were conducted to test robustness of our results.

Study III

The aim was to investigate the association between dementia (exposure) and all-cause 7-day readmission risk (outcome) as well as reasons for readmission (outcome) in people with at

least one infection index admission. Secondary outcomes were 30- and 90-day all-cause readmissions. The study unit was admissions. Two exposure groups were analyzed: Infection index admissions of people with dementia, and of people without dementia (reference group).

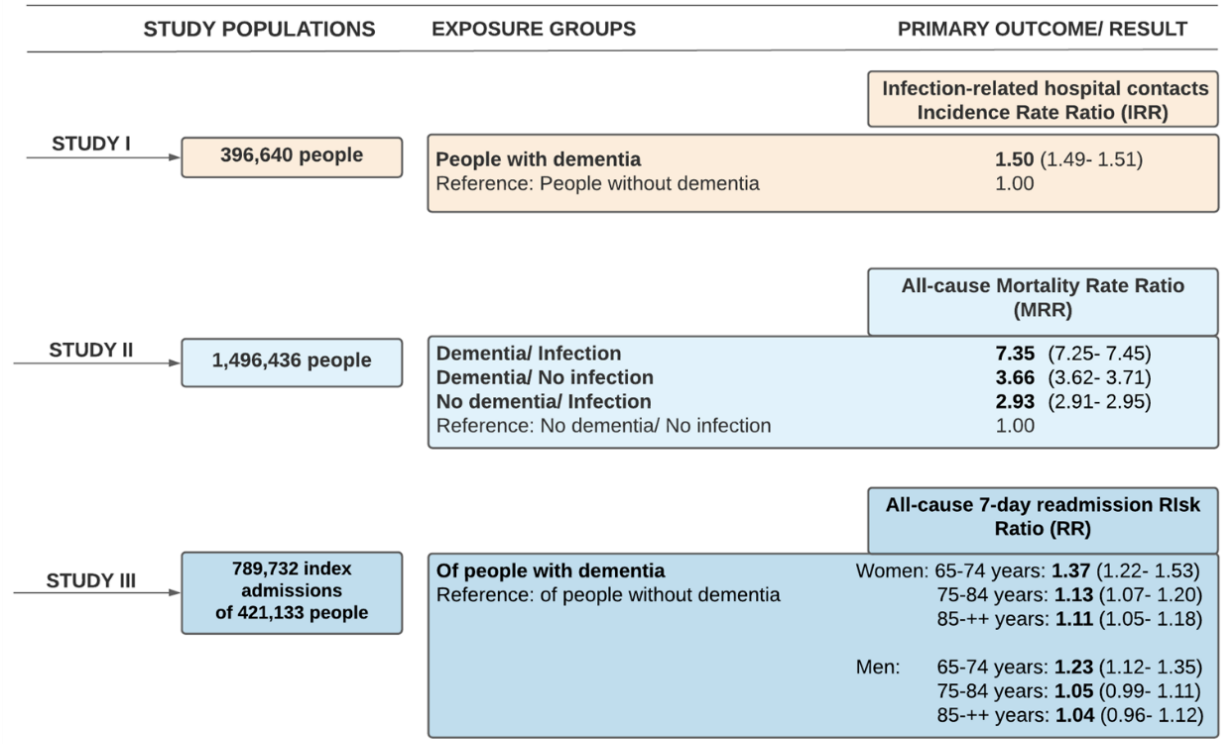
All-cause 7-day readmission was defined as an admission for any reason occurring within seven days of the discharge date of an infection index admission. For each readmission, the primary diagnoses were grouped into a) Any infection, further subdivided into: Linked infections (primary diagnosis of index admission and readmission were of the same infection site); sepsis; and other infections. b) Primary readmission diagnoses not of an infection were grouped as disease categories in the ICD-10 manual (e.g. other respiratory disease).[95] These are referred to as "reasons for readmission". Each infection index admission could be counted as both that and as a readmission for a previous one. A follow-up period of seven days (for secondary outcomes 30 and 90 days) was the risk period. If dementia was registered during follow-up, the infection index admission was not counted as such but was eligible to be counted as a readmission for a previous infection index admission of a person without dementia.

We used a generalized estimation equation model with a Poisson distribution and a log link function to estimate Risk Ratios (RR) between exposure groups, with 95% CI and stratified by sex and age. To account for repeated measures i.e. multiple admissions per person, the person was the random effect in the model. Due to possible competing risk of death, and because censoring was not possible, we computed mortality RRs. Each index admission could result in a readmission, death or neither. Seven-day readmission risks were estimated for infection sites. If there were primary diagnoses of several infection sites recorded in the same infection index admission, it was represented in several sites. Finally, in each infection site, we calculated the percentage of readmissions within each group of reasons for readmissions. If a readmission included multiple primary diagnoses that belonged to several groups of reasons for readmission, then we presented that readmission in all groups. Finally, three adjustment models were used (as in studies I and II and additionally adjusting for LOS). Age-strata are also adjusted for age. In a sensitivity analysis, we investigated whether readmission and mortality were different following index admissions due to other causes than infections.

4. RESULTS SUMMARY

Figure 4 presents the study populations and results' summary. In study I, 396,640 people with and without dementia were followed for 2,322,528 PYs (129,660 people with dementia followed for 403,744 PYs). In study II, 1,496,436 people with and without dementia were followed for 12,739,135 PYs (112,565 people with dementia followed for 354,456 PYs). In study III, the population was 421,133 people with at least one acute inpatient index admission for an infection (total of 789,732 index admissions eligible for 7-day readmissions), with and without dementia (34,599 people with dementia, and 72,103 index admissions with dementia). In summary, compared with people without dementia, people with dementia had a 1.5 higher rate for infection-related hospital contacts, had increased mortality following a first infection (7.35 higher mortality compared with the reference population), and the risk for readmissions was higher following infection index admissions of people with dementia (particularly for ages 65-74 years).

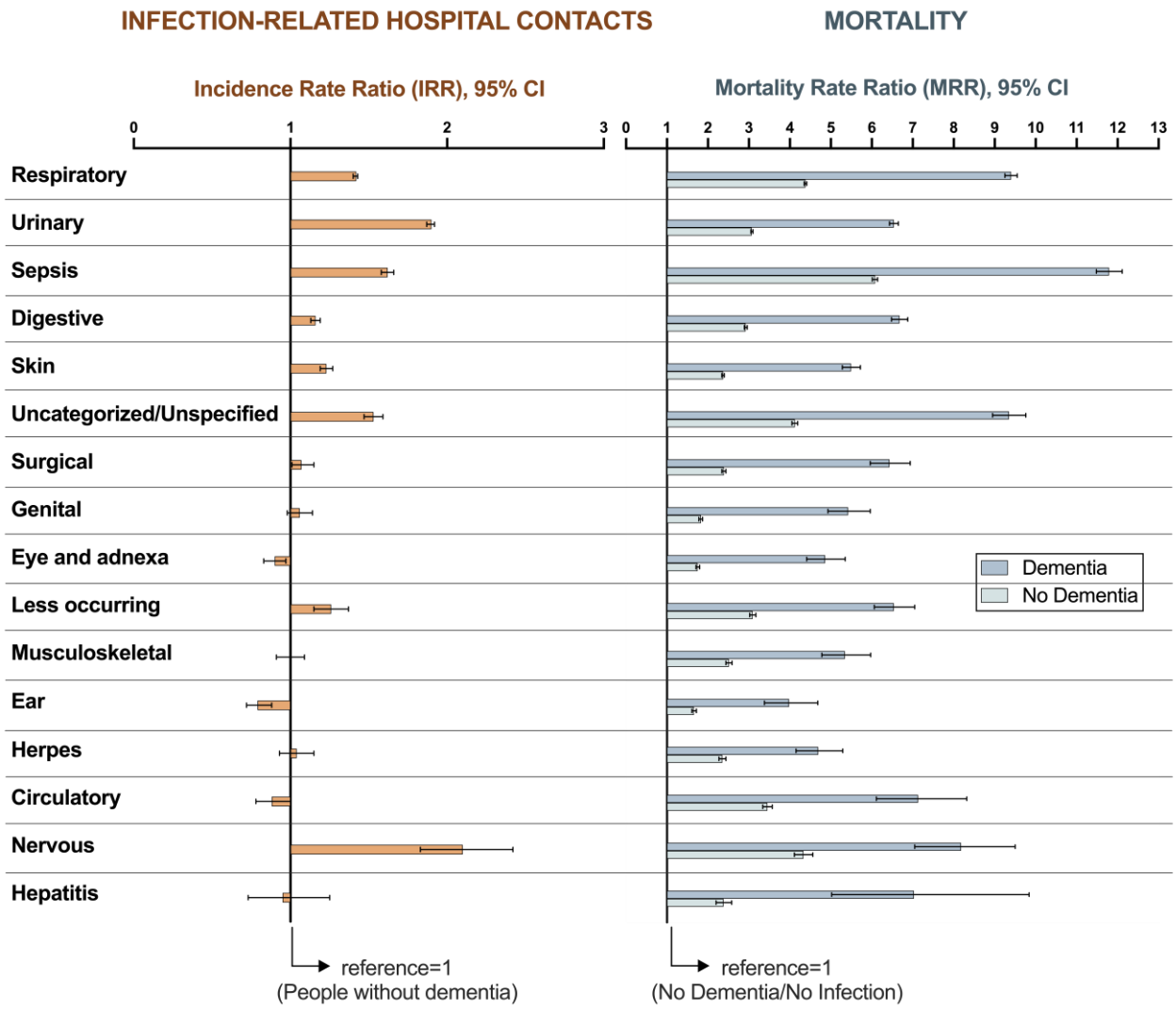
Figure 3. Summary of the study population and results of each of the three studies



	Study I	Study II	Study III
Total, Pyrs	2,322,528	12,739,135	-
Dementia, N	129,660	112,565	34,599 (72,103 index admissions with dementia)
Dementia, pyrs	403,744	354,456	-

Results from analyses by infection sites showed such associations in most but not all sites. Specific results for infection sites are presented in the following three sections for each of the studies. Figure 4 presents results in each infection site from study I (rates of hospital contacts) and study II (mortality). Infection sites are ordered by most to least frequent in our cohort data. Results from study III on readmission risks are presented later in Figure 5.

Figure 4. Results of studies I and II for each infection site



In each of the studies, majority of the entire study population and people with dementia were women (of people with dementia: 62% in study I and II, and 58% in study III). Mean age of incident dementia in our cohort (studies I and II) was 82 years.

Study I: Dementia identified as a risk factor for infection-related hospital contacts

During the study period, there were 97,586 infection-related hospital contacts (outcome) in people with dementia, and 280,848 contacts in people without dementia.

The fully adjusted IRR of any infection-related hospital contact was 1.5-fold higher in people with dementia compared with people without dementia (IRR= 1.50, 95% CI 1.49- 1.51).

The most frequent infections in people with and without dementia were those of the respiratory and urinary tracts. IRRs for most infections were significantly increased in people with dementia. The highest were for infections of the nervous system (IRR=2.10, 95% CI 1.83- 2.24), followed by those of the urinary system, sepsis, uncategorized infections, and infections of the respiratory system (IRR=1.42, 95% CI 1.40- 1.43). Infections of the genital and musculoskeletal systems as well as herpes and hepatitis were not significant, although herpes infections and those of the genital systems were slightly increased, while the other two were slightly decreased. Infections of the eye and ear and of the circulatory system showed decreased IRRs in people with dementia compared with those without.

IRRs for any infection were higher in men with dementia (1.62, 95% CI 1.61- 1.64) than they were in women with dementia (1.42, 95% CI 1.40- 1.43); were highest among the youngest in the cohort (65-69 years); and decreased with increasing age, remaining significantly higher in people with than without dementia in all age groups (65-69 years IRR= 2.50, 95% CI 2.36- 2.65; 90+ years IRR=1.19, 95% CI 1.17- 1.21). Five years prior to index date, a larger proportion of people with dementia than without had infection-related hospital contacts, with the biggest difference particularly seen during the year prior to index date (16.5% of people with dementia at index date vs 7.5% of those without dementia at index date).

Controlling for civil status and highest attained educational level slightly decreased the observed IRRs, while further adjustment for CCI had a smaller impact on the IRRs, although also decreasing the observed IRRs. Rates in people with and without dementia increased with higher CCI scores, but the relative rates were highest when comparing between people with no comorbidities. In a sensitivity analysis, the IRR for inpatient hospital admissions was 1.54 (95% CI 1.53- 1.55) while

the IRR for outpatient contacts was 1.12 (95% CI 1.09- 1.14). In the remaining sensitivity analyses, results showed robustness to any decisions we made for definitions and categorizations.

Study II: Increased short- and long-term mortality following infections in dementia

During the study period, there was a total of 575,260 deaths (outcome) in the cohort, where most deaths (77.4%) were in the Dementia/Infection exposure group.

The fully adjusted MRRs for the Dementia/Infection group was 7.35 (95% CI 7.25- 7.45) compared with the reference group, while the MRR was 2.93 (95% CI 2.91- 2.95) for the No dementia/Infection group. MRRs were higher in men than in women, when each compared with their respective reference group. The Synergy Index of 1.383 showed the presence of excess mortality in the Dementia/Infection group, bigger than the sum of the mortality risks following infections alone or dementia alone.

The most frequent infections in the study population were those of the respiratory urinary and tracts (as also observed in Study I). The MRRs for each of the infection sites were higher in people with dementia than without, when compared with the reference group without dementia or infections. The highest MRRs were seen following sepsis, and the lowest were seen following ear infections. The Synergy Index for each of the infection sites showed that some infections sites presented an excess mortality in people with dementia, while others showed statistically insignificant results. However, all these were in the same direction, except for herpes and ear infections (Figure 3 in study II).

Looking at the time since first infection (Figure 4 in study II), MRRs were higher in the Dementia/Infection group than No dementia/Infection in all time periods analyzed. MRRs were highest within the first 30 days of first infection (short-term mortality) and remained higher in the Dementia than No Dementia group even after 10 years of first infection (long-term mortality).

The adjustment models showed that adjusting for civil status and highest attained educational level made little difference on the observed MRRs and adjustment for CCI decreased the MRRs. Mortality rates were highest in the highest CCI score for all exposure groups. The relative mortality rate between people with and without dementia (all with infections) was however highest when

comparing people with no comorbidities. The sensitivity analyses yielded MRRs that were only slightly different than the ones observed in the main analysis.

Study III: Hospital readmissions following infections in dementia

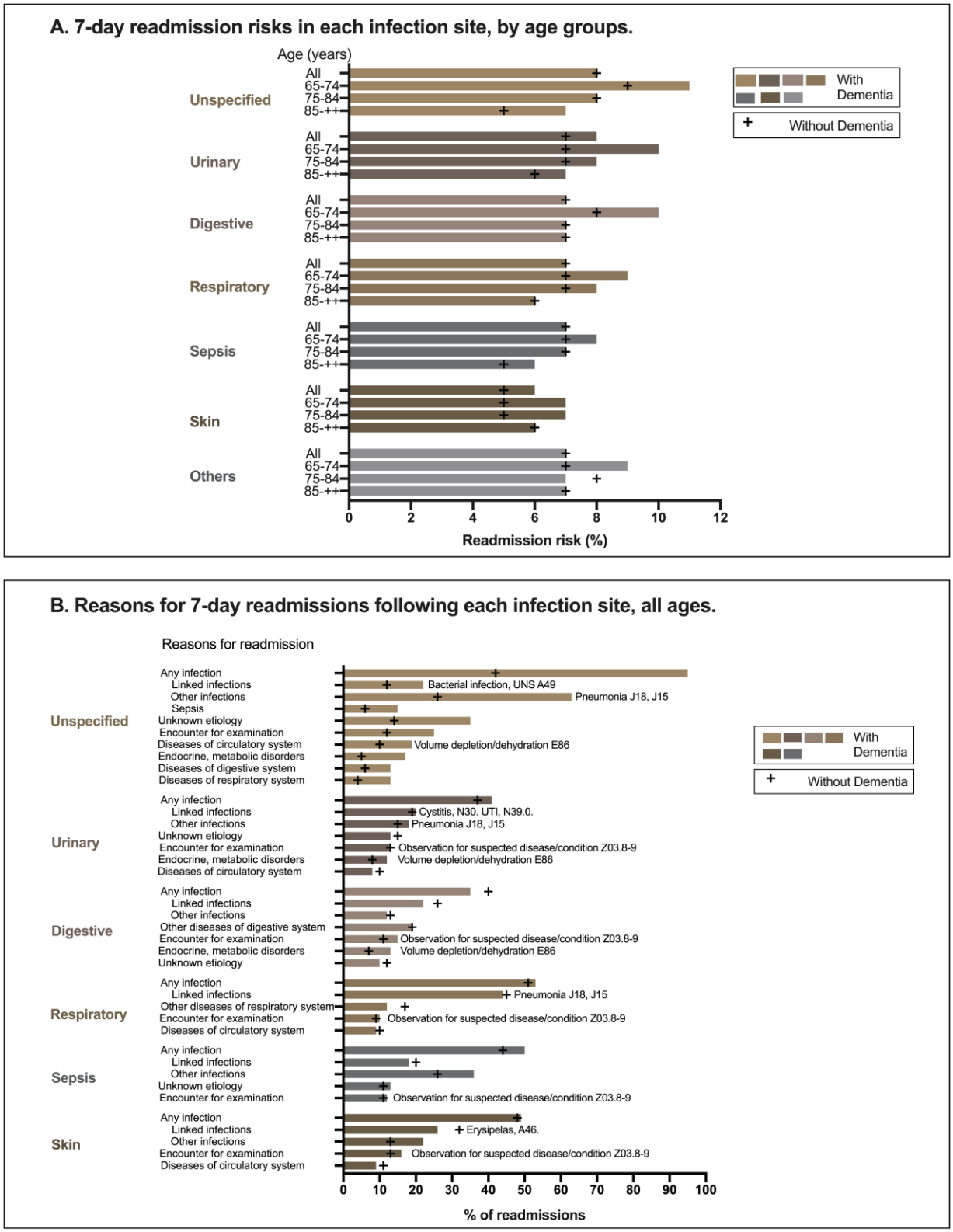
During the study period, there was a total of 55,303 readmissions within seven days (primary outcome), 161,550 readmissions in 30 days, and 259,745 readmissions in 90 days (secondary outcomes). Regarding death (competing risk in this study), there was a total of 78,732 deaths in seven days, 97,027 in 30 days, and 108,328 in 90 days. Interactions with sex and age were significant and results are stratified and presented accordingly.

The fully adjusted 7-day readmission RRs (readmission risk following infection index admissions of people with dementia relative to readmission risk following infection index admissions of people without dementia) were 1.37 (95% CI: 1.22 to 1.53) for women and 1.23 (95% CI: 1.12 to 1.35) for men in the youngest age group of the cohort (65-74 years). In the 75-84 years and ≥85 years age groups, 7-day readmission RRs were also increased in women, and a statistically insignificant yet increased RR was observed in men. Seven-day mortality RRs were also increased in women and men in all age groups (and higher in men).

For the secondary outcomes of 30- and 90- day readmissions, the observed RRs remained significantly increased in the youngest age group of the cohort in women only and were lower than those observed for the 7-day readmission outcome. The 30- and 90- day readmission RRs were statistically insignificant or slightly decreased in the 75-84 age group for both women and men. Finally, in the oldest age group, 30- and 90-day readmission RRs were overall slightly decreased in women and men.

We observed a trend where readmission RRs were highest within seven days and in the youngest age group and got smaller both with increasing age and with longer follow-up period (Figures 3 and 4 in study III). For mortality, the observed trend is that RRs were highest within 90 days and in the youngest age group, and similar to readmission RRs, these got smaller with increasing age, but unlike readmission RRs' trend, mortality RRs got larger with longer follow-up period.

Figure 5. Seven-day readmission risk by infection site reprinted from Janbek et al [96]



Category "Others" pooled infection sites with <2000 infection index admissions. If an index admission had primary diagnoses of multiple infection sites, it was categorized in multiple sites. Presented reasons for readmissions are those that comprised ≥10%. Primary readmission diagnoses are those that comprised ≥50% of all primary diagnoses.

Results also showed that higher 7-day readmission risks for people with dementia than those for people without dementia were seen across all infection sites and mainly in the youngest age group (65-74 years). The most common reason for 7-day readmissions was any infection (including linked infections and other infections), and reasons varied across infection sites. Most notably, for unspecified infections, all presented reasons for readmission were higher in people with dementia than without (Figure 5). Here, of all readmissions of people with dementia, 95% were due to infection (22% due to unspecified infections, 63% due to other infections of which pneumonia was the most common, and 15% due to sepsis), and of all readmissions of people without dementia, 42% were due to infection. Another reason for readmission that was notably more frequent (in more than one infection site) in people with dementia than those without was volume depletion/dehydration. We also found that for linked infections in all infection sites, the most common primary readmission diagnosis was also the most common infection index admission primary diagnosis.

Adjustment for civil status and highest attained educational level made essentially no changes to the readmission and mortality RRs, while further adjustment for CCI yielded larger (yet only very slightly) readmission RRs and larger mortality RRs.

Finally, in our sensitivity analysis, readmission and mortality RRs following index admissions for causes other than infections were overall smaller than those observed in our main analysis for infection index admissions, and mostly insignificant (e.g. 7-day readmission RR in women in the age group 65-74 was 1.03, 95% CI 0.95- 1.11; and in men 1.04 with 95% CI 0.98- 1.11).

5. DISCUSSION

In this section, I will discuss the results of the three studies, divided into four subsections. In the first, I will discuss the increased rate of infection-related hospital contacts in people with dementia; in the second and third, I will discuss the two adverse outcomes following infections (mortality and readmissions); and in the last subsection, I will present the knowledge gained in this thesis for the infection sites. Throughout, I directly compare estimates from our studies to those of previous work where there were relevant previous studies. Studies that only reported on outcomes for specific infections are discussed later in "Infection Sites". Of note, all relevant previous work on mortality and readmission was focused on selected infections.

Infection-related hospital contacts in dementia

People with dementia have 50% increased risk of infection-related hospital contacts compared with people without dementia, and infections may be an early sign of dementia. Perhaps the most relevant studies to compare with are by Phelan et al[35] and Tolpannen et al[44] that investigated incidence rates of hospitalizations in people with and without dementia where infections were one category of hospitalization diagnoses. For this category, the authors reported rate ratios of 1.31 (95% CI 1.11- 1.53) in people with AD[44] and 2.01 (95% CI 1.15- 3.52) in people with dementia,[35] both compared with those without AD or dementia. One other study by Tuppin et al found a 1.90 hospital admission risk following infectious disease (95% CI 1.7- 2.2) in people with dementia relative to those without.[37] Our findings are consistent with these and magnitudes varied (as well as the size of CIs) due to varying infection code algorithms included, focus of AD in one study, and methodological differences. Other studies also found increased risk of hospitalization for any infection in people with dementia than those without dementia[40] or without AD.[42]

Such increased risk reflects possible pitfalls in dementia care. It also begs the question of whether biological mechanisms underlying interactions between infections and dementia have a role for these pitfalls and thus contribute to explaining our findings. Such interactions could include that infections develop faster and more seriously in people with dementia (i.e. they may be sicker than others) due to e.g. frailty, increased central nervous system vulnerability to metabolic effects of such acute infections,[35] and it's been proposed that an impaired blood brain barrier may predispose them to infections.[22,23]

Pitfalls in dementia care that can be behind increased risk of infection-related hospital contacts may be taking place over several stages.

The first is infection prevention. As presented in the background, people with dementia may be more susceptible to infections due to several patient and social factors. These include altered hygienic habits and reduced self-care such as ensuring proper hydration, nutrition, and mobility for which people with dementia need external and specialized care.[20,24] Thus, failure in dementia care to address such factors and prevent infections may cause more frequent infections, which may be what is reflected in our observed increased rates in hospital contacts in people with dementia.

The second is infection detection i.e. identifying early signs of infection. Challenges in communicating symptoms of infections in people with dementia, together with atypical symptoms of an infection[27,97] means that often, the only visible sign of an infection is a change in the person's mental state, or confusion that accompanies an infection.[24] Such behavioral symptoms might be misattributed to dementia rather than the underlying infection.[30] Failure to identify these as infection signs (or as signs that prompt assessment for an infection) leads to the infection remaining undetected until it reaches a severity point that requires a hospital contact. It can be the caregivers or care personnel (e.g. at a nursing home) who overlook early signs of infections, meaning that the person never presents to the healthcare system (i.e. primary care) before the infection becomes severe. Alternatively, the person may present to the primary care and if infection signs are not identified (e.g. misattributed to dementia), the infection may be undetected. Regrettably, our data don't indicate whether it's one or the other. It's been previously shown that people with dementia are actually less likely to have primary care contacts,[98] while other studies showed the opposite.[37] Identifying what the case is for infections is crucial for shaping interventions.

The third is infection management i.e. providing care for the dementia patient with a detected infection. People with dementia need external care to carry out daily activities that are crucial for proper infection management e.g. hydration, nutrition, toilet habits, and adherence to infection treatment. Lack of such care, together with the possible biological interactions between infections and dementia, may lead to severe infections or their consequences requiring a hospital contact.

In total, our findings are likely a combination of more frequent infections than in people without dementia, and that these are more frequently resulting in hospital contact. Therefore, this reflects an equity issue in attitudes and the receipt of needed care. The healthcare system is responsible to ensure proper healthcare for everyone, also considering the aforementioned possible pitfalls in dementia care even when these are not directly perceived as attributed to the healthcare service but are simply a patient characteristic. For example, if people with dementia are less likely to present to the healthcare system (primary care) for their infections, awareness is needed of patient characteristics and disabilities that may hinder such healthcare seeking patterns. Thus, awareness of the need for more specialized and personalized care for people with dementia is required.

However, another plausible explanation for the observed increased risk could be that people with dementia are hospitalized as soon as something wrong is suspected (i.e. perhaps not severe infections), or they are over-diagnosed. We did not have data on infection severity at the time of the hospital contact. However, the risk for inpatient admissions was substantially higher (54%) than for outpatient contacts (12%), indicating that infections may be left undetected until severe (i.e. require an inpatient admission). Previous studies documented decreased outpatient visits but increased inpatient admissions for people with dementia for all causes,[37,44] but did not focus on infections. While our results do not show decreased outpatient contact rates, they were lower for such contacts than for inpatient admissions. Further, the excess mortality following infections (in studies II and III) together with our finding that infection-related hospital contacts were increased even before a dementia diagnosis may also indicate that people with dementia have more severe infections at time of hospitalization (and not a case of unnecessary hospitalization).

Highest risks of infection-related hospital contacts were in the youngest dementia patients (65-74 years), consistently with previous studies on all-cause hospitalization[37] and those for UTIs, pneumonia, sepsis, and infectious disease.[40] Older dementia patients may be less likely to be hospitalized. Firstly, accompanying confusion or delirium are more likely to be misattributed to dementia rather than suspected as a sign for underlying condition (i.e. infection) in older patients.[40,99] Secondly, for older patients with dementia, general practitioners, care personnel, and family members may be more reluctant to hospitalize,[100] especially in advanced stages of dementia, nursing home residents, and terminal patients.[101] For these patients, weighing hospitalization and treatment burden against benefits is often at the core of dementia care.[101] Often,

decisions to hospitalize are parallel to decisions to treat e.g. pneumonia requires IV treatment at the hospital.[102] Here, treatment goals shift between function maintenance, comfort, and life prolongation and several ethical and treatment considerations come into play (e.g. antimicrobial resistance). Decisions not to hospitalize older dementia patients, together with increased contacts in older patients without dementia thus explains the observed decrease in risks with increasing age. Of note, our observed rate ratios decreased only slightly (39%) when we removed people who died within a year of the index date. Thus, results do not reflect hospitalization in end of life only.

We also observed that rate ratios were higher for men, which may reflect higher incidence rates for the most common infection (respiratory infections) in men with dementia, as previously reported.[99] Moreover, highest rate ratios were for people with dementia and no comorbidities (compared with those without dementia or comorbidities), which means that the increased risk for infection-related hospital contacts is most pronounced for people with dementia who are less severely burdened with other diseases, likely suggesting that our findings can be attributed to dementia disease and its consequences.

Factors related to dementia pathology (e.g. declines in cognitive and functional abilities) that increase vulnerability to infections are already present years before a dementia diagnosis is registered. Thus, increased infection-related hospital contacts in the previous five years may be "red flags" for a coming dementia diagnosis. Our findings may also reflect episodes of e.g. delirium that accompany severe infections increase the chance that a person is investigated for and subsequently diagnosed with dementia. It can also be that these episodes may accelerate the cognitive decline process and unmask a clinical dementia, which has been underway already.[103,104] Whether infections accelerate cognitive decline or possibly cause dementia is being continuously investigated,[60,63,105,106] however our study cannot and does not claim this, but rather encourages further investigations on the matter.

Adverse outcomes; mortality

Increased mortality risk (studies II and III) can be explained and further built on in the context of a) dementia care prior to, during, and following the hospital contact with infection; and b) possible biological and pathological mechanisms underlying interactions between infections and dementia.

Regarding dementia care, prior to a hospital contact, the lack of timely infection detection may result in severe infections and severity may be a reason for increased mortality in people with dementia. During the hospital contact, diagnostic challenges of infections may result in poor management and treatment of the infection, leaving it untreated and eventually leading to increased mortality. Studies have shown that failure to identify the site of infection or the pathogen – in sepsis – results in increased mortality, and so does ineffective antibiotic treatment (due to possible misdiagnosis).[55,107] Following a hospital contact with a severe infection, people with dementia may become even more reliant on help from others, their functional levels decline further, and their overall health deteriorates increasing the risk for further complications and adverse events.

Regarding possible biological mechanisms, while the short-term increased mortality (within 30 days of an infection) may well be attributed to the infection itself, the observed increased long-term mortality – especially after 10 years of an infection – may be more reflective of a long-term impact of an infection on overall health or on neurodegeneration. It has been hypothesized that infections play a role in cognitive decline and dementia progression,[106] which may ultimately increase mortality.[108] Deterioration in cognition due to e.g. delirium accompanying a severe infection may accelerate cognitive decline in people with dementia,[109] and may also explain increased mortality.[110] A recent study found that infection-related hospitalizations in nursing home residents were associated with immediate and persistent cognitive decline,[111] and other studies have documented cognitive decline following an infectious episode in persons who did not have dementia.[112,113] Further, previous studies have also documented increased mortality in people with dementia regardless of failures in infection management during the hospital contact[55] and despite treatment.[57] Thus, perhaps just getting a severe infection leads to increased mortality, possibly through its impact on dementia progression. Further, in study II, we noted an excess mortality due to the interaction of infection and dementia that went beyond the risk of mortality for infections alone or for dementia alone or even the sum of the two risks. Such an interaction may be indicative of a biological interaction[92] in the combination of infections and dementia and may support infections' role in dementia pathology.

In total, the infection might start a cascade of events (including cognitive decline and overall poorer health) that each on their own and all together lead to increased short- and long-term mortality. This has been referred to previously as "cascade iatrogenesis", which describes the serial

development of several events/complications that have been set in motion by what seemed to be an innocuous first event.[114] In this case, one infection could be the trigger for such events. This is in keeping with our finding that increased mortality was also seen in our study (in the same magnitude) in people who only had one infection during the study period.

In study II, an infection included primary or secondary diagnoses during inpatient and outpatient contacts. It is therefore possible that the observed increased mortality could be attributed to the primary reason for the hospital contact (where an infection was also diagnosed), especially if such primary reasons differed in people with and without dementia. However, in study III, we estimated mortality risks following inpatient admissions where an infection was the primary admission reason. Here, mortality risks were also substantially more increased for people with dementia.

Mortality was higher in men (studies II and III) and highest in the youngest age group (study III, following acute admissions only), consistent with previous findings.[55,58,115,116] It's also relevant to note the increased mortality in people with dementia and no infection, compared with the general population, as also previously reported.[108] Further, we noted that the reported increased mortality was despite comorbidities, as also previously documented in people with dementia and no infection,[117] and in one study also people with dementia and sepsis.[55] Thus likely attributing mortality risk to dementia and the interaction with infections.

Adverse outcomes; readmission

Another adverse outcome of hospitalization with infections in people with dementia is readmissions. If a person is acutely hospitalized and the reason is treated, and discharge appropriately managed, then ideally, we would see zero – or realistically – close to zero readmissions. If this is not the case and if a person's risk of readmission is then also higher because the person has dementia, we have an issue.

The observed increased risk of 7-day readmission in people with dementia compared with those without can be either due to the quality of healthcare provided to the patient upon hospitalization, or due to patient characteristics, and the interplay of these is important.[118] This issue revolves around dementia care prior to, during, and following hospitalization with an infection.

First, acute hospitalizations with severe infections (due to e.g. delayed diagnosis) leads to poorer health and further declines in functional levels which can result in complications that may lead to readmission within a short period of time.[51] Examples of such complications are malnutrition[119] and dehydration.[120] We found in our study that dehydration was a common reason for 7-day readmissions after infections and was a notably more common reason in people with dementia.

Second, challenges in infection diagnosis may result in misdiagnosis during hospitalization, thus leaving the infection undertreated and results in a readmission shortly after discharge.[33] Further, poor discharge planning for dementia patients may also increase readmission risk.

Third, impaired cognition, further declines in functional levels, and lack of caregiver support post discharge may hinder treatment compliance and ability to follow discharge plan.[33,121] This would also leave the infection undertreated and result in readmission.

The most common reason for readmission in people with dementia was infections. These included both linked infections (of the same site as the initial infection), and other infections (of a different site than the initial infection). This supports these issues of possible misdiagnoses of infections, inappropriate discharge planning, and insufficient post-discharge care.

Finally, hospitalizations for patients with dementia might put them at higher risk for a new infection (hospital-acquired infections), which is in keeping with our finding that "other" or "new" infections were a common reason for readmission. These "other/ new" infections could have been hospital-acquired or a resulting complication of the initial infection, which might be more common in people with dementia.[51] However evidence on this is scarce, and generally, there is a lack of evidence on whether the risk of hospital-acquired infections for people with dementia is higher, and thus this remains speculative. Previous research has shown that associations between hospital-acquired infections and readmissions in older adults (without focus on dementia) were not explained by factors related to vulnerability to infection and readmission risk, but rather were likely due to failure in treatment and post-care transitions from the hospital.[52]

Readmission risks were higher for people with dementia than without in the youngest of the cohort and decreased with increasing age, consistent with previous findings.[40,49] This trend may be in

keeping with the reluctance of hospitalizations in older dementia patients and nursing home residents. Previous evidence is inconsistent regarding whether readmission risks were lower for nursing home residents.[33,48,52,122]

Overall, the readmission risk disappears in longer follow-up periods, partly explained by the increased competing risk of death.

Readmission risk ratio was higher for women with dementia than men. There is not much data to compare this with. Two previous studies (not focused on infections) documented that women with dementia were at lower risk for 30-day readmission[33,123] but were at higher risk for three month readmission.[123] In one of the studies, the authors found that risk factors associated with readmission also varied by sex, and what predicted the risk for men (e.g. fewer cohabitants) was not a predictor for women.[123] Thus, the discrepancies between our results and the two studies could be due to different factors (not assessed in our study), or be because we focused on infection admissions while the previous ones were on all-cause admissions.

Finally, in our study III, readmissions risks in people with dementia (compared with those without) were higher after a hospitalization for an infection rather than for other causes than infections. This further highlights the excessive burden of infections in dementia. However, grouping all other causes may have masked that risks were decreased for some causes and increased for others.

We noted in our study that index admissions of people with dementia were with less comorbidities than for people without dementia. However, this does not directly reflect the comorbidity burden in people with dementia since people without dementia also had markedly lower mortality and could thus accumulate more comorbidities than people with dementia. At least one previous study has noted the same trend in people with and without dementia hospitalized for sepsis.[55]

Infection sites

Infections investigated in the studies of this thesis are of course different from each other and the underlying mechanisms for the investigated outcomes vary per infection site and type, thus the point here was not to claim a common pathway between all infections that explains the outcomes, but rather to comprehensively include them all, to compare them and provide new knowledge on

where the focus should be. Looking at the different infection sites and the difference in risks will hopefully allow for hypotheses and further investigation of underlying factors and mechanisms.

Most frequent infections in people with and without dementia were of the respiratory and urinary systems and sepsis, as also previously documented in literature.[16,17] Increased hospital contacts, readmissions, and mortality have been shown for these infections and our results are consistent with such findings (detailed below). However, direct comparison of such associations in people with and without dementia for other infections are close to non-existent.

In our studies, the most frequent infections after the three already mentioned were infections of the digestive site, skin infections, and other uncategorized/ unspecified infections. Readmission risks were only calculated site-specific for these six most frequent sites that all showed increased 7-day readmission risk in people with dementia (especially in the youngest). In all these six sites, there were also increased rates of hospital contacts and mortality in people with dementia as well as excess mortality. Similar trends were observed for nervous infections, surgical infections, and those that were less occurring in each of the studies.

For the remaining infection sites, there were no increased rates of hospital contacts, and while all sites showed higher mortality in people with dementia than in people without dementia, these infection sites had no excess mortality due to interaction with dementia (except for genital infections). Insignificant – or decreased – estimates can be attributed to small sample sizes for some of these sites, or to actual differences in the observed outcomes in these sites e.g. differences in symptom expression and visibility. Also, if decisions to hospitalize differ between people with and without dementia for certain infections, then they will remain undetected in our study.

It is interesting that nine infection sites showed an increase in both rates of hospital contacts and excess mortality, while neither were increased in the remaining sites (except the genital site). One could cautiously speculate on a link between the outcomes where increased risk of hospital contacts in people with dementia indicates more severe infections that also result in excess mortality. However, due to small sample sizes in some sites, and considerations regarding the use of the synergy index to estimate excess mortality, this remains purely a speculation.

I would like to draw attention to the uncategorized/ unspecified infections. Majority of these are diagnoses of e.g. general bacterial infection. For these, there was a 53% increased rate for hospital contacts, they had the second highest mortality rate in people with dementia as well as an increased excess mortality, 7-day readmission risks after such infections were the highest of all sites, and unlike other sites, all reasons for readmission were notably higher in people with dementia than without. Most notably, 95% of all readmissions were also due to an infection. The three studies together indicate that people with dementia are more likely to have hospital contacts where an unspecific diagnosis of an infection is given (in keeping with the diagnostic challenges) and that such possible misdiagnosis results in an increased readmission risk and higher mortality. Indeed, it's been shown previously that not identifying the infection site or pathogen in people with dementia hospitalized with sepsis showed an even more increased mortality.[55] Misdiagnosis may lead to failure of treatment, and ineffective antibiotic treatment has previously been shown to also increase mortality.[107]

The highest rates for infection-related hospital contacts among all sites were seen for nervous infections, of which most the common were bacterial meningitis and viral encephalitis. Both have could be mistaken for a dementia disease, as they may present with similar clinical symptoms.[124] However, we did not find that a dementia diagnosis was recorded close to a diagnosis of one of these infections. Also, important to note are the wide CIs and small sample size in the nervous infections site. This is a finding that has not been previously reported and needs further investigation.

All infections showed increased mortality in people with dementia. Infections generally seen as non-life threatening (e.g. eye and ear infections) also increase a person with dementia's risk of dying. This should not be phrased as dying *from* an infection but rather *following* an infection. As mentioned above, infections may trigger a cascade of adverse events that ultimately result in death.[114] Whether an infection is that first event and what series of following complications occur is where the value lies. This further highlights the importance of looking at all types of infections.

The external validity of our findings for each infection site is difficult to explore since there are few previous studies to date, and these only included pneumonia (mainly), followed by UTIs, sepsis, and in a few also gastroenteritis. Phelan et al. reported a rate ratio of 1.88 (95% CI 1.25-

2.82) for hospital admissions with bacterial pneumonia and 3.38 (95% CI 1.93- 5.93) for UTI in people with dementia.[35] In our study, respiratory infections showed a rate ratio of 1.42 (95% CI 1.40- 1.43) and 1.90 (95% CI 1.87- 1.92) for urinary infections. This is a consistent trend with findings of Phelan et al but with varying magnitudes. This is likely due to methodological differences, difference in infection algorithm and categorization, and study population difference (hence the wide CIs in the previous study). As for outcomes of mortality, the two most relevant studies were by Bouza et al[55] and Graversen et al.[49] Bouza et al found a 1.32 odds ratio (OR) for in-hospital mortality after sepsis in people with dementia compared with those without.[55] In our study II, sepsis showed the highest MRRs, but the two studies cannot be directly compared. The study by Graversen et al reported a 30-day MRR of 2.29 (95% CI 2.21- 2.37) following pneumonia admission in people with dementia.[49] In our study, respiratory infections showed an MRR of 9.40 in people with dementia, a much higher rate probably mainly because the reference group in our study was people with no infections unlike theirs. In the same study by Graversen et al reported a 7% increased 30-day readmission rate in people with dementia (following pneumonia admissions), that was highest in the first days immediately after discharge and highest in the youngest cohort members.[49] As we did not investigate 30-day readmission risks for infection sites in our study, we cannot directly compare findings. Nevertheless, consistently, we found higher 7-day readmission risks in people with dementia relative to those without for respiratory infections, especially for the youngest in the cohort. Consistently, one other relevant study, by Knox et al also found increased OR for readmission after pneumonia for people with dementia relative to those without (OR 2.9, 95% CI 1.93- 4.40).[48]

Additionally, several other studies (generally smaller and based on selected population groups) have consistently reported increased hospitalization for people with dementia where common reasons were UTIs,[32,34,37,38,40,45] pneumonia,[32,34,37,40] sepsis,[32,40] and gastroenteritis.[37,38] Such studies also reported increased mortality and readmission risks following pneumonia (mainly) and in a few also UTIs and sepsis.[33,47,50,51,56,125]

Strengths and limitations

Detailed strengths and limitations are discussed in each paper. Here, an overview of the main strengths and limitations are presented to give a better context to the interpretation of our findings.

All studies in this thesis were based on registry data, which have several strengths: 1) these cover the entire Danish population, and record all civil/administrative information on the population continuously as well as the vast majority of all healthcare contacts due to the free of charge services for everyone; 2) data have high validity and completeness for epidemiological research, although it varies depending on the data and specific diagnoses used;[73,126–129] 3) common issues of non-participation or loss to follow-up were practically negligible;[128] and 4) data allow to study the entire nation as one dynamic cohort.[73] The latter gives statistical power, which means we get precise estimates without the risk of overlooking small effects (hence no risk of random error). This also means that statistical significance might result from possibly clinically irrelevant associations, and thus results are discussed thoroughly. Our studies also presented important methodological refinement over previous work. In addition to the mentioned points above, we assessed rates of hospital contacts and mortality from recorded incident dementia and for 15 years. Utilizing the entire nation allowed for comparison of population rates of outcomes between multiple groups and with appropriate reference populations e.g. people with and without dementia, people with and without infection-related hospital contacts. We also used time varying adjustments which allowed for proper prospective follow up. Calendar year as a time-dependent variable was included, which accounted for any coding or registration practices over the years. Moreover, we conducted several sensitivity analyses to test the robustness of our findings. Finally, we do not claim causality from our reported associations. Nevertheless, findings from such nationwide and population-based observational studies with high validity (both internal and external) over 15 years provide a solid building block on which future research can build important hypotheses.

Important to note however is that registry data were not originally collected for research purposes, which can mean possible issues of information bias, residual confounding, and lack of some information interesting to include for specific studies. I will present these within the coming subsections: information on dementia, information on infections, confounding, and other limitations.

Information on dementia

Dementia diagnosis in the NPR has a high validity as shown in a validation study conducted based on patient records and interviews that found that a registered dementia diagnosis was correct in 86% of the patients.[127] However, information bias is important to consider here. A registered

dementia was defined as either a diagnosis or a redeemed anti-dementia medication. Further, a mini review from 2009 showed that prescription data in the NPrR are both valid and reliable for epidemiologic research on the use of medicine.[130] Since diagnoses given in the primary care setting are not available in the registries, medication redemption in the NPrR may be used as proxy for diagnosis. Not everyone diagnosed with dementia would get medication, and thus if a person was diagnosed outside of the public secondary healthcare setting (no registered diagnosis with an ICD code) and did not redeem anti-dementia medication, this remains undetected in the registries. Further, people living with dementia may not all be diagnosed. These could be cases in early stages of dementia not yet diagnosed, cases not seeking help thus not diagnosed, and cases in advanced stages of dementia for whom a diagnosis may have been deemed unnecessary. In 2015, there were around 36,000 people living with dementia in Denmark, and the estimated number is around 80,000.[9] In total, such information bias may have resulted in misclassification which was likely non-differential and our results in this case would be under-estimated. To limit this, in study I, we chose to match each person with dementia with three randomly chosen people with dementia, and in the remaining studies, the reference group was big enough to avoid the effect of possible misclassification.

Registered diagnoses of the subtypes of dementia are of low validity and thus subtypes were not used in any of the studies of this thesis.[127,131] We also did not have information on dementia severity or cognitive and functional measures at the time of diagnosis or longitudinally. Although we included incident dementia cases (except in study III), people with dementia are diagnosed at different severity stages, and this means that included dementia cases were in different stages of severity and our defined date of diagnosis does not mark the onset of disease. Lack of information on all these dementia disease-specific factors probably did not directly bias our findings, however investigating these could have resulted in more detailed findings relevant for identifying specific patient risk groups, as well as furthering understanding of possible underlying biological mechanisms in the interactions between infections and dementia. Increased mortality generally,[132–134] and due to pneumonia, have been found to be related to dementia subtypes,[135] but what subtype shows better survival is somewhat inconsistent (e.g. AD was shown to result in favorable survival,[132–134] but in one study it was shown to increase pneumonia-associated in death).[135] Further, the role of these factors for the risk of hospitalizations (all-cause and including infections) remains inconsistent or generally inconclusive[34,35,41,100,136] but points towards no difference across

subtypes.[46] Interactions between dementia subtypes and different infection types is also of interest to further understanding on dementia pathology, and to shape targeted interventions reducing adverse outcomes according to infection type.

Lastly, we did not include dementia in Parkinson's disease in our definition using ICD codes. However, we did include cholinesterase inhibitors medication group. These are prescribed for AD, Lewy body dementia, and dementia in Parkinson's disease. As such, our dementia cohort could include some persons with dementia in Parkinson's disease.

Information on infections

There is generally a lack of validation studies on infection diagnosis codes in NPR, which means that what the results reflect is registered infection diagnoses rather than the presence or absence of the infection. Perhaps the best and most relevant example is UTIs. These are commonly over-diagnosed and overtreated due to diagnosis difficulties[45] resulting possibly in over-estimation of the presence of the UTI among older adults and people with dementia, particularly if a more liberal approach in diagnosis is practiced in people with dementia. However, our data did identify everyone in the cohort who had an infection-related hospital contact. From available validation studies on infection diagnoses in the NPR, the positive predictive value (PPV) ranged between 72% to 98%, depending on the infection type.[137–139] Bacteremia and septicemia showed lower PPV in three studies.[140–142] Generally, broader categorization of infection types had higher validity than for specific types[137,139] hence the decision in our studies to categorize infections in broader infection sites. Further, two studies have shown higher validity in more recent years (2011/2012 vs 1994-2000).[141,142] However, since PPVs are highly dependent on the prevalence of the disease (the infections investigated) in the study population, results from the mentioned studies may not be directly comparable with those in dementia patients or the elderly population as a whole, and variation in the validity of the types of infections is expected due to a different infection susceptibility profile in the elderly (and especially those with dementia) vs younger adult populations or other specific patient groups (e.g. cancer patients).

We did not have information on infection severity or on infection diagnoses in the primary care. Infections in the primary care were not included in our studies because the focus was on hospital contacts, and because diagnoses in the primary care are not recorded in the national registries. One

could of course use redeemed anti-microbials as a proxy for infection, however that also comes with challenges such as precisely identifying the specific infection. We did not distinguish infection discharge diagnoses by relevant groupings such as community vs hospital acquired infections, medical vs surgical patients, and by type of pathogen i.e. bacterial, viral. We also did not investigate the impact of co-infections for our outcomes. Like the dementia disease-specific factors we did not have information on, these information on infections probably did not directly bias our reported associations but investigating these could have important value that explains our results further. Research on primary care infections can further our understanding on whether patients with dementia are presented to the primary care but not managed adequately or whether they do not present at all. It can also show whether infections treated only in the primary care are also associated with adverse outcomes in similar ways as hospitalizations. Investigating severity of infections both in primary care and at time of hospitalization is necessary for determining its role in both readmission and mortality risks. Another interesting factor to explore is whether certain combinations of infections are more common in people with dementia and if adverse outcomes are more serious in such combinations. Finally, distinguishing community- from hospital-acquired infections is important for shaping future interventions.

Confounding

The lack of data on potentially important confounders such as lifestyle factors, frailty, nursing home admission, medication use, and delirium could have explained part of the observed associations. We accounted for education and civil status that are related to lifestyle. However, information on these for some individuals in our cohort was missing, and lead to suboptimal adjustment for these factors. Generally, older cohorts in our studies meant that many people were registered with low education according to our categorization, and re-classification of these might have been relevant. Further, we did not include information on economic status (income) which may have accounted for some of the associations as well as it's been shown to predict mortality.[143] In total, socio-economic status was likely not ideally accounted for, and residual confounding remained. As for the remaining potential confounders, more thorough considerations are warranted. Frailty and reduced activities of daily living, polypharmacy, and delirium are all related to dementia,[144,145] have been documented as risk factors for excess mortality (and some indications for further cognitive decline e.g. for delirium and frailty),[109,144,146–149] and for all-cause and infection-related hospitalizations.[100,148,150,151] Similarly, nursing home admissions is a potential

confounder and may serve as a proxy for dementia severity and – as discussed earlier – decisions and hospitalization patterns may be altered there and distort our associations.[100,101]

We did not include information on these factors because 1) we did not have data to measure activities of daily living or frailty (often includes measures of e.g. weight loss, muscle grip, mobility)[146,148,152,153] 2) available data on nursing home admissions is of low validity,[154] and 3) while listed factors might potentially have a confounding effect, the relationship with dementia might be complex and need careful considerations where concepts may e.g. overlap and diminish the effect of the studied exposures. Further, inclusion of these would result in multiple timelines as they would need to be included time-dependently and can complicate interpretation of results.

Nevertheless, these certainly give important information on our explored associations. For example, targeted interventions may benefit from understanding the degree of impact that self-care and dependency on external care has on our outcomes. Such knowledge can translate into establishing competent care that meets the individualized needs of people with dementia.[146,153] Accounting for delirium can give better understanding of the role of infections in e.g. cognitive decline where at least one recent study found that hospitalization without delirium did not influence cognitive decline.[109] Further, a paper reflecting on our study I has been published bringing to light important considerations regarding dementia, infection, frailty, and delirium.[145] These were presented as loops with infection at the center, and marked the complexity of these phenomena where future – especially interdisciplinary – research is key to start disentangling these loops.

We did not have genetic information in our data, and research into whether apolipoprotein E (ApoE4) allele may explain increased predisposition to severe infection and mortality in people with dementia and ApoE4 would be interesting, as some research has suggested,[155] including that on COVID-19 has suggested.[156] In this regard, such information can further understanding of the underlying mechanisms between infections/ inflammation and cognitive decline. The interaction of ApoE4 and inflammatory markers e.g. c-reactive protein for cognitive outcomes is continuously tested.[157,158]

Other limitations

A selection bias called Berkson's bias should also be considered.[159,160] The more you go to the hospital, the more you're likely to have your infections detected, and the more likely you are to get a dementia diagnosis. This is somewhat represented in our analysis in study I, where five years prior to a dementia diagnosis, more people had infection-related hospital contacts. Dementia could have been more easily detected and recorded due to repeated hospitalizations.

It is also important to note that although we adjusted for calendar year, civil status, and education, I have not discussed outcomes reported in this thesis with focus on these factors. This is due to the missing information for some people in the cohort on civil status and education. As for calendar year, although interesting, a time trend discussion of our outcomes would be influenced by parallel timeline of age and possibly dementia disease progression.

Finally, we stratified by sex and age in all our studies, but not in the infection sites. Differences between sexes and across ages in the healthcare seeking/ provision patterns for the different infections, or in the underlying biological mechanisms of our investigated outcomes could thus regrettably not be noted. Further research needs to address whether such differences exist, and for which infections.

Methodological considerations and reflections

Here I provide explanations and reflections over some decisions made in our studies. These are: Poisson regression, the choice of the synergy index for estimation of additive interaction in study II, adjustment for the CCI, choosing all-cause mortality, and relative vs absolute risk measures.

First, we used the Poisson regression model to analyze outcome incidence rates in studies I and II. The Poisson model is equivalent to the more familiar Cox Proportional Hazards model, but it does not have underlying assumptions of proportionality.[90] Poisson regression only assumes constant piecewise rates i.e. constant rates in the periods used (e.g. during one calendar year). As we have chosen small time periods, we made sure to fulfill the assumption. Further, a Poisson model more easily reduces large data into event counts and person years.[90]

Second, the interpretation of the synergy index in study II is not straightforward since it assumes no residual unmeasured confounding.[161] Although it does show that there might be biological (or

causal)[92] interaction between infections and dementia, it may still be reflective of the underlying unmeasured factors. Nevertheless, the synergy index has been recommended in clinical epidemiology for its possible value for public health.[92]

Third, in all our studies, we adjusted for the CCI which has a PPV between 82-100% in NPR.[162] Management of patients with chronic diseases is continuously evolving, and the population is aging and living longer with chronic disease, and perhaps living with more severe conditions as well. Therefore, the weights of such diseases for the risk of mortality could change.[163] There are continuous discussions about appropriate weights for each disease in the CCI[164–167] and its performance compared with others such as the Elixhauser Index[168,169] and the CCI may lead to risk over-adjustment. Further, the CCI only includes diseases diagnosed in the secondary care settings, and patients who were living with e.g. diabetes that was controlled at the GP's office would not be identified in our cohort members. In all our studies, we presented three adjustment models. The fully adjusted model included the CCI, and its inclusion or exclusion did not impact the conclusions, although its inclusion did impact mortality estimates, and less so with infection-related hospital contacts or readmissions. The CCI was included time-dependently to account for changes in comorbidities over time and the added risk of such changes on our outcomes, especially mortality. The CCI was developed based on mortality predictions, and adjustment for it for other outcomes than mortality might not have been ideal. Nevertheless, the CCI is the most widely used measure for comorbidity burden and can serve well at least for comparison of studies.

Fourth, when investigating mortality outcome following infections, we did not investigate whether infections were a cause of death. The Causes of Death Registry has not been validated, and all-cause mortality was used instead because information was almost 100% complete[75,170] and because we were interested in short- and long-term mortality rather than the cause of death only.

Finally, in all our studies, we used relative risk estimates. Additionally, using absolute risk measures (perhaps most relevant is the Population Attributable Fraction) could provide additional relevant public health information. However, absolute risk measures assume little or no residual confounding/ bias and are often misinterpreted to indicate causality.[171,172] Nevertheless, with cautious interpretation, such measures supplement relative risk estimates and provide additional indications for the findings' external validity/ generalizability to other populations.[173]

5. IMPLICATIONS

Future research implications

Our studies have generated several important insights which have made it possible to ask numerous additional key questions. In this section, I highlight recommendations for future research that will in one way or another help clarify points raised throughout this thesis.

Future research is needed to advance knowledge on the possible underlying biological mechanisms in our associations, and to identify specific risk groups which can in turn be translated into needed interventions.

I present here first a summary of factors discussed throughout this thesis that are relevant for our investigated outcomes. These include:

1) Dementia disease-specific factors: Severity stage, subtypes, and measures of cognition and functional levels.
2) Infection-related factors: Infections in the primary care setting, severity of infections, co-infections, and relevant groupings such as community vs hospital acquired infections, medical vs surgical patients, and by type of pathogen i.e. bacterial, viral.
3) Other disease, patient-related, social, and healthcare service factors: frailty, nursing home admission, medication use, delirium, socio-economic factors, lifestyle, social environment, and genetic influences.

These factors should also be investigated for their role across the different types of infections. All infection sites need to be further investigated, especially those highlighted in our studies but not previously investigated (e.g. nervous and unspecified infections).

Further, exploration of the events that occur between a hospital contact with an infection and death (cascade iatrogenesis) is needed. One possibility could be to map the path(s) between that first infection and death with all events (both social and health related) and their interactions identified. This can contribute to generating relevant hypotheses to be tested, which can explain the excess mortality and aid in shaping interventions.

Evidence on antibiotic prescribing appropriateness in people with dementia is limited, especially for a spectrum of all infections and should be a research priority.[57,68,102,174] Antibiotics may be associated with adverse outcomes such as gastrointestinal discomfort, allergic reactions, and most importantly antimicrobial resistance.[174]

Further, sitting with these "big data" really highlights the need for qualitative data to better understand the attitudes and thought processes that take place when general practitioners/ physicians, family members, and healthcare personnel surrounding people with dementia go through complex decision making regarding symptom recognition, hospitalization, and treatment. The most obvious example and one that is continuously researched is the decisions to treat in advanced stages of dementia and for particularly weak and frail patients. Another example is attitudes of people with dementia and their caregivers towards e.g. home help services which is crucial to consider when shaping interventions. A lack of evidence for such experiences has previously been noted and highlighted.[175]

Finally, future research focused on assessing the global burden of infections in dementia is key for prioritization of recourses and to inform policy makers. This includes investigating the incidence rates of infections and hospitalizations with infections over the years and in multiple healthcare systems/countries. Moreover, the burden of infections should be put in context of other events/diseases, to understand its relative magnitude among other comorbidities.

While this thesis was not about whether infections cause dementia, it highlights the need for further research on the possible role of all types of infections in dementia pathology (causing/ accelerating dementia) and the underlying biological mechanisms of infection dementia interactions.

Clinical and public health implications

Findings from the three studies in this thesis carry important implications for dementia care and emphasize the need for infection prevention, closer attention, and specialized care for people with dementia prior to, during, and following an infection-related hospital contact.

I'm writing this thesis during the COVID-19 pandemic which has taught us – if anything – that focus on preventing an infection is both the first line of defense and is a reasonable place to start.

Many infections are potentially preventable and focusing on infection prevention is key. Sometimes drastic measures such as a full societal lockdown are undertaken to protect from excess deaths especially for vulnerable persons in the society. COVID-19 came as an immediate threat and so action was also immediate. If we approach all infections in people with dementia as a COVID-19 situation, considering the obvious adverse outcomes, it becomes clear that immediate attention is warranted. Infection preventive measures should include targeting the modifiable risk factors and tailoring interventions to patient needs while considering their characteristics (e.g. race, socio-economic background). Examples are ensuring proper hygiene and nutrition,[25] deprescribing medication that may cause drug induced acquired immunodeficiency,[24] and ensuring competent care personnel.

Next, hospitalization (and readmission) prevention is another area for intervention where identifying early signs of infection is key. Whether increased hospitalization is a result of infection diagnosis failure in the primary care, or whether people with dementia do not even present in the primary care for their infections, the implication is clear: people with dementia need more specialized and personalized care that e.g. takes into account that they may not seek care for an infection on their own. In a nursing home setting, this may mean that people with dementia should be in close contact with a physician that can spot any changes that may warrant assessment for an infection. In the Netherlands, nursing homes employ elderly care physicians who have the nursing home as their principal site of practice, and therefore see the patients regularly.[176] One study showed that nursing homes with on-site nurse practitioners reduced hospitalizations for pneumonia, UTIs, and gastroenteritis by more than 50% in residents with dementia, and less for residents without dementia.[38] Further, it's been previously shown that education programs for care professionals on the timely diagnosis and early treatment of sepsis resulted in reduced mortality.[177]

Unfortunately, efforts to reduce hospitalization and rehospitalization in people with dementia have to date been generally ineffective,[12,178–180] with exceptions noted in the coming section. Infections are often complications of other disease and can be acquired during hospitalization. Interventions should therefore also consider other events/ diseases when targeting hospitalization. Because of multimorbidity in people with dementia, this obviously makes such efforts quite complex.

During and following a hospital contact, specialized care provided for the patient with dementia is crucial to limit negative outcomes and ensure a high quality of life. Indeed, several studies have noted that post discharge home care was a common factor in interventions with some levels of success for reducing readmissions in older adults generally,[179,181,182] while at least one study reported the opposite in people with dementia.[33] Further, another previous study found that specialized aftercare programs for sepsis survivors (without focus on dementia) reduced the otherwise markedly increased five-year mortality.[70] Further, focusing attention towards support of the caregiver has shown potential for targeting hospitalization and adverse outcomes in people with dementia.[183] Additionally, vaccinations for people with dementia (and caregivers) might reduce hospitalization for severe infections and negative outcomes like mortality.[184]

Finally, an important public health perspective sheds light on the current and future burden of hospital care use. One recent study has estimated that – assuming no changes – the number of hospital days for people 70+ years of age will account for almost 60% of all hospital days by the year 2050 in Denmark.[185] This, together with the estimated rise in the number of people living with dementia in the coming decades,[4] is major, and emphasizes the urgent need to focus attention towards prevention of avoidable hospitalizations (focus point: infections) in people with dementia.

Interdisciplinary way forward

Infection prevention, specialized care, proper infection management, and appropriate care during and following infection-related hospital contacts should be at the core of dementia care. "Proper" and "appropriate" are intentionally chosen terms that include considerations of patient characteristics and wishes, as well as caregiver wishes, and the burden of versus need for treatment.[11,14,174] As Sir William Osler said: "The good physician treats the disease; the great physician treats the patient who has the disease."

Optimizing infection management and providing appropriate care for people with dementia calls for a strong collaboration across disciplines of geriatrics, neurology, psychology, infection disease specialists, pharmacists, primary care practitioners, and in advanced stages, experts in palliative care.[13,186] For example, hospital-based interventions that aim to decrease readmissions or mortality would have limited impact if they did not include collaboration with the patient's family, and the nursing home that the patient is discharged to.[187] Another example is including a clinical

pharmacist in the health care team for patients with dementia,[118,188,189] which in one study reduced drug-related readmissions.[189] So interdisciplinary care tailored to the needs of the person with dementia and their caregivers may reduce adverse outcomes after a hospital contact.[14,118] When we think of the multifactorial aspect of the risk of infections in people with dementia as well as the risk of adverse outcomes following a hospital contact with an infection, it becomes crystal clear that the way forward is an interdisciplinary approach (e.g. need for social support, nutrition management, physical therapy for possible deterioration of physical function).[30] Indeed, studies that noted the success of post discharge home care have emphasized the required advanced levels of collaboration between all involved agents.[179] Home health services would not be able to on their own meet patient needs post discharge, further highlighting the need for interdisciplinary efforts.[33]

Successful interdisciplinary efforts should not only span different disciplines of medical care (geriatrics, neurology, primary care), but also cross to e.g. social care professionals and the responsible entities e.g. municipalities. Such interdisciplinary collaborations can be referred to as case management teams. These include professionals and agents that work together, and not just side by side or in combination, to integrate the complexity of needs of patients with dementia into an individualized service delivery plan.[3,13] The lancet commission has reviewed effectiveness of case management in people with dementia and found an overall low to moderate positive impact on patients' quality of life and adverse outcomes.[3] However, heterogeneity between case management approaches is noted.[3] Since such approaches are dependent on evidence on what works well in dementia care, there also needs to be focus on interdisciplinary approach in research.

The call for interdisciplinary approach also applies to research needs, where parties from across disciplines of geriatrics; neurology; public health and epidemiology; sociology; and infectious disease need to come together to bridge knowledge and build solid evidence that is translated to clinical practice and interventions. Additionally, research utilizing quantitative, big data, and administrative health data should be supplemented with and mapped together with qualitative research and clinical randomized trials to align research needs. Perhaps the first step is raising awareness of these needs to better facilitate future collaborations that acknowledge the cruciality of coming together. Finally, we need system wide policy changes that can encourage and push for a patient-oriented interdisciplinary intervention approaches, particularly focused on this potentially preventable and very common issue (infections).

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STUDY I

Dementia identified as a risk factor for infection-related hospital contacts in a national, population-based and longitudinal matched-cohort study

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Dementia identified as a risk factor for infection-related hospital contacts in a national, population-based and longitudinal matched-cohort study

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The aim of this study was to investigate the association between incident dementia and rates of infection-related hospital contacts. We conducted a registry- and population-based matched-cohort study of all Danish residents who were born in or before 1950, included from 1 January 2000 or their 65th birthday (whichever came later), who were alive and resided in Denmark at the start of the study, excluding those who had received a dementia diagnosis before 1 January 2000 or their 65th birthday (n = 1,712,100). A total of 129,660 people (403,744 person years) with incident dementia were matched with 297,476 people (1,918,784 person years) without dementia. Incidence rate ratios (IRRs) of infection-related hospital contacts were calculated using Poisson regression, by infection type, sex and age. The IRR for any infection-related contact in dementia was 1.5, was highest for nervous and urinary system infections and sepsis, decreased with increasing age and was higher in men. More people with than without dementia had contacts five years before the index date. Our findings show that dementia is a risk factor for infection-related hospital contacts and infections might be an early sign of dementia.

Infections are common in older people, can lead to hospitalization[1–3] and can often be terminal events[4]. It is expected that older persons are more vulnerable to infections[5] due to the clinical impact of immunological aging[5,6], frailty[7] and physiological changes such as nutritional status[8]. People with dementia may have increased sensitivity to infections, possibly due to altered hygienic habits and decreased mobility resulting from cognitive impairment. Furthermore, the difficulty in observing typical clinical signs of infection in older people[9], and the reduced ability of people with cognitive impairment to communicate infectious symptoms[10,11], may lead to frequent hospitalization with infections.

Previous epidemiological studies have shown increased all-cause hospitalization for people with dementia[12], of which infections generally[13], or infections of the respiratory and urinary tracts specifically, were among the most common causes[2,3,14–18]. However, these studies were based on selected populations. The aim of the current study was to compare the rates of infection-related hospital contacts (that is, contacts (or interactions) of an individual with a hospital as the result of an infection) in people with and without dementia, in a prospectively followed-up nationwide cohort, to investigate the association between incident dementia and rates of infection-related hospital contacts, as well as the differences in rates across the different infection types.

An understanding of which infections are behind increased hospital contacts in people with dementia is crucial for public health knowledge that can shape targeted interventions and aid in ensuring a better quality of life for people living with dementia.

Results

The source population included 1,712,100 people (Fig. 1), where 129,660 people had a dementia diagnosis and were matched with 297,476 people without a dementia diagnosis on or before the index date. The index date was defined as the date when a person was diagnosed with dementia during the study period. Each person diagnosed with dementia was matched to three randomly chosen people on sex and age who did not have a registered dementia diagnosis on or before their date of diagnosis. This diagnosis date was assigned as the index date for people with and without dementia and marked the start of follow-up. For fewer than five people with a dementia diagnosis, it was not possible to match three people without a diagnosis, so these people were matched with fewer than three people or not included in the final cohort. In addition, some of the people without dementia served as a matching pair for more than one person with dementia. Matching therefore yielded 388,976 pairs. Of those without dementia on or before the index date, 266,980 people remained free of a dementia diagnosis during follow-up, while 30,496 people were registered with dementia, censored and then matched to people without dementia. These 30,496 people are included in the total number of people diagnosed with dementia during the study period (that is, 129,660); therefore, the total sample size was 396,640 unique individuals.

Total follow-up was 403,744 person years for people with dementia and 1,918,784 person years for people without dementia. Table 1 presents the matching characteristics at the index date and person years of follow-up (Supplementary Table 6 presents time at risk in the remaining covariates).

The most frequent infections were those of the respiratory and urinary systems and sepsis. Figure 2 and Table 2 presents fully adjusted incidence rate ratios (IRRs) for people with dementia for any infection-related hospital contact, as well as by infection site category. The IRR of any contact was 1.5 (95% confidence interval (CI) = 1.49–1.51), meaning that the incidence of infection was 1.5-fold higher in people with dementia compared with those

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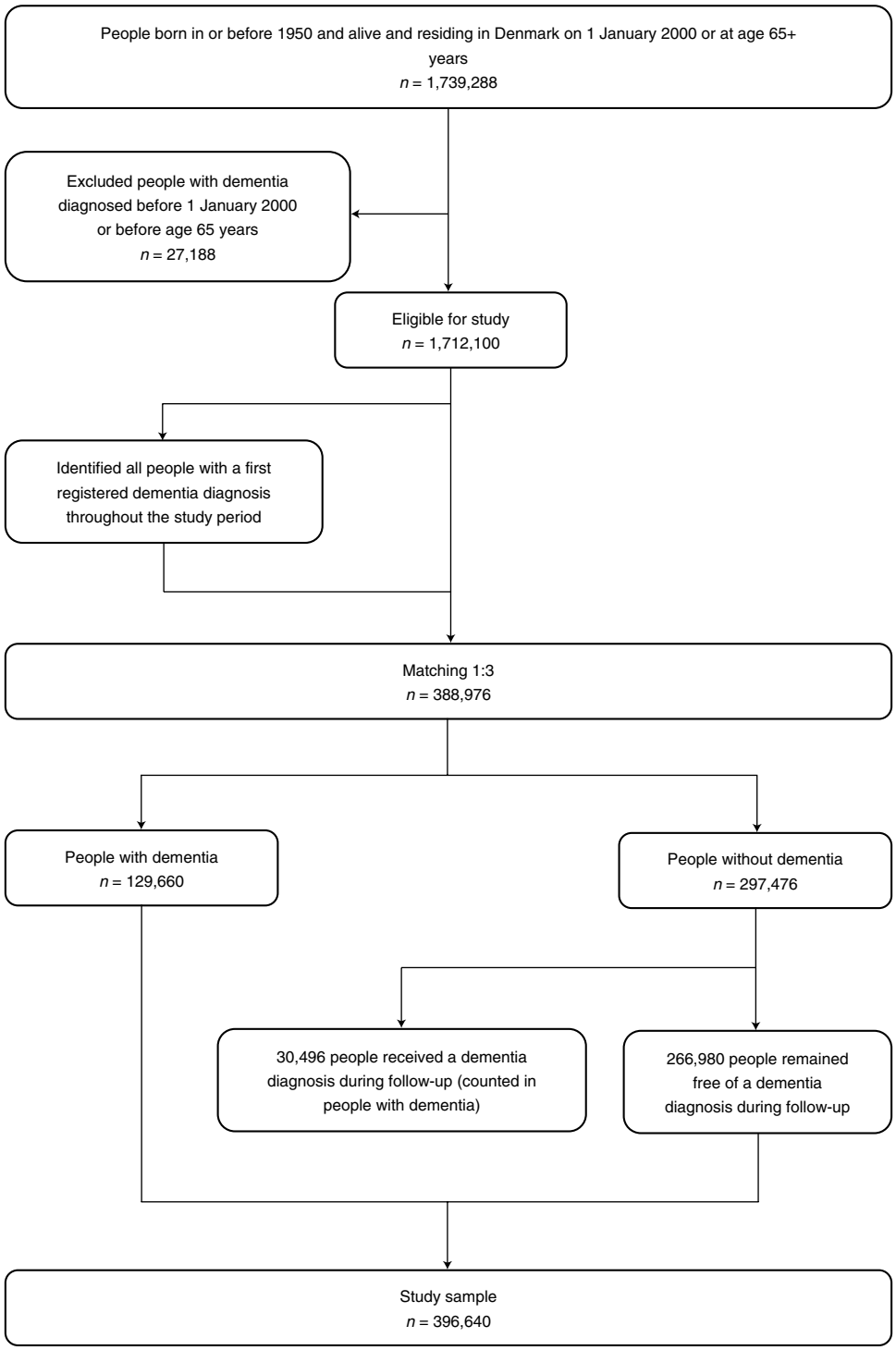

Fig. 1 | Cohort population flow chart. Of a total of 1,712,100 people eligible for the study, 129,660 were identified with a first registered dementia diagnosis during the study period and were matched using a ratio of one to three (where possible; see main text) to people who did not have a registered dementia diagnosis during this time. Matching resulted in 388,976 pairs. There were 129,660 unique individuals with a registered dementia diagnosis and 297,476 matched unique individuals without. Of the matched people without dementia at the index date, 30,496 people were registered with a dementia diagnosis after the index date and were counted among the 129,660 people with dementia, while 266,980 matched persons remained free of a dementia diagnosis throughout the follow-up period. The total sample size thus consisted of 396,640 unique individuals.

without. IRRs were highest for infections of the nervous and urinary systems and sepsis, and were also significantly higher in the remaining sites in people with dementia compared with those without, except for infections of the eye, ear and circulatory system (where IRRs were significantly higher in people without dementia). IRRs for herpes, hepatitis and infections of the genital and musculoskeletal systems were not significant (Supplementary Table 7).

Figure 3 presents IRRs stratified by sex and by age. Compared with their respective reference groups, IRRs were higher in men. IRRs were more than twofold in the youngest age group and

Table 1 | Matching characteristics of age and sex in people with and without dementia

Matching characteristic	People with dementia				People without dementia			
	n at index date	Pyrs	*n* contacts	Rate	*n* at index date	Pyrs	*n* contacts	Rate
Total	129,660	403,744	97,586	241.7	297,476	1,918,784	280,848	146.4
Sex								
Women	80,315	265,053	57,026	215.2	179,977	1,217,335	168,286	138.2
Men	49,345	138,691	40,560	292.4	117,499	701,450	112,562	160.5
Age (years)								
65–69	7,872	13,967	2,690	192.6	22,522	46,958	2,348	50.0
70–74	14,874	42,292	8,752	206.9	39,959	159,554	11,339	71.1
75–79	25,996	76,689	16,792	219.0	63,912	317,677	30,734	96.7
80–84	34,578	107,020	26,397	246.7	77,287	483,713	63,833	132.0
85–89	30,237	101,642	26,399	259.7	62,127	516,026	88,818	172.1
90+	16,103	62,135	16,556	266.5	31,669	394,857	83,776	212.2

Rates were calculated as the rate per 1,000 person years at risk (Pyrs).

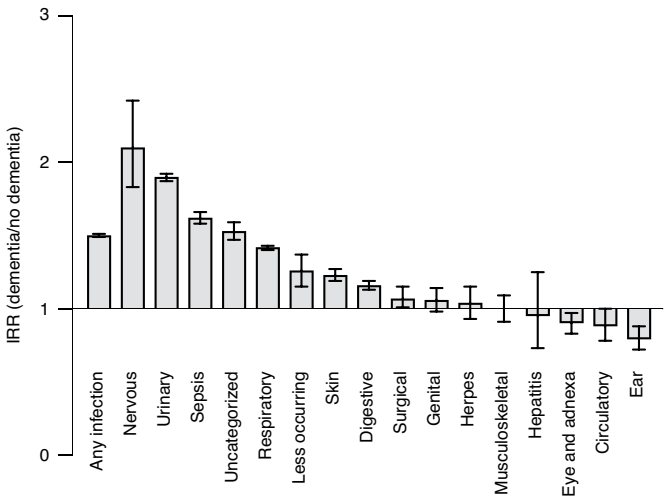

Fig. 2 | IRRs of infection-related hospital contacts, by infection site category, in people with dementia. IRRs are plotted for any infection-related hospital contact, as well as by infection site category, in people with dementia. For the reference group (people without dementia), the IRR is equal to 1 (as indicated by the solid black vertical line). Error bars represent 95% CIs. IRRs were estimated using Poisson regression. A two-sided type 1 error of 5% was considered statistically significant. Total person years at risk (Pyrs) were 403,744 in people with dementia and 1,918,784 in people without dementia. The IRRs presented are adjusted for sex, age, calendar year, civil status, highest educational level attained and CCI. All adjustment models, along with the resulting IRRs, CIs and *P* values, are presented in Supplementary Table 7. Note that the sum of the number of contacts from each infection site does not equal the number for any infection because in some cases multiple contacts for different infection site categories occurred on the same date. These were counted separately for each infection site category, but would count for only one in the total for any infection, thus giving a slightly smaller sum. The most frequent uncategorized infections in our cohort were unspecified bacterial and viral infections. The most frequent less-occurring infections included *Clostridium perfringens*, infectious unspecified gastroenteritis and colitis.

dropped with increasing age to 1.2-fold in the oldest age group (Supplementary Table 8).

In all analyses, the IRRs decreased slightly following adjustment for covariates (Supplementary Tables 7 and 8).

Figure 4 presents the percentage of people with and without dementia with infection-related hospital contacts during the 5 years before the index date. A higher percentage of people with dementia than without dementia had contacts. Percentages markedly increased for people with dementia closer to the index date, with the highest percentage during the year before the index date (16.5% compared with 7.5% for people without dementia).

Lastly, we performed seven sensitivity analyses (see Methods for a description of each). Models 1–5 showed no major influence on our results; for example, in model 4, similar IRRs were observed whether the infection was a primary or secondary diagnosis during the hospital contact. In model 6, inpatient admissions resulted in an IRR for any infection of 1.54 (95% CI = 1.53–1.55), whereas outpatient visits resulted in an IRR of 1.12 (95% CI = 1.09–1.14). Finally, in model 7, the use of a modified Charlson comorbidity index (CCI; weight of human immunodeficiency virus (HIV) reduced from 6 to 1) did not change the estimates (Supplementary Table 9).

Discussion

In this nationwide, longitudinal and population-based matched-cohort study of people aged 65 years or older, dementia diagnosis was associated with an increased rate of infection-related hospital contacts, where people with dementia had a 1.5-fold increased rate compared with people without dementia. Rates were higher in men and were increased across most, but not all, infection sites. The most frequent infections were those of the respiratory and urinary systems and sepsis, and the rates of these were highest in people with dementia. During the 5 years before a registered dementia diagnosis, a higher percentage of people with a registered dementia diagnosis than without one had infection-related hospital contacts, particularly during the year before the index date. Our findings contribute to the small amount of existing literature on associations between dementia and risk of infections. In our study, we comprehensively investigated the rates of infection-related hospital contacts across all infections following a diagnosis of incident dementia and until death or for a period of 15 years using prospectively collected and highly valid national registry data. Our results are generally consistent with previous studies, although they are not directly comparable. In one study, hospital discharge diagnoses did not differ between people with and without Alzheimer's disease except for infectious diseases, where 40.8% of hospitalized patients with Alzheimer's disease had pneumonia or another infectious disease compared with 27.2% of patients who did not have Alzheimer's disease[13]. Previous studies investigating associations

Table 2 | Frequency and rates of infection-related hospital contacts, by infection site category, in people with dementia

	Number of contacts		Rate per 1,000 Pyrs		IRR (95% CI)
	Dementia	No dementia	Dementia	No dementia	Dementia/no dementia
Any infection	97,586	280,848	241.7	146.4	1.50 (1.49–1.51)
Nervous	309	571	0.8	0.3	2.10 (1.83–2.42)
Urinary	35,277	83,796	87.4	43.7	1.90 (1.87–1.92)
Sepsis	9,431	24,443	23.4	12.7	1.62 (1.58–1.66)
Uncategorized	3,686	10,723	9.1	5.6	1.53 (1.47–1.59)
Respiratory	39,538	116,433	97.9	60.7	1.42 (1.40–1.43)
Less occurring	709	2,374	1.8	1.2	1.26 (1.15–1.37)
Skin	4,711	16,929	11.7	8.8	1.23 (1.19–1.27)
Digestive	7,677	28,180	19.0	14.7	1.16 (1.13–1.19)
Surgical	1,177	4,500	2.9	2.3	1.07 (1.01–1.15)
Genital	836	3,583	2.1	1.9	1.06 (0.98–1.14)[a]
Herpes	438	1,841	1.1	1.0	1.04 (0.93–1.15)[a]
Musculoskeletal	609	2,578	1.5	1.3	1.00 (0.91–1.09)[a]
Hepatitis	68	239	0.2	0.1	0.95 (0.73–1.25)[a]
Eye and adnexa	799	4,030	2.0	2.1	0.90 (0.83–0.97)
Circulatory	317	1,416	0.8	0.7	0.88 (0.78–1.00)
Ear	483	2,741	1.2	1.4	0.79 (0.72–0.88)

[a]Non-significant.

with all-cause hospitalization have only looked at infections of the urinary tract, pneumonia and sepsis, which are among the common hospitalization causes in people with dementia[2,3,14–21].

To our knowledge, no previous studies have investigated other infections or compared the rates of several types of infections. We thus extend previous knowledge and report that people with dementia have substantially increased rates of infections generally, and of several infection types. Our findings confirm that infections of the respiratory and urinary systems and sepsis are most frequent, and the rates of these infections are highest in people with dementia. We also identified increased IRRs for other infection types in people with dementia (infections of the nervous and digestive systems, infections of the skin, surgical infections and uncategorized and less-occurring infections). Of the infections we studied, the IRR for infections of the nervous system was the highest; however, these results were based on a small sample size, hence the observed wide CI. Most hospital contacts associated with infections of the nervous system, both in people with and without dementia, were cases of bacterial meningitis and viral encephalitis. It has been shown that some symptoms of encephalitis and meningitis could be mistaken for dementia, and one might expect that most of the cases with such infections occurred on or very close to the registered dementia diagnosis. However, we did not find this to be the case in our study (data not shown), and future research is needed to confirm and clarify such associations.

The observed increased IRRs in people with dementia in our study could be due to the deleterious effects of dementia on expressive language and symptom perception, which can impair people's ability to express and communicate symptoms of infections. This can subsequently create diagnostic challenges for clinicians in the primary care setting, leading to infections being left undiagnosed for longer and later requiring hospitalization, particularly as dementia progresses[22]. Moreover, our findings could reflect the increased sensitivity of people with dementia to contracting infections, where cognitive impairments result in altered hygienic habits, decreased mobility and reliance on external care. We found that IRRs were substantially higher for inpatient than outpatient infection-related hospital contacts, suggesting that the severity of infections plays an important role in explaining the observed increased IRRs in people with dementia, where inpatient infection-related hospital contacts reflect more severe episodes of infections than outpatient contacts. While outpatient infection-related hospital contacts were also higher in people with dementia than in those without, they were substantially lower compared with inpatient contacts.

We found that IRRs decreased with increasing age, which could reflect clinicians' reluctance to hospitalize older people with dementia and comorbidities, to decrease burdensome hospital transitions, adverse hospitalization outcomes and aggressive treatments. This is particularly true for people who are terminally ill, have advanced dementia or reside in nursing homes, as was reported in one Dutch study[23]. These individuals might not be referred to hospitals, and incidences of infection might therefore remain undetected in our population, resulting in lower than expected rates. In contrast, one study reported no differences in hospitalization during the last month before death between nursing home residents with and without dementia where infections were the leading cause of such hospitalizations[24]. It is also possible that the decreasing IRRs with increasing age could be explained by elevated rates of infection among people without dementia as well in older age.

Moreover, hospitalization patterns may differ with the type of infection; for some infections, clinicians might be more reluctant to refer a patient to hospital and such infections would therefore be handled in the primary care setting and remain undetected in our study. If such hospitalization patterns differ for people with and without dementia, it is possible that these led to the insignificant rates observed for some of the infection types in our study.

After excluding the data for everyone who died within 1 year of the index date, IRRs in people with dementia decreased only slightly, indicating that the observed rates could not be attributable to increased infections at the terminal stage of life only. Moreover, the increased IRRs may reflect an increased rate of all-cause hospitalization in people with dementia, where infections were diagnosed. However, we have shown that the rates are not just a

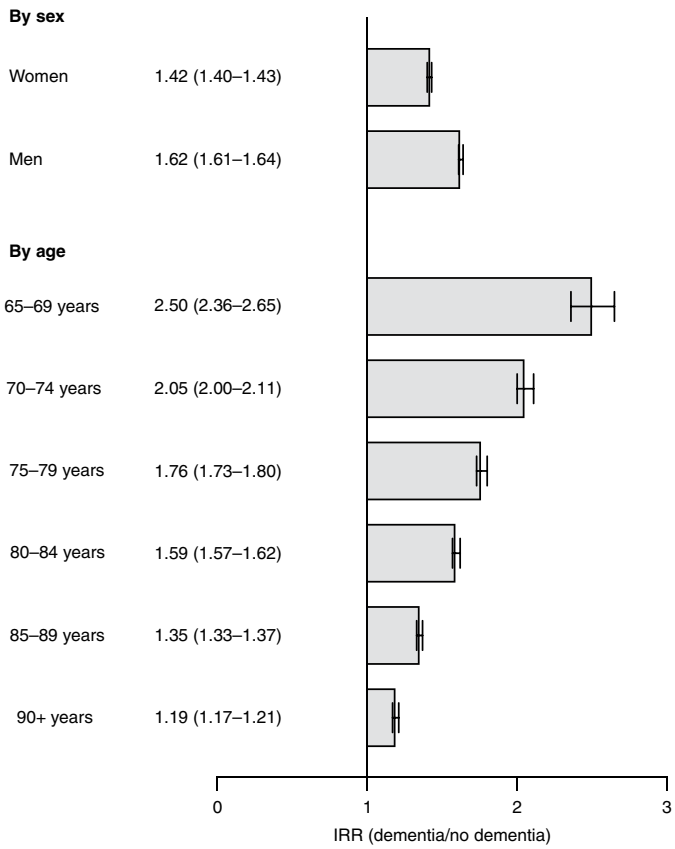

Fig. 3 | IRRs by sex and age group in people with dementia. IRRs are listed for any infection-related hospital contact by sex and age group in people with dementia. For the reference group (people without dementia), the IRR is equal to 1 (as indicated by the solid black vertical line). Error bars represent 95% CIs. IRRs were estimated using Poisson regression. A two-sided type 1 error of 5% was considered statistically significant. Total person years at risk were 403,744 in people with dementia and 1,918,784 in people without dementia. Detailed distributions of person years at risk, number of infections and rates across the two sexes and all age groups are presented in Table 1. The IRRs presented are adjusted for sex or age (whichever is not plotted), as well as calendar year, civil status, highest educational level attained and CCI. All adjustment models with the resulting IRRs, CIs and *P* values are presented in Supplementary Table 8.

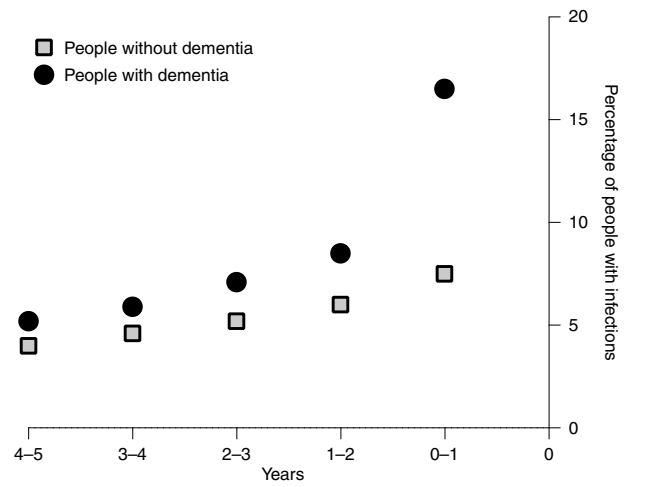

Fig. 4 | Infection-related hospital contacts during the 5 years before the index date. Percentages of people with and without dementia who had infection-related hospital contacts during the 5 years before the index date.

reflection of increased hospitalization for other events (where the infection was a secondary diagnosis) since the IRRs were similar when infections were the primary or secondary diagnosis during the hospital contact. Increased infection-related hospital contacts in people with dementia were already seen 5 years before the dementia diagnosis date. Cognitive impairment is likely to have started years before a registered dementia diagnosis and, as such, the increased percentage of people with infection-related hospital contacts before a dementia diagnosis might reflect the consequences of impaired cognition that put people with dementia at risk for infections (for example, altered hygienic habits and reliance on external care). The observed increase up to 5 years before a dementia diagnosis may also reflect people presenting with infections associated with confusion and delirium who were subsequently more likely to be diagnosed with dementia during such hospital contacts. Because of this observed increase, we propose that infection-related hospital contacts could be an early sign of dementia. Finally, with growing literature on associations between infections and dementia incidence[25–30], one could also speculate that the observed increase in rates of infection-related hospital contacts in the period before a dementia diagnosis might identify infections as risk factors for dementia, although our analysis cannot confirm such associations, and longer periods of follow-up between infections and dementia diagnosis are needed to establish such evidence.

Our findings provide knowledge on which infections are behind increased rates of hospital contacts in people with dementia. Such knowledge points to the need for developing tools and measures that aid in the prevention of infections in people with dementia. People with dementia who also have reduced functional abilities and impaired memory may consequently forget to drink, eat or follow agreed plans or daily routines. Focus on ensuring proper hygiene, as well as healthy habits of hydration and food intake, in people with dementia is key to better management of susceptibility to infections. Moreover, there is a need to develop measures to aid the recognition of early signs and symptoms of different infections so that hospitalizations are prevented. This demands that people with dementia are offered and receive specialized care by personnel who are well equipped and educated to recognize early signs of infections. Finally, research efforts need to identify patient-related characteristics (such as living status, functional abilities and so on) that may be particularly linked to increased susceptibility to infections. The identification of these can aid the development of specific and targeted interventions for infection prevention. To date, infections such as pneumonia and sepsis have been increasingly researched, resulting in the provision of crucial evidence that is used to shape targeted interventions for people with dementia. As such, our comprehensive exploration of all infection types is a building block to encourage and advance research on other important infections.

Strengths and limitations

Several limitations in our study should be addressed. First, we did not investigate the subtypes of dementia due to the low validity of such data in the registries[31]. Moreover, dementia is generally underdiagnosed, so several cases could have gone undetected[32,33]. For example, the number of dementia cases in our cohort represents the registered population rate; however, a recent Danish study showed a prevalence of 36,000 registered dementia cases in 2015 compared with an expected prevalence of around 83,000–89,000 (refs. [34,35]).

We also lacked information on the severity stage of dementia at the time of diagnosis and at the time of the hospital contact. Similarly, we lacked information on the severity stage of the

infection at the time of the hospital contact and could thus not investigate whether the threshold for a hospital contact with an infection was the same for people with and without dementia. However, the results from our sensitivity analyses suggest that the severity of infections plays an important role in explaining the observed increased IRRs in people with dementia, as previously discussed. Second, all of the infections included in our study were severe and treated and led to a hospital contact (inpatient hospital admission or an outpatient hospital visit). We have no information on infections that were handled in the primary care setting only (because this information could only be obtained through prescription data, which include all redeemed prescription medications and lack diagnostic information); thus, our results should be interpreted as such. Furthermore, outpatient hospital contacts are registered as a treatment period (from the date of the first contact to the date of the last contact) rather than each hospital contact. Consequently, if treatment periods for infections of outpatient contacts differed between people with and without dementia, this could have affected our rates. Third, we did not include information on nursing home residency due to the lack of validity of such data[36]. Lastly, as with all observational studies, the possibility of residual confounding (for example, lifestyle factors and frailty) cannot be excluded. The impact of frailty on the incidence of infections among people with dementia could be a crucial explanatory factor for our findings (rather than comorbidities alone) as it takes into account additional factors that we lacked information on.

It is also important to mention several strengths. First, with the study's prospective and population-based design and long follow-up period, biases arising from common issues of nonresponse, selection or loss of follow-up were limited. Moreover, we used a 1:3 matching ratio, thus limiting potential bias arising from having undetected cases of dementia in the reference group. Second, the data in the national registries on dementia and infections are valid and complete, thus limiting potential information bias[31,37]. This means that, although cases of undiagnosed dementia would have been missed, every single case of diagnosed dementia in the population would have been registered and included in our study. Third, we had data on several key covariates, such as calendar year, to control for time trends in dementia diagnosis and healthcare utilization patterns over the follow-up period[31]. Fourth, we comprehensively investigated all infection sites. Finally, we conducted several sensitivity analyses to test the robustness of our data to any decisions we had made.

Conclusion

People with dementia have higher infection-related hospital contact rates compared with people without dementia. This is the case for infections generally and across most, but not all, infection sites. Rates were higher in men and decreased with increasing age. Even 5 years before a dementia diagnosis, more people had infection-related hospital contacts. Our findings highlight the need for increased awareness by clinicians, caregivers and other healthcare personnel of the risk of infection-related hospitalization in people with dementia. Future efforts need to identify specific factors that the risk could be attributed to in people with dementia (for example, nutritional and living status), to further our understanding of the possible mechanistic pathways that link dementia and infections.

Methods

Study design and population. We conducted a nationwide, longitudinal, registry- and population-based matched-cohort study using the Danish national registries. The source population was all Danish residents born in or before 1950, as identified from the Danish Civil Registration System[38]. People in the source population were included in the study from 1 January 2000 if they were at least 65 years old, or otherwise from their 65th birthday from 1 January 2000 and onwards. People had to be alive and resided in Denmark at the time of inclusion into the study. We excluded people with a dementia diagnosis registered before 1 January 2000 or before the age of 65 years, thus focusing on late-onset incident dementia.

On the date that a person was diagnosed with dementia (the index date), they were matched on sex and age (using their birth date ± 90 days) to three randomly chosen people without a registered dementia diagnosis on or before the index date. This date marked the start of follow-up.

Danish law does not require ethics committee approval or informed patient consent for registry-based studies[39]. This study is part of a project that has been approved by the Danish Data Protection Agency, Statistics Denmark and the Danish Health and Medicines Authority.

Dementia. We defined first registered dementia diagnosis using the International Classification of Diseases codes from the Danish National Patient Registry[40] and Psychiatric Central Research Register[41], or a first redeemed prescription for an anti-dementia medication from the Danish National Prescription Registry[42] (Supplementary Table 1).

Infection-related hospital contacts. Infection-related hospital contacts were defined as any in- or outpatient hospital contact registered in the Danish National Patient Registry with a primary or secondary discharge diagnosis of infection (Supplementary Tables 2–4). A hospital contact was defined as an acute or planned inpatient admission or outpatient visit. In cases where admissions or visits were registered on the same admission date or the same discharge date (+1 day) as the previous registered admission or visit, we collapsed these into one record representing an entire episode of care from first admission to the date of discharge from the hospital, such that any administrative registrations and transfers between departments in the hospital were counted as one record or 'contact'.

Diagnosis codes were categorized as follows: sepsis; eye and adnexa; ear; circulatory; respiratory; digestive; skin; musculoskeletal; urinary; genital; nervous; surgical; herpes; hepatitis; uncategorized; and less occurring. People with multiple hospital contacts with infections were represented in multiple site categories. We did not include diagnosis codes for HIV, which we already included in the CCI[43]. We relied on previous literature[44,45] and expert knowledge for the categorization process (Supplementary Methods).

To avoid counting re-hospitalizations for the same infection episode, we counted infection-related hospital contacts for new infections as defined in the Supplementary Methods. In all analyses (except sensitivity analysis model 3), we used a cleaned up dataset where the data were cleaned such that we counted and reported on each episode of care as one hospital contact, creating one hospital record for a patient from initial admission to final discharge, and accounting for any transfers between hospital departments and other administrative registrations that would have resulted in multiple records for the same hospital contact (the data clean-up process is detailed in the Supplementary Methods).

Confounding factors. Data on all covariates were obtained from the national registries and defined following Statistics Denmark methods. Covariates were either fixed or time-dependent variables and included age (time dependent), sex (fixed), civil status (time dependent; defined as married, single, divorced or widowed), highest educational level attained (fixed at age 65 years; defined as low, medium or high), comorbidities (time dependent; defined using the CCI as 0, 1, 2, 3 or ≥4; Supplementary Table 5) and calendar year (time dependent).

Statistical analyses. Matching characteristics for people with and without dementia at the index date were presented as numbers and person years at risk during follow-up.

Follow-up was from the index date until the date of death, immigration or 31 December 2015 (whichever came first). For matched people without dementia at the index date, the follow-up also terminated on the date of a registered dementia diagnosis, at which point they were censored and assigned three new matched people without dementia.

Two exposure groups were investigated in all analyses: people with and without dementia. IRRs of infection-related hospital contacts were calculated using Poisson regression models in people with dementia (the reference group was people without dementia; IRR = 1). IRRs were calculated by infection site, sex and age similarly. Poisson regression analysis does not assume that the data follow any distribution and we only assumed constant rates in the time periods we used (that is, age and calendar year), which were small enough periods to ensure that the constant rates were fulfilled. The logarithm of the estimate (IRR) was normally distributed and the 95% CIs followed this normal distribution (represented as error bars in Figs. 2 and 3).

Three IRR models were used in all of the analyses: (1) adjusted for sex, age and calendar year; (2) further adjusted for civil status and highest attained educational level; and (3) further adjusted for CCI.

To explore whether infection-related hospital contacts increased in people with dementia during the period before the dementia diagnosis, we calculated the percentage of people with contacts (with and without dementia) before the assigned index date during the periods 0–1 years, 1–2 years, 2–3 years, 3–4 years and 4–5 years.

To test the robustness of our data to any arbitrary definitions, we conducted a series of sensitivity analyses. In model 1, we excluded all diagnosis codes unspecific to an infection alone (Supplementary Methods). In model 2, we changed the definition of one infection-related hospital contact from a period of 90 days to either 7, 14 or 30 days, and from a period of 1 year to 6 months.

In model 3, we calculated IRRs without data clean up. In model 4, we calculated IRRs separately for contacts where the infection was a primary or secondary diagnosis (Supplementary Methods). In model 5, we excluded all people with and without dementia who died within 1 year of the index date, to test whether the observed rates were attributed to rates in the terminal phase of life only. In model 6, we calculated IRRs separately for inpatient admission and outpatient visit contacts (Supplementary Methods). Finally, in model 7, we modified the CCI by changing the weight of HIV (from 6 to 1) and repeated adjustment model 3 with this modified CCI, to test whether the CCI was overestimating HIV's adverse prognosis.

A two-sided type 1 error of 5% was considered statistically significant. Analyses were performed using SAS 9.4 (SAS Institute). All data were handled in an anonymized form, as is the standard procedure for research using Danish national registries on the platform Statistics Denmark[46]. This paper adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting standards (Supplementary Table 10).

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

All of the data used in this study are derived from the Danish National and Public Health registries. These data are collected and stored by the relevant authorities and cannot be made public or accessed by unauthorized parties. Access to such data is given via standard rules and regulations of data access outlined by the Danish Data Protection Agency and Danish Health Data Authority.

Code availability

SAS software version 9.4 was used for analysis and coding relating to all of the methods used in this study. We used the procedure PROC GENMOD.

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Author contributions

J.J., G.W. and N.F.-M. conceived of the study concept and performed the literature review. All authors designed the study. J.J. and N.F.-M. prepared and defined the data related to the infection codes. J.J. and T.M.L. performed the statistical analyses. J.J. wrote the manuscript as outlined by J.J. and G.W. All authors contributed equally to data interpretation and critical review of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection
Data analysis	SAS software version 9.4 was used to analyse and code for all methods used in this study. We used the procedure PROC GENMOD.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

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All data used in this study are derived from the Danish national and public health registries that are collected and stored by relevant authorities and cannot be made public or accessed by unauthorized parties. Access to such data is given via standard rules and regulations of data access outlined by the Danish Data Protection Agency and the Danish Health Data Authority.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The sample size comprised of the entire Danish population aged 65 years or older from the year 2000. As such, no sample calculation was performed.
Data exclusions	Exclusion criteria were pre-specified, and were the following: People who had a dementia diagnosis registered before the age of 65 years or before the year 2000. Rationale behind this was follow only people with incident and late-onset dementia.
Replication	We describe in detail and step by step our sample size and definition of all variables included. We include all ICD-10 codes used to define infections and for each infection site category, making replication of our methods and findings possible. Replication of experiments is not relevant for our type of study, however, when our statistical analyses were all checked through running our SAS code again, replication was successful and yielded the same results and exact confidence intervals and significance levels (exact p values).
Randomization	Allocation to te exposure groups was done using dates of the exposure investigated (dementia diagnosis date).
Blinding	Blinding is not relevant to our study since it is based on national health registry data that is already collected and stored, and no allocation to experimental groups was performed.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
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☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	The source population included 1 712 100 people, where 129 660 people had a dementia diagnosis and were matched with 297 476 people without a dementia diagnosis on or prior to index date (of which 266 980 people remained free of a dementia diagnosis during follow-up while 30 496 people were registered with dementia, censored and matched to people without dementia). Matching yielded 388 976 pairs. Total follow-up was 403 744 person years for people with dementia and 1 918 784 for people without dementia. At index date, majority of people with and without dementia were women and in the age group 80-84 years (age distribution was similar for the men, where majority were in the age group 80-84 years). These are the matching characteristics of the sample population. All relevant covariates are described in our study in detail using person-years for each covariate level and with number of infection-related hospital contacts per level.
Recruitment	No recruitment was perfomed. The data is based on national health registries, and as such, common biases of self-selection or loss to follow-up are avoided.
Ethics oversight	This study uses data derived from Danish national health registries, Danish law does not require ethics committee approval or informed patient consent for registry-based studies. The study is part of a project that has been approved by the Danish Data Protection Agency, Statistics Denmark, and the Danish Health and Medicine Authority.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Supplementary information

Dementia identified as a risk factor for infection-related hospital contacts in a national, population-based and longitudinal matched-cohort study

In the format provided by the authors and unedited

Dementia identified as a risk factor for infection-related hospital contacts in national population-based, longitudinal matched cohort study

Janet Janbek, Niels Frimodt-Møller, Thomas Munk Laursen, Gunhild Waldemar

Supplementary material

Table 1. International Classification of Diseases (ICD) -8 and 10 codes for dementia diagnosis and Anatomical Therapeutic Chemical Classification (ATC) codes for anti-dementia medication.

Dementia type	**ICD-8 code**	**ICD-10 code**
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
Medication	**ATC code**	
Cholinesterase inhibitors		
Donepezil	N06DA02	
Rivastigmine	N06DA03	
Galantamine	N06DA04	
Glutamate-receptor antagonists		
Memantine	N06DX01	

Dementia was defined as a first registered dementia diagnosis using the ICD codes from the Danish National Patient Registry and the Psychiatric Central Research Registry, or a first redeemed prescription for an anti-dementia medication from the Danish National Prescription Registry. ICD codes for a dementia diagnosis reflect diagnosis in the secondary care setting. If a person with dementia was identified by a redeemed anti-dementia medication but with no registered ICD code of dementia, then this person had been diagnosed in the primary care setting. If a person gets a diagnosis of dementia in the primary care setting and does not redeem an anti-dementia medication, then this dementia diagnosis remains undetected in our registries.

Supplementary Methods: Process of defining infections (selection of ICD codes, categorization of infection codes and data cleaning)

1. We first included all ICD-10 codes that were used in previous Danish epidemiological studies, using the Danish National Patient Register (excluding A and B codes; refer to point 3.6 below for these).
2. We additionally scanned through all ICD-10 codes using the Danish website icdpedia.dk and WHO's official ICD-10 code manual: https://icd.who.int/browse10/2016/en#/U82-U85
3. Expert knowledge in infectious diseases was used to guide the process of including or excluding codes as well as scanning through the Danish webpage sundhed.dk and pubmed publications, as follows:

   3.1. We excluded all codes from letter categories C (Neoplasms); F (Mental and behavioural disorders); O (Pregnancy, childbirth and the puerperium); P (Certain conditions originating in the perinatal period); Q (Congenital malformations, deformations and chromosomal abnormalities); V and Y (External causes of morbidity and mortality) and U (Codes for special purposes).
   3.2. We excluded all codes which were not infections and diseases not caused by an infection.
   3.3. We excluded all codes where an infection was secondary; an unlikely cause of the disease or where the disease was in majority of reported cases due to non-infectious causes; was due to medication or chemicals (toxic); was due to trauma; was due to allergy/allergic reactions; was due to or related to autoimmune diseases.
   3.4. We also excluded all granulomas and eosinophilic infections.
   3.5. Unspecific infections, and diseases due to several causes including an infectious cause were included in our analyses, and these are marked in yellow throughout this document. Refer to supplementary table 13 for the sensitivity analysis model where these were removed.
   3.6. We included all A and B codes and ran a frequency analysis in our sample population. We then chose all A and B codes that occurred 500 times or more over our study period (Table 2).
   Rationale: Based on the assumption that these specific infections with specified pathogens are rare in the Danish population, or that these diagnoses are generally not used in our population.
   3.7. We excluded all diagnosis types marked as "referring diagnosis" in the Danish National Patient Registry.
4. A list of all ICD-10 codes was agreed on by 2 of the authors (JJ, NFM) (Table 3).

5. Categorization:

We categorized all included infection codes by infection site based on the ICD-10 official manual https://icd.who.int/browse10/2016/en#/U82-U85 and guided by expert knowledge and categorization process in previous Danish studies that used infection codes from the Danish National Patient Registry.
Rationale: This is to limit any misclassification errors between the diagnostic codes of specific infections within each site (e.g. different types of urinary infections). We assumed that categorizing infection diagnostic codes by infection site would limit errors arising from incorrectly diagnosing a specific infection (i.e. the underlying assumption is that an error is more likely to happen within an infection site than across sites. An example is diagnosing a specific urinary infection, where a misclassification among the codes is possible, but limited across another site such as diagnosing a urinary infection versus a respiratory or skin one). Another underlying assumption here is that all specific codes within each site are dependent on and related to each other.

Categorization was made as follows (Table 4):

5.1. All ICD-10 codes with start letters H, I, J, K, L, M, N, G and T were categorized as in the ICD-10 manual (an exception was splitting genital and urinary codes).
5.2. All ICD-10 codes with start letters A and B and that were frequently occurring in our sample population (refer to point 3.6. above for rationale) were categorized per infection site category. These indicate major infectious disease categories in the ICD-10 manual.

5.3. Codes for sepsis were put in a separate site category and these codes were taken out from the other site categories. All A and B codes that were of sepsis were included regardless of their occurrence frequency in our population.
5.4. A category: "Uncategorized" was used for all codes which did not fit in the defined categories.
5.5. Another category "less occurring" was used for all ICD-10 codes with start letters A and B and which occurred less than 500 times in our sample population (refer to point 3.6. above for rationale).
5.6. Infection codes of herpes and hepatitis were put in two separate categories. All A and B codes that were of herpes and hepatitis were included regardless of their occurrence frequency in our population.
Rationale: Infection codes for herpes and hepatitis: 1) Recent literature has pointed out the role of herpes infections specifically in dementia and Alzheimer's disease; 2) Because these infections are seen as life-long infections and are thus different than other infections categorized together in each infection site (i.e. These infections are not "episodes" that occur such as a urinary tract infection, but instead occur once and individuals with these infections will be referred to using terms such as "expressed symptoms" or "break-outs" instead of "episodes" used for the remaining infections.
5.7. We excluded ICD-10 codes for HIV infections, and these were included in the Charlson Comorbidity Index.
Rationale: HIV affects the immune system leading to an impaired immune response. Thus, this suppression of the immune system makes people with HIV more receptive to other infections.[1]

6. Initial clean-up of data:

Due to the nature of the admissions' registered in the Danish national Patient Registry, we cleaned up the data. Within each of the categories, an individual may have had several hospital contacts on the same date. To clean-up such data, where an individual had a registered admission date (in- or out-patient) on the same date as a previous discharge date or a previous admission date (+1 day), these were considered one hospital contact where we used the first admission date and last discharge date to define the period of the contact. Inpatient contacts always triumphed outpatient contacts, in situations where an inpatient contact's admission was on the same date as a previous outpatient contact discharge. This was to limit counting hospital contacts more than once when these were the same hospital contact where several administrative processes or transfers between hospital departments caused the multiple contacts. This dataset is referred to as the "cleaned dataset" in paper. All analyses in our study (except for sensitivity analysis model 3) were performed based on this cleaned up dataset.

7. Infection-related hospital contact definition:

Within each infection site category, an infection-related hospital contact was defined as each hospital contact with a start date >90 days following a prior discharge date in the same site category. This was an arbitrarily chosen period, to exclude readmissions for the same infection. Exceptions were made for infections such as tuberculosis, osteomyelitis, arthritis and where an infection was registered as chronic. For such infections, we counted one year (365 days) instead of 90 days to define a new infection, based on the longer period required clinically to treat an episode of such infections. These are highlighted in green in Tables 2-4 below. Hepatitis and Herpes infections were counted as ever or never for each person. We then pooled infections of all sites into "any infection" by combining data from each infection site category.

8. Infection- related hospital contacts by primary and secondary diagnoses and by in- and outpatient contacts:
To test whether observed rates in people with dementia were majorly due to hospitalization to other events where infections were a secondary diagnosis, we calculated IRRs separately for hospital contacts where the infection was the primary diagnosis and where it was a secondary diagnosis. We then also tested whether IRRs differed based on whether the infection-related hospital contact was an inpatient admission or an outpatient visit, as a proxy for infection severity. For these analyses, we did not define an infection-related hospital contact as in point 7 above since that included grouping several hospital contacts into one which subsequently grouped primary and secondary diagnosis of several hospital contacts into one. We used a cleaned-up dataset for this analysis as detailed in point 6 above.

Table 2. All A, B codes occurring in sample population 500 times or more.

ICD-10 Code	Category	ICD-10 Code	Category	ICD-10 Code	Category
DA020	Digestive	DA021	Sepsis	DA029	Uncategorized
DA045	Digestive	DA047	Digestive	DA049	Digestive
DA081	Digestive	DA084	Digestive	DA090	Digestive
DA099	Digestive	DA150†	Respiratory	DA153†	Respiratory
DA159†	Respiratory	DA182†	Respiratory	DA310	Respiratory
DA319	Respiratory	DA400	Sepsis	DA403	Sepsis
DA408	Sepsis	DA409	Sepsis	DA410	Sepsis
DA411	Sepsis	DA412	Sepsis	DA414	Sepsis
DA415	Sepsis	DA418	Sepsis	DA419	Sepsis
DA419B	Sepsis	DA419C	Sepsis	DA469	Skin
DA480	Uncategorized	DA481	Respiratory	DA488	Uncategorized
DA490	Uncategorized	DA491	Uncategorized	DA498	Uncategorized
DA499	Uncategorized	DA499A	Uncategorized	DA630	Genital
DA689	Uncategorized	DA692	Uncategorized	DA869	Nervous
DA879	Nervous	DA881	Uncategorized	DB001	Herpes
DB004	Herpes	DB005	Herpes	DB009	Herpes
DB022	Herpes	DB023	Herpes	DB028	Herpes
DB029	Herpes	DB079	Skin	DB169	Hepatitis
DB178	Hepatitis	DB181	Hepatitis	DB182	Hepatitis
DB199	Hepatitis	DB259	Nervous	DB309	Eye
DB349	Uncategorized	DB351	Skin	DB353	Skin
DB359	Skin	DB369	Uncategorized	DB370	Digestive
DB372	Skin	DB373	Genital	DB377	Sepsis
DB378	Uncategorized	DB378C	Digestive	DB379	Uncategorized
DB440	Respiratory	DB441	Respiratory	DB499	Skin
DB599	Respiratory	DB869	Skin	DB909†	Uncategorized
DB919	Musculoskeletal	DB956	Uncategorized	DB956A	Uncategorized
DB961	Uncategorized	DB962	Uncategorized	DB965	Uncategorized
DB999	Uncategorized				

† Infections with longer treatment period and counted as a new infection with a period of one year in between each infection. Refer to point 7 above.

Table 3. List of all ICD-10 codes of infections included in our study

ICD-10 Category	ICD-10 codes
H. Eye and adnexa	H000, H000A, H000B, H000C, H000D, H010, H018, H019, H030, H031, H040, H043, H043A, H043B, H043C, H043D, H043E, H043F, H044†, H044A†, H050, H050A, H050B, H050C†, H050D, H050E, H051†, H061, H100, H102, H103, H104†, H105, H108, H109, H130, H131, H132, H150, H151, H160A, H161, H161A, H161B, H161C, H161D, H161E, H161F, H161G, H162, H162A, H162B, H163, H168, H169, H181¥, H184B¥, H191, H191A, H191C, H192, H192L, H192M, H193¥, H193A, H193C¥, H200¥, H201†¥, H202¥, H208¥, H209¥, H220, H300¥, H301¥, H302¥, H309¥, H308¥, H320, H350E¥, H440, H440A, H440B, H441, H441A, H441B, H441C, H441D, H441E, H451, H469C¥, H481¥
H. Ear and mastoid process	H600, H600A, H601, H601B, H602, H603, H603A, H603B, H603C, H608, H608A†, H609, H610, H610A, H620, H621, H622, H623, H624, H650, H650A, H651, H651C, H651D, H652†, H653†, H654†, 654C†, H659, H660, H660A, H661†, H662†, H663†, H664, H669, H670, H671, H678, H680, H700, H701†, H702, H708, H709, H730, H730A, H731†, H750, H830¥, H940
I. Circulatory	I301, I301A, I301B, I301C, I301D, I301E, I308¥, I309¥, I320, I321, I328¥, I330, I339, I389, I398, I400, I408¥, I408A, I409¥, I410, I411, I412, I430, I514¥, I514B†¥, I520, I521, I681
J. Respiratory	J009, J010, J011, J012, J013, J014, J018, J019, J020, J020A, J028, J029, J029A, J029B, J029C, J030, J038, J039, J039A, J039B, J039C, J039D, J039E, J039F, J040, J040A, J040B, J040C, J040D, J041, J042, J050, J051, J060, J068, J069, J091, J091A, J091B, J100, J101, J101A, J101B, J101C, J108, J108A, J110, J111, J111A, J111B, J111C, J118, J118B, J118D, J120, J121, J122, J123, J128, J128A, J129, J139, J139A, J139B, J149, J149A, J149B, J150, J151, J152, J153, J154, J155, J156, J156A, J157, J158, J159, J160, J168, J170, J171, J172, J173, J178, J180, J181, J182¥, J188, J189, J200, J200A, J201, J201A, J202, J202A, J203, J203A, J204, J204A, J205, J205A, J206, J206A, J207, J207A, J208, J208A, J209, J209A, J210, J211, J218, J219, J229, J311†, J312†, J320†, J321†, J322†, J323†, J324†, J328†, J329†, J340, J340A, J340B, J340D, J340I, J340J, J350†, J369, J370†, J370A, J370B, J370C, J371†, J383C, J383D, J387G, J390, J390A, J390B, J390C, J391, J391A, J391B, J391C, J398A, J409¥, J410†, J411†, J418†, J429A†, J429B†, J440†, J441†¥, J659†, J850, J851, J852, J853, J860, J869, J950A, J985D¥, J986D

K. Digestive	K040, K040A, K040B, K041, K041A, K044, K045†, K046, K047, K047A, K047B, K050, K051†, K051A, K051B, K051C, K052, K052A, K052B, K052C, K053†, K053A, K053B†, K102, K102A, K102B, K102C†, K102D†, K102G, K102H, K112, K112A, K112B†, K112C, K112D, K113, K113A, K113B, K113C, K113D, K121, K121A, K121B, K121C, K122, K122A, K122B, K130A, K130B, K130C¥, K130D¥, K130E¥, K130F, K130G, K140, K140A, K140B, K140D, K209¥, K209A, K221C, K230†, K231, K298¥, K352, K353, K353A, K353B, K358, K358A, K358B, K358C, K369†, K379, K401, K404, K411, K414, K421, K431, K434, K437, K441, K451, K451B, K451C, K451D, K451E, K451F, K451G, K451H, K451I, K451J, K451K, K451L, K451M, K461, K570, K570A, K570B, K570C, K572, K572A, K572B, K572C, K573E, K573F, K574, K578, K610, K610A, K610B, K611, K611A, K612, K613, K614, K628I, K628L, K628N, K630, K650, K650A, K650B, K650C, K650D, K650E, K650F, K650G, K650H, K650I, K650J, K650K, K650L, K650M, K650N, K650O, K650P, K658, K658A, K658F, K658I, K659, K670, K671, K672, K673†, K678, K720A¥, K720E¥, K720F¥, K730¥, K731¥, K732¥, K738¥, K739¥, K750, K750A, K750B, K750C, K750D, K751, K759A¥, K770, K803, K803A, K803B, K803C, K804A, K804C, K804E, K810A, K810B, K810C, K810D, K830, K830A, K830B, K830C, K830D, K830E, K830G, K858A, K858D, K858E, K858F, K861A†, K930†, K931,
L. Skin and subcutaneous tissue	L009, L009A, L009B, L009C, L010, L010A, L010B, L010C, L011, L020, L020A, L020B, L020C, L021, L021A, L021B, L021C, L022, L022A, L022B, L022C, L022D, L022E, L022F, L022G, L022H, L022I, L022J, L022K, L022L, L022M, L022N, L022O, L022P, L022Q, L022R, L022S, L022T, L023, L023A, L023B, L023C, L024, L024A, L024B, L024C, L024D, L024E, L024F, L024G, L024H, L024I, L024J, L024K, L024L, L024M, L028, L028A, L028B, L028C, L029, L029A, L029B, L029C, L030, L030A, L030B, L030C, L030D, L030E, L030F, L030G, L030H, L030I, L030J, L030K, L031, L031A, L031B, L031C, L031D, L031E, L031F, L031G, L031H, L031I, L032, L033, L033A, L033B, L033C, L033D, L033E, L033F, L038, L038A, L038B, L039, L040, L040A, L040B, L040C, L041, L042, L042A, L043, L048, L049, L050, L080, L080A, L080B, L080C, L081, L088, L088C, L088D, L089, L303, L738, L738A, L738H
M. Musculoskeletal and connective tissue	M000†, M000A†, M000B†, M001†, M001A†, M001B†, M002†, M002A†, M002B†, M008†, M009†, M010†, M011†, M012†, M013†, M014†, M015†, M016†, M018†, M462†, M463, M463A, M464, M465, M465A†, M490†, M491†, M492†, M493†, M600, M600A, M601, M608¥, M608A, M608A1, M609¥, M630, M631, M632, M650, M651, M680, M680G, M680H, M710, M711, M726, M729A, M730, M731, M792B¥, M860†, M861†, M862†, M863†, M864†, M865†, M865A†, M866†, M868†, M868A, M869†, M869A, M869B, M869C, M900†, M901, M902

N. Urinary	N080, N109A, N109B, N109C, N110†, N110A†, N111†, N111A†, N111B†, N118†¥, N118A†, N118B†, N118C†, N118D†, N119†, N129, N136, N136A, N136B, N136C, N136D, N136E, N151, N151A, N151B, N160, N200I, N201I, N209A, N220, N291, N300, N302†, N308, N308A, N308B, N308C, N308E, N308F, N308G, N308J, N308K, N309, N330†, N340, N340B, N340C, N341, N342, N342G, N343¥, N370, N390
N.Genital	N410, N411†, N412, N412A, N413, N413A, N418, N419, N431, N432¥, N433¥, N449C, N450, N450A, N450B, N450C, N459, N459A, N459B†, N459C, N459D, N459E, N481, N481A, N481B, N481C, N481D, N482, N482A, N482B, N482C, N482D, N482E, N482F, N482G, N482H, N490, N491, N491A, N491B, N492, N492A, N492B, N492C, N492D, N498, N498A, N498B, N498C, N498M, N499¥, N511K, N511L, N512, N619¥, N619A, N619B, N619E, N700, N700A, N700B, N700C, N700D, N700E, N700F, N700G, N701†, N701A†, N701B†, N701C, N701D†, N701E, N701F, N701G†, N701H†, N709, N709A, N709B, N709C, N710, N710A, N710C, N710D, N710E, N710F, N710A, N711†, N711A†, N711B†, N711D†, N711E†, N711F†, N719, N729, N729A, N729B, N729C, N729D, N729E, N729F, N730, N730A, N730B, N730C, N730D, N730E, N731†, N731A†, N731B†, N731C†, N731D†, N731E†, N732, N732A, N732B, N732C, N732D, N732E, N733, N733A, N734†, N734A†, N735, N735A, N738, N738A, N738B, N738C, N739, N740†, N741†, N741A, N742, N743, N744, N748, N751, N758A, N758B, N758C, N760, N760B, N760C, N760D, N760E, N761†, N761A†, N761B, N761C†, N761D, N761E, N762, N762A, N763†, N763A†, N763B, N764, N764A, N764B, N764C, N764D, N764E, N765, N766, N766A, N768, N768A, N768B, N768C, N770, N771, N771P, N771Q, N771R, N778
G. Nervous	G000, G001, G002, G003, G008, G008A, G008B, G009, G009A, G019, G020, G021, G028, G030, G031, G032, G038, G039, G040, G040A, G041, G042, G042A, G042B, G048, G048A, G048B, G048C, G049, G049A, G049B¥, G049C¥, G049D, G050, G050P, G050R, G050S, G051, G051U, G051V, G051X, G052, G052K, G052L, G052M, G052N, G058, G060, G060A, G060B, G060C, G060E, G060F, G061, G061A, G061C, G061F, G062, G062A, G062C, G079, G079A, G079B, G089, G630, G734, G940
T. Surgical	T793, T801, T802, T802A, T802D, T802D1, T802G, T814, T814A, T814B, T814C, T814D, T814F, T814G, T814H, T814I, T814J, T814P, T814P1, T814U, T814X, T826, T826A, T827, T827A, T827B, T827I, T827P, T835, T835A, T835B, T835C, T836, T836A, T836B, T836C, T845, T845A, T846, T846A, T847, T857, T857A, T874, T880, T880A
Z. Factors influencing health status and contact with health services	Z229¥
R. Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	DR572, R827¥, R827B¥
D. Blood and blood-forming organs and certain disorders involving the immune mechanism	D733, D762
E. Endocrine, nutritional and metabolic diseases	E321, E236A

¥ Unspecific infections, and diseases due to several causes including an infectious cause were included in our analyses. Refer to point 3.5. above and to supplementary table 9 for the sensitivity analysis model where these were removed. † Infections with longer treatment period and counted as a new infection with a period of one year in between each infection. Refer to point 7 above. †: Infections that belong to both groups marked with yellow and green.

Table 4. Infection site categories and ICD-10 codes

Infection site category	ICD-10 codes
- Sepsis	R572, J950A, T880A, T802D, T802D1, T814D, A419, A419B, A419C, A415, A410, A412, A409, A267*, A021, A403, A411A*, B377, A400, A414, A327*, A401*, A418, A408, A411, A415A*, A392A*, A282B*, A402*, A207*, A227*, A413*, A427*, A548G*
- Eye and adnexa	Until H60 (except herpes: H191)
- Ear	H60 and forward
- Circulatory	I
- Respiratory	J (except sepsis: J950A), A150, A153, A159, A182, A310, A319, A481, B440, B441, B599
- Digestive	K (except hepatitis: K720A, K720E, K720F, K730, K731, K732, K738, K739, K759A), A020, A045, A047, A049, A081, A084, A090, A099, B370, B378C
- Skin	L, A469, B079, B351, B353, B359, B372, B499, B869
- Musculoskeletal	M, B919
- Urinary	Until N39, R827, R827B
- Genital	N41 and forward, A630, B373
- Nervous	G, A869, A879, B259
- Surgical	T (except sepsis: T880A, T802D, T802D1, T814D)
- Uncategorized	A029, A480, A488, A490, A491, A498, A499, A499A, A689, A692, A881, B349, B369, B378, B379, B909, B956, B956A, B961, B962, B965, B999, Z229, D733, D762, E321, E236A
- Less occurring	Remaining A, B codes not categorized elsewhere in this table. (Of these, the following were exceptions to count as described in point 7 above: A151†, A152†, A154†, A155†, A156†, A157†, A158†, A162B†,A162C†, A192†, A692A†, A393†, A242†, B572†, B381†, B391†, B401†, B573†)
Herpes	H191, B029, B028, B023, B001A*, B009, B004, B004A*, A609*, B001B*, B022, B021*, B001, B003*, B005, A601B*, B002A*, A600*, A601*, B008*, B020*, B020A*, A601A*, B000*, B007*, B027*, A601C*, B001C*, DB002*, B002B*, B002C*
Hepatitis	K720A, K720E, K720F, K730, K731, K732, K738, K739, K759A, B182, B169A*, B180*, B169, B251*, B181, B150*, B159*, B178, B199, B188*, B161*, B160*, B162*, B171*, B189*, B190*, B159A*, B170*, B172*, B581*, B179*

*Codes occurring less than 500 times in our population. † Infections with longer treatment period and counted as a new infection with a period of one year in between each infection. Refer to point 7 above.

Table 5. Charlson Comorbidity Index

Comorbidity	Weight	ICD codes included
Myocardial infarction	1	410, I21, I22, I23
Congestive heart failure	1	42709, 42710, 42711, 42719, 42899, 78249, I50, I110, I130, I132
Peripheral vascular disease	1	440, 441, 442, 443, 444, 445, I70, I71, I72, I73, I74, I77
Cerebrovascular disease	1	430- 4398, I60- I69, G45, G46
Chronic pulmonary disease	1	490-493, 515-518, J40-J47, J60-J67, J684, J701, J703, J841, J920, J961, J982, J983
Connective tissue disease	1	712, 716, 734, 446, 13599, M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
Ulcer disease	1	53091, 53098, 531-534, K221, K25-K28
Mild liver disease	1	571, 57301, 57304, B18, K700-K703, K709, K71, K73, K74, K760
Diabetes I and II without complications	2	24900, 24906, 24907, 24909, 25000, 25006, 25007, 25009, E100, E101, E109, E110, E111, E119
Hemiplegia	2	344, G81, G82
Moderate to severe renal disease	2	403, 404, 580-585, 59009, 59319, 75310-75319, 792, I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Diabetes with complications	2	24901-24905, 24908, 25001-25005, 25008, E102-E108, E112-E118
Any tumor	2	140-194, C00-C75
Leukemia	2	204-207, C91-C95
Lymphoma	2	200-203, 27559, C81-C86, C88, C90, C96
Moderate to severe liver disease	3	07000, 07002, 07004, 07006, 07008, 57300, 45600-45609, B150, B160, B162, B190, K704, K72, K766, I85
Metastatic solid tumor	3	195-198, 199, C76-C80
*AIDS	6	07983, B21-B24

Charlson Comorbidity Index[2] is based on 19 chronic diseases (Listed in the table are 18 diseases due to exclusion of dementia from the list in this study). For each disease, a person is given a score between one and six depending on the severity of the disease and the associated risk of dying. The scores of all diseases are then summed up to give an index.
* Modified CCI used in sensitivity analysis model 7 changes the weight of HIV from 6 to 1.

Table 6. Characteristics table

Characteristic	People with dementia			People without dementia		
	Pyrs	N Contacts	Rate	Pyrs	N Contacts	Rate
Calendar year						
2000-2004	64 494	15 472	239.9	244 567	26 940	110.2
2005-2009	140 625	31 513	224.1	636 235	83 370	131.0
2010-2015	198 625	50 601	254.8	1 037 982	170 538	164.3
Education						
High	47 864	2 336	253.6	9 213	6 339	132.4
Medium	141 864	6 547	223.0	29 361	16 631	117.2
Low	1 201 912	63 133	237.4	265 918	166 289	138.4
Missing	527 144	25 570	257.6	99 252	91 589	173.7
Civil status						
Married	102 585	16 417	160.0	528 297	44 363	84.0
Divorced	32 411	6 041	186.4	123 489	13 824	111.9
Single	17 159	2 983	173.8	82 657	7 816	94.6
Widowed	169 121	26 261	155.3	833 348	90 020	108.0
Missing	82 468	45 884	556.4	350 994	124 825	355.6
CCI						
0	149 749	19 518	130.3	846 947	49 340	58.3
1	93 054	21 697	233.2	375 994	56 974	151.5
2	70 490	18 613	264.1	334 556	56 327	168.4
3	37 885	13 309	351.3	159 355	41 835	262.5
4 and above	52 566	24 449	465.1	201 933	76 372	378.2

Table 7. Incidence rate ratios of any infection-related hospital contact and by infection site categories in people with dementia

	IRR People with dementia/people without dementia (95% CI)					
	Model 1[a]	P value	Model 2[b]	P value	Model 3[c]	P value
Any infection	1.77 (1.75, 1.78)	≤0.00001	1.59 (1.57, 1.60)	≤0.00001	1.50 (1.49, 1.51)	≤0.00001
By infection site						
Respiratory	1.73 (1.71, 1.75)	≤0.00001	1.52 (1.50, 1.53)	≤0.00001	1.42 (1.40, 1.43)	≤0.00001
Urinary	2.16 (2.13, 2.18)	≤0.00001	1.99 (1.96, 2.01)	≤0.00001	1.90 (1.87, 1.92)	≤0.00001
Digestive	1.36 (1.32, 1.39)	≤0.00001	1.23 (1.20, 1.26)	≤0.00001	1.16 (1.13, 1.19)	≤0.00001
Sepsis	2.03 (1.98, 2.07)	≤0.00001	1.71 (1.67, 1.75)	≤0.00001	1.62 (1.58, 1.66)	≤0.00001
Skin	1.39 (1.35, 1.44)	≤0.00001	1.30 (1.26, 1.35)	≤0.00001	1.23 (1.19, 1.27)	≤0.00001
Uncategorized	1.81 (1.74, 1.88)	≤0.00001	1.62 (1.56, 1.68)	≤0.00001	1.53 (1.47, 1.59)	≤0.00001
Less occurring	1.49 (1.37, 1.62)	≤0.00001	1.34 (1.23, 1.45)	≤0.00001	1.26 (1.15, 1.37)	≤0.00001
Hepatitis	1.30 (0.99, 1.70)	0.06652	1.15 (0.88, 1.51)	*0.32147	0.95 (0.73, 1.25)	*0.72591
Herpes	1.17 (1.05, 1.30)	0.00388	1.09 (0.98, 1.21)	*0.10266	1.04 (0.93, 1.15)	*0.50031
Genital	1.15 (1.07, 1.24)	0.00032	1.11 (1.03, 1.20)	0.00634	1.06 (0.98, 1.14)	*0.14137
Eye	0.95 (0.88, 1.03)	*0.22382	0.93 (0.86, 1.00)	*0.05879	0.90 (0.83, 0.97)	0.00469
Ear	0.83 (0.76, 0.92)	0.00018	0.82 (0.74, 0.90)	0.00004	0.79 (0.72, 0.88)	≤0.00001
Nervous	2.56 (2.23, 2.95)	≤0.00001	2.24 (1.95, 2.58)	≤0.00001	2.10 (1.83, 2.42)	≤0.00001
Circulatory	1.11 (0.98, 1.25)	*0.11079	0.96 (0.85, 1.08)	*0.48583	0.88 (0.78, 1.00)	0.04283
Musculoskeletal	1.16 (1.06, 1.27)	0.00141	1.07 (0.98, 1.17)	*0.15293	1.00 (0.91, 1.09)	*0.98732
Surgical	1.24 (1.17, 1.33)	≤0.00001	1.15 (1.08, 1.23)	0.00003	1.07 (1.01, 1.15)	0.03294

IRR for any infection-related hospital contact and by infection site categories in people with dementia (reference group: people without dementia, IRR=1). IRRs were estimated using Poisson regression. A 2-sided type 1 error of 5% was considered statistically significant. Person years at risk in people with dementia= 403 744, in people without dementia=1 918 784. *non-significant IRR. [a] Adjusted for sex, age and calendar year. [b] Further adjusted for civil status and highest educational level attained. [c] Further adjusted for CCI. No adjustments were made for multiple comparisons. CI= Confidence interval; IRR= Incidence Rate Ratio.

Table 8. Incidence rate ratios by sex and by age groups in people with dementia

	IRR People with dementia/people without dementia (95% CI)		
	Model 1[a]	**Model 2[b]**	**Model 3[c]**
By sex			
Women	1.64 (1.62, 1.66)	1.49 (1.47, 1.50)	1.42 (1.40, 1.43)
Men	1.97 (1.95, 2.00)	1.75 (1.73, 1.77)	1.62 (1.61, 1.64)
By age groups (years)			
65-69	3.86 (3.65, 4.08)	3.37 (3.18, 3.56)	2.50 (2.36, 2.65)
70-74	2.93 (2.85, 3.01)	2.54 (2.47, 2.61)	2.05 (2.00, 2.11)
75-79	2.29 (2.25, 2.33)	2.02 (1.98, 2.05)	1.76 (1.73, 1.80)
80-84	1.90 (1.88, 1.93)	1.70 (1.68, 1.73)	1.59 (1.57, 1.62)
85-89	1.55 (1.53, 1.57)	1.39 (1.37, 1.41)	1.35 (1.33, 1.37)
90+	1.30 (1.28, 1.33)	1.19 (1.17, 1.21)	1.19 (1.17, 1.21)

IRR for any infection-related hospital contact by sex and by age groups in people with dementia (reference group: people without dementia, IRR=1). IRRs were estimated using Poisson regression. A 2-sided type 1 error of 5% was considered statistically significant. Person years at risk in people with dementia= 403 744, in people without dementia=1 918 784. Detailed person years at risk, number of contacts and rates/1000 person years in women and men and in all age groups presented here, are presented in Table 1 in the paper. All IRRs p≤0.00001. [a] Adjusted for sex, age and calendar year. [b] Further adjusted for civil status and highest educational level attained. [c] Further adjusted for CCI. CI= Confidence interval; IRR= Incidence Rate Ratio.

Table 9. Sensitivity analysis models: Incidence rate ratios in people with dementia

Model	N contacts		Rate per 1000 pyrs		IRR People with dementia/people without dementia (95% CI)		
	Dementia	No dementia	Dementia	No dementia	Model 1[a]	Model 2[b]	Model 3[c]
Original model	97 586	280 848	241.7	146.4	1.77 (1.75, 1.78)	1.59 (1.57, 1.60)	1.50 (1.49, 1.51)
1	94 484	267 231	234.0	139.3	1.80 (1.79, 1.82)	1.62 (1.61, 1.63)	1.53 (1.52, 1.54)
2a	108 787	312 906	269.4	163.1	1.76 (1.75, 1.78)	1.58 (1.57, 1.59)	1.49 (1.48, 1.50)
2b	106 563	306 275	263.9	159.6	1.76 (1.75, 1.78)	1.58 (1.57, 1.59)	1.49 (1.48, 1.50)
2c	103 313	296 952	255.9	154.8	1.77 (1.75, 1.78)	1.59 (1.57, 1.60)	1.49 (1.48, 1.50)
3	139 909	414 589	346.5	216.1	1.71 (1.70, 1.72)	1.53 (1.52, 1.54)	1.44 (1.43, 1.45)
4a	71 295	200 126	176.6	104.3	1.81 (1.79, 1.83)	1.63 (1.62, 1.64)	1.53 (1.52, 1.55)
4b	47 446	139 309	117.5	72.6	1.73 (1.71, 1.74)	1.53 (1.51, 1.54)	1.44 (1.42, 1.45)
5	81 832	268 102	208.1	140.9	1.58 (1.57, 1.60)	1.47 (1.46, 1.48)	1.39 (1.38, 1.40)
6a	101 700	280 771	251.9	146.3	1.85 (1.83, 1.86)	1.64 (1.63, 1.65)	1.54 (1.53, 1.55)
6b	10 891	42 832	27.0	22.3	1.25 (1.22, 1.27)	1.18 (1.16, 1.21)	1.12 (1.09, 1.14)
7	-	-	-	-	-	-	1.50 (1.49, 1.51)

Sensitivity analysis models for IRRs in people with dementia (reference group: people without dementia, IRR=1). IRRs were estimated using Poisson regression. A 2-sided type 1 error of 5% was considered statistically significant**. Model 1**: Removal of ICD-10 codes that were unspecific to an infection alone (highlighted in yellow in supplementary Table 3). **Model 2a**: Redefining each infection-related hospital contact with a start date >7 days following a prior discharge date in the same site category and for infections with a longer treatment, a period of six months was used. **Model 2b**: The period was changed from 7 days to 14 days. **Model 2c**: The period was changed from 14 days to 30 days. **Model 3**: We used the raw data to calculate IRRs for any infection-related hospital contact without data clean up as described in point 6 in the Supplementary Methods. **Model 4a:** Calculating IRRs for hospital contacts where an infection was a primary diagnosis. **Model 4b:** Calculating IRRs for hospital contacts where an infection was a secondary diagnosis. **Model 5:** Exclusion of everyone who died within 1 year after index date**. Model 6a:** Calculating IRRs for inpatient infection-related hospital contacts. **Model 6b:** Calculating IRRs for outpatient infection-related hospital contacts. **Model 7:** Repetition of the original model where adjustment model 3 used modified CCI where HIV was given a weight of 1 instead 6. Person years at risk in people with dementia= 403 744, in people without dementia=1 918 784, in model 5: Person years at risk in people with dementia=393 208, in people without dementia= 1 903 359. All IRRS p≤0.00001. [a] Adjusted for sex, age and calendar year. [b] Further adjusted for civil status and highest educational level attained. [c] Further adjusted for CCI. CI= Confidence interval; IRR= Incidence Rate Ratio.

Table 10.STROBE Statement—Checklist of items that should be included in reports of cohort studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)

Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Supplementary material references

1. Deeks SG, Overbaugh J, Phillips A, Buchbinder S. HIV infection. Nat Rev Dis Prim [Internet]. 2015 Dec 1;1(1):15035. Available from: http://www.nature.com/articles/nrdp201535

2. Brusselaers N, Lagergren J. The Charlson Comorbidity Index in Registry-based Research. Methods Inf Med [Internet]. 2017 Jan 24;56(5):401–6. Available from: http://www.thieme-connect.de/DOI/DOI?10.3414/ME17-01-0051

STUDY II

Increased short- and long-term mortality following infections in dementia, a nationwide registry-based cohort study

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Abstract

BACKGROUND: Mortality following infections in dementia has not yet been comprehensively explored. The aim of this cohort study was to investigate the short- and long-term mortality following infections in dementia.

METHODS: Follow-up was from January 1, 2000, or the 65-year birthday until death, immigration or December 31, 2015. Exposure was incident dementia and a first infection. The outcome was all-cause mortality. Mortality rate ratios (MRR) were calculated using poisson regression in four exposure groups (Dementia yes/no, Infection yes/no) by sex, infection site, and time since infection.

RESULTS: 1,496,436 people were followed with 12,739,135 person years. MRR in Dementia/Infection was 7.35 (95% CI, 7.25 to 7.45) and was increased for infections of all sites. Increased mortality was short- (30 days) and long-term (10 years).

CONCLUSIONS: Increased mortality in people with dementia identifies them as a particularly vulnerable group who need clinical attention.

Keywords: Infection; Dementia; Mortality; Registry-based study; Epidemiology.

Introduction

The role of infections in dementia remains insufficiently explored. Infections can have severe consequences in elderly people and particularly in those with dementia. People with dementia have a higher all-cause mortality and the cause may be different than in people without dementia.[1] One of such causes is infections.[2–12] Specifically, infections of the respiratory tract and sepsis have been shown to be causes of death in people with dementia[2–6,11,12] and an increased mortality months after such infections[7–9] as well as a shorter survival probability[10] have been reported. However, studies that investigated mortality and survival over time following infections are few and were based on selected populations (eg, nursing home residents,[8–10] end-stage dementia[7]), had small sample sizes,[7,8,10] and mainly focused on pneumonia.[7–10]

Thus, it is not known whether infections have a long-term impact on mortality in people with dementia. Consequences of severe infections may extend well beyond the period immediately following an infection as observed in previous studies in people without dementia that showed an increased mortality following severe infections and sepsis, observed up to five years following an infection.[13–16] Therefore, it is important and highly relevant to investigate the long-term mortality in people with dementia, especially due to the lack of such data in literature to date. Understanding the influence of infections on the clinical time-course of dementia is key for the identification of vulnerable patient groups, thus, optimizing clinical management and applying possible preventive measures.

The aim of this study was to investigate the impact of infections on the short- and long-term mortality in people with and without dementia and to specifically examine the differences in infection sites.

Methods

Study population

We conducted a nationwide registry-based cohort study using prospectively collected data from Danish national registries. The cohort population was all residents born in or before 1950, identified from the Civil Registration System.[17] People were included in the cohort from January 1, 2000, if they were at least 65 years old, or from the date they turned 65 years old between January 1, 2000, and December 31, 2015 (start of follow-up). Everyone was alive and resided in Denmark at start of follow-up and people with a dementia diagnosis registered before that were excluded to focus on late-

onset incident dementia. We also excluded people with hospital contacts with infections during five years before start of follow-up to establish a washout period.

Danish law does not require ethics committee approval or informed patient consent for registry-based studies.

Dementia definition

Dementia was defined as a first registered dementia diagnosis using the International Classification of Diseases (ICD) codes from the Danish National Patient Registry[18] and the Psychiatric Central Research Registry,[19] or a first redeemed prescription for an anti-dementia medication from the Danish National Prescription Registry[20] (Table 1 in the Supplement).

Infections definition

We used hospital contacts with infections as a proxy variable to define infections. A hospital contact with infections was defined as any in- or outpatient contact registered in the Danish National Patient Registry with a primary or secondary discharge diagnosis of an infection (Tables 2-4 in the Supplement). In this paper, we will use the term infections throughout.

We categorized all diagnosis codes according to infection site, into: Sepsis; Eye and adnexa; Ear; Circulatory; Respiratory; Digestive; Skin; Musculoskeletal; Urinary; Genital; Nervous; Surgical; Uncategorized (eg, Bacterial infections without site specification); Less occurring; Herpes; and Hepatitis. We did not include diagnosis codes for HIV infections which were already included in the Charlson Comorbidity index (CCI).[21] We relied on previous literature[22,23] and expert knowledge for the categorization process (Methods in the Supplement).

We only used first infections defined as a first hospital contact with an infection after start of follow-up. If the dementia diagnosis was registered on the same date as a hospital contact with an infection, then this was counted as a dementia diagnosis and as the first infection.

Outcome- Mortality

The primary outcome was all-cause mortality, identified from the registered date of death in the Civil Registration System.[17]

Covariates

Data on covariates were obtained from the national registries and were either fixed at the start of follow-up or time-dependent. These were age (time-dependent), sex (fixed), civil status (time-dependent), highest educational level attained at age 65 years (fixed), comorbidities (time-

dependent), and calendar year (time-dependent). Civil status was defined as married, unmarried, divorced, or widowed. Highest educational level attained was defined as low, medium, and high (detailed in legend of Table 6 in the Supplement). Comorbidities were defined using the CCI[21] as zero, one, two, three, and four and above (Table 5 in the Supplement).

Statistical analysis

Characteristics were presented with person-years at risk, number of deaths, and mortality rate/1000 person years in the exposure groups.

Four exposure groups were investigated: Dementia/No Infection, Dementia/Infection, No Dementia /Infection, and No Dementia/No Infection. Follow-up was from the date of inclusion into the study until the date of death, immigration, or the end of follow-up on December 31, 2015. Mortality rate ratios (MRR) were calculated for all-cause mortality from a first infection using Poisson regression models with the logarithm of the person years at risk as an offset variable in all exposure groups, stratified by sex, and with the No Dementia/No Infection as the reference group in all analyses. This model is equivalent to a Cox Regression model.[24,25] We subdivided the Dementia and Infection group into two levels, depending on whether the infection occurred after or before a dementia diagnosis. Dementia and infections were included as time-dependent variables. We fitted three analysis models: One adjusted for age, sex, and calendar year; the second further adjusted for civil status and highest attained educational level; and the third model further adjusted for CCI.

<u>By infection site</u>

MRRs were similarly calculated by infection site category. We added another level (MRR for infections of other sites that occurred prior to the first infection of the site category) to get an estimate for infections of each site category independently of other infections and relative to the general population without an infection.

<u>Additive interaction</u>

We tested for statistical interaction between dementia and infections (for any infection and by infection site categories) on an additive scale using the synergy index calculated using the fully adjusted MRRs. This was calculated as previously described.[26–29]We used the template provided by Andersson et al [29] (Figure 1 in the Supplement).

By time since first infection

To investigate short- and long-term mortality following infections, we calculated MRRs by time since first infection stratified by sex in all exposure groups and with No Dementia/No Infection as the reference group. Time at risk was divided as: within 30 days of first infection, 30 days to one year, one to five years, five to 10 years, and after 10 years. We also calculated MRRs by time since first infection of the different site categories stratified by sex. In each infection site category, we added a level for infections for other sites as described earlier. Due to the small sample sizes in some infection site categories, we only analyzed six categories (respiratory, urinary, digestive, sepsis, skin, and uncategorized infections) and divided the time at risk into: within 30 days of first infection, 30 days to one year, one to five years, and after five years. Years were calculated based on 365 days.

Sensitivity analyses

To test the robustness of our data to any decisions we made, we conducted several sensitivity analyses: a) We excluded ICD-10 codes which were unspecific to an infection (Methods in the Supplement); b) We changed our exclusion criteria and kept people with hospital contacts due to infections during five years prior to start of follow-up; c) We modelled CCI continuously to test whether our categorization influenced results; d) For the analysis by time since first infection, we conducted a sub-group analysis of people with only one infection (defined by a data cleaning process detailed in the Supplement), to investigate the long-term mortality in the absence of repeated or a mixture of infections.

Post hoc analysis

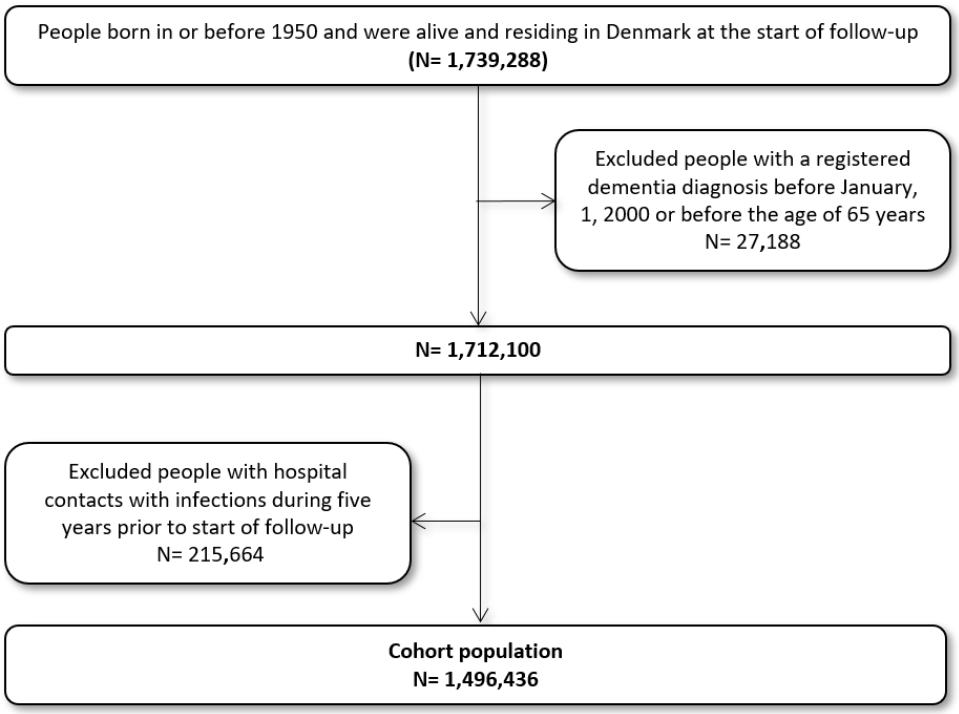
Based on our results from the time since first infection analysis, we divided the time period between 30 days and one year into: within 30 days, 30 days to three months, three to six months, six to nine months, nine months to one year, and more than one year (months were calculated based on 30 days and one year based on 365 days). To test whether dementia alone explained the increased long-term mortality observed in our time since infection analysis, we analyzed MRRs by time since dementia diagnosis in Dementia/Infection group with reference to Dementia/No Infection group. We analyzed this in a separate model to avoid multiple different timelines, model complication and the interpretation of results.

In all analyses, a 2-sided type 1 error of 5% was considered statistically significant. Analyses were performed using SAS 9.4 (SAS Institute Inc).

Results

The cohort included 1,496,436 people (Figure 1) with 12,739,135 person years of follow-up (average follow-up per person= 8.5 years). Of the cohort population, 54% were women. During the study period, 112,565 people were registered with dementia with 354,456 person years of follow-up and 518,880 people had infections (4.5% of the cohort were registered with dementia and infections). At the end of follow-up, there were 575,260 deaths in the cohort. The proportion of deaths was 77.4% in Dementia/Infection group, 56.1% in No Dementia/Infection, 67.4% in Dementia/No Infection and 25.7% in the reference group (Table 1). Table 6 in the Supplement presents cohort characteristics for all exposure groups.

Figure 1. Cohort population flowchart



The fully adjusted MRR for the Dementia/Infection (after dementia) group was 7.35 (95% CI, 7.25 to 7.45) compared with the reference group (No Dementia/No Infection), while MRR in the No Dementia/Infection group was 2.93 (95% CI, 2.91 to 2.95) and in the Dementia/No Infection group 3.66 (95% CI, 3.62 to 3.71). Compared with their respective reference groups, MRRs were higher in men than in women (Table 1). Interactions by sex were highly significant ($p \leq 0.00001$) but with small effect sizes.

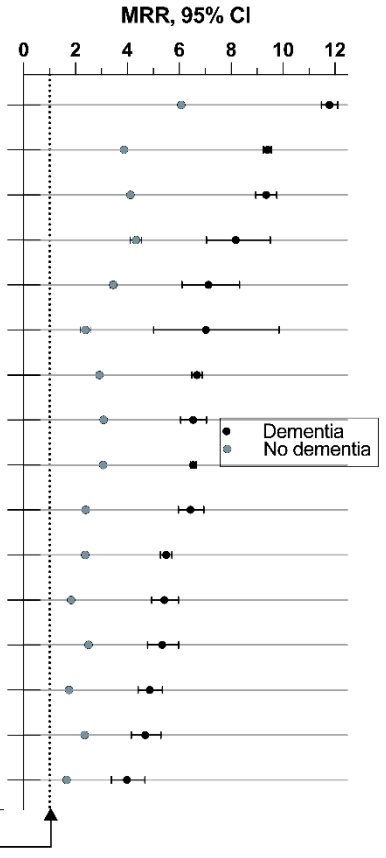
Table 1. Mortality rate ratios in cohort population stratified by sex

	Exposure groups	N	%	Pyrs at risk	N deaths	MRR model 1[a], 95% CI		MRR model 2[b], 95% CI		MRR model 3[c], 95% CI	
All	**Dementia**	112,565		354,456	82,537						
	Infection (after)	30,323	26.9	57,940	24,894	10.61	(10.47, 10.76)	10.69	(10.54, 10.83)	**7.35**	(7.25, 7.45)
	Infection (before)	36,853	32.7	89,162	27,070	7.78	(7.67, 7.88)	7.85	(7.74, 7.95)	4.78	(4.72, 4.84)
	No Infection	45,389	40.3	207,354	30,573	4.01	(3.96, 4.06)	4.07	(4.02, 4.12)	**3.66**	(3.62, 3.71)
	No Dementia	1,383,871		12,384,679	492,723						
	Infection	451,704	32.6	1,864,623	253,355	4.68	(4.65, 4.71)	4.75	(4.72, 4.78)	**2.93**	(2.91, 2.95)
	No Infection	932,167	67.4	10,520,056	239,368	1 (ref)		1 (ref)		1 (ref)	
	Total	1,496,436		12,739,135	575,260						
Women	**Dementia**	70,162		233,809	51,027						
	Infection (after)	18,364	26.2	38,408	14,914	9.48	(9.32, 9.65)	9.55	(9.38, 9.72)	**6.76**	(6.64, 6.88)
	Infection (before)	22,415	31.9	57,345	16,275	7.26	(7.14, 7.39)	7.32	(7.20, 7.45)	4.67	(4.59, 4.75)
	No Infection	29,383	41.9	138,056	19,838	3.94	(3.88, 4.00)	3.98	(3.92, 4.04)	**3.67**	(3.61, 3.73)
	No Dementia	744,402		6,953,106	257,446						
	Infection	237,376	31.9	1,022,965	131,513	4.56	(4.52, 4.60)	4.61	(4.57, 4.65)	**2.94**	(2.92, 2.97)
	No Infection	507,026	68.1	5,930,141	125,933	1 (ref)		1 (ref)		1 (ref)	
Men	**Dementia**	42,403		120,646	31,510						
	Infection (after)	11,959	28.2	19,532	9980	12.51	(12.25, 12.77)	12.63	(12.37, 12.90)	**8.29**	(8.12, 8.47)
	Infection (before)	14,438	34.0	31,817	10,795	8.50	(8.33, 8.67)	8.61	(8.44, 8.79)	4.91	(4.81, 5.01)
	No Infection	16,006	37.7	69,297	10,735	4.04	(3.96, 4.12)	4.13	(4.05, 4.22)	**3.59**	(3.52, 3.67)
	No Dementia	639,469		5,431,574	235,277						
	Infection	214,328	33.5	841,659	121,842	4.81	(4.77, 4.85)	4.91	(4.87, 4.95)	**2.91**	(2.88, 2.93)
	No Infection	425,141	66.5	4,589,915	113,435	1 (ref)		1 (ref)		1 (ref)	

Bolded MRRs are mainly the focus of this paper. Abbreviations: CI, confidence interval; MRR, mortality rate ratio; N, number; Pyrs, personyears; ref, reference group. [a] Adjusted for sex, age, and calendar year. [b] Further adjusted for highest attained educational level and civil status; $p \leq 0.00001$ for all MRRs. [c] Further adjusted for Charlson Comorbidity Index.

Figure 2. Mortality rate ratios by infection site

Infection site	N		Pyrs at risk		N deaths		MRR model 3[c], 95% CI	
	Dementia	No dementia	Dementia	No dementia	Dementia	No dementia	Dementia	No dementia
Sepsis	6790	62,050	7339	124,499	5737	43,307	**11.79** (11.48, 12.11)	6.08 (6.01, 6.14)
Respiratory	20,111	233,295	28,230	752,435	17,073	154,574	**9.40** (9.25, 9.55)	3.87 (3.85, 3.90)
Uncategorized	2778	26,407	3702	71,738	2076	14,616	**9.35** (8.95, 9.76)	4.12 (4.05, 4.19)
Nervous	220	2674	376	9022	173	1460	**8.18** (7.05, 9.50)	4.33 (4.11, 4.56)
Circulatory	238	5916	317	20,460	162	3361	**7.13** (6.11, 8.32)	3.45 (3.34, 3.57)
Hepatitis	44	1331	85	5880	34	618	**7.03** (5.02, 9.84)	2.38 (2.20, 2.58)
Digestive	5391	88,426	10,034	344,675	4332	47,540	**6.68** (6.48, 6.88)	2.92 (2.89, 2.96)
Less occurring	866	13,595	1549	50,948	679	6987	**6.54** (6.06, 7.05)	3.09 (3.02, 3.17)
Urinary	18,699	140,979	36,468	496,708	15,059	86,579	**6.54** (6.43, 6.65)	3.07 (3.05, 3.10)
Surgical	870	20,884	1743	90,928	661	9635	**6.43** (5.96, 6.94)	2.39 (2.34, 2.44)
Skin	3219	52,866	7097	231,504	2429	25,013	**5.49** (5.28, 5.72)	2.37 (2.34, 2.40)
Genital	595	17,663	1418	94,188	427	6460	**5.42** (4.93, 5.96)	1.83 (1.78, 1.87)
Musculoskeletal	418	9201	893	39,128	311	4427	**5.34** (4.78, 5.97)	2.51 (2.44, 2.59)
Eye and adnexa	558	15,953	1390	91,579	413	6096	**4.86** (4.41, 5.35)	1.75 (1.71, 1.80)
Herpes	340	6448	795	28,384	262	3245	**4.69** (4.15, 5.29)	2.35 (2.27, 2.44)
Ear	197	8539	560	54,790	144	3366	**3.98** (3.38, 4.68)	1.66 (1.61, 1.72)
No infections	45,389	932,167	207,354	10,520,056	30,573	239,368	3.66 (3.62, 3.71)	1 (reference)



MRR is presented for each infection site (without other infections) that occurred after a dementia diagnosis relative to the general population without an infection (reference group: no dementia/no infection, MRR = 1), adjusted for sex, age, calendar year, highest attained educational level, civil status, and Charlson Comorbidity Index. Site categories are in ascending order by MRR. Refer to Table S7for the complete analysis models. CI, confidence interval; MRR, mortality rate ratio; N, number; Pyrs, person-years.

Figure 2 presents the MRR for infections of each infection site (without other infections) that occurred after a dementia diagnosis relative to the general population without an infection. MRRs in each of the site categories were higher in the Dementia and Infection than the Infection only group. Highest ratios were seen for sepsis followed by infections in the respiratory system, uncategorized infections, nervous, and circulatory systems. (Table 7 in the Supplement). Estimates of additive interactions between dementia and infections are presented in Figure 3. The synergy index for any infection was 1.383 (95% CI, 1.360 to 1.407) and was highest for infections in the respiratory system followed by uncategorized infections, sepsis, and surgical infections. A non-significant synergy index was seen for infections of the eye, musculoskeletal and circulatory systems as well as for herpes, hepatitis and ear infections.

Figure 3. Synergy index for any infection and in all infection

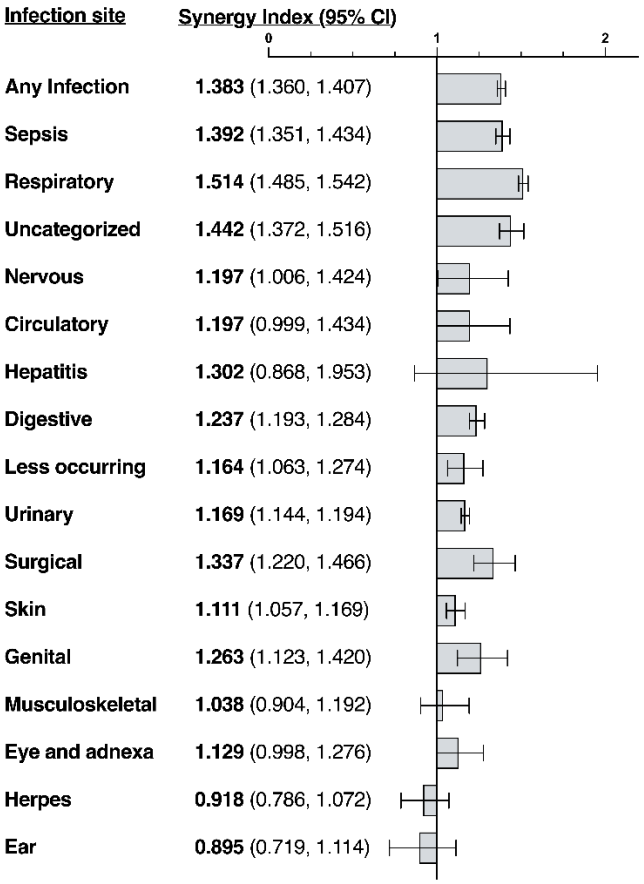
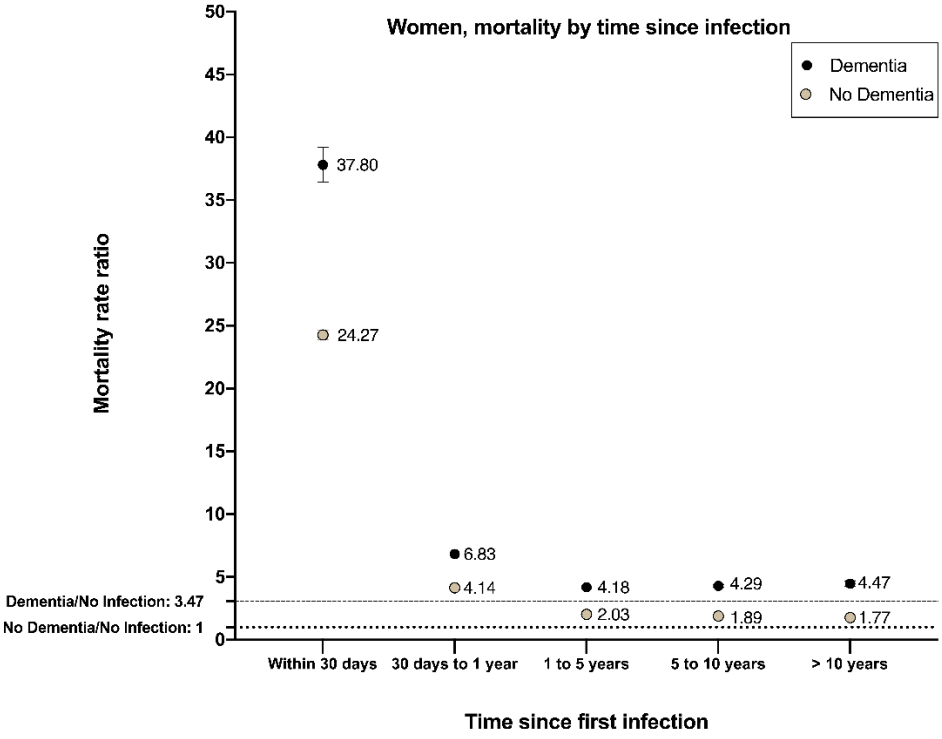
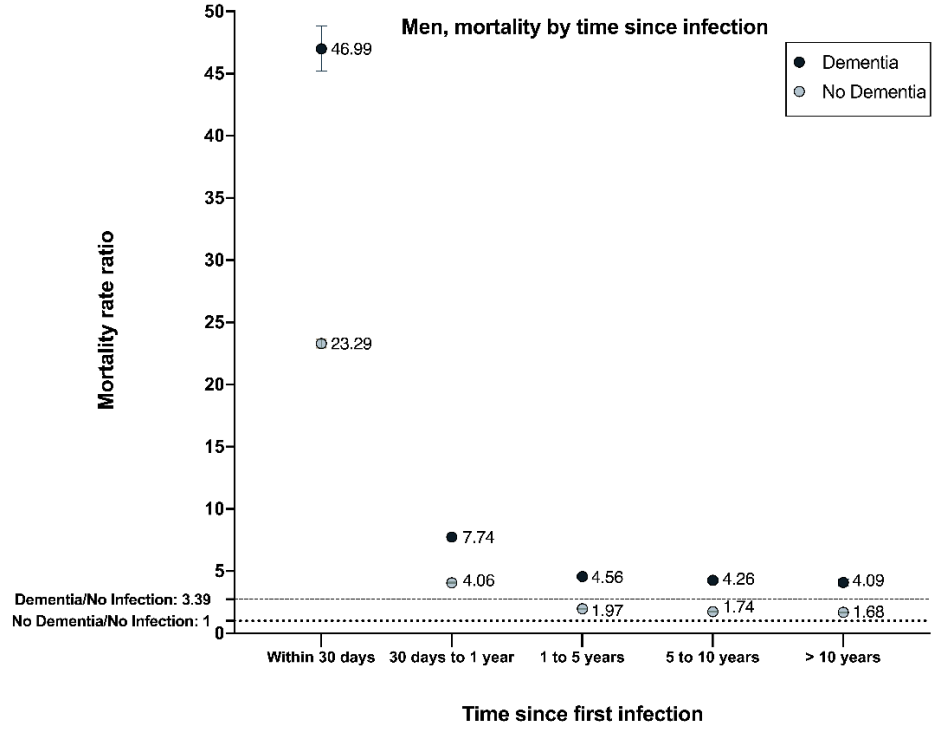


Figure presents the calculated synergy index (S) for estimation of the excess mortality between dementia and infections that is beyond the mortality risk from infections or dementia alone and is beyond the added sum of the two mortality risks. S can range from 0 to infinity, where S=1 indicates no interaction or exact additivity, S>1 indicates positive interaction or more than additivity, and S<1 indicates negative interaction or less than additivity. Error bars represent the 95% confidence intervals (CI). Infection sites are ordered as in Figure2. S was calculated from the fully adjusted mortality rate ratios (MRRs) in the 4 main exposure groups. For any infection, MRR=7.35 was used to calculate S.

Figure 4. Mortality rate ratios (MRRs) by time since first infection in women (a) and men (b)



(a)



(b)

Error bars represent the 95% confidence intervals. MRRs presented for groups: dementia/infection (infection after dementia), no dementia/infection, dementia/no infection, and no dementia/no infection (reference group), adjusted for sex, age, calendar year, highest attained educational level, civil status, and Charlson Comorbidity Index. Refer to Tables S8andS9for the complete analysis model.

Figure 4A-B presents MRRs by time since first infection in women and men, respectively. MRRs for the Dementia and Infection group were higher than for the Infection only group in all time periods, were highest within 30 days of first infection and remained higher after 10 years of first infection (Tables 8-9 in the Supplement).

Similar trends were seen in each of the 6 infection site categories analyzed (Tables 10- 11 in the Supplement).

Results from the sensitivity analyses showed very slight changes in the observed MRRs (Tables 12-16 in the Supplement).

Results from our post-hoc analysis showed that MRRs remained highest within 30 days of first infection and were higher for the Dementia/Infections group than the No Dementia/Infection group (Table 17, Fig 2 in the Supplement). In our second post-hoc analysis, results showed increased MRRs in the Dementia/Infection compared with Dementia/No Infection groups across all time periods (Table 18, Fig 3 in the Supplement).

Discussion

In this prospective nationwide cohort study with a 15-year follow-up period, we showed a more than 7-fold overall increased mortality in elderly people with dementia and infections and found evidence for a synergistic interaction between dementia and infections on mortality risk. Mortality was increased in this group for infections of all sites, with varying magnitudes and significant synergistic interactions were seen in most but not all sites. Additionally, increased mortality in people with dementia was both short- and long-term.

A synergy index of 1.383 shows excess mortality risk in people with both dementia and infections that is beyond the mortality risk from either dementia or infections alone and is beyond the added sum of the two mortality risks. The synergy index for interaction on the additive scale has been recommended in clinical epidemiology due to its potential implications for public health.[27] Implications of our study identify people with dementia as a vulnerable group in relation to infections. It is however important to note that the synergistic effect might also be attributed to differences in several psychosocial characteristics of people with dementia, as discussed below, which remain unmeasured in our study and may explain the additive interaction result in people with dementia and infections.

It is difficult to directly compare our results to those of previous studies since to our knowledge, this is the first study that investigated short- and long-term impact of several different infections on mortality in dementia using a large nationwide cohort. Previous studies have reported an increased six-month and one-year mortality after pneumonia in patients with dementia.[7–9] Pneumonia was also found to be a common cause of death in dementia and recent reviews have reported a twofold increased pneumonia-associated death in people with dementia.[6,11,12] Sepsis was also found to increase the risk of in-hospital death in patients with dementia[4] and identified dementia as a risk factor for in-hospital mortality due to sepsis.[3] Consistently, we also found that highest MRRs were seen in people with dementia and sepsis as well as infections in the respiratory system.

Mortality estimates from literature for infections other than pneumonia and sepsis are lacking, as is a comparison between these and all other infections. Our study showed that increased mortality was higher in all infection sites and MRRs ranged from 11.79 in people with dementia and sepsis to 3.98 in those with dementia and ear infections. However, synergistic interactions with dementia were seen in most but not all infection sites. In some sites, smaller sample sizes when calculating the synergy index could have led to wider confidence intervals and therefore shown insignificance.

Our results showed an increased mortality that was highest within 30 days of first infection in people with dementia and remained markedly higher than in people without dementia after 10 years following a first infection. We then showed in our sub-group analysis that this long-term impact was present even in people without co-occurring or recurring infections. We further showed in our post hoc analysis an increased long-term mortality in the Infection compared with No Infection group in dementia, suggesting that infections continue to play a role long-term.

Several explanations of our findings are plausible. People with dementia have a different psycho-social profile and hospitalization without support from relatives, together with poorer physical health and dependency on external-care following severe infections may increase frailty and lead to a decline in functional levels,[30,31] thus explain the observed increased and excess mortality. Consistently, one study found that the effect of dementia on mortality was lower after accounting for frailty.[32] The severity of infections at the time of hospital contact was unknown in our study due to lack of data, thus the differences in MRRs could reflect health care attitudes towards people with dementia with possibly more severe infections at the time of the hospital contact than those without dementia, due to delayed diagnosis of the infection or a delayed presentation of symptoms.[33] It is also possible that due to challenges in observing moderate infections in people with dementia, they may present to the

hospital with an infection earlier than those without dementia. Moreover, since the hospital contacts we investigated also included secondary diagnoses of infections, one could speculate that in those cases the observed increased mortality was driven by the primary reason for the hospital contact during which an infection was also diagnosed, if such reasons differed between people with and without dementia.[33]

It is reasonable to attribute increased mortality risk to infections, particularly within the first 30 days following an infection. However, for the observed long-term mortality (particularly after 10 years), infections may play less of a direct role. This is a surprising finding and even though we do not directly attribute the increased mortality to exposure to that first infection and do not interpret it as such, we do believe that our findings shed light on possible long-term consequences of severe infections in people with dementia that ultimately led to increased mortality. Consequences of severe infections may extend well beyond the period immediately following an infection as documented previously in literature where severe infections were associated with an increased mortality up to five years post infection (in people without focus on dementia).[13–16] A study investigating long-term mortality in sepsis survivors has concluded that survivors retain mortality risk both from the index (first) hospitalization with sepsis and also accumulate additional risk following hospital-discharge.[16] Therefore, consequences and risk factors that may independently be associated with increased long-term mortality observed in our study are crucial to investigate in future research and may guide targeted interventions.

Additionally, a growing recent attention has been directed towards the involvement of infections in the neurodegenerative process and the pathogenesis of dementias.[34] A bidirectional relationship between cognitive function and pneumonia has been demonstrated where a decrease in cognitive status was reported to increase the risk of pneumonia and that following a pneumonia episode, cognitive decline was accelerated,[35] a relationship that may be common to all infections. It could be hypothesized based on our findings that infections in dementia impact the neurodegeneration process and worsen dementia. With the plausibility of several explanations for the observed increased and excess mortality, we do not conclude on causality between infections in dementia and mortality, and our findings should be interpreted in light of the points discussed in this paper.

Strengths and limitations

Our study has limitations important to draw attention to. First, we were unable to investigate the different subtypes of dementia due to the low validity of such data.[36] Moreover, dementia is generally

under-diagnosed in our population as in other populations and so several cases undetected in the registries.[33,37] We also lacked information on the severity stage of dementia at the times of diagnosis, the hospital contact with an infection, and death.

Second, we do not know if the threshold for a hospital contact with an infection was the same for people with and without dementia which could be a determining factor for the observed increased and excess mortality. Infections in our study were only the severe and treated ones that led to a hospital contact and our results should be interpreted as such. We only investigated first infections in our analyses and the impact of recurrent or co-occurring infections on mortality was not estimated.

Third, we did not include information on nursing home residency due to the lack of validity of such data.[38] Such information could have clarified our results since people in nursing homes could have altered patterns of medical care and decision-making regarding hospitalization. Lastly, as with all observational studies, the possibility of residual confounding cannot be excluded (eg, lifestyle factors).

Our study also has several strengths. First, it is a large nationwide cohort study, and with its long follow-up and use of prospectively collected data, biases arising from common issues of nonresponse, selection, or loss of follow-up were limited. Second, we investigated both short- and long-term mortality after several different infections. Third, data on dementia and infections in the national registries were complete and valid thus limiting potential information bias.[36,39] We only investigated all-cause mortality using the valid and almost 100% complete data[17] to avoid any misclassifications of the underlying causes of death.[40] Fourth, we included several covariates, including calendar year to control for time-trends in dementia diagnosis over the follow-up period.[36] Finally, we conducted several sensitivity analyses to ensure robustness of our data to any decisions we have made and found essentially no changes to our estimates in the several models.

Conclusion

Mortality is substantially increased in people with dementia following infections of all sites. This increase was observed both short- (within 30 days) and long-term (after 10 years). Although we do not directly attribute the increased mortality after 10 years of first infection to that first infection, we believe that our findings reflect that possible consequences of infections, specifically in people dementia, are associated with a long-term increased mortality, and research into which factors or events this increase may be attributed to is crucial. Our findings identify people with dementia and

infections as a vulnerable group and steps towards better clinical management of infections should be identified. Future research that builds hypotheses on the role of infections in the pathogenesis of dementia as well as investigates possible mechanistic pathways involved is needed to clarify the associations that we report.

Acknowledgements

Author contributions

Study concept and the literature review were done by JJ, GW and NFM. JJ, GW and TML designed the study. JJ, CSM and NFM prepared and defined the data related to infection codes. Statistical analyses were done by JJ and TML. JJ wrote the manuscript as outlined by JJ and GW together, and all authors equally contributed to data interpretation and to the critical review of the manuscript.

Disclosure of conflicts of interest

None.

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Data sharing statement

The data included in the current study are all derived from the Danish public health registries and cannot be shared with the public.

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Increased short- and long-term mortality following infections in dementia, a nationwide registry-based cohort study

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Supplementary Material

Online supplement material

Table 1. International Classification of Diseases (ICD) 8 and 10 codes for dementia diagnosis and Anatomical Therapeutic Chemical Classification (ATC) codes for anti-dementia medication.

Dementia type	**ICD-8 code**	**ICD-10 code**
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
Medication	**ATC code**	
Cholinesterase inhibitors		
Donepezil	N06DA02	
Rivastigmine	N06DA03	
Galantamine	N06DA04	
Glutamate-receptor antagonists		
Memantine	N06DX01	

Dementia was defined as a first registered dementia diagnosis using the ICD codes from the Danish National Patient Registry and the Psychiatric Central Research Registry, or a first redeemed prescription for an anti-dementia medication from the Danish National Prescription Registry. ICD codes for a dementia diagnosis reflect diagnosis in the secondary care setting. If a person with dementia was identified by a redeemed anti-dementia medication but with no registered ICD code of dementia, then this person had been diagnosed in the primary care setting. If a person gets a diagnosis of dementia in the primary care setting and does not redeem an anti-dementia medication, then this dementia diagnosis remains undetected in our registries.

Method: Process of defining infections (selection of ICD codes, categorization of infection codes and data cleaning)

1. We first included all ICD-10 codes that were used in previous Danish epidemiological studies, using the Danish National Patient Register (excluding A and B codes; refer to point 3.6 below for these).
2. We additionally scanned through all ICD-10 codes using the Danish website icdpedia.dk and WHO's official ICD-10 code manual: https://icd.who.int/browse10/2016/en#/U82-U85
3. Expert knowledge in infectious diseases was used to guide the process of including or excluding codes as well as scanning through the Danish webpage sundhed.dk and pubmed publications, as follows:

   3.1. We excluded all codes from letter categories C (Neoplasms); F (Mental and behavioral disorders); O (Pregnancy, childbirth and the puerperium); P (Certain conditions originating in the perinatal period); Q (Congenital malformations, deformations and chromosomal abnormalities); V and Y (External causes of morbidity and mortality) and U (Codes for special purposes).
   3.2. We excluded all codes which were not infections and diseases not caused by an infection.
   3.3. We excluded all codes where an infection was secondary; an unlikely cause of the disease or where the disease was in majority of reported cases due to non-infectious causes; was due to medication or chemicals (toxic); was due to trauma; was due to allergy/allergic reactions; was due to or related to autoimmune diseases.
   3.4. We also excluded all granulomas and eosinophilic infections.
   3.5. Unspecific infections, and diseases due to several causes including an infectious cause were included in our analyses, and these are marked in yellow throughout this document. Refer to Table A.12 for the sensitivity analysis model where these were removed.
   3.6. We included all A and B codes and ran a frequency analysis in our sample population. We then chose all A and B codes that occurred 500 times or more over our study period (Table A.2).
   Rationale: Based on the assumption that these specific infections with specified pathogens are rare in the Danish population, or that these diagnoses are generally not used in our population.
   3.7. We excluded all diagnosis types marked as "referring diagnosis" in the Danish National Patient Registry.
4. A list of all ICD-10 codes was agreed on by 3 of the authors (JJ, CSM, NFM) (Table A.3).

5. Categorization:

We categorized all included infection codes by infection site based on the ICD-10 official manual https://icd.who.int/browse10/2016/en#/U82-U85 and guided by expert knowledge and categorization process in previous Danish studies that used infection codes from the Danish National Patient Registry.
Rationale: This is to limit any misclassification errors between the diagnostic codes of specific infections within each site (e.g. different types of urinary infections). We assumed that categorizing infection diagnostic codes by infection site would limit errors arising from incorrectly diagnosing a specific infection (i.e. the underlying assumption is that an error is more likely to happen within an infection site than across sites. An example is diagnosing a specific urinary infection, where a misclassification among the codes is possible, but limited across another site such as diagnosing a urinary infection versus a respiratory or skin one). Another underlying assumption here is that all specific codes within each site are dependent on and related to each other.

Categorization was made as follows (Table A.4):

5.1. All ICD-10 codes with start letters H, I, J, K, L, M, N, G and T were categorized as in the ICD-10 manual (an exception was splitting genital and urinary codes).
5.2. All ICD-10 codes with start letters A and B and that were frequently occurring in our sample population (refer to point 3.6. above for rationale) were categorized per infection site category.

5.3. Codes for sepsis were put in a separate site category and these codes were taken out from the other site categories. All A and B codes that were of sepsis were included regardless of their occurrence frequency in our population.
5.4. A category: "Uncategorized" was used for all codes which did not fit in the defined categories.
5.5. Another category "less occurring" was used for all ICD-10 codes with start letters A and B and which occurred less than 500 times in our sample population (refer to point 3.6. above for rationale).
5.6. Infection codes of herpes and hepatitis were put in two separate categories. All A and B codes that were of herpes and hepatitis were included regardless of their occurrence frequency in our population.
Rationale: Infection codes for herpes and hepatitis: 1) Recent literature has pointed out the role of herpes infections specifically in dementia and Alzheimer's disease; 2) Because these infections are seen as life-long infections and are thus different than other infections categorized together in each infection site (i.e. These infections are not "episodes" that occur such as a urinary tract infection, but instead occur once and individuals with these infections will be referred to using terms such as "expressed symptoms" or "break-outs" instead of "episodes" used for the remaining infections.
5.7. We did not include ICD-10 codes for HIV infections which were instead included in the Charlson Comorbidity Index.
Rationale: HIV affects the immune system leading to an impaired immune response. Thus, this suppression of the immune system makes people with HIV more receptive to other infections.[1]

6. Initial clean-up of data:

Prior to counting new infections, and due to the nature of the admissions' registered in the Danish National Patient Registry, we cleaned up the data. Within each of the categories, an individual may have had several hospital contacts on the same date. To clean-up such data, where an individual had a registered admission date (in- or out-patient) on the same date as a previous discharge date or a previous admission date (+1 day), these were considered one hospital contact where we used the first admission date and last discharge date to define the period of the contact. Inpatient contacts always triumphed outpatient contacts, in situations where an inpatient contact's admission was on the same date as a previous outpatient contact discharge. This was to limit counting hospital contacts more than once when these were the same hospital contact where several administrative processes or transfers between hospital departments caused the multiple contacts. This dataset is referred to as the "cleaned dataset" in paper.

Table 2. All A, B codes occurring in sample population 500 times or more.

ICD-10 Code	Category	ICD-10 Code	Category	ICD-10 Code	Category	ICD-10 Code	Category
A020	Digestive	A411	Sepsis	A499	Uncategorized	B370	Digestive
A045	Digestive	A412	Sepsis	A499A	Uncategorized	B378	Uncategorized
A047	Digestive	A414	Sepsis	A630	Genital	B378C	Digestive
A049	Digestive	A415	Sepsis	A692	Uncategorized	B379	Uncategorized
A081	Digestive	A418	Sepsis	A869	Nervous	B869	Skin
A084	Digestive	A419	Sepsis	B022	Herpes	B909	Uncategorized
A090	Digestive	A419B	Sepsis	B023	Herpes	B919	Musculoskeletal
A099	Digestive	A419C	Sepsis	B028	Herpes	B956A	Uncategorized
A150	Respiratory	A469	Skin	B029	Herpes	B962	Uncategorized
A403	Sepsis	A481	Respiratory	B079	Skin	B999	Uncategorized
A409	Sepsis	A490	Uncategorized	B182	Hepatitis		
A410	Sepsis	A498	Uncategorized	B349	Uncategorized		

Table 3. List of all ICD-10 codes of infections included in our study

Category	ICD-10 codes
H. Eye and adnexa	H000, H000A, H000B, H000C, H000D, H010, H018, H019, H030, H031, H040, H043, H043A, H043B, H043C, H043D, H043E, H043F, H044, H044A, H050, H050A, H050B, H050C, H050D, H050E, H051, H061, H100, H102, H103, H104, H105, H108, H109, H130, H131, H132, H150, H151, H160A, H161, H161A, H161B, H161C, H161D, H161E, H161F, H161G, H162, H162A, H162B, H163, H168, H169, H181, H184B, H191, H191A, H191C, H192, H192L, H192M, H193, H193A, H193C, H200, H201, H202, H208, H209, H220, H300, H301, H302, H309, H308, H320, H350E, H440, H440A, H440B, H441, H441A, H441B, H441C, H441D, H441E, H451, H469C, H481
H. Ear and mastoid process	H600, H600A, H601, H601B, H602, H603, H603A, H603B, H603C, H608, H608A, H609, H610, H610A, H620, H621, H622, H623, H624, H650, H650A, H651, H651C, H651D, H652, H653, H654, 654C, H659, H660, H660A, H661, H662, H663, H664, H669, H670, H671, H678, H680, H700, H701, H702, H708, H709, H730, H730A, H731, H750, H830, H940
I. Circulatory	I301, I301A, I301B, I301C, I301D, I301E, I308, I309, I320, I321, I328, I330, I339, I389, I398, I400, I408, I408A, I409, I410, I411, I412, I430, I514, I514B, I520, I521, I681
J. Respiratory	J009, J010, J011, J012, J013, J014, J018, J019, J020, J020A, J028, J029, J029A, J029B, J029C, J030, J038, J039, J039A, J039B, J039C, J039D, J039E, J039F, J040, J040A, J040B, J040C, J040D, J041, J042, J050, J051, J060, J068, J069, J091, J091A, J091B, J100, J101, J101A, J101B, J101C, J108, J108A, J110, J111, J111A, J111B, J111C, J118, J118B, J118D, J120, J121, J122, J123, J128, J128A, J129, J139, J139A, J139B, J149, J149A, J149B, J150, J151, J152, J153, J154, J155, J156, J156A, J157, J158, J159, J160, J168, J170, J171, J172, J173, J178, J180, J181, J182, J188, J189, J200, J200A, J201, J201A, J202, J202A, J203, J203A, J204, J204A, J205, J205A, J206, J206A, J207, J207A, J208, J208A, J209, J209A, J210, J211, J218, J219, J229, J311, J312, J320, J321, J322, J323, J324, J328, J329, J340, J340A, J340B, J340D, J340I, J340J, J350, J369, J370, J370A, J370B, J370C, J371, J383C, J383D, J387G, J390, J390A, J390B, J390C, J391, J391A, J391B, J391C, J398A, J409, J410, J411, J418, J429A, J429B, J440, J441, J659, J850, J851, J852, J853, J860, J869, J950A, J985D, J986D
K. Digestive	K040, K040A, K040B, K041, K041A, K044, K045, K046, K047, K047A, K047B, K050, K051, K051A, K051B, K051C, K052, K052A, K052B, K052C, K053, K053A, K053B, K102, K102A, K102B, K102C, K102D, K102G, K102H, K112, K112A, K112B, K112C, K112D, K113, K113A, K113B, K113C, K113D, K121, K121A, K121B, K121C, K122, K122A, K122B, K130A, K130B, K130C, K130D, K130E, K130F, K130G, K140, K140A, K140B, K140D, K209, K209A, K221C, K230, K231, K298, K352, K353, K353A, K353B, K358, K358A, K358B, K358C, K369, K379, K401, K404, K411, K414, K421, K431, K434, K437, K441, K451, K451B, K451C, K451D, K451E, K451F, K451G, K451H, K451I, K451J, K451K, K451L, K451M, K461, K570, K570A, K570B, K570C, K572, K572A, K572B, K572C, K573E, K573F, K574, K578, K610, K610A, K610B, K611, K611A, K612, K613, K614, K628I, K628L, K628N, K630, K650, K650A, K650B, K650C, K650D, K650E, K650F, K650G, K650H, K650I, K650J, K650K, K650L, K650M, K650N, K650O, K650P, K658, K658A, K658F, K658I, K659, K670, K671, K672, K673, K678, K720A, K720E, K720F, K730, K731, K732, K738, K739, K750, K750A, K750B, K750C, K750D,

Category	ICD-10 codes
	K751, K759A, K770, K803, K803A, K803B, K803C, K804A, K804C, K804E, K810A, K810B, K810C, K810D, K830, K830A, K830B, K830C, K830D, K830E, K830G, K858A, K858D, K858E, K858F, K861A, K930, K931,
L. Skin and subcutaneous tissue	L009, L009A, L009B, L009C, L010, L010A, L010B, L010C, L011, L020, L020A, L020B, L020C, L021, L021A, L021B, L021C, L022, L022A, L022B, L022C, L022D, L022E, L022F, L022G, L022H, L022I, L022J, L022K, L022L, L022M, L022N, L022O, L022P, L022Q, L022R, L022S, L022T, L023, L023A, L023B, L023C, L024, L024A, L024B, L024C, L024D, L024E, L024F, L024G, L024H, L024I, L024J, L024K, L024L, L024M, L028, L028A, L028B, L028C, L029, L029A, L029B, L029C, L030, L030A, L030B, L030C, L030D, L030E, L030F, L030G, L030H, L030I, L030J, L030K, L031, L031A, L031B, L031C, L031D, L031E, L031F, L031G, L031H, L031I, L032, L033, L033A, L033B, L033C, L033D, L033E, L033F, L038, L038A, L038B, L039, L040, L040A, L040B, L040C, L041, L042, L042A, L043, L048, L049, L050, L080, L080A, L080B, L080C, L081, L088, L088C, L088D, L089, L303, L738, L738A, L738H
M. Musculoskeletal and connective tissue	M000, M000A, M000B, M001, M001A, M001B, M002, M002A, M002B, M008, M009, M010, M011, M012, M013, M014, M015, M016, M018, M462, M463, M463A, M464, M465, M465A, M490, M491, M492, M493, M600, M600A, M601, M608, M608A, M608A1, M609, M630, M631, M632, M650, M651, M680, M680G, M680H, M710, M711, M726, M729A, M730, M731, M792B, M860, M861, M862, M863, M864, M865, M865A, M866, M868, M868A, M869, M869A, M869B, M869C, M900, M901, M902
N. Urinary	N080, N109A, N109B, N109C, N110, N110A, N111, N111A, N111B, N118, N118A, N118B, N118C, N118D, N119, N129, N136, N136A, N136B, N136C, N136D, N136E, N151, N151A, N151B, N160, N200I, N201I, N209A, N220, N291, N300, N302, N308, N308A, N308B, N308C, N308E, N308F, N308G, N308J, N308K, N309, N330, N340, N340B, N340C, N341, N342, N342G, N343, N370, N390
N.Genital	N410, N411, N412, N412A, N413, N413A, N418, N419, N431, N432, N433, N449C, N450, N450A, N450B, N450C, N459, N459A, N459B, N459C, N459D, N459E, N481, N481A, N481B, N481C, N481D, N482, N482A, N482B, N482C, N482D, N482E, N482F, N482G, N482H, N490, N491, N491A, N491B, N492, N492A, N492B, N492C, N492D, N498, N498A, N498B, N498C, N498M, N499, N511K, N511L, N512, N619, N619A, N619B, N619E, N700, N700A, N700B, N700C, N700D, N700E, N700F, N700G, N701, N701A, N701B, N701C, N701D, N701E, N701F, N701G, N701H, N709, N709A, N709B, N709C, N710, N710A, N710C, N710D, N710E, N710F, N710A, N711, N711A, N711B, N711D, N711E, N711F, N711A, N719, N729, N729A, N729B, N729C, N729D, N729E, N729F, N730, N730A, N730B, N730C, N730D, N730E, N731, N731A, N731B, N731C, N731D, N731E, N732, N732A, N732B, N732C, N732D, N732E, N733, N733A, N734, N734A, N735, N735A, N738, N738A, N738B, N738C, N739, N740, N741, N741A, N742, N743, N744, N748, N751, N758A, N758B, N758C, N760, N760B, N760C, N760D, N760E, N761, N761A, N761B, N761C, N761D, N761E, N762, N762A, N763, N763A, N763B, N764, N764A, N764B, N764C, N764D, N764E, N765, N766, N766A, N768, N768A, N768B, N768C, N770, N771, N771P, N771Q, N771R, N778
G. Nervous	G000, G001, G002, G003, G008, G008A, G008B, G009, G009A, G019, G020, G021, G028, G030, G031, G032, G038, G039, G040, G040A, G041, G042, G042A, G042B, G048, G048A, G048B, G048C, G049, G049A, G049B, G049C, G049D, G050, G050P, G050R, G050S, G051, G051U, G051V, G051X, G052, G052K, G052L, G052M, G052N, G058, G060, G060A, G060B, G060C, G060E, G060F, G061, G061A, G061C, G061F, G062, G062A, G062C, G079, G079A, G079B, G089, G630, G734, G940

Category	ICD-10 codes
T. Surgical	T793, T801, T802, T802A, T802D, T802D1, T802G, T814, T814A, T814B, T814C, T814D, T814F, T814G, T814H, T814I, T814J, T814P, T814P1, T814U, T814X, T826, T826A, T827, T827A, T827B, T827I, T827P, T835, T835A, T835B, T835C, T836, T836A, T836B, T836C, T845, T845A, T846, T846A, T847, T857, T857A, T874, T880, T880A
Z. Factors influencing health status and contact with health services	Z229
R. Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	DR572, R827, R827B
D. Blood and blood-forming organs and certain disorders involving the immune mechanism	D733, D762
E. Endocrine, nutritional and metabolic diseases	E321, E236A

Codes marked in yellow: Unspecific infections, and diseases due to several causes including an infectious cause were included in our analyses. Refer to point 3.5. above and to Table A.12 for the sensitivity analysis model where these were removed.

Table 4. Infection site categories and ICD-10 codes

Categories by infection site	ICD-10 codes
- Sepsis	R572, J950A, T880A, T802D, T802D1, T814D, A419, A419B, A419C, A415, A410, A412, A409, A267[a], A021, A403, A411A[a], B377, A400, A414, A327[a], A401[a], A418, A408, A411, A415A[a], A392A[a], A282B[a], A402[a], A207[a], A227[a], A413[a], A427[a], A548G[a]
- Eye and adnexa	Until H60 (except herpes: H191)
- Ear	H60 and forward
- Circulatory	I
- Respiratory	J (except sepsis: J950A), A150, A481
- Digestive	K (except hepatitis: K720A, K720E, K720F, K730, K731, K732, K738, K739, K759A), A020, A045, A047, A049, A081, A084, A090, A099, B370, B378C
- Skin	L, A469, B079, B869
- Musculoskeletal	M, B919
- Urinary	Until N39, R827, R827B,
- Genital	N41 and forward, A630
- Nervous	G, A869
- Surgical	T (except sepsis: T880A, T802D, T802D1, T814D)
- Uncategorized	A490, A498, A499, A499A, A692, B349, B378, B379, B909, B956A, B962, B999, Z229, D733, D762, E321, E236A
- Less occurring	Remaining A, B codes not categorized elsewhere in this table.
Herpes	H191, B029, B028, B023, B001A[a], B009, B004, B004A[a], A609[a], B001B[a], B022, B021[a], B001, B003[a], B005, A601B[a], B002A[a], A600[a], A601[a], B008[a], B020[a], B020A[a], A601A[a], B000[a], B007[a], B027[a], A601C[a], B001C[a], DB002[a], B002B[a], B002C[a]
Hepatitis	K720A, K720E, K720F, K730, K731, K732, K738, K739, K759A, B182, B169A[a], B180[a], B169, B251[a], B181, B150[a], B159[a], B178, B199, B188[a], B161[a], B160[a], B162[a], B171[a], B189[a], B190[a], B159A[a], B170[a], B172[a], B581[a], B179[a]

[a]Codes occurring less than 500 times in our population.

Figure 1. Calculation of the additive interaction

	Infection	Dementia	Infection&Dementia
Regr. coefficients	1,07500	1,29746	1,99470
Cov Infection	0,00001	0,00001	0,00001
Cov Dementia	0,00001	0,00004	0,00001
Cov Infection&Deme	0,00001	0,00001	0,00005

Exposure	*RR*	*Lower*	*Upper*
Infection	2,930	2,912	2,948
Dementia	3,660	3,616	3,705
Infection&Dementia	7,350	7,251	7,450

Measure	*Estimate*	*Lower*	*Upper*
RERI	1,760	1,659	1,861
AP	0,239	0,228	0,251
S	1,383	1,360	1,407

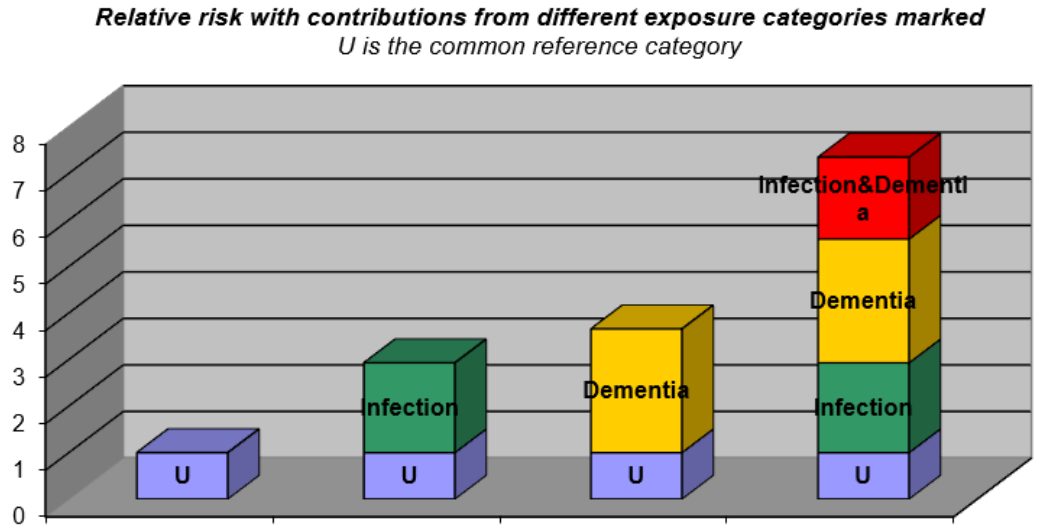


Figure presents the calculation method used to estimate the synergy index. Other additive measure estimates are presented in the figure, but only the Synergy Index was reported in our study. Numbers were obtained using the covariate matrix and the fully adjusted Mortality Rate Ratios yieled by the poisson regression model describd in our study. The template is taken from the paper by Andersson et al. [2] and is explained in detail there. Lower and upper correspond to lower and upper 95% confidence intervals. RERI= relative excess risk due to interaction; AP= attributable proportion due to interaction; SI= Synergy Index.

Table 5. Charlson Comorbidity Index

Comorbidity	Weight	ICD codes included
Myocardial infarction	1	410, I21, I22, I23
Congestive heart failure	1	42709, 42710, 42711, 42719, 42899, 78249, I50, I110, I130, I132
Peripheral vascular disease	1	440, 441, 442, 443, 444, 445, I70, I71, I72, I73, I74, I77
Cerebrovascular disease	1	430- 4398, I60- I69, G45, G46
Chronic pulmonary disease	1	490-493, 515-518, J40-J47, J60-J67, J684, J701, J703, J841, J920, J961, J982, J983
Connective tissue disease	1	712, 716, 734, 446, 13599, M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
Ulcer disease	1	53091, 53098, 531-534, K221, K25-K28
Mild liver disease	1	571, 57301, 57304, B18, K700-K703, K709, K71, K73, K74, K760
Diabetes I and II without complications	2	24900, 24906, 24907, 24909, 25000, 25006, 25007, 25009, E100, E101, E109, E110, E111, E119
Hemiplegia	2	344, G81, G82
Moderate to severe renal disease	2	403, 404, 580-585, 59009, 59319, 75310-75319, 792, I12, I13, N00-N05, N07, N11, N14, N17-N19, Q61
Diabetes with complications	2	24901-24905, 24908, 25001-25005, 25008, E102-E108, E112-E118
Any tumor	2	140-194, C00-C75
Leukemia	2	204-207, C91-C95
Lymphoma	2	200-203, 27559, C81-C86, C88, C90, C96
Moderate to severe liver disease	3	07000, 07002, 07004, 07006, 07008, 57300, 45600-45609, B150, B160, B162, B190, K704, K72, K766, I85
Metastatic solid tumor	3	195-198, 199, C76-C80
AIDS	6	07983, B21-B24

Charlson Comorbidity Index[3] is based on 19 chronic diseases (Table lists 18 diseases due to removal of Dementia from the list in this study). For each disease, a person is given a score between one and six depending on the severity of the disease and the associated risk of dying. The scores of all diseases are then summed up to give an index.

Table 6. Cohort characteristics in the exposure groups and across all covariates.

Characteristic	Dementia. Total pyrs= 354,456									No Dementia. Total pyrs= 12,384,679					
	Infection (after dementia)			Infection (before dementia)			No Infection			Infection			No Infection		
	Pyrs	Deaths	rate	Pyrs	Deaths	rate	Pyrs	Deaths	rate	Pyrs	Deaths	rate	Pyrs	Deaths	rate
Age (years)															
65-69	1152	313	271.6	1362	225	165.2	9076	441	48.6	218,175	19,407	89.0	3,799,358	34,792	9.2
70-74	5002	1482	296.3	6804	1192	175.2	24,852	1618	65.1	422,751	34,683	82.0	2,678,001	37,439	14.0
75-79	9702	3384	348.8	15,942	3324	208.5	42,479	3953	93.1	446,843	46,323	103.7	1,881,440	42,017	22.3
80-84	15,139	5999	396.3	23,962	6339	264.5	55,509	7166	129.1	373,999	53,782	143.8	1,221,115	43,826	35.9
85-89	15,841	7374	465.5	24,652	8197	332.5	48,918	9068	185.4	251,749	50,540	200.8	643,825	39,372	61.2
90+	11,102	6342	571.2	16,440	7793	474.0	26,520	8327	314.0	151,107	48,620	321.8	296,317	41,922	141.5
Sex															
Women	38,408	14,914	388.3	57,345	16,275	283.8	138,056	19,838	143.7	1,022,965	131,513	128.6	5,930,141	125,933	21.2
Men	19,532	9980	511.0	31,817	10,795	339.3	69,297	10,735	154.9	841,659	121,842	144.8	4,589,915	113,435	24.7
Calendar year															
2000-2004	7307	3802	520.3	6991	2419	346.0	39,230	6691	170.6	262,266	52,278	199.3	3,186,706	100,788	31.6
2005-2009	20,105	8808	438.1	28,060	8614	307.0	74,670	11,269	150.9	594,538	83,208	140.0	3,126,727	71,990	23.0
2010-2015	30,528	12,284	402.4	54,111	16,037	296.4	93,453	12,613	135.0	1,007,819	117,869	117.0	4,206,623	66,590	15.8
Civil status															
Divorced	6091	2383	391.3	9888	2794	282.6	18,882	2435	129.0	207,992	27,395	131.7	1,101,463	23,603	21.4
Married	17,555	7675	437.2	27,859	7598	272.7	74,881	8611	115.0	864,304	90,808	105.1	5,908,060	84,704	14.3
Missing	25	<10	319.8	11	<10	174.9	185	25	135.1	1685	273	162.0	139,261	10,421	74.8
Single	3437	1525	443.7	4672	1648	352.7	10,867	1873	172.4	95,683	16,953	177.2	577,722	19,292	33.4
Widowed	30,831	13,303	431.5	46,731	15,028	321.6	102,539	17,629	171.9	694,959	117,926	169.7	2,793,550	101,348	36.3
Education															
High	1262	571	452.6	2266	564	248.9	4532	537	118.5	56,363	5035	89.3	362,020	4521	12.5
Low	37,015	14,411	389.3	60,665	16,250	267.9	138,065	16,176	117.2	1,371,715	162,337	118.3	7,729,177	132,494	17.1
Medium	4110	1438	349.9	6399	1497	233.9	15,754	1595	101.2	177,710	15,497	87.2	1,222,876	13,398	11.0
Missing	15,554	8474	544.8	19,832	8759	441.7	49,003	12,265	250.3	258,836	70,486	272.3	1,205,983	88,955	73.8
CCI															
0	17,441	5986	343.2	20,713	3967	191.5	99,876	11,009	110.2	538,991	21,341	39.6	6,628,043	59,002	8.9
1	14,525	6017	414.3	21,021	5517	262.4	45,995	7236	157.3	402,600	37,390	92.9	1,604,659	41,213	25.7
2	10,627	4825	454.0	17,494	5191	296.7	32,968	5668	171.9	368,484	48,362	131.2	1,367,354	48,670	35.6
3	6425	3161	492.0	11,651	4171	358.0	13,777	2918	211.8	212,433	40,086	188.7	430,505	28,971	67.3
4+	8922	4905	549.8	18,281	8224	449.9	14,737	3742	253.9	342,116	106,176	310.4	489,494	61,512	125.7

Pyrs= Person years at risk; Deaths= Number of deaths; Rate= Rate per 1000 person years at risk; CCI= Charlson Comorbidity Index. Education represents the highest attained educational level categorized as low: “Primary and lower and upper secondary education”, medium: “Short cycle tertiary and bachelor or equivalent”, high: “Master or equivalent and doctoral or equivalent”, and unknown: “Not elsewhere classified” (as defined by Statistics Denmark).

Table 7. Complete analysis model for mortality rate ratios by infection site.

Site	Exposure groups		N	Pyrs	N deaths	MRR model 1[a]	MRR model 2[b]	MRR model 3[c]
Respiratory	**Dementia**	Infection (After dementia)	20,111	28,230	17,073	14.92 (14.68, 15.15)	15.01 (14.77, 15.25)	9.40 (9.25, 9.55)
		Infection (Before dementia)	15,895	34,234	12,137	9.19 (9.03, 9.37)	9.26 (9.09, 9.43)	5.16 (5.06, 5.26)
		Infection of other sites	31,170	84,638	22,754	6.83 (6.74, 6.93)	6.90 (6.81, 7.00)	4.77 (4.70, 4.84)
	No Dementia	Infection	233,295	752,435	154,574	6.82 (6.77, 6.87)	6.89 (6.84, 6.94)	3.87 (3.85, 3.90)
		Infection of other sites	218,409	1,112,188	98,781	3.16 (3.14, 3.19)	3.22 (3.19, 3.25)	2.17 (2.16, 2.19)
Urinary	**Dementia**	Infection (After dementia)	18,699	36,468	15,059	10.07 (9.90, 10.24)	10.15 (9.98, 10.32)	6.54 (6.43, 6.65)
		Infection (Before dementia)	15,978	36,096	12,078	8.21 (8.06, 8.37)	8.24 (8.09, 8.39)	4.91 (4.82, 5.01)
		Infection of other sites	32,499	74,537	24,827	8.83 (8.71, 8.95)	8.92 (8.80, 9.04)	5.84 (5.76, 5.92)
	No Dementia	Infection	140,979	496,708	86,579	5.24 (5.19, 5.28)	5.28 (5.24, 5.33)	3.07 (3.05, 3.10)
		Infection of other sites	310,725	1,367,915	166,776	4.46 (4.43, 4.49)	4.54 (4.51, 4.57)	2.88 (2.86, 2.90)
Digestive	**Dementia**	Infection (After dementia)	5391	10,034	4332	11.20 (10.86, 11.54)	11.30 (10.96, 11.64)	6.68 (6.48, 6.88)
		Infection (Before dementia)	6145	14,630	4355	7.88 (7.65, 8.12)	8.01 (7.77, 8.25)	4.64 (4.50, 4.78)
		Infection of other sites	55,640	122,437	43,277	8.87 (8.77, 8.96)	8.93 (8.84, 9.03)	5.81 (5.75, 5.87)
	No Dementia	Infection	88,426	344,675	47,540	4.91 (4.86, 4.96)	4.99 (4.94, 5.04)	2.92 (2.89, 2.96)
		Infection of other sites	363,278	1,519,948	205,815	4.64 (4.61, 4.67)	4.70 (4.67, 4.73)	2.94 (2.92, 2.96)
Sepsis	**Dementia**	Infection (After dementia)	6790	7339	5737	20.59 (20.05, 21.14)	20.80 (20.26, 21.36)	11.79 (11.48, 12.11)
		Infection (Before dementia)	3214	6484	2326	9.60 (9.21, 10.00)	9.70 (9.31, 10.11)	5.09 (4.89, 5.31)
		Infection of other sites	57,172	133,279	43,901	8.36 (8.27, 8.45)	8.43 (8.34, 8.52)	5.49 (5.43, 5.55)
	No Dementia	Infection	62,050	124,499	43,307	11.76 (11.63, 11.88)	11.93 (11.80, 12.06)	6.08 (6.01, 6.14)
		Infection of other sites	389,654	1,740,125	210,048	4.20 (4.17, 4.23)	4.26 (4.23, 4.29)	2.69 (2.67, 2.71)
Skin	**Dementia**	Infection (After dementia)	3219	7097	2429	8.68 (8.34, 9.04)	8.67 (8.33, 9.02)	5.49 (5.28, 5.72)
		Infection (Before dementia)	4407	10,386	3169	7.91 (7.63, 8.19)	7.98 (7.70, 8.27)	4.78 (4.61, 4.95)
		Infection of other sites	59,550	129,618	46,366	9.02 (8.92, 9.11)	9.09 (9.00, 9.19)	5.84 (5.78, 5.90)
	No Dementia	Infection	52,866	231,504	25,013	3.88 (3.82, 3.93)	3.92 (3.87, 3.97)	2.37 (2.34, 2.40)
		Infection of other sites	398,838	1,633,119	228,342	4.79 (4.76, 4.82)	4.86 (4.83, 4.89)	3.01 (2.99, 3.03)
Uncategorized	**Dementia**	Infection (After dementia)	2778	3702	2076	15.51 (14.85, 16.20)	15.68 (15.02, 16.38)	9.35 (8.95, 9.76)
		Infection (Before dementia)	1754	3660	1172	8.65 (8.17, 9.17)	8.72 (8.23, 9.23)	4.90 (4.63, 5.19)
		Infection of other sites	62,644	139,739	48,716	8.78 (8.69, 8.88)	8.86 (8.77, 8.95)	5.69 (5.63, 5.75)
	No Dementia	Infection	26,407	71,738	14,616	7.38 (7.26, 7.51)	7.49 (7.36, 7.62)	4.12 (4.05, 4.19)
		Infection of other sites	425,297	1,792,885	238,739	4.59 (4.56, 4.61)	4.65 (4.62, 4.68)	2.89 (2.87, 2.91)
Surgical	**Dementia**	Infection (After dementia)	870	1743	661	10.28 (9.53, 11.10)	10.30 (9.55, 11.12)	6.43 (5.96, 6.94)
		Infection (Before dementia)	1211	3002	822	7.86 (7.34, 8.42)	7.97 (7.45, 8.54)	4.43 (4.13, 4.74)
		Infection of other sites	65,095	142,357	50,481	8.93 (8.84, 9.02)	9.00 (8.91, 9.10)	5.77 (5.71, 5.83)
	No Dementia	Infection	20,884	90,928	9635	4.24 (4.15, 4.32)	4.32 (4.23, 4.41)	2.39 (2.34, 2.44)
		Infection of other sites	430,820	1,773,695	243,720	4.70 (4.67, 4.73)	4.77 (4.74, 4.80)	2.96 (2.94, 2.98)
Eye	**Dementia**	Infection (After dementia)	558	1390	413	7.41 (6.73, 8.16)	7.46 (6.77, 8.22)	4.86 (4.41, 5.35)
		Infection (Before dementia)	1378	3694	894	6.21 (5.81, 6.63)	6.28 (5.88, 6.71)	3.98 (3.72, 4.25)

Site	Exposure groups		N	Pyrs	N deaths	MRR model 1[a]	MRR model 2[b]	MRR model 3[c]
		Infection of other sites	65,240	142,018	50,657	9.01 (8.92, 9.10)	9.08 (8.99, 9.18)	5.81 (5.75, 5.87)
	No Dementia	Infection	15,953	91,579	6096	2.41 (2.35, 2.47)	2.46 (2.40, 2.52)	1.75 (1.71, 1.80)
		Infection of other sites	435,751	1,773,045	247,259	4.79 (4.76, 4.82)	4.86 (4.83, 4.89)	2.99 (2.97, 3.01)
Genital	**Dementia**	Infection (After dementia)	595	1418	427	8.16 (7.42, 8.97)	8.16 (7.42, 8.97)	5.42 (4.93, 5.96)
		Infection (Before dementia)	1177	2847	774	7.52 (7.01, 8.07)	7.65 (7.12, 8.21)	4.55 (4.24, 4.89)
		Infection of other sites	65,404	142,836	50,763	8.98 (8.89, 9.07)	9.05 (8.96, 9.14)	5.79 (5.73, 5.85)
	No Dementia	Infection	17,663	94,188	6460	2.55 (2.49, 2.61)	2.61 (2.55, 2.68)	1.83 (1.78, 1.87)
		Infection of other sites	434,041	1,770,435	246,895	4.79 (4.76, 4.82)	4.85 (4.82, 4.88)	2.98 (2.97, 3.00)
Less occurring	**Dementia**	Infection (After dementia)	866	1549	679	11.78 (10.93, 12.71)	11.91 (11.04, 12.84)	6.54 (6.06, 7.05)
		Infection (Before dementia)	937	2276	638	7.69 (7.11, 8.31)	7.85 (7.26, 8.48)	4.55 (4.21, 4.92)
		Infection of other sites	65,373	143,277	50,647	8.91 (8.82, 9.01)	8.99 (8.89, 9.08)	5.76 (5.70, 5.82)
	No Dementia	Infection	13,595	50,948	6987	5.21 (5.09, 5.34)	5.31 (5.19, 5.44)	3.09 (3.02, 3.17)
		Infection of other sites	438,109	1,813,675	246,368	4.67 (4.64, 4.70)	4.74 (4.71, 4.77)	2.93 (2.91, 2.95)
Muscul.	**Dementia**	Infection (After dementia)	418	893	311	9.17 (8.20, 10.25)	9.38 (8.39, 10.49)	5.34 (4.78, 5.97)
		Infection (Before dementia)	655	1612	453	7.73 (7.05, 8.48)	7.78 (7.09, 8.53)	4.15 (3.78, 4.55)
		Infection of other sites	66,103	144,596	51,200	8.94 (8.85, 9.03)	9.01 (8.92, 9.10)	5.77 (5.72, 5.83)
	No Dementia	Infection	9201	39,128	4427	4.19 (4.07, 4.32)	4.24 (4.11, 4.36)	2.51 (2.44, 2.59)
		Infection of other sites	442,503	1,825,496	248,928	4.69 (4.66, 4.72)	4.76 (4.73, 4.79)	2.95 (2.93, 2.96)
Ear	**Dementia**	Infection (After dementia)	197	560	144	5.76 (4.89, 6.78)	5.92 (5.03, 6.98)	3.98 (3.38, 4.68)
		Infection (Before dementia)	776	2015	532	6.87 (6.31, 7.48)	6.97 (6.40, 7.59)	4.71 (4.33, 5.13)
		Infection of other sites	66,203	144,526	51,288	8.97 (8.88, 9.06)	9.05 (8.95, 9.14)	5.78 (5.72, 5.84)
	No Dementia	Infection	8539	54,790	3366	2.22 (2.15, 2.30)	2.27 (2.19, 2.35)	1.66 (1.61, 1.72)
		Infection of other sites	443,165	1,809,834	249,989	4.75 (4.73, 4.78)	4.82 (4.79, 4.85)	2.97 (2.95, 2.99)
Herpes	**Dementia**	Infection (After dementia)	340	795	262	7.86 (6.96, 8.87)	8.98 (7.07, 9.01)	4.69 (4.15, 5.29)
		Infection (Before dementia)	556	1430	388	6.57 (5.94, 7.26)	6.63 (6.00, 7.32)	4.27 (3.86, 4.71)
		Infection of other sites	66,280	144,876	51,314	8.95 (8.86, 9.04)	9.03 (8.93, 9.12)	5.77 (5.71, 5.83)
	No Dementia	Infection	6448	28,384	3245	3.71 (3.58, 3.84)	3.76 (3.63, 3.89)	2.35 (2.27, 2.44)
		Infection of other sites	445,256	1,836,239	250,110	4.70 (4.67, 4.73)	4.77 (4.74, 4.80)	2.95 (2.93, 2.96)
Circulatory	**Dementia**	Infection (After dementia)	238	317	162	14.36 (12.31, 16.75)	14.80 (12.69, 17.27)	7.13 (6.11, 8.32)
		Infection (Before dementia)	278	730	224	8.42 (7.39, 9.60)	8.84 (7.75, 10.08)	4.07 (3.57, 4.64)
		Infection of other sites	66,660	146,054	51,578	8.92 (8.83, 9.01)	8.99 (8.90, 9.08)	5.76 (5.70, 5.82)
	No Dementia	Infection	5916	20,460	3361	6.28 (6.07, 6.50)	6.53 (6.31, 6.76)	3.45 (3.34, 3.57)
		Infection of other sites	445,788	1,844,163	249,994	4.67 (4.64, 4.70)	4.73 (4.70, 4.76)	2.93 (2.91, 2.95)
Nervous	**Dementia**	Infection (After dementia)	220	376	173	14.44 (12.44, 16.77)	14.74 (12.70, 17.12)	8.18 (7.05, 9.50)
		Infection (Before dementia)	227	573	160	9.41 (8.06, 10.98)	9.52 (8.15, 11.12)	5.75 (4.92, 6.71)
		Infection of other sites	66,729	146,153	51,631	8.91 (8.82, 9.00)	8.98 (8.89, 9.08)	5.75 (5.69, 5.80)
	No Dementia	Infection	2674	9022	1460	7.02 (6.66, 7.39)	7.22 (6.86, 7.60)	4.33 (4.11, 4.56)
		Infection of other sites	449,030	1,855,601	251,895	4.67 (4.65, 4.70)	4.74 (4.71, 4.77)	2.93 (2.91, 2.95)
Hep ati	**Dementia**	Infection (After dementia)	44	85	34	12.65 (9.04, 17.71)	12.75 (9.11, 17.85)	7.03 (5.02, 9.84)
		Infection (Before dementia)	69	133	55	15.09 (11.58, 19.65)	15.56 (11.94, 20.26)	7.40 (5.68, 9.63)

Site	Exposure groups		N	Pyrs	N deaths	MRR model 1[a]	MRR model 2[b]	MRR model 3[c]
	No Dementia	Infection of other sites	67,063	146,883	51,875	8.92 (8.83, 9.01)	8.99 (8.90, 9.08)	5.75 (5.69, 5.81)
		Infection	1331	5880	618	5.06 (4.67, 5.47)	5.12 (4.73, 5.54)	2.38 (2.20, 2.58)
		Infection of other sites	450,373	1,858,743	252,737	4.68 (4.65, 4.71)	4.75 (4.72, 4.78)	2.94 (2.92, 2.96)
	Dementia	No Infections	45,389	207,354	30,573	4.01 (3.96, 4.06)	4.07 (4.02, 4.12)	3.67 (3.63, 3.72)
	No Dementia	No Infections	932,167	10,520,056	239,368	1 (ref)	1 (ref)	1 (ref)

MRRs presented for each infection site category in the exposure groups: Dementia/Infection (Subdivided to: i.Infection either after or before dementia and ii. Infections of other sites); No Dementia/Infection (subdivided to into infection of the site and infections of other sites); Dementia/No Infection; No Dementia/No Infection (ref). Infection of other sites refers to any infection of a different site category that occurred prior to the infection of the site of interest. [a]Adjusted for sex, age, and calendar year. [b]Further adjusted for highest attained educational level and civil status. [c]Further adjusted for CCI. Site categories ordered in an ascending order by numbers in the dementia group (not adjusted and do not take time at risk into account and are only meant for descriptive purposes). $p \leq 0.00001$ for all MRRs listed in the table. N= Number; MRR= Mortality rate ratio; Pyrs= Person years at risk; ref= reference group.

Table 8. Mortality rate ratios by time since first infection in women- complete analysis model.

Exposure groups				Pyrs	N deaths	MRR model 1[a]	MRR model 2[b]	MRR model 3[c]
Dementia	Infection	Within 30 days	After dementia	1360	2985	51.95 (50.09, 53.88)	52.45 (50.57, 54.40)	37.81 (36.45, 39.21)
			Before dementia	72	93	28.90 (23.58, 35.42)	28.87 (23.56, 35.38)	20.93 (17.08, 25.65)
		30 days to 1 yr	After dementia	12,091	4801	9.45 (9.18, 9.73)	9.54 (9.26, 9.82)	6.83 (6.63, 7.03)
			Before dementia	2353	897	9.45 (8.85, 10.10)	9.49 (8.89, 10.14)	6.38 (5.97, 6.81)
		1 yr to 5 yrs	After dementia	33,371	8775	6.02 (5.88, 6.15)	6.05 (5.92, 6.18)	4.18 (4.09, 4.28)
			Before dementia	13,465	3817	6.84 (6.62, 7.07)	6.91 (6.68, 7.13)	4.27 (4.13, 4.41)
		5 yrs to 10 yrs	After dementia	18,100	5339	6.64 (6.46, 6.83)	6.68 (6.49, 6.87)	4.29 (4.17, 4.41)
			Before dementia	8189	2379	6.99 (6.71, 7.28)	7.04 (6.75, 7.33)	4.21 (4.04, 4.38)
		>10 yrs	After dementia	4829	1530	7.09 (6.74, 7.46)	7.16 (6.81, 7.54)	4.47 (4.25, 4.70)
			Before dementia	1923	573	7.45 (6.86, 8.09)	7.58 (6.98, 8.23)	4.49 (4.14, 4.88)
	No Infection			138,056	19,838	3.74 (3.68, 3.80)	3.78 (3.72, 3.84)	3.47 (3.42, 3.52)
No Dementia	Infection	Within 30 days		20,128	21,731	37.04 (36.50, 37.58)	37.37 (36.83, 37.91)	24.27 (23.91, 24.62)
		30 days to 1 yr		187,126	33,387	6.32 (6.24, 6.39)	6.38 (6.30, 6.46)	4.14 (4.09, 4.20)
		1 yr to 5 yrs		508,731	46,776	3.15 (3.11, 3.18)	3.18 (3.14, 3.21)	2.03 (2.01, 2.05)
		5 yrs to 10 yrs		248,387	23,669	3.02 (2.97, 3.06)	3.05 (3.00, 3.09)	1.89 (1.87, 1.92)
		>10 yrs		58,593	5950	2.89 (2.81, 2.97)	2.92 (2.84, 3.00)	1.77 (1.72, 1.82)
	No Infection			5,930,141	125,933	1 (ref)	1 (ref)	1 (ref)

MRRs in women are presented in exposure groups: Dementia/infection (sub-divided into whether infections came before or after dementia); Dementia/No Infection; No Dementia/Infection and No Dementia/No Infection (reference group). [a]Adjusted for sex, age, and calendar year. [b]Further adjusted for highest attained educational level and civil status. [c]Further adjusted for CCI. All MRRs p≤0.00001. Years were calculated based on 365 days. Highlighted MRRs are those presented in graphs (figure 3) in paper. MRR= Mortality rate ratio; Yr= Year; N deaths= Number of deaths; Pyrs= Person years; ref= reference group.

Table 9. Mortality rate ratios by time since first infection in men- complete analysis model.

Exposure groups				Pyrs	N deaths	MRR model 1[a]	MRR model 2[b]	MRR model 3[c]
Dementia	Infection	Within 30 days	After dementia	852	2636	68.94 (66.31, 71.67)	70.10 (67.43, 72.88)	46.99 (45.20, 48.85)
			Before dementia	43	73	34.87 (27.72, 43.87)	34.57 (27.48, 43.49)	22.17 (17.62, 27.89)
		30 days to 1 yr	After dementia	6916	3490	11.46 (11.08, 11.85)	11.60 (11.21, 12.00)	7.74 (7.49, 8.01)
			Before dementia	1403	731	11.96 (11.12, 12.87)	12.01 (11.17, 12.92)	7.10 (6.60, 7.63)
		1 yr to 5 yrs	After dementia	16,838	5317	7.18 (6.98, 7.38)	7.20 (7.00, 7.40)	4.56 (4.44, 4.69)
			Before dementia	8028	2899	8.27 (7.97, 8.59)	8.41 (8.10, 8.73)	4.71 (4.53, 4.88)
		5 yrs to 10 yrs	After dementia	8613	2769	7.30 (7.02, 7.58)	7.35 (7.07, 7.63)	4.26 (4.10, 4.43)
			Before dementia	4798	1621	7.70 (7.33, 8.09)	7.86 (7.48, 8.26)	4.29 (4.08, 4.50)
		>10 yrs	After dementia	2704	856	7.07 (6.60, 7.56)	7.20 (6.73, 7.70)	4.09 (3.82, 4.37)
			Before dementia	1153	383	7.65 (6.92, 8.47)	7.86 (7.11, 8.70)	4.09 (3.70, 4.52)
	No Infection			69,297	10,735	3.81 (3.73, 3.88)	3.89 (3.81, 3.97)	3.39 (3.32, 3.46)
No Dementia	Infection	Within 30 days		17,625	21,530	38.75 (38.18, 39.32)	39.31 (38.74, 39.89)	23.29 (22.94, 23.63)
		30 days to 1 yr		161,252	33,045	6.71 (6.63, 6.80)	6.83 (6.75, 6.92)	4.06 (4.01, 4.11)
		1 yr to 5 yrs		422,549	43,063	3.26 (3.23, 3.30)	3.32 (3.28, 3.36)	1.97 (1.95, 1.99)
		5 yrs to 10 yrs		196,683	19,502	2.88 (2.83, 2.92)	2.94 (2.89, 2.99)	1.74 (1.71, 1.77)
		>10 yrs		43,550	4702	2.75 (2.67, 2.84)	2.83 (2.75, 2.92)	1.68 (1.63, 1.73)
	No Infection			4,589,915	113,435	1 (ref)	1 (ref)	1 (ref)

MRRs in men are presented in exposure groups: Dementia/infection (sub-divided into whether infections came before or after dementia); Dementia/No Infection; No Dementia/Infection and No Dementia/No Infection (reference group). [a]Adjusted for sex, age, and calendar year. [b]Further adjusted for highest attained educational level and civil status. [c]Further adjusted for CCI. All MRRs p≤0.00001. Years were calculated based on 365 days. Highlighted MRRs are those presented in graphs (figure 3) in paper. MRR= Mortality rate ratio; Yr= Year; N deaths= Number of deaths; Pyrs= Person years; ref= reference group.

Table 10. Mortality rate ratios by time since first infection of several infection sites in women

Site	Exposure groups	MRR model 3					
		Infection of the site category				Infections of other sites	No infection
		Within 30 days	30 days to 1 yr	1 yr to 5 yrs	>5 yrs		
Respiratory	**Dementia**						
	Infection (After dementia)	59.73 (57.55, 61.98)	8.34 (8.03, 8.66)	4.91 (4.73, 5.09)	5.13 (4.71, 5.58)	4.50 (4.43, 4.58)	3.57 (3.51, 3.62)
	Infection (Before dementia)	4.99 (4.58, 5.43)	4.85 (4.62, 5.10)	4.66 (4.49, 4.83)	4.83 (4.59, 5.09)		
	No Dementia						
	Infection	35.95 (35.37, 36.54)	4.97 (4.89, 5.05)	2.47 (2.44, 2.51)	2.27 (2.23, 2.31)	2.19 (2.17, 2.22)	1 (ref)
Urinary	**Dementia**						
	Infection (After dementia)	21.73 (20.56, 22.96)	7.16 (6.91, 7.41)	4.74 (4.60, 4.89)	5.22 (4.90, 5.56)	5.41 (5.31, 5.52)	3.63 (3.57, 3.69)
	Infection (Before dementia)	4.74 (4.44, 5.06)	4.62 (4.44, 4.80)	4.72 (4.57, 4.88)	4.76 (4.50, 5.03)		
	No Dementia						
	Infection	12.25 (11.92, 12.59)	4.44 (4.37, 4.52)	2.30 (2.27, 2.34)	2.23 (2.18, 2.28)	2.85 (2.82, 2.88)	1 (ref)
Digestive	**Dementia**						
	Infection (After dementia)	33.04 (30.31, 36.00)	7.70 (7.22, 8.22)	4.41 (4.16, 4.69)	5.07 (4.44, 5.79)	5.45 (5.37, 5.52)	3.64 (3.58, 3.69)
	Infection (Before dementia)	5.23 (4.46, 6.14)	4.36 (4.02, 4.72)	4.35 (4.11, 4.60)	4.32 (4.01, 4.67)		
	No Dementia						
	Infection	22.41 (21.72, 23.13)	4.72 (4.61, 4.83)	2.05 (2.01, 2.10)	1.87 (1.82, 1.93)	2.92 (2.89, 2.94)	1 (ref)
Sepsis	**Dementia**						
	Infection (After dementia)	114.76 (108.85,120.99)	9.57 (8.89, 10.30)	4.40 (4.06, 4.77)	4.14 (3.45, 4.99)	5.21 (5.13, 5.28)	3.64 (3.58, 3.69)
	Infection (Before dementia)	5.73 (4.87, 6.75)	4.80 (4.29, 5.38)	4.44 (4.06, 4.87)	5.28 (4.58, 6.07)		
	No Dementia						
	Infection	90.47 (88.52, 92.46)	7.25 (7.05, 7.46)	2.56 (2.48, 2.65)	2.30 (2.18, 2.41)	2.68 (2.66, 2.71)	1 (ref)
Skin	**Dementia**						
	Infection (After dementia)	15.53 (13.25, 18.21)	5.96 (5.46, 6.52)	4.44 (4.13, 4.78)	4.66 (3.98, 5.46)	5.54 (5.46, 5.61)	3.66 (3.60, 3.72)
	Infection (Before dementia)	5.82 (4.75, 7.12)	4.38 (3.97, 4.83)	4.56 (4.26, 4.88)	4.83 (4.39, 5.32)		
	No Dementia						
	Infection	9.74 (9.15, 10.36)	3.57 (3.45, 3.69)	2.10 (2.04, 2.16)	1.94 (1.88, 2.02)	2.99 (2.97, 3.02)	1 (ref)
Uncategorized	**Dementia**						
	Infection (After dementia)	55.01 (49.48, 61.15)	9.45 (8.56, 10.43)	5.00 (4.48, 5.58)	4.82 (3.75, 6.21)	5.43 (5.35, 5.50)	3.66 (3.61, 3.72)
	Infection (Before dementia)	6.85 (5.39, 8.71)	4.45 (3.84, 5.17)	4.29 (3.80, 4.84)	4.31 (3.59, 5.19)		
	No Dementia						
	Infection	32.85 (31.28, 34.49)	6.53 (6.28, 6.79)	2.36 (2.26, 2.47)	1.98 (1.85, 2.12)	2.90 (2.87, 2.92)	1 (ref)

MRRs in women in 6 site categories. MRRs presented for each infection site category in the exposure groups: Dementia/Infection (Subdivided to: i.Infection either after or before dementia); No Dementia/Infection (subdivided to into infection of the site and infections of other sites); Dementia/No infection; No Dementia/No Infection (ref), fully adjusted for sex, age, calendar year, highest attained educational level, civil status, and CCI. All MRRs p≤0.00001. Years calculated based on 365 days. MRR= Mortality rate ratio; Yr(s)= Year(s); ref= reference group.

Table 11. Mortality rate ratios by time since first infection of several infection sites in men

Site	Exposure groups	MRRs model 3					
		Infection of the site category				Infections of other sites	No infection
		Within 30 days	30 days to 1 yr	1 yr to 5 yrs	>5 yrs		
Respiratory	**Dementia**						
	Infection (After dementia)	66.01 (63.57, 68.54)	8.78 (8.44, 9.14)	5.35 (5.13, 5.58)	4.73 (4.23, 5.28)	4.57 (4.46, 4.68)	3.51 (3.44, 3.58)
	Infection (Before dementia)	5.98 (5.49, 6.52)	5.23 (4.97, 5.50)	4.96 (4.77, 5.16)	4.66 (4.38, 4.96)		
	No Dementia						
	Infection	33.23 (32.71, 33.76)	4.99 (4.92, 5.06)	2.39 (2.35, 2.42)	2.14 (2.10, 2.18)	1.96 (1.93, 1.98)	1 (ref)
Urinary	**Dementia**						
	Infection (After dementia)	23.09 (21.52, 24.78)	7.68 (7.34, 8.04)	5.30 (5.07, 5.54)	5.72 (5.10, 6.42)	6.11 (5.99, 6.23)	3.57 (3.50, 3.65)
	Infection (Before dementia)	5.43 (4.91, 6.02)	5.04 (4.76, 5.33)	5.08 (4.83, 5.34)	4.39 (4.02, 4.80)		
	No Dementia						
	Infection	11.99 (11.60, 12.39)	4.55 (4.46, 4.64)	2.32 (2.27, 2.36)	2.03 (1.97, 2.09)	2.83 (2.80, 2.86)	1 (ref)
Digestive	**Dementia**						
	Infection (After dementia)	27.29 (24.34, 30.59)	7.62 (7.04, 8.26)	4.53 (4.18, 4.91)	5.53 (4.52, 6.77)	6.14 (6.03, 6.24)	3.56 (3.49, 3.64)
	Infection (Before dementia)	5.58 (4.48, 6.96)	4.81 (4.35, 5.31)	4.85 (4.51, 5.20)	4.69 (4.27, 5.15)		
	No Dementia						
	Infection	17.37 (16.76, 18.00)	4.57 (4.47, 4.69)	2.09 (2.04, 2.14)	1.78 (1.72, 1.84)	2.89 (2.86, 2.92)	1 (ref)
Sepsis	**Dementia**						
	Infection (After dementia)	85.73 (81.14, 90.57)	9.45 (8.83, 10.11)	5.41 (5.01, 5.83)	5.44 (4.46, 6.64)	5.72 (5.62, 5.82)	3.58 (3.51, 3.65)
	Infection (Before dementia)	6.08 (5.14, 7.19)	5.36 (4.85, 5.92)	5.11 (4.69, 5.56)	4.45 (3.79, 5.23)		
	No Dementia						
	Infection	59.35 (58.09, 60.64)	6.51 (6.35, 6.67)	2.49 (2.42, 2.56)	2.05 (1.95, 2.16)	2.62 (2.59, 2.64)	1 (ref)
Skin	**Dementia**						
	Infection (After dementia)	13.31 (10.79, 16.42)	6.13 (5.49, 6.83)	4.83 (4.39, 5.31)	6.31 (5.05, 7.89)	6.22 (6.12, 6.33)	3.59 (3.52, 3.66)
	Infection (Before dementia)	5.43 (4.39, 6.71)	4.71 (4.21, 5.27)	4.50 (4.16, 4.87)	5.84 (5.29, 6.46)		
	No Dementia						
	Infection	7.73 (7.23, 8.26)	3.08 (2.97, 3.19)	1.90 (1.85, 1.96)	1.86 (1.79, 1.93)	3.00 (2.97, 3.03)	1 (ref)
Uncategorized	**Dementia**						
	Infection (After dementia)	46.50 (41.31, 52.35)	9.27 (8.35, 10.30)	6.05 (5.38, 6.80)	5.79 (4.21, 7.96)	6.03 (5.93, 6.13)	3.59 (3.52, 3.66)
	Infection (Before dementia)	10.72 (8.42, 13.65)	4.84 (4.18, 5.60)	5.39 (4.72, 6.15)	4.52 (3.67, 5.57)		
	No Dementia						
	Infection	26.70 (25.43, 28.03)	6.18 (5.96, 6.41)	2.41 (2.31, 2.51)	1.96 (1.82, 2.10)	2.86 (2.83, 2.89)	1 (ref)

MRRs in men in 6 site categories. MRRs presented for each infection site category in the exposure groups: Dementia/Infection (Subdivided to: i.Infection either after or before dementia); No Dementia/Infection (subdivided to into infection of the site and infections of other sites); Dementia/No infection; No Dementia/No Infection (ref), fully adjusted for sex, age, calendar year, highest attained educational level, civil status, and CCI. All MRRs p≤0.00001. Years calculated based on 365 days. MRR= Mortality rate ratio; Yr(s)= Year(s); ref= reference group.

Table 12. Sensitivity analysis model 1; removal of ICD-10 codes unspecific to an infection

Exposure groups		N	Pyrs	N deaths	MRR model 1[a], 95% CI	MRR model 2[b], 95% CI	MRR model 3[c], 95% CI
All	**Dementia**	114,104	358,958	83,782			
	Infection (after)	30,906	58,287	25,399	10.53 (10.39, 10.67)	10.59 (10.45, 10.73)	7.38 (7.28, 7.48)
	Infection (before)	36,028	86,654	26,545	7.64 (7.54, 7.74)	7.70 (7.60, 7.80)	4.77 (4.71, 4.84)
	No Infection	47,170	214,017	31,838	3.96 (3.91, 4.01)	4.01 (3.96, 4.06)	3.64 (3.60, 3.69)
	No Dementia	1,403,318	12,534,403	503,810			
	Infection	441,636	1,772,864	251,163	4.72 (4.69, 4.75)	4.78 (4.75, 4.81)	2.99 (2.97, 3.00)
	No Infection	961,682	10,761,539	252,647	1 (ref)	1 (ref)	1 (ref)
Women	**Dementia**	70,957	236,256	51,666			
	Infection (after)	18,641	38,638	15,158	9.37 (9.21, 9.54)	9.42 (9.26, 9.59)	6.76 (6.64, 6.88)
	Infection (before)	22,009	55,987	16,021	7.11 (6.99, 7.23)	7.16 (7.04, 7.28)	4.64 (4.56, 4.72)
	No Infection	30,307	141,631	20,487	3.88 (3.82, 3.94)	3.92 (3.86, 3.98)	3.63 (3.58, 3.69)
	No Dementia	753,055	7,020,776	262,608			
	Infection	232,787	982,697	130,387	4.54 (4.50, 4.58)	4.58 (4.55, 4.62)	2.96 (2.93, 2.98)
	No Infection	520,268	6,038,079	132,221	1 (ref)	1 (ref)	1 (ref)
Men	**Dementia**	43,147	122,703	32,116			
	Infection (after)	12,265	19,650	10,241	12.43 (12.18, 12.69)	12.50 (12.25, 12.76)	8.37 (8.20, 8.54)
	Infection (before)	14,019	30,667	10,524	8.38 (8.20, 8.55)	8.45 (8.28, 8.63)	4.92 (4.82, 5.03)
	No Infection	16,863	72,386	11,351	4.00 (3.92, 4.08)	4.07 (3.99, 4.15)	3.58 (3.51, 3.65)
	No Dementia	650,263	5,513,626	241,202			
	Infection	208,849	790,167	120,776	4.92 (4.87, 4.96)	5.00 (4.96, 5.05)	3.00 (2.97, 3.03)
	No Infection	441,414	4,723,459	120,426	1 (ref)	1 (ref)	1 (ref)

Analysis based on a sample population of 1,517,422 individuals in the cohort. [a]Adjusted for sex, age, and calendar year. [b]Further adjusted for highest attained educational level and civil status. [c]Further adjusted for CCI. MRRs in four exposure groups are presented: Dementia/Infection (sub-divided into whether infections came before or after dementia), Dementia/No Infection, No Dementia/Infection, and No Dementia/No Infection. All MRRs p≤0.00001. N= Number; Pyrs= Person years; MRR= Mortality rate ratio; ref= reference group.

Table 13. Sensitivity analysis model 2; inclusion of people with infections during 5 years before start of follow-up

Exposure groups		N	Pyrs	N deaths	MRR model 1[a], 95% CI		MRR model 2[b], 95% CI		MRR model 3[c], 95% CI	
All	**Dementia**	129,662	403,745	96,428						
	Infection (after)	34,773	107,624	33,211	10.55	(10.42, 10.68)	10.56	(10.43, 10.70)	7.22	(7.13, 7.31)
	Infection (before)	44,533	66,970	28,784	7.94	(7.84, 8.03)	7.96	(7.87, 8.06)	4.79	(4.74, 4.85)
	No Infection	50,356	229,151	34,433	4.03	(3.98, 4.07)	4.06	(4.02, 4.11)	3.64	(3.60, 3.68)
	No Dementia	1,582,438	13,797,994	600,449						
	Infection	553,957	2,281,875	320,943	4.80	(4.78, 4.83)	4.84	(4.82, 4.87)	2.96	(2.94, 2.98)
	No Infection	1,028,481	11,516,119	279,506	1 (ref)		1 (ref)		1 (ref)	
Women	**Dementia**	80,316	265,053	59,234						
	Infection (after)	20,953	44,199	17,167	9.41	(9.26, 9.57)	9.43	(9.28, 9.59)	6.64	(6.53, 6.75)
	Infection (before)	26,954	69,117	19,846	7.38	(7.27,7.50)	7.40	(7.29, 7.52)	4.66	(4.59, 4.73)
	No Infection	32,409	151,737	22,221	3.95	(3.89, 4.01)	3.98	(3.92, 4.04)	3.64	(3.59, 3.70)
	No Dementia	845,077	7,697,562	312,947						
	Infection	289,275	1,245,873	165,965	4.68	(4.64, 4.72)	4.71	(4.67, 4.74)	2.97	(2.95, 2.99)
	No Infection	555,802	6,451,689	146,982	1 (ref)		1 (ref)		1 (ref)	
Men	**Dementia**	49,346	138,692	37,194						
	Infection (after)	13,820	22,771	11,617	12.45	(12.21, 12.70)	12.49	(12.24, 12.73)	8.16	(8.00, 8.32)
	Infection (before)	17,579	38,507	13,365	8.72	(8.56, 8.89)	8.79	(8.63, 8.95)	4.97	(4.88, 5.06)
	No Infection	17,947	77,414	12,212	4.08	(4.00, 4.16)	4.14	(4.07, 4.22)	3.58	(3.51, 3.64)
	No Dementia	737,361	6,100,432	287,502						
	Infection	264,682	1,036,002	154,978	4.93	(4.89, 4.97)	5.00	(4.96, 5.04)	2.94	(2.92, 2.97)
	No Infection	472,679	5,064,430	132,524	1 (ref)		1 (ref)		1 (ref)	

Analysis based on a sample population of 1,712,100 individuals in the cohort. [a]Adjusted for sex, age, and calendar year. [b]Further adjusted for highest attained educational level and civil status. [c]Further adjusted for CCI. MRRs in four exposure groups are presented: Dementia/Infection (sub-divided into whether infections came before or after dementia), Dementia/No Infection, No Dementia/Infection, and No Dementia/No Infection. All MRRs p≤0.00001. N= Number; Pyrs= Person years; MRR= Mortality rate ratio; ref= reference group.

Table 14. Mortality rate ratios when modelling the Charlson Comorbidity Index as a continuous variable

Exposure groups		MRR model 3
All	**Dementia**	
	Infection (After dementia)	7.25 (7.16, 7.35)
	Infection (Before dementia)	4.64 (4.57, 4.70)
	No Infection	3.65 (3.61, 3.70)
	No Dementia	
	Infection	2.86 (2.84, 2.88)
	No Infection	1 (ref)
Women	**Dementia**	
	Infection (After dementia)	6.72 (6.61, 6.84)
	Infection (Before dementia)	4.56 (4.48, 4.64)
	No Infection	3.67 (3.61, 3.72)
	No Dementia	
	Infection	2.89 (2.87, 2.92)
	No Infection	1 (ref)
Men	**Dementia**	
	Infection (After dementia)	8.11 (7.94, 8.28)
	Infection (Before dementia)	4.72 (4.62, 4.82)
	No Infection	3.57 (3.50, 3.65)
	No Dementia	
	Infection	2.81 (2.79, 2.84)
	No Infection	1 (ref)

MRR model fully adjusted for sex, age, calendar year, highest attained educational level, civil status, and CCI. All MRRs p≤0.00001. MRR= Mortality rate ratio; CI= Confidence interval; ref= reference group.

Table 15. Mortality rate ratios by time since infection in a subgroup of women with one infection

Exposure groups				Pyrs	N deaths	MRR model 1[a]	MRR model 2[b]	MRR model 3[c]
Dementia	Infection	Within 30 days	After dementia	748	2430	58.13 (55.83, 60.53)	58.55 (56.24, 60.96)	42.92 (41.22, 44.69)
			Before dementia	30	64	35.40 (27.71, 45.24)	35.18 (27.53, 44.95)	24.30 (19.01, 31.04)
		30 days to 1 yr	After dementia	5917	2837	8.72 (8.40, 9.05)	8.78 (8.46, 9.12)	6.53 (6.29, 6.78)
			Before dementia	855	349	7.84 (7.06, 8.71)	7.84 (7.06, 8.71)	5.60 (5.04, 6.22)
		1 yr to 5 yrs	After dementia	13,546	3859	5.09 (4.93, 5.26)	5.10 (4.94, 5.27)	3.88 (3.76, 4.01)
			Before dementia	3870	1004	4.78 (4.49, 5.09)	4.82 (4.53, 5.13)	3.44 (3.23, 3.66)
		5 yrs to 10 yrs	After dementia	5238	1531	5.47 (5.20, 5.76)	5.48 (5.21, 5.76)	4.16 (3.95, 4.37)
			Before dementia	1989	432	4.85 (4.42, 5.34)	4.88 (4.44, 5.37)	3.61 (3.29, 3.97)
		>10 yrs	After dementia	1222	304	5.55 (4.96, 6.22)	5.62 (5.02, 6.29)	4.61 (4.12, 5.16)
			Before dementia	437	76	4.83 (3.86, 6.05)	5.01 (4.00, 6.28)	3.99 (3.18, 4.99)
	No Infection			123,583	19,873	3.32 (3.27, 3.37)	3.35 (3.30, 3.40)	3.10 (3.05, 3.14)
No Dementia	Infection	Within 30 days		9351	17,798	53.39 (52.55, 54.25)	53.85 (53.00, 54.71)	34.10 (33.56, 34.65)
		30 days to 1 yr		80,358	18,138	6.87 (6.77, 6.98)	6.94 (6.84, 7.05)	4.63 (4.55, 4.70)
		1 yr to 5 yrs		194,672	16,145	2.57 (2.53, 2.61)	2.60 (2.55, 2.64)	1.81 (1.78, 1.84)
		5 yrs to 10 yrs		85,129	5477	2.03 (1.97, 2.09)	2.06 (2.00, 2.11)	1.51 (1.47, 1.55)
		>10 yrs		19,898	977	1.57 (1.47, 1.67)	1.59 (1.49, 1.70)	1.20 (1.12, 1.28)
	No Infection			5,117,110	126,260	1 (ref)	1 (ref)	1 (ref)

MRRs in a sub-group of women who only had one infection throughout the study period, presented in exposure groups: Dementia/Infection (sub-divided into whether infections came before or after dementia), Dementia/No Infection, No Dementia/Infection, and No Dementia/No Infection (reference group). N= 1,228,963 individuals (women and men) with either one infection only or no infections (268,096 individuals were excluded who had more than one infection throughout the study period out of the total of 518,880 individuals with infections, thus a total of 250,784 individuals had one infection only). [a]Adjusted for sex, age, and calendar year. [b]Further adjusted for highest attained educational level and civil status. [c]Further adjusted for CCI. All MRRs p≤0.00001. Years were calculated based on 365 days. MRR= Mortality rate ratio; Yr= Year; N deaths= Number of deaths; Pyrs= Person years; ref= reference group.

Table 16. Mortality rate ratios by time since infection in a subgroup of men with one infection

Exposure groups				Pyrs	N deaths	MRR model 1[a]	MRR model 2[b]	MRR model 3[c]
Dementia	Infection	Within 30 days	After dementia	419	2150	84.96 (81.39, 88.69)	85.77 (82.16, 89.84)	57.64 (55.21, 60.17)
			Before dementia	17	49	43.77 (33.08, 57.92)	42.92 (32.43, 56.79)	28.17 (21.29, 37.27)
		30 days to 1 yr	After dementia	2843	1804	10.83 (10.33, 11.35)	10.85 (10.35, 11.37)	7.68 (7.33, 8.05)
			Before dementia	429	227	9.25 (8.12, 10.54)	9.25 (8.12, 10.53)	5.74 (5.04, 6.54)
		1 yr to 5 yrs	After dementia	5509	1845	5.90 (5.64, 6.18)	5.88 (5.61, 6.15)	4.22 (4.03, 4.42)
			Before dementia	2086	678	5.98 (5.54, 6.45)	6.16 (5.71, 6.64)	4.01 (3.72, 4.32)
		5 yrs to 10 yrs	After dementia	2123	618	5.75 (5.31, 6.23)	5.76 (5.32, 6.24)	4.28 (3.95, 4.64)
			Before dementia	1091	270	5.08 (4.50, 5.72)	5.14 (4.56, 5.79)	3.46 (3.07, 3.90)
		>10 yrs	After dementia	604	141	5.26 (4.46, 6.20)	5.42 (4.59, 6.39)	4.31 (3.66, 5.09)
			Before dementia	246	49	5.11 (3.86, 6.76)	5.03 (3.80, 6.66)	3.18 (2.40, 4.20)
	No Infection			59,066	10,761	3.47 (3.40, 3.54)	3.53 (3.46, 3.60)	3.08 (3.02, 3.15)
No Dementia	Infection	Within 30 days		7862	17,571	59.20 (58.26, 60.16)	59.91 (58.96, 60.89)	34.21 (33.66, 34.77)
		30 days to 1 yr		66,154	16,362	7.22 (7.10, 7.34)	7.35 (7.23, 7.47)	4.50 (4.42, 4.57)
		1 yr to 5 yrs		155,600	13,319	2.57 (2.53, 2.62)	2.63 (2.58, 2.67)	1.74 (1.71, 1.77)
		5 yrs to 10 yrs		64,636	3925	1.78 (1.72, 1.83)	1.82 (1.76, 1.88)	1.30 (1.26, 1.35)
		>10 yrs		14,752	685	1.36 (1.26, 1.47)	1.41 (1.31, 1.52)	1.08 (1.00, 1.16)
	No Infection			3,886,174	113,708	1 (ref)	1 (ref)	1 (ref)

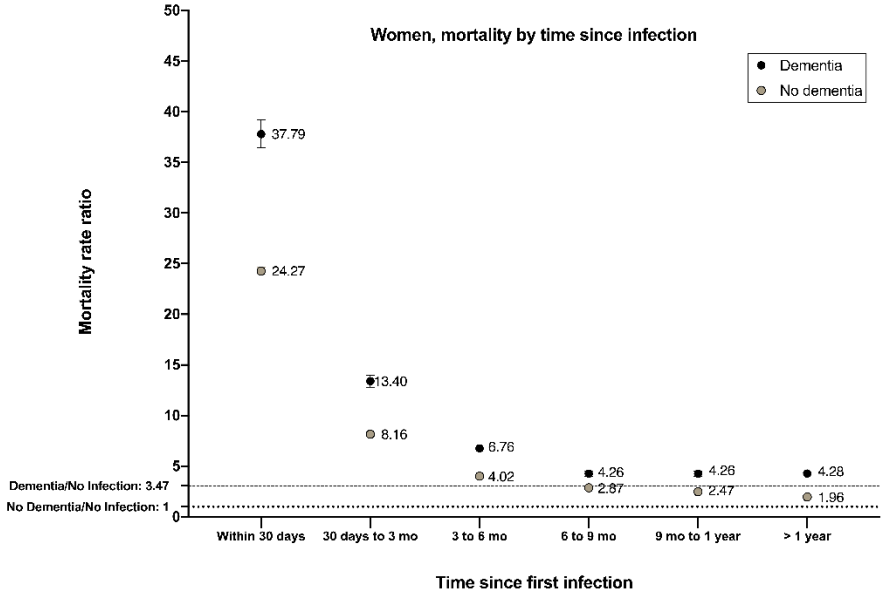
MRRs in a sub-group of men who only had one infection throughout the study period, presented in exposure groups: Dementia/Infection (sub-divided into whether infections came before or after dementia), Dementia/No Infection, No Dementia/Infection, and No Dementia/No Infection (reference group). N= 1,228,963 individuals (women and men)s with either one infection only or no infections (268,096 individuals were excluded who had more than one infection throughout the study period out of the total of 518,880 individuals with infections, thus a total of 250,784 individuals had one infection only). [a]Adjusted for sex, age, and calendar year. [b]Further adjusted for highest attained educational level and civil status. [c]Further adjusted for CCI. All MRRs p≤0.00001. Years were calculated based on 365 days. MRR= Mortality rate ratio; Yr= Year; N deaths= Number of deaths; Pyrs= Person years; ref= reference group.

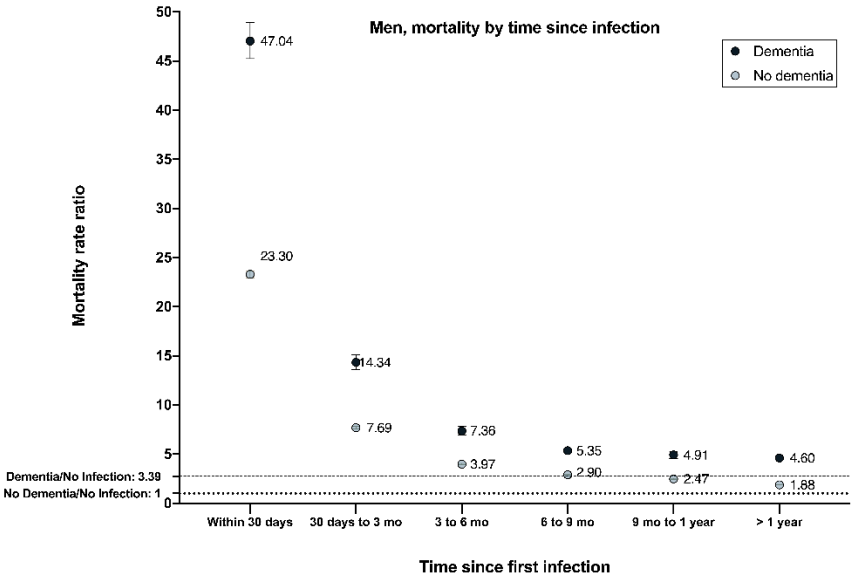
Table 17. Mortality rate ratios in women and men by time since first infection within 30 days to after 1 year

Exposure groups				Women			Men		
				Pyrs	N deaths	MRR model 3	Pyrs	N deaths	MRR model 3
Dementia	Infection	30 days	After dementia	1360	2985	37.79 (36.44, 39.20)	852	2636	47.04 (45.25, 48.91)
			Before dementia	72	93	20.94 (17.08, 25.66)	43	73	22.19 (17.64, 27.92)
		30 days to 3 mo	After dementia	2557	1977	13.40 (12.81, 14.01)	1515	1422	14.34 (13.60, 15.11)
			Before dementia	126	99	13.94 (11.45, 16.98)	75	87	15.46 (12.53, 19.07)
		3 to 6 mo	After dementia	3737	1460	6.76 (6.42, 7.12)	2166	1045	7.36 (6.93, 7.83)
			Before dementia	180	99	8.53 (7.00, 10.38)	113	89	10.39 (8.44, 12.80)
		6 to 9 mo	After dementia	3725	928	4.26 (3.99, 4.54	2124	753	5.35 (4.98, 5.75)
			Before dementia	130	83	10.46 (8.43, 12.97)	81	60	10.14 (7.88, 13.07)
		9 mo to 1 yr	After dementia	3872	977	4.26 (4.00, 4.54)	2170	716	4.91 (4.56, 5.29)
			Before dementia	116	75	9.89 (7.88, 12.40)	75	49	8.83 (6.67, 11.68)
		>1 yr	After dementia	40,992	11,295	4.28 (4.20, 4.37)	19,999	6385	4.60 (4.49, 4.72)
			Before dementia	38,884	11,118	4.22 (4.14, 4.31)	22,136	7460	4.35 (4.25, 4.46)
	No Infection			138,056	19,838	3.47 (3.41, 3.52)	69,297	10,735	3.39 (3.33, 3.46)
No Dementia	Infection	30 days		20,128	21,731	24.27 (23.92, 24.63)	17,625	21,530	23.30 (22.95, 23.65)
		30 days to 3 mo		37,101	13,154	8.16 (8.02, 8.31)	32,250	12,679	7.69 (7.55, 7.83)
		3 to 6 mo		51,979	8973	4.02 (3.94, 4.11)	44,949	9021	3.97 (3.89, 4.06)
		6 to 9 mo		49,051	6049	2.87 (2.80, 2.95)	42,148	6145	2.90 (2.82, 2.97)
		9 mo to 1 yr		48,995	5211	2.47 (2.40, 2.54)	41,905	5200	2.47 (2.40, 2.54)
		>1 yr		815,711	76,395	1.96 (1.94, 1.98)	662,782	67,267	1.88 (1.86, 1.90)
	No Infection			5,930,141	125,933	1 (ref)	4,589,915	113,435	1 (ref)

MRRs presented in groups: Dementia/Infection (subdivided into whether infections came before or after dementia), Dementia/No Infection, No Dementia/Infection, and No Dementia/No Infection. MRRs were fully adjusted for sex, age, calendar year, highest attained educational level, civil status, and CCI. Time periods of 3, 6 and 9 months were calculated based on 30 days/month. One year was calculated based on 365 days. All MRRs are of significance (p=<.00001). Highlighted MRRs are presented in figure 1 below. MRR= Mortality rate ratio; Mo= months; Yr= Year; N deaths= Number of deaths; Pyrs= Person years; ref= reference group.

Figure 2. Post hoc analysis: Mortality rate ratios by time since first infection in women and men





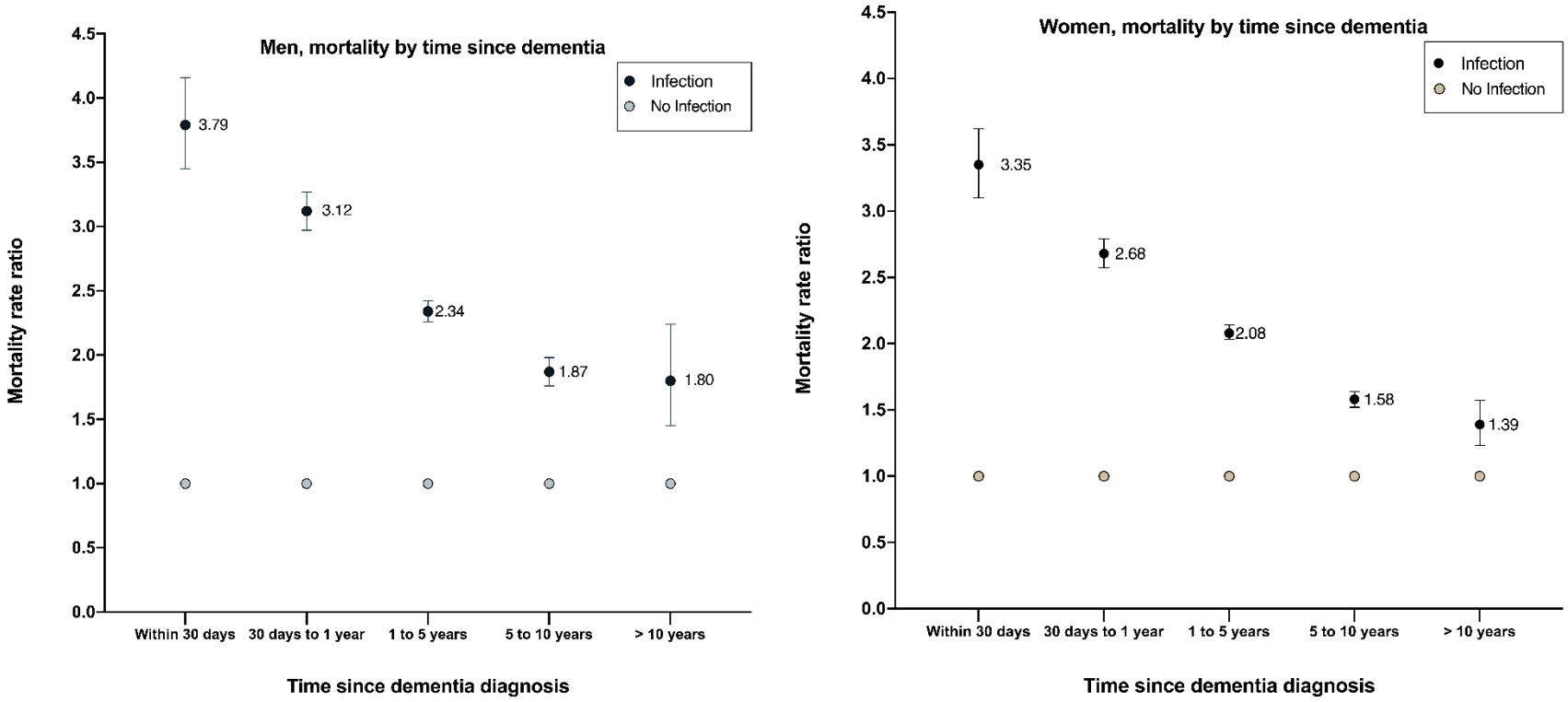
Error bars represent the 95% confidence intervals.

Table 18. Mortality Rate Ratios in women and men with dementia by time since dementia diagnosis

Time since dementia diagnosis	Exposure group	Women			Men		
		Pyrs	N deaths	MRR model 3	Pyrs	N deaths	MRR model 3
Within 30 days	Infection	2068	1986	3.35 (3.10, 3.62)	1287	1566	3.79 (3.45, 4.16)
	No infection (ref)	3557	958	1 (ref)	2092	643	1 (ref)
30 days to 1 yr	Infection	20,326	6670	2.68 (2.57, 2.79)	12,117	5311	3.12 (2.97, 3.27)
	No infection (ref)	34,020	39s10	1 (ref)	19,404	2617	1 (ref)
1 to 5 yrs	Infection	54,686	15,846	2.08 (2.03, 2.14)	29,376	10,540	2.34 (2.26, 2.42)
	No infection (ref)	78,357	10,172	1 (ref)	39,242	5727	1 (ref)
5 to 10 yrs	Infection	16,952	6046	1.58 (1.52, 1.64)	7841	3093	1.87 (1.76, 1.98)
	No infection (ref)	20,428	4360	1 (ref)	7963	1632	1 (ref)
>10 yrs	Infection	1720	641	1.39 (1.23, 1.57)	728	265	1.80 (1.45, 2.24)
	No infection (ref)	1694	438	1 (ref)	596	116	1 (ref)

MRRs presented in groups: Dementia/Infection with refernce to Dementia/No Infection in each time period. MRRs were fully adjusted for sex, age, calendar year, highest attained educational level, civil status, and CCI. A year was calculated based on 365 days. All MRRs are of significance (p=<.00001). Because time since dementia is highly correlated with age and calendar time, we repeated this analysis in 2 other models where we excluded adjustment for age in one model, and for calendar year in another model. Results only slightly changed the presented MRRs in this table (not shown). **This analysis model is not directly comparable to the MRR by time since infection model due to different time lines (time since infection and since dementia diagnosis), and results should be interpreted separately**. MRR= Mortality rate ratio; Yr= Year; N deaths= Number of deaths; Pyrs= Person years; ref= reference group.

Figure 3. Mortality rate ratios in women and men by time since dementia diagnosis.



Error bars represent the 95% confidence intervals.

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STUDY III

Hospital readmissions following infections in dementia: a nationwide and registry-based cohort study

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Abstract

INTRODUCTION: We aimed to investigate readmission risks following infections in dementia; identify types of infections behind risks; and highlight reasons for readmissions.

METHODS: Acute inpatient hospital admissions for infections in Danish residents included from January 1, 2000 or age 65 years. Primary outcomes: 7-day readmissions risk ratios (RR, Risk following infection index admissions of people with dementia relative to those of people without dementia); risks by infection site; and reasons for readmission. Secondary outcomes: 30- and 90-day readmission risks. Competing risk of death was estimated.

RESULTS: 7-day readmission RR was increased in all ages and highest in the youngest (Women RR 1.37, 95% confidence interval [CI] 1.22-1.53; Men RR 1.23, 95% CI: 1.12-1.35). RRs got smaller with increasing age and longer follow up. Most notable common readmissions were for infections and dehydration in dementia.

DISCUSSION: We conclude on a substantially increased readmission risk in people with dementia than those without, particularly within 7 days, and for the youngest in the cohort. Readmission risks were higher for infection index admissions than for admissions for other causes than infection, and readmissions were mostly due to infections. Findings highlight the burden of infections in people with dementia and call for in-depth investigations of determinants related to readmission risks, to inform public policy and identify avenues for interventions that can decrease or prevent potentially avoidable readmissions.

Introduction

Unplanned acute hospital readmissions in persons with dementia place them at increased risk for adverse outcomes and result in poor health as well as burdening the health care system. Readmissions are also used as a measure of quality of health care provided during hospitalization and post discharge.[1] It is therefore crucial to identify avenues for interventions to effectively decrease or prevent readmissions, especially in vulnerable groups such as those living with dementia and particularly for common and potentially preventable reasons for hospitalization such as infections. Infections can result in health complications[2,3] and are linked to excess mortality.[4] Importantly, these are potentially preventable and therefore represent an efficient place to focus interventions.

However, despite the well-known impact, relatively little is known about hospitalization trajectories for people with dementia who get admitted for an infection, and surprisingly little is documented in literature.

One study reported a 1.16 risk ratio of 30-day readmission,[5] another an odds ratio of 2.9,[6] and the third a 7% increased risk following pneumonia hospitalization in people with dementia.[7] Additionally, another study showed that dementia was one of the risk factors for readmissions following pneumonia.[8] However, no study has comprehensively compared readmissions following all types of infections in people with and without dementia and in population-based cohorts. Such knowledge is crucial for understanding the impact of infections on dementia, to shape public health practice and policy.

To contribute to such knowledge, we aimed to investigate readmission risks (7, 30, and 90 days) following acute inpatient hospital admissions for infections in people with and without dementia; to identify types of infections linked to such risks; and to highlight reasons for readmissions.

Materials and methods

Study design and population

We conducted a nationwide registry-based cohort study using prospectively collected data from the Danish national registries. The population was people born in or before 1950, identified from the Danish Civil Registration System. People were included in the study from 1 January 2000 if they were at least 65 years old, or otherwise from the date they turned 65 years old between 1 January 2000 and 31 December 2015. People were alive (at the start of the study) and residing in Denmark

(during the study period) and had at least one registered hospital inpatient admission in the Danish National Patient Register (DNPR) [9] after start of the study. We excluded everyone with a dementia diagnosis registered before the age of 65 years. To allow for complete follow up, an exclusion based on admission date was set for each readmission period. Admissions occurring on or after 24 December 2015, 1 December 2015, and 02 October 2015 were excluded for 7, 30, and 90 days respectively.

Admissions definition

Data were extracted from the DNPR by identifying inpatient acute (unplanned) hospital records and the primary discharge ICD-10 diagnosis codes. Each hospital record is registered with an admission and discharge date. Transfers between hospital departments during one admission would result in multiple records. Hospital records that occurred on the same admission or discharge date (+1 day) as the previous record were counted as a single record. As such, an admission was defined as an inpatient acute hospitalization that represented one complete period of hospitalization from first admission date to last discharge date. Moreover, because we combined hospital records into one admission, each admission could be registered in our study's dataset with several primary discharge diagnoses.

Except for the first admission in the study period for each person, admissions were eligible to be both an index admission for future readmissions and a readmission for prior index admissions as defined below.

Infection index admissions definition

Infection index admissions were defined as inpatient acute admissions with a primary discharge diagnosis of an infection (using ICD-10 codes).

Infection index admissions were categorized using the ICD-10 codes according to the system in which the infection is located as classified in the ICD-10 manual (e.g. respiratory), and categories are referred to as "infection sites" throughout this paper (Table S1). Previous literature[10,11] and expert knowledge guided this categorization. We removed diagnosis codes for HIV infections which were instead included in the Charlson Comorbidity index (CCI).[12] Details of choosing infection codes and categorization are previously described.[4]

Exposure: Dementia diagnosis

The date of dementia diagnosis was defined as a first registered diagnosis at age 65 years or older using ICD codes, or a first redeemed anti-dementia medication prescription (Table S2), as previously described. [4]

Outcomes: Readmissions and reasons for readmission

The primary outcomes were 7-day readmission, and reasons for readmission. Readmissions were defined as any registered admission (regardless of the primary diagnosis) that occurred within 7 days of the infection index admission's discharge date. Thus, these were all-cause readmissions, referred to as "readmissions" throughout this paper.

Based on their primary discharge diagnoses, readmissions were categorized into the following groups referred to as "Reasons for readmission":

a) Any infection (primary readmission diagnosis was of any infection). This group was subdivided into: Linked infections (primary readmission diagnosis was of an infection in the same infection site category as that of the infection index admission); Other infections (primary readmission diagnosis was of an infection that was not in the same infection site category as that of the infection index admission); and sepsis (primary readmission diagnosis was sepsis). When the infection index admission's primary diagnosis was sepsis, then this category was omitted from reasons for readmission since sepsis in that case was categorized as "Linked infections".
b) The remaining primary readmission diagnoses which were not of an infection were categorized according to the disease system categories in the ICD-10 manual (e.g. other respiratory disease, other circulatory disease).[13]

The secondary outcome was 30- and 90-day readmission (all-cause readmissions).

Competing risk of death

Due to the competing risk of death before readmission, we investigated death as an outcome (registered date of death).

Covariates

Covariates were obtained from the national registries, and were: age, sex, civil status, highest educational level attained, comorbidities (CCI, previously described[4]), hospital length of stay (LOS), and the calendar year. All covariates were fixed on the date of each infection index admission.

Data analyses

Baseline characteristics were presented for infection index admissions of people with dementia and without. The study unit was admissions. We used a generalized estimating equation (GEE) model with a Poisson distribution, a log link function and with individuals' identification number as the random effect to account for repeated measures (PROC GENMOD in SAS 9.4). We estimated risk ratios (RR) of readmission and mortality (risks in infection index admissions of people with dementia relative to risks in infection index admissions of people without dementia), with 95% confidence intervals (CIs). Each infection index admission could result in readmission, death, or neither. We tested interactions with sex and age and stratified our main analyses accordingly. Examples of data coding and outcome definitions are presented in Figure S1.

Infection index admissions were classified into two groups: 1) Of people with dementia: infection index admissions where a patient was already registered with a dementia diagnosis prior to or on the discharge date of the admission; and 2) Of people without dementia. Following this definition, if infection index admissions were of people with dementia, then the following readmission was referred to as a readmission of people with dementia. If a dementia diagnosis was registered within the follow up period (7, 30, or 90 days) of an infection index admission then it was not counted as such but was still eligible to be counted as a readmission (Figure S1).

Three adjustment models were used: Model 1 adjusted for sex, age, and calendar year; model 2 further adjusted for civil status, highest attained educational level, and LOS; and model 3 further adjusted for CCI.

Infection sites

To compare 7-day readmission risks across infection sites (of the infection index admission), we estimated risks in each infection site and by age groups, for infection sites with 2000 or more infection index admissions (an arbitrarily chosen cut point based on the frequency of infection index admissions of each site in the study population), and pooled the remaining sites into "other sites". In

case one infection index admission had primary diagnoses of multiple infection sites, then the same infection index admission was categorized in multiple infection sites.

Reasons for readmission

For each infection site, we calculated the percentage of readmissions within each group of reasons for readmissions. Due to data regulations, we only presented reasons for readmissions that comprised at least 10%. Within each reason for readmission, if one primary readmission diagnosis comprised more than 50% of all primary diagnoses, then we presented that diagnosis. In case there was more than one primary readmission diagnosis that fell under multiple groups of reasons for readmission, then that readmission was presented in all the groups. We did not present percentages by age groups due to small numbers.

Sensitivity analysis

To explore whether risks were different after index admissions for other causes than infection, we performed a sensitivity analysis where we investigated readmission and mortality RRs following all index admissions without a primary diagnosis of an infection.

All analyses were performed using SAS 9.4 and a 2-sided type 1 error of 5% was considered statistically significant. Danish law does not require ethics committee approval or informed patient consent for registry-based studies. Data were handled anonymously using the server of Statistics Denmark.

Results

Baseline characteristics and outcome summary

Figure 1 presents the study sample. A total of 789,732 infection index admissions (421,133 people) eligible for 7-day readmissions were included. Of these, 783,119 (418,507 people) and 769,042 (412,823 people) infection index admissions were eligible for 30- and 90-day readmissions, respectively. In each of the follow-up periods, 9% of infection index admissions were of people with dementia. Table 1 presents a description of infection index admissions eligible for 7-day readmissions and Table S3 presents these for 30- and 90-day readmissions. Of infection index admissions of people with dementia, 55% were of women (and 51% in infection index admissions of people without dementia). Most infection index admissions of people with and without dementia were of people 75-84 years of age. Socio-demographic and disease characteristics were similar in all follow-up periods.

There were 55,303 readmissions in 7 days (10% were of people with dementia), 161,550 readmissions in 30 days, and 259,745 readmissions in 90 days (for each, 8% were of people with dementia). A total of 78,732 deaths were recorded in 7 days (14% were of people with dementia), 97,027 in 30 days, and 108,328 in 90 days (for each, 16% were of people with dementia) (Table S4). Interactions with age were significant in all follow-up periods, and only in 7 days for interactions with sex (Table S5).

Figure 1. Flow chart of study

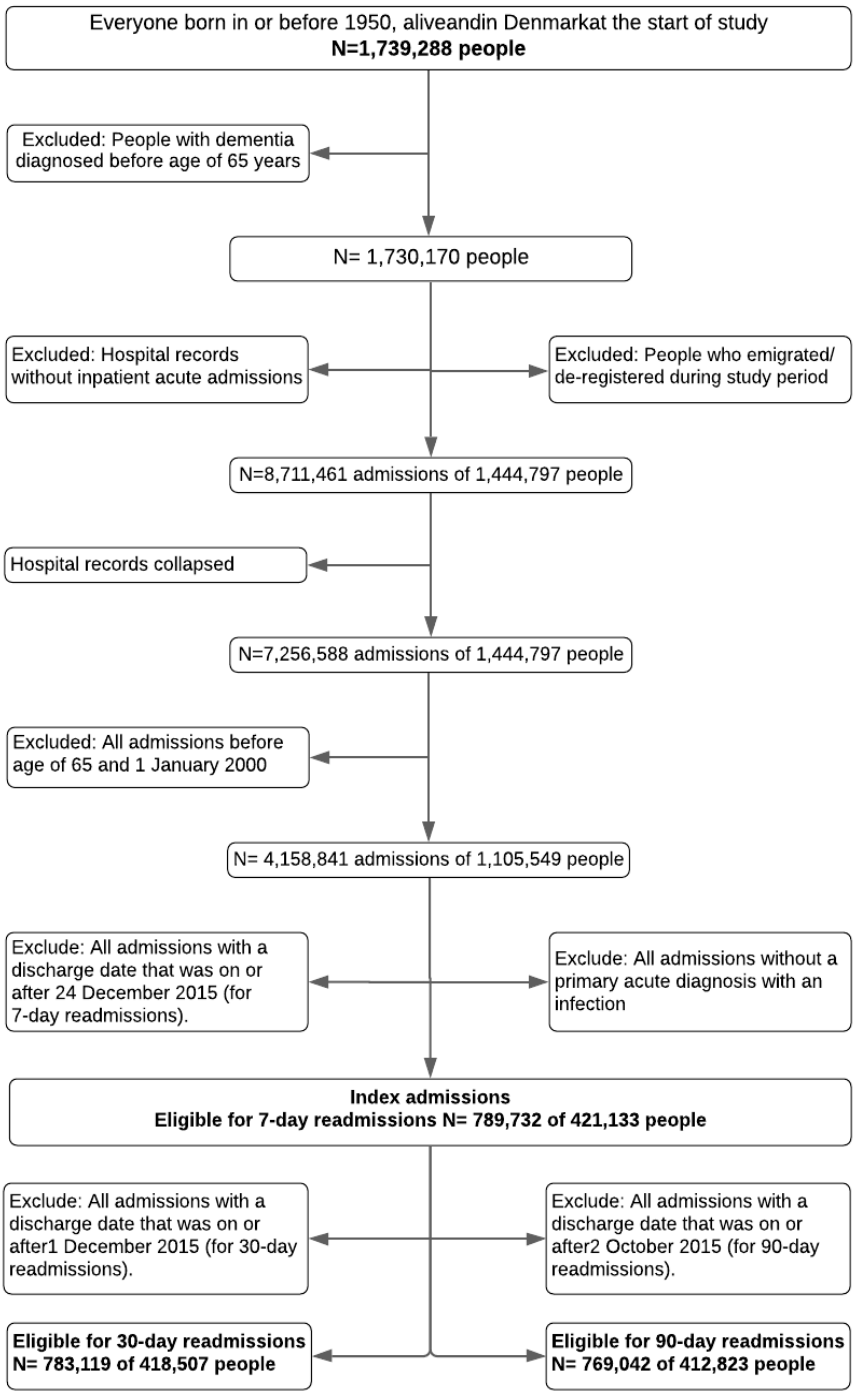


Table 1. Baseline characteristics for infection index admissions eligible for 7-day readmissions (of people with and without dementia)

Characteristic	Level	With dementia		Without dementia	
Total, N (%)[a]	Index admissions	72,103	(9.1)	717,629	(90.9)
	People	34,599	(8.2)	386,534	(91.8)
Sex, Women N (%)	Index admissions	39,935	(55.4)	364,102	(50.7)
	People	20,102	(58.1)	199,664	(51.7)
Age, years N (%)	65-74	8752	(12.1)	275,098	(38.3)
	75-84	32,952	(45.7)	287,827	(40.1)
	85-++	30,399	(42.2)	154,704	(21.6)
Calendar year, N (%)	2000-2004	13,938	(19.3)	176,535	(22.4)
	2005-2009	22,085	(30.6)	207,226	(26.2)
	2010-2015	36,080	(50.0)	333,868	(46.5)
Civil status, N (%)	Married	25,693	(35.6)	322,550	(45.0)
	Unmarried	4227	(5.90)	40,516	(5.7)
	Widowed	33,723	(46.8)	260,705	(36.3)
	Divorced	8428	(11.7)	93,183	(13.0)
	Unknown	32	(0.04)	675	(0.1)
Education, N (%)	Low	46,528	(64.5)	525,068	(73.2)
	Medium	4661	(6.5)	54,927	(7.7)
	High	1792	(2.5)	16,803	(2.3)
	unknown	19,122	(26.5)	120,831	(16.8)
LOS, days, Mean (SD)		7.9	(10.2)	8.6	(11.3)
CCI, N (%)	0	14,488	(20.1)	113,511	(15.8)
	1	15,968	(22.2)	149,492	(20.8)
	2	13,806	(19.2)	143,052	(19.9)
	3	9901	(13.7)	102,058	(14.2)
	4+	17,940	(24.9)	209,516	(29.2)
Infection site, N (%)	Respiratory	35,006	(48.6)	389,603	(54.3)
	Urinary	18,854	(26.2)	97,081	(13.5)
	Sepsis	8598	(11.9)	69,662	(9.71)
	Digestive	4446	(6.2)	63,485	(8.9)
	Skin	2987	(4.1)	44,211	(6.2)
	Unspecified	2037	(2.8)	19,118	(2.7)
	Surgical	824	(1.1)	16,689	(2.3)
	Less occurring	422	(0.6)	7348	(1.0)
	Genital	360	(0.5)	7459	(1.0)
	Musculoskeletal	301	(0.4)	6560	(0.9)
	Herpes	203	(0.3)	3300	(0.5)
	Nervous	192	(0.3)	2613	(0.4)
	Circulatory	184	(0.3)	6337	(0.9)
	Eye	57	(0.1)	1570	(0.2)
	Ear	31	(0.04)	879	(0.1)
	Hepatitis	25	(0.03)	745	(0.1)

Table presents baseline sociodemographic and disease characteristics of infection index admissions of people with dementia (With dementia) and of infection index admissions of people without dementia (without dementia). Infection index admissions are those eligible for 7-day readmissions, and characteristics of infection index admissions which were also eligible for 30-and 90-day readmissions are described in Table S3. Abbreviations: LOS, hospital length of stay; SD, standard deviation; CCI, Charlson Comorbidity Index. [a] Percentage of all infection index admissions, and all people. Education: highest educational level attained was defined as low (primary school), medium (upper secondary, business high school, vocational internship and main course), and high (short-term further education, middle-range education, bachelor's degree, extended education and research degree). Infection sites are ordered from highest to lowest frequency in the exposure groups.

Readmission and mortality risk ratios

Infection index admissions of people with dementia showed an increased risk for readmission and mortality in women (Figure 2) and men (Figure 3) compared with infection index admissions of people without dementia. This risk varied in magnitude across follow-up periods and age groups, with the 7-day readmission RR in the age group 65-74 years being 1.37 (95% CI: 1.22 to 1.53) in women and 1.23 (95% CI: 1.12 to 1.35) in men. Seven-day readmission RRs got smaller with increasing age but remained significantly increased in all age groups, except for ≥75-year-old men, where RRs were insignificant.

The 30- and 90-day readmission RRs were also significantly increased in the 65-74 years age group in women (30-day readmission RR in women 1.14 with 95% CI: 1.05 to 1.24, men: 1.06 with 95% CI: 0.99 to 1.12; 90-day readmission RR in women 1.10 with 95% CI: 1.03 to 1.18, men 1.03 with 95% CI: 0.97 to 1.08), while in the older age groups, these were either insignificant or slightly decreased (Figures 2-3). Mortality RRs were significantly increased in all age groups and follow-up periods and got larger with longer follow-up. The highest were observed in the 65-74 years age group and in 90 days (Women, fully adjusted RR 1.90, 95% CI: 1.75-2.06; Men, fully adjusted RR 1.99, 95% CI: 1.86 to 2.12). Tables A.6-9 present the complete analysis models.

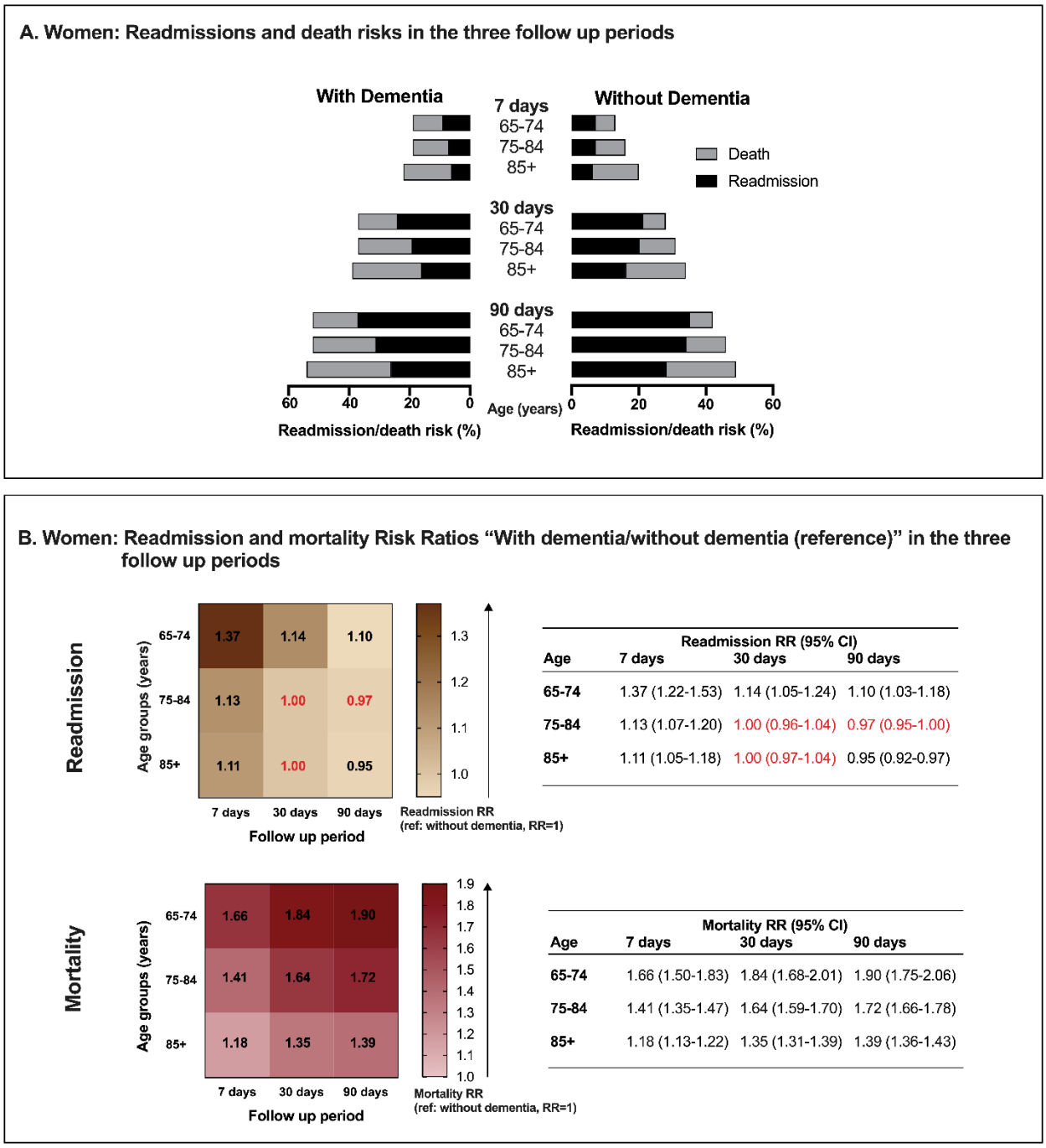
Readmission risks in infection sites

Seven-day readmission risks were higher following infection index admissions of people with dementia in the 65-74 years age group for all infection sites (7-11%), than following those of people without dementia (5-9%). For all sites, risks were more notably different across age groups following infection index admissions of people with dementia than without (Figure 4A).

Reasons for readmission

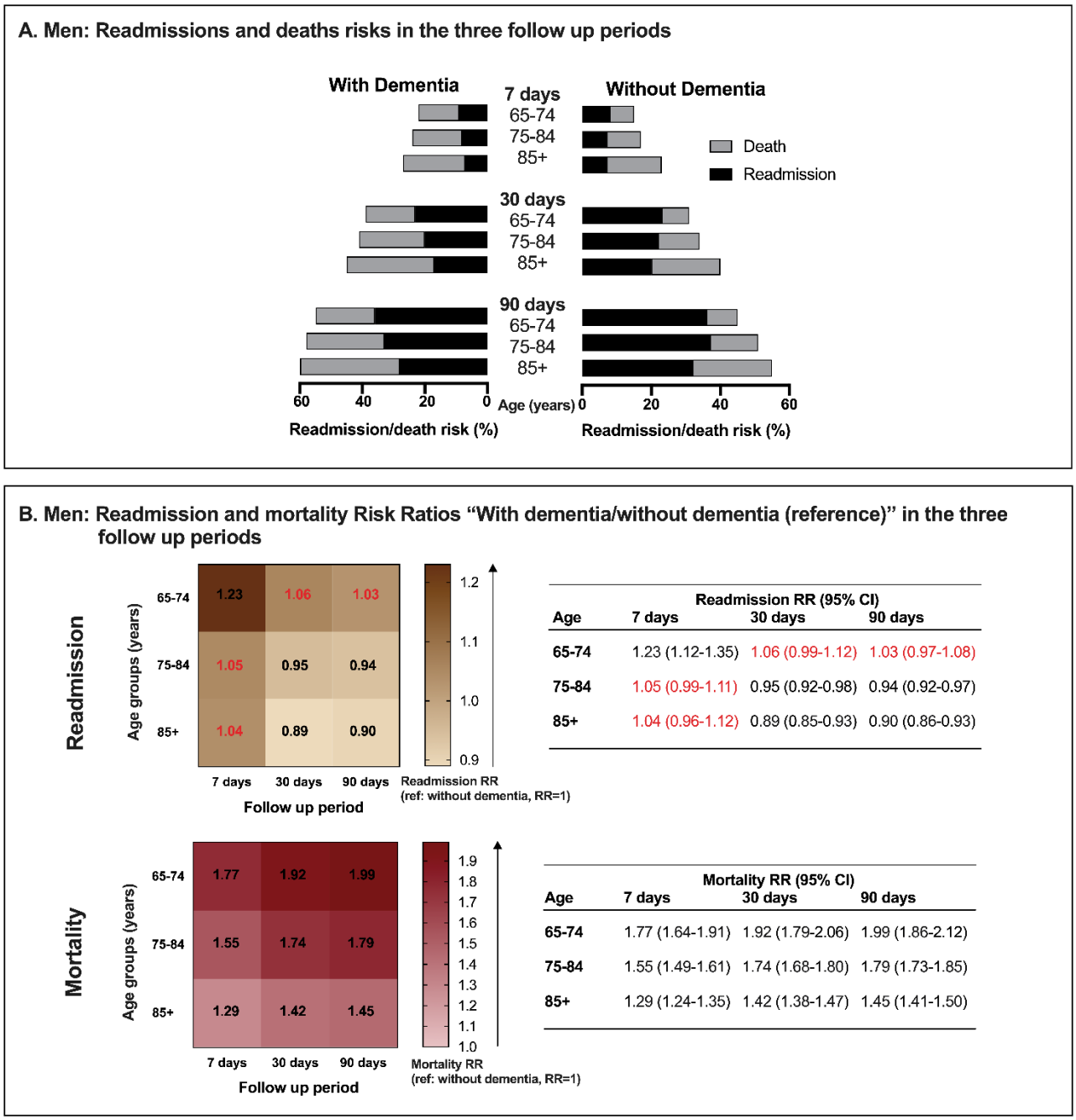
Reasons for 7-day readmissions varied depending on the infection site and most common reason in all sites was infection (Figure 4B). The most notable difference was for unspecified infections. Here, of all readmissions of people with dementia, 95% were due to infection (22% due to unspecified infections and 63% due to other infections of which pneumonia was the most common), while of readmissions of people without dementia, 42% were due to infection. Additionally, volume depletion/dehydration was a more common reason for readmissions of people with dementia (12-17% after admissions with unspecified, urinary, and digestive infections), than for those of people without dementia (5-8%). For linked infections in all sites, the most common primary readmission diagnosis was the same as the most common infection index diagnosis (data not shown).

Figure 2. Women, readmission, and mortality.



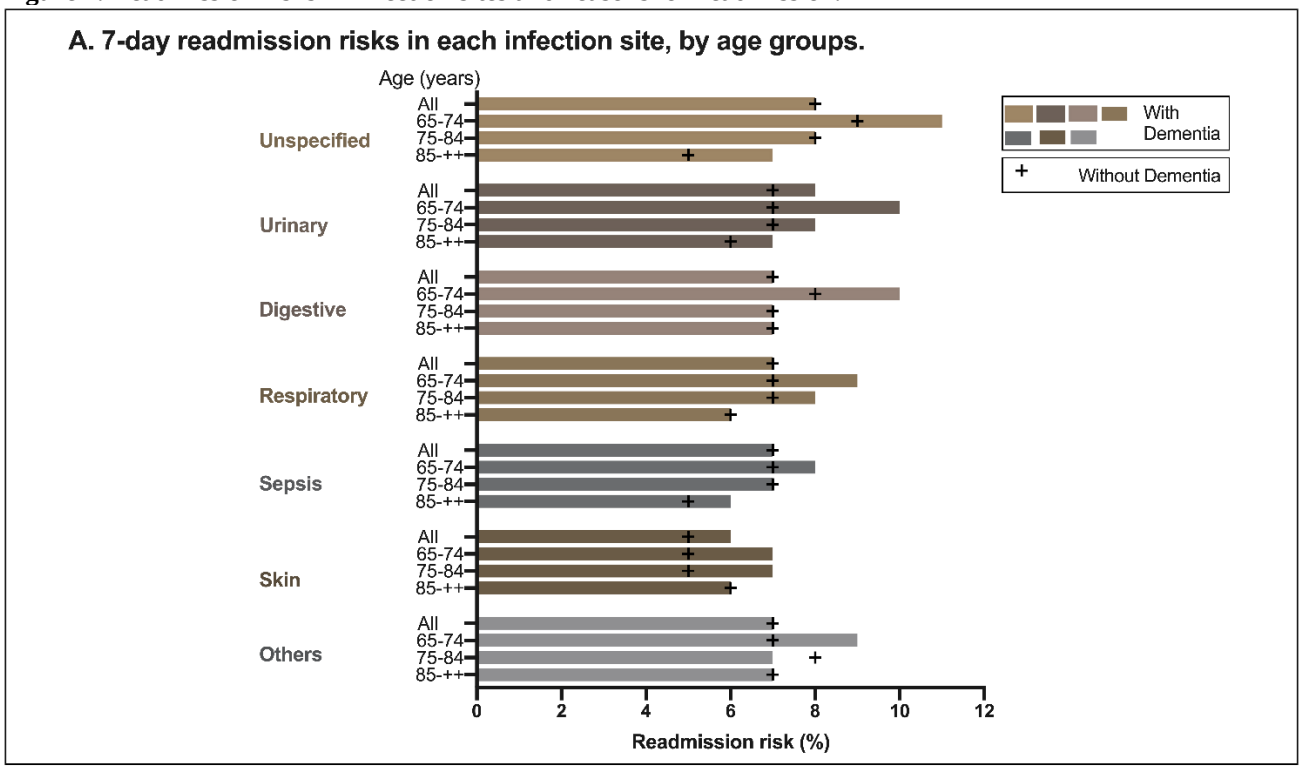
Panel (a) presents the risks of readmission and death in infection index admissions of people with dementia (With dementia) and of infection index admissions of people without dementia (Without dementia) in women in the follow-up periods and across age groups. Panel (b) presents the fully adjusted readmission risk ratios (RRs) (top heat map) and mortality RRs (bottom heat map) for women in all follow-up periods (horizontal x-axes) and across the age groups (vertical y-axes). RRs are the ratios of risk in infection index admissions of people with dementia/risk in infection index admissions of people without dementia. The fully adjusted model was for age, sex, calendar year, civil status, highest attained educational level, length of stay, and Charlson Comorbidity Index. Each cell in the two heat maps represents RR estimates and colors increase in intensity with increasing RR. Numbers inside each cell are the RRs as presented in the adjacent tables to each of the heat maps where 95% confidence intervals (95% CIs) are also presented. Numbers in cells that are in red represent those with insignificant RRs. Infection index admissions that were eligible for more than one of the follow-up periods were represented in multiple periods in our analyses. Full analysis model is presented in Tables S6–S7.

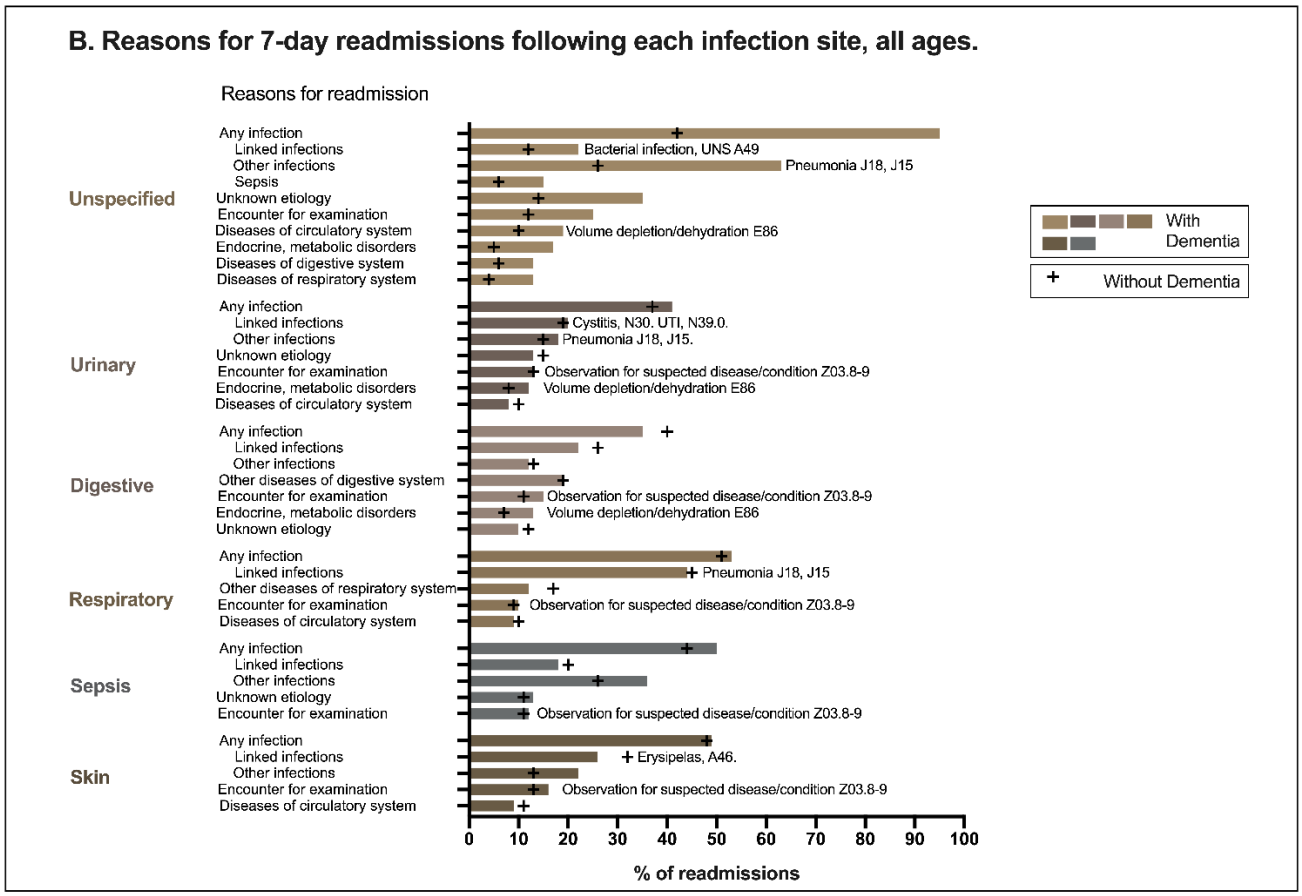
Figure 3. Men, readmission, and mortality.



Panel (a) presents the risks of readmission and death in infection index admissions of people with dementia (With dementia) and of infection index admissions of people without dementia (Without dementia) in men in the follow-up periods and across age groups. Panel (b) presents the fully adjusted readmission risk ratios (RRs) (top heat map) and mortality RRs (bottom heat map) for men in all follow-up periods (horizontal x-axes) and across the age groups (vertical y-axes). RRs are the ratios of risk in infection index admissions of people with dementia/risk in infection index admissions of people without dementia. The fully adjusted model was for age, sex, calendar year, civil status, highest attained educational level, length of stay, and Charlson Comorbidity Index. Each cell in the two heat maps represents RR estimates and colors increase in intensity with increasing RR. Numbers inside each cell are the RRs as presented in the adjacent tables to each of the heat maps where 95% confidence intervals (95% CIs) are also presented. Numbers in cells that are in red represent those with insignificant RRs. Infection index admissions that were eligible for more than one of the follow-up periods were represented in multiple periods in our analyses. Full analysis model is presented in Tables S8,S9.

Figure 4. Readmission risks in infection sites and reasons for readmission.





Panel (a) presents the 7-day readmission risks following infection index admissions of each of the infection sites and stratified by age groups. The category "Others" pooled all infection sites described in the Methods section, which had less than 2000 infection index admissions. Infection sites are ordered from the highest to the lowest readmission risk in all age groups, with the category "Others" at the end. In case one infection index admission had primary diagnoses of multiple infection sites, then the same infection index admission was categorized in multiple infection sites. Panel (b) presents the reasons for 7-day readmissions in each of the infection sites, in all age groups. For each infection site we calculated the percentage of readmissions within each group of reasons for readmissions. Within each reason for readmission, if one primary readmission diagnosis comprised more than 50% of all primary diagnoses, then we presented that diagnosis in text adjacent to the bars together with the ICD-10 codes. In any case where there was more than one primary readmission diagnosis that fell under multiple groups of reasons for readmission, then that readmission was presented in all the groups. In both panels (a) and (b), the bars present the readmission risk (panel a) and percentage of readmissions (panel b) following infection index admissions of people with dementia (With dementia), and the plus signs present readmission risks and the percentage of readmissions following infection index admissions of people without dementia (Without dementia)

Sensitivity analysis

Seven-day readmission and mortality RRs were lower than those observed in infection index admissions (Readmission RR in 65-74 years, women 1.03 with 95% CI: 0.95 to 1.11; men 1.04 with 95% CI: 0.98 to 1.11). Trends for readmission and mortality RRs were also different where readmission RRs got smaller with increasing age, while mortality RRs got larger with increasing age and with longer follow up (Figures S2, S3).

All three adjustment models showed the same trends for readmission and mortality RRs. Adjustment for the CCI increased readmission RRs and mortality RRs.

Discussion

In this nationwide and population-based cohort study, we emphasize three major findings: 1) Infection index admissions of people with dementia were 37% more likely to result in 7-day readmissions in the 65-74 years age group in women (and 11-13% in older age groups), and 23% in men (and insignificantly 4-5% in older age groups), compared with infection index admissions of people without dementia; 2) Readmission and mortality RRs were higher following infection index admissions than those for other causes than infection; and 3) Readmission risks of people with dementia were notably higher in the 65-74 years age group in all infection sites, and readmissions were mostly due to infection.

Our results are generally consistent with previous studies in that readmission risk is elevated in people with dementia after hospitalization for any reason (reviewed in [2,14]) but results cannot be directly comparable due to our focus on hospitalizations for infections specifically. A few studies reported an increased 30-day readmission risk in people with dementia following pneumonia,[5,6,8] and a recent Danish study showed that such risks were primarily within the first days after discharge and were

highest amongst the youngest in the cohort.[7] Our results on 7-day readmission risks after admissions for respiratory infections (of which majority were for pneumonia) were consistent with previous findings, however varied in risk magnitude due to different study design and follow-up period.

Our results do not explain why the readmissions are occurring and which factors may determine these causally. However, there are several plausible explanations to our findings. First, people with dementia present with atypical signs of infection and have reduced ability to express their symptoms, particularly in older age and advanced stages of dementia. This contributes to challenges in identifying early symptoms of infection and subsequently delay infection diagnosis[15] and result in more severe infections at the time of admission. Severe infections may further deteriorate functional and cognitive abilities of a person with dementia and an overall poorer health may result in complications that subsequently lead to readmissions.[3] For example, we showed that volume depletion was a more common reasons for readmission in people with dementia than without, consistent with findings from a recent study.[16] Another complication may be hospital-acquired infections in people with dementia.

Second, challenges in diagnosing infections can result in misdiagnosis and consequent failure of treatment and thus readmissions. Our results showed that readmission risks following unspecified infections (e.g. general bacterial infection) were notably higher in people with dementia than without, indicating that subsequent readmissions are possibly due to the improper diagnosis of the infection.

Third, impaired cognition and functional abilities, especially if further deteriorated by the hospitalization for a severe infection, can challenge compliance with instructions after discharge that require the patient's involvement in complex decision making and adjustments of routines and medication intake. Such a challenge can result in the undertreatment of the infection, leaving it unresolved and lead to readmission. Our finding that readmissions were commonly due to linked infections may be indicative of unresolved infections, a finding previously documented in the general elderly population in one study.[17]

In all infection sites, readmission risk was higher in people with dementia than without, particularly in the age group 65-74 years, indicating that observed readmission RRs were not likely attributed to one infection site only.

Because death is a competing risk, readmission estimates should be interpreted considering the mortality RRs, and the readmission RRs getting smaller with longer follow-up could be explained by

the increasing mortality. It could also be interpreted that 7 days is a critical period where more readmissions occur for people with dementia than without, whereas in 30 and 90 days, more readmissions occur for people without dementia and thus explain the observed reduction in RRs in those periods.

An important confounder that we could not investigate is placement in nursing homes, where hospitalization patterns may be altered, particularly for people with dementia for whom hospitalization events can be more destabilizing[18] and where decisions by care personnel and caregivers may favor avoidance of hospitalizations.[19] Readmission RR's pattern across ages can thus be explained by placement in nursing homes (and not by the competing risk of death, since mortality RRs also got smaller with increasing age). This is supported by our results in Figures 2A and 2B where readmission risks decreased more steeply with older age for infection index admissions of people with dementia than without. Moreover, younger people with dementia (who are more likely to be living at home) might be prioritized and deemed to more likely benefit from hospitalization for infections and treatment, and thus experience more readmissions after infections.

Readmissions can either be due to the quality of care provided during hospitalization, patient characteristics, or the interaction of the two. [14] Understanding such interactions is a crucial research priority as such knowledge can pave the way to develop appropriate measures to decrease and possibly prevent readmissions. Such measures include identifying early infection symptoms; ensuring proper diagnosis and treatment of the infection at the initial hospitalization; ensuring successful discharge planning and transition from the hospital to community settings; and applying preventive measures for potentially preventable infections and complications following infection (e.g. dehydration).

Strengths and limitations

Interpretation of our findings should be considered within several constraints. First and most importantly, we did not have data on nursing home residency, due to their low validity.[20] Second, although we identified all registered dementia cases in Denmark, dementia is generally under-registered,[21,22] and we assume that our estimates of risks and ratios were thus underestimated. Third, we did not have information on the severity stage of dementia at diagnosis or at the time of each index admission. Infection index admissions of people with dementia were those with prevalent and incident dementia, so some people with a first registered dementia diagnosis prior to start of study might have had hospital admissions that were not counted in our study. Similarly, the threshold of

infection severity at the time of index admission and readmission was unknown, and it was unknown whether the threshold was different in people with and without dementia. Fourth, due to small sample sizes in some infection sites, we were unable to explore these further. Fifth, admissions that occurred 1 day following the index admissions were counted as a single hospitalization and not a readmission, as we could not reliably distinguish internal transfers between hospital sections and actual discharge with readmission within one day. Lastly, residual confounding is always an important limitation to observational studies, and information on factors such as lifestyle and living status that we did not have could boost our understanding of determinants of readmissions and provide evidence for interventive strategies.

It is also important to note our study's strengths. Given the population- and registry-based design, we had complete and valid data on all dementia cases registered in the country, as well as all hospital admissions and deaths.[23,24] Further, with the long follow-up period (up to 15 years), we captured all acute inpatient hospital admissions for individuals. Loss to follow up and selection bias common in observational studies were minimal in ours. Lastly, we considered the competing risk of death and interpreted our findings considering these risks.

Conclusion

We conclude on a substantially increased readmission risk in people with dementia than those without, particularly during the period immediately following discharge, and for the youngest in the cohort. Readmission risks were higher for infection index admissions than for admissions for other causes than infection, and readmissions were mostly due to infections. Thus, findings highlight the burden of infections in people with dementia. We urge in-depth investigations of determinants related to readmission risks, to identify avenues for interventions that can decrease or prevent potentially avoidable readmissions.

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Authors' contributions: Study concept and the literature review were done by JJ, GW and NFM. All authors designed the study. JJ and NFM prepared and defined the data related to infection codes. Statistical analyses were done by JJ and TML. JJ wrote the manuscript as outlined by JJ and GW together, and all authors equally contributed to data interpretation and to the critical review of the manuscript.

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Conflicts of interest/Competing interests: GW reports consultancy work for Hoffman-La-Roche.

Data availability statement: All data used in this study are derived from the Danish national health registry record and cannot be shared with the public. Data access requires authorization by The Danish Data Protection Agency, The Danish Health Authority, The Danish Health Data Authority, The Danish Medicines Authority, and Statistics Denmark.

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Hospital readmissions following infections in dementia, a nationwide and registry-based cohort study

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Supplementary Material

Table S.1 Infection site categories and ICD-10 codes

Infection site category	ICD-10 codes
- Sepsis	R572, J950A, T880A, T802D, T802D1, T814D, A419, A419B, A419C, A415, A410, A412, A409, A267*, A021, A403, A411A*, B377, A400, A414, A327*, A401*, A418, A408, A411, A415A*, A392A*, A282B*, A402*, A207*, A227*, A413*, A427*, A548G*
- Eye and adnexa	Until H60 (except herpes: H191)
- Ear	H60 and forward
- Circulatory	I
- Respiratory	J (except sepsis: J950A), A150, A481
- Digestive	K (except hepatitis: K720A, K720E, K720F, K730, K731, K732, K738, K739, K759A), A020, A045, A047, A081, A084, A090, A099, B370
- Skin	L, A469, DA269
- Musculoskeletal	M, B919
- Urinary	Until N39, R827, R827B
- Genital	N41 and forward, A630
- Nervous	G, A869
- Surgical	T (except sepsis: T880A, T802D, T802D1, T814D)
- Uncategorized	A490, A498, A499, A499A, A692, A881, B349, B378, B999, Z229, D733, D762, E321, E236A
- Less occurring	Remaining A, B codes not categorized elsewhere in this table.
- Herpes	H191, B029, B028, B023, B001A*, B009, B004, B004A*, A609*, B001B*, B022, B021*, B001, B003*, B005, A601B*, B002A*, A600*, A601*, B008*, B020*, B020A*, A601A*, B000*, B007*, B027*, A601C*, B001C*, DB002*, B002B*, B002C*
- Hepatitis	K720A, K720E, K720F, K730, K731, K732, K738, K739, K759A, B182, B169A*, B180*, B169, B251*, B181, B150*, B159*, B178, B199, B188*, B161*, B160*, B162*, B171*, B189*, B190*, B159A*, B170*, B172*, B581*, B179*

Detailed process of choosing infection codes and categorization is described in the supplementary material of our previous study [1]

*Codes occurring less than 500 times in our population.

Table S.2 International Classification of Diseases (ICD) -8 and 10 codes for dementia diagnosis and Anatomical Therapeutic Chemical Classification (ATC) codes for anti-dementia medication.

Dementia type	**ICD-8 code**	**ICD-10 code**
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
Medication	**ATC code**	
Cholinesterase inhibitors		
Donepezil	N06DA02	
Rivastigmine	N06DA03	
Galantamine	N06DA04	
Glutamate-receptor antagonists		
Memantine	N06DX01	

Dementia was defined as a first registered dementia diagnosis using the ICD codes from the Danish National Patient Registry and the Psychiatric Central Research Registry, or a first redeemed prescription for an anti-dementia medication from the Danish National Prescription Registry. ICD codes for a dementia diagnosis reflect diagnosis in the secondary care setting. If a person with dementia was identified by a redeemed anti-dementia medication but with no registered ICD code of dementia, then this person had been diagnosed in the primary care setting. If a person gets a diagnosis of dementia in the primary care setting and does not redeem an anti-dementia medication, then this dementia diagnosis remains undetected in our registries.

Figure S.1 Data coding- what is counted as readmissions?

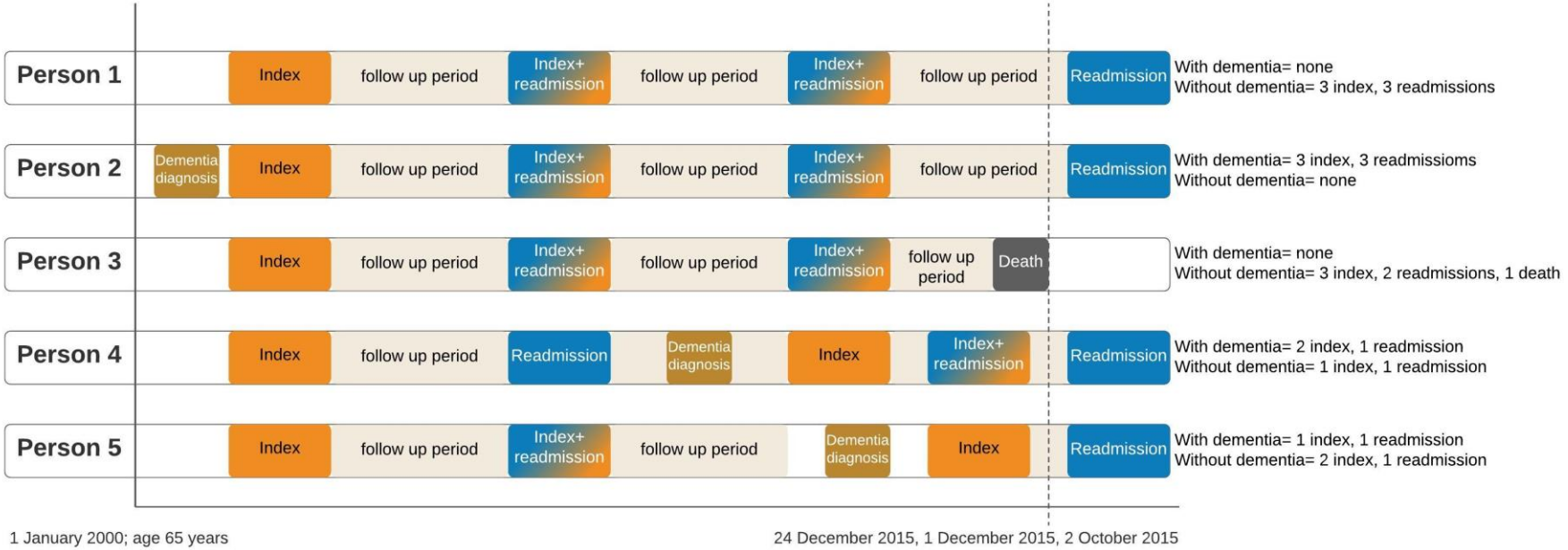


Figure present the process of how admissions were coded how outcomes were counted, in 5 different scenarios represented by 5 persons. The study unit was admissions and not persons. The follow up period represents 7, 30, or 90 days. Index are admissions that were counted as infection index admissions, and index+ readmission are admissions that were counted as both an infection index admission and an all-cause readmission in our analyses. The dotted vertical line is the end of study period for each of the follow up periods (24 December 2015 for 7-day readmissions; 1 December 2015 for 30-day readmissions; and 1 October 2015 for 90-day readmissions), that were chosen to ensure that all index admissions counted in our study had the complete follow up period (at risk for readmissions or deaths). If a date of a dementia diagnosis was recorded prior to the start of study, then the person's first infection index admission is categorized as with existing dementia (with dementia) regardless of which date before start of study it was recorded on. The method is described in the article text, in the Methods section.

Table S.3 Baseline characteristics of the study sample of index admissions eligible for 30- and 90-day readmissions.

		Eligible for 30-day readmissions				Eligible for 90-day readmissions			
Characteristic	**Level**	**With dementia**		**Without dementia**		**With dementia**		**Without dementia**	
Total, N (%)*	Index admissions	71,673	(9.2)	711,446	(90.9)	70,682	(9.2)	698,360	(90.8)
	People	34,922	(8.3)	383,585	(91.7)	35,380	(8.6)	377,443	(91.4)
Sex, Women N (%)	Index admissions	39,705	(55.4)	360,941	(50.7)	39,171	(55.4)	354,324	(50.7)
	People	20,298	(58.1)	198,097	(51.6)	20,519	(58.0)	194,902	(51.6)
Age, years N (%)	65-74	8703	(12.1)	273,242	(38.4)	8568	(12.1)	269,053	(38.5)
	75-84	32,780	(45.7)	285,258	(40.1)	32,357	(45.8)	279,914	(40.1)
	85-++	30,190	(42.1)	152,946	(21.5)	29,757	(42.1)	149,393	(21.4)
Calendar year, N (%)	2000-2004	13,938	(19.5)	176,099	(24.8)	13,938	(19.7)	175,293	(25.1)
	2005-2009	22,085	(30.8)	206,610	(29.0)	22,085	(31.3)	205,536	(29.4)
	2010-2015	35,650	(49.7)	328,737	(46.2)	34,659	(49.0)	317,531	(45.5)
Civil status, N (%)	Married	25,537	(35.6)	319,880	(45.0)	25,179	(35.6)	314,126	(45.0)
	Unmarried	4196	(11.7)	40,128	(5.6)	4138	(5.9)	39,305	(5.6)
	Widowed	33,534	(5.9)	258,457	(36.3)	33,099	(46.8)	253,871	(36.4)
	Divorced	8374	(46.8)	92,314	(13.0)	8234	(11.7)	90,405	(13.0)
	Unknown	32	(0.04)	667	(0.1)	32	(0.1)	653	(0.1)
Education, N (%)	Low	46,166	(64.4)	520,341	(73.1)	45,357	(64.2)	510,288	(73.1)
	Medium	4630	(6.5)	54,364	(7.6)	4543	(6.4)	53,122	(7.6)
	High	1779	(2.5)	16,630	(2.3)	1750	(2.5)	16,226	(2.3)
	unknown	19,098	(26.7)	120,111	(16.9)	19,032	(26.9)	118,724	(17.0)
LOS, days, Mean (SD)		7.0	(11.3)	6.8	(10.4)	7.0	(11.4)	6.9	(10.4)
CCI, N (%)	0	14,405	(20.1)	112,559	(15.8)	14,229	(20.1)	110,519	(15.8)
	1	15,891	(22.2)	148,278	(20.8)	15,696	(22.2)	145,971	(20.9)
	2	13,720	(19.1)	141,922	(19.9)	13,539	(19.2)	139,351	(20.0)
	3	9853	(13.7)	101,189	(14.2)	9702	(13.7)	99,355	(14.2)
	4+	17,804	(24.8)	207,498	(29.2)	17,516	(24.8)	203,164	(29.1)

Table presents baseline socio-demographic characteristics of infection index admissions of people with dementia (with dementia), and of people without dementia (without dementia). Infection index admissions are those eligible for 30- and 90-day readmissions. *percentage of all infection index admissions, and all people. Education: Highest educational level attained was defined as low (primary school), medium (upper secondary, business high school, vocational internship and main course), and high (short-term further education, middle-range education, bachelor's degree, extended education and research degree).

Table S.4 Summary of all outcomes in the exposure groups and in all three follow up periods

Outcome	Follow-up period		
	7 days (total index admissions= 789,732)	**30 days (total index admissions= 783,119)**	**90 days (total index admissions= 769,042)**
Total readmissions	55,303	161,550	259,745
With dementia (%)	5291 (10)	13,553 (8)	21,555 (8)
Without dementia (%)	50,012 (90)	147,997 (92)	238,190 (92)
Total deaths	78,732	97,027	108,328
With dementia (%)	10,940 (14)	15,205 (16)	17,647 (16)
Without dementia (%)	67,792 (86)	81,822 (84)	90,681 (84)

Table presents outcomes of all-cause readmission and all-cause mortality in the exposure groups: With dementia= Infection index admissions of people with dementia; and Without dementia= Infection index admissions of people without dementia.

Table S.5 Table with interactions

Outcome, interaction term	Follow-up period		
	7 days	**30 days**	**90 days**
Readmission			
Dementia*sex	0.0436	0.0558	0.9955
Dementia*age	<.0001	<.0001	<.0001
Mortality			
Dementia*sex	<.0001	0.0116	0.0897
Dementia*age	<.0001	<.0001	<.0001

Table S.6 Women, complete analysis model for readmission risk ratios

Age (years)	With dementia N readmissions	%	Without dementia N readmissions	%	RR 1 (95% CI)	p	RR 2 (95% CI)	p	RR 3 (95% CI)	p
All-cause 7-day readmission										
All women	2834	7	23,723	7	1.14 (1.09- 1.18)	<.0001	1.14 (1.09- 1.18)	<.0001	1.15 (1.11- 1.20)	<.0001
65-74	349	9	8844	7	1.37 (1.22- 1.53)	<.0001	1.37 (1.22- 1.53)	<.0001	1.37 (1.22- 1.53)	<.0001
75-84	1236	7	9580	7	1.11 (1.05- 1.18)	0.0006	1.11 (1.05- 1.18)	0.0004	1.13 (1.07- 1.20)	<.0001
85+	1249	6	5299	6	1.10 (1.03- 1.17)	0.0025	1.10 (1.03- 1.17)	0.0027	1.11 (1.05- 1.18)	0.0006
All-cause 30-day readmission										
All women	7249		70,868		1.01 (0.98- 1.03)	0.709	1.00 (0.98- 1.03)	0.7253	1.02 (0.99-1.04)	0.1875
65-74	886	24	27,319	21	1.15 (1.06- 1.25)	0.0011	1.15 (1.06- 1.25)	0.0013	1.14 (1.05- 1.24)	0.0012
75-84	3234	19	28,819	20	0.98 (0.95- 1.02)	0.3297	0.98 (0.95- 1.02)	0.4022	1.00 (0.96- 1.04)	0.9503
85+	3129	16	14,730	16	0.99 (0.95- 1.03)	0.517	0.99 (0.95- 1.03)	0.581	1.00 (0.97- 1.04)	0.8824
All-cause 90-day readmission										
All women	11,459		115,519		0.97 (0.95- 0.99)	0.0021	0.97 (0.95- 0.99)	0.0015	0.98 (0.96- 1.00)	0.0148
65-74	1354	37	43,761	35	1.10 (1.01- 1.19)	0.0224	1.10 (1.02- 1.18)	0.018	1.10 (1.03- 1.18)	0.0063
75-84	5143	31	47,159	34	0.96 (0.93- 0.99)	0.0052	0.96 (0.93- 0.99)	0.0074	0.97 (0.95- 1.00)	0.0619
85+	4962	26	24,599	28	0.93 (0.91- 0.96)	<.0001	0.93 (0.91- 0.96)	<.0001	0.95 (0.92- 0.97)	0.0001

CI= Confidence Interval; N= Number; p= p-value; With dementia= Infection index admissions of people with dementia; Without dementia= Infection index admissions of people without dementia; RR= All-cause readmission Risk Ratio (risk for infection index admissions of people with dementia relative to risk for infection index admissions of people without dementia).

Table S.7 Women, complete analysis model for mortality risk ratios

Age (years)	With dementia N deaths	%	Without dementia N deaths	%	RR 1 (95% CI)	p	RR 2 (95% CI)	p	RR 3 (95% CI)	p
All-cause 7-day mortality										
All women	5508		32,625		1.26 (1.23- 1.29)	<.0001	1.27 (1.23- 1.30)	<.0001	1.30 (1.26- 1.33)	<.0001
65-74	381	10	7339	6	1.66 (1.50- 1.83)	<.0001	1.65 (1.49- 1.82)	<.0001	1.66 (1.50- 1.83)	<.0001
75-84	2102	12	12,784	9	1.36 (1.30- 1.42)	<.0001	1.37 (1.31- 1.43)	<.0001	1.41 (1.35- 1.47)	<.0001
85+	3025	16	12,502	14	1.15 (1.11- 1.19)	<.0001	1.15 (1.11- 1.20)	<.0001	1.18 (1.13- 1.22)	<.0001
All-cause 30-day mortality										
All women	7898		39,757		1.44 (1.41- 1.47)	<.0001	1.45 (1.42- 1.49)	<.0001	1.49 (1.45- 1.52)	<.0001
65-74	495	13	8566	7	1.84 (1.69- 2.01)	<.0001	1.83 (1.68- 1.99)	<.0001	1.84 (1.68- 2.01)	<.0001
75-84	2970	18	15,297	11	1.59 (1.53- 1.65)	<.0001	1.60 (1.55- 1.66)	<.0001	1.64 (1.59- 1.70)	<.0001
85+	4433	23	15,894	18	1.32 (1.28- 1.35)	<.0001	1.32 (1.29- 1.36)	<.0001	1.35 (1.31-1.39)	<.0001
All-cause 90-day mortality										
All women	9336		44,522		1.50 (1.47- 1.53)	<.0001	1.51 (1.48- 1.54)	<.0001	1.54 (1.51- 1.57)	<.0001
65-74	564	15	9429	7	1.90 (1.75- 2.06)	<.0001	1.89 (1.74- 2.05)	<.0001	1.90 (1.75- 2.06)	<.0001
75-84	3480	21	16,970	12	1.67 (1.61- 1.72)	<.0001	1.68 (1.62- 1.74)	<.0001	1.72 (1.66- 1.78)	<.0001
85+	5292	28	18,123	21	1.36 (1.33- 1.40)	<.0001	1.37 (1.34- 1.41)	<.0001	1.39 (1.36- 1.43)	<.0001

CI= Confidence Interval; N= Number; p= p-value; With dementia= Infection index admissions of people with dementia; Without dementia= Infection index admissions of people without dementia; RR= Mortality Risk Ratio (risk for infection index admissions of people with dementia relative to risk for infection index admissions of people without dementia).

Table S.8 Men, complete analysis model for readmission risk ratios

Age (years)	With dementia N readmissions	%	Without dementia N readmissions	%	RR 1 (95% CI)	p	RR 2 (95% CI)	p	RR 3 (95% CI)	p
All-cause 7-day readmission										
All men	2457		26,289		1.06 (1.01- 1.10)	0.0122	1.06 (1.01- 1.10)	0,0113	1.08 (1.04- 1.13)	0.0002
65-74	451	9	11,233	8	1.22 (1.11- 1.34)	<.0001	1.21 (1.10- 1.33)	<.0001	1.23 (1.12- 1.35)	<.0001
75-84	1230	8	10,709	7	1.02 (0.96- 1.08)	0.5454	1.02 (0.96- 1.08)	0.4772	1.05 (0.99- 1.11)	0.1041
85+	776	7	4347	7	1.01 (0.94- 1.09)	0.7427	1.02 (0.94- 1.10)	0.6681	1.04 (0.96- 1.12)	0.3381
All-cause 30-day readmission										
All men	6304		77,129		0.94 (0.91- 0.97)	<.0001	0.94 (0.91- 0.97)	<.0001	0.96 (0.93- 0.98)	0.0018
65-74	1159	23	32,939	23	1.05 (0.98- 1.12)	0.1503	1.04 (0.98- 1.11)	0.1975	1.06 (0.99- 1.12)	0.0949
75-84	3265	20	31,904	22	0.92 (0.89- 0.96)	<.0001	0.93 (0.89- 0.96)	<.0001	0.95 (0.92- 0.98)	0.0054
85+	1880	17	12,286	20	0.87 (0.83- 0.92)	<.0001	0.87 (0.83- 0.92)	<.0001	0.89 (0.85- 0.93)	<.0001
All-cause 90-day readmission										
All men	10,096		122,671		0.94 (0.92- 0.96)	<.0001	0.94 (0.92- 0.96)	<.0001	0.95 (0.93- 0.97)	<.0001
65-74	1774	36	51,770	36	1.02 (0.96- 1.08)	0.4823	1.02 (0.96- 1.08)	0.5551	1.03 (0.97- 1.08)	0.3486
75-84	5241	33	51,049	37	0.92 (0.90- 0.95)	<.0001	0.93 (0.90- 0.95)	<.0001	0.94 (0.92- 0.97)	<.0001
85+	3081	28	19,852	32	0.88 (0.85- 0.92)	<.0001	0.89 (0.85- 0.92)	<.0001	0.90 (0.86- 0.93)	<.0001

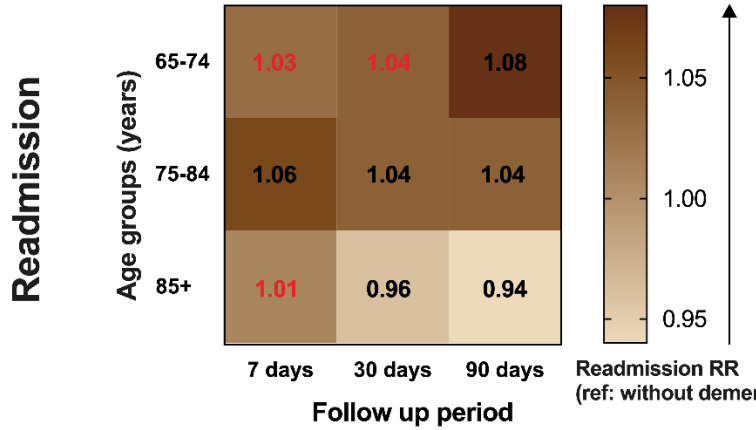
CI= Confidence Interval; N= Number; p= p-value; With dementia= Infection index admissions of people with dementia; Without dementia= Infection index admissions of people without dementia; RR= All-cause readmission Risk Ratio (risk for infection index admissions of people with dementia relative to risk for infection index admissions of people without dementia).

Table S.9 Men, complete analysis model for mortality risk ratios

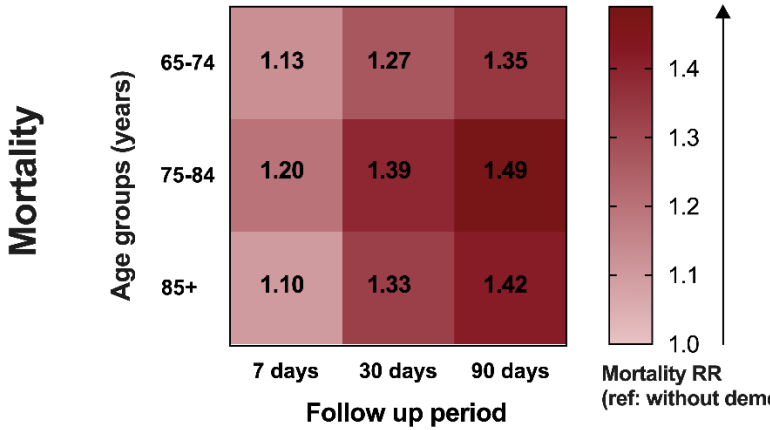
Age (years)	With dementia N deaths	%	Without dementia N deaths	%	RR 1 (95% CI)	p	RR 2 (95% CI)	p	RR 3 (95% CI)	p
All-cause 7-day mortality										
All men	5432		35,167		1.42 (1.38- 1.45)	<.0001	1.42 (1.38- 1.46)	<.0001	1.47 (1.43- 1.51)	<.0001
65-74	636	13	9920	7	1.77 (1.64- 1.91)	<.0001	1.73 (1.60- 1.86)	<.0001	1.77 (1.64- 1.91)	<.0001
75-84	2547	16	14,883	10	1.49 (1.43- 1.55)	<.0001	1.49 (1.44- 1.55)	<.0001	1.55 (1.49- 1.61)	<.0001
85+	2249	20	10,364	16	1.26 (1.21- 1.31)	<.0001	1.27 (1.22- 1.32)	<.0001	1.29 (1.24- 1.35)	<.0001
All-cause 30-day mortality										
All men	7307		42,065		1.57 (1.53- 1.60)	<.0001	1.57 (1.54- 1.61)	<.0001	1.62 (1.58- 1.66)	<.0001
65-74	810	16	11,617	8	1.91 (1.79- 2.04)	<.0001	1.87 (1.75- 2.00)	<.0001	1.92 (1.79- 2.06)	<.0001
75-84	3425	21	17,631	12	1.67 (1.62- 1.73)	<.0001	1.68 (1.63- 1.74)	<.0001	1.74 (1.68- 1.80)	<.0001
85+	3072	28	12,817	20	1.38 (1.34- 1.43)	<.0001	1.40 (1.35- 1.45)	<.0001	1.42 (1.38- 1.47)	<.0001
All-cause 90-day mortality										
All men	8311		46,159		1.60 (1.57- 1.64)	<.0001	1.61 (1.58- 1.65)	<.0001	1.66 (1.62- 1.69)	<.0001
65-74	912	19	12,641	9	1.98 (1.86- 2.11)	<.0001	1.93 (1.82- 2.06)	<.0001	1.99 (1.86- 2.12)	<.0001
75-84	3879	25	19,254	14	1.72 (1.67- 1.78)	<.0001	1.73 (1.68- 1.78)	<.0001	1.79 (1.73- 1.85)	<.0001
85+	3520	32	14,264	23	1.41 (1.37- 1.46)	<.0001	1.43 (1.38- 1.47)	<.0001	1.45 (1.41- 1.50)	<.0001

CI= Confidence Interval; N= Number; p= p-value; With dementia= Infection index admissions of people with dementia; Without dementia= Infection index admissions of people without dementia; RR=Mortality Risk Ratio (risk for infection index admissions of people with dementia relative to risk for infection index admissions of people without dementia).

Figure S.2 Women, readmission and mortality RR following index admissions for other causes than infection



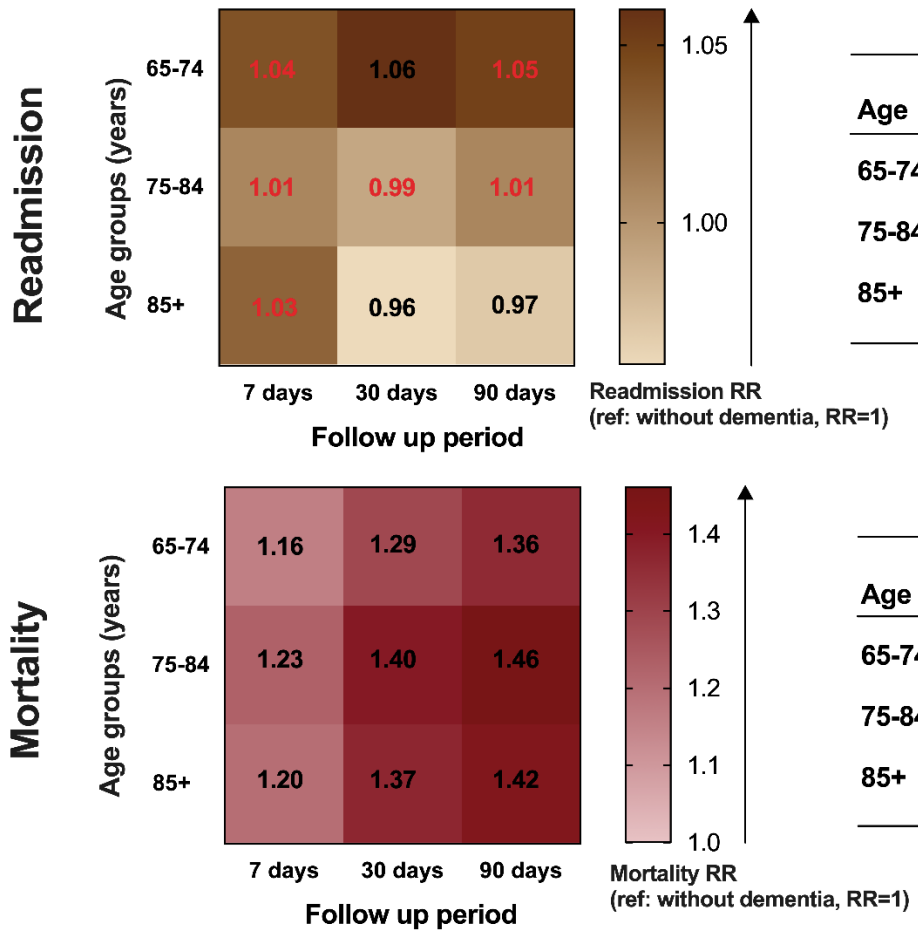
Age	Readmission RR (95% CI) 7 days	30 days	90 days
65-74	1.03 (0.95-1.11)	1.04 (0.98-1.10)	1.08 (1.02-1.14)
75-84	1.06 (1.02-1.09)	1.04 (1.02-1.06)	1.04 (1.03-1.06)
85+	1.01 (0.97-1.04)	0.96 (0.94-0.98)	0.94 (0.92-0.96)



Age	Mortality RR (95% CI) 7 days	30 days	90 days
65-74	1.13 (1.05-1.21)	1.27 (1.19-1.34)	1.35 (1.28-1.43)
75-84	1.20 (1.16-1.23)	1.39 (1.36-1.42)	1.49 (1.46-1.53)
85+	1.10 (1.07-1.13)	1.33 (1.31-1.35)	1.42 (1.40-1.44)

Figure presents the fully adjusted readmission (top heat map) and mortality (bottom heat map) RRs for women in all follow up periods (horizontal x-axes) and across the age groups (vertical y-axes), following index admissions with other causes than infections. RRs are the ratios of risk in index admissions of people with dementia/risk in index admissions of people without dementia. The fully adjusted model was for age, sex, calendar year, civil status, highest attained educational level, length of stay and CCI. Each cell in the two heat maps represents RR estimates and colors increase in intensity with increasing RR. Numbers inside each cell are the RRs as presented in the adjacent tables to each of the heat maps where 95% confidence intervals are also presented. Numbers in cells that are in red represent those with insignificant RRs. Index admissions that were eligible for more than one of the follow-up periods were represented in multiple periods in our analyses. Abbreviations: RR=Risk Ratio; CI= confidence interval.

Figure S.3 Men, readmission and mortality RR following index admissions for other causes than infection



Age	Readmission RR (95% CI) 7 days	30 days	90 days
65-74	1.04 (0.98-1.11)	1.06 (1.01-1.11)	1.05 (1.00-1.10)
75-84	1.01 (0.97-1.04)	0.99 (0.96-1.01)	1.01 (1.00-1.03)
85+	1.03 (0.99-1.08)	0.96 (0.93-0.99)	0.97 (0.95-0.99)

Age	Mortality RR (95% CI) 7 days	30 days	90 days
65-74	1.16 (1.10-1.23)	1.29 (1.23-1.35)	1.36 (1.30-1.42)
75-84	1.23 (1.20-1.27)	1.40 (1.37-1.43)	1.46 (1.43-1.50)
85+	1.20 (1.16-1.24)	1.37 (1.33-1.40)	1.42 (1.39-1.45)

Figure presents the fully adjusted readmission (top heat map) and mortality (bottom heat map) RRs for men in all follow up periods (horizontal x-axes) and across the age groups (vertical y-axes), following index admissions with other causes than infections. RRs are the ratios of risk in index admissions of people with dementia/risk in index admissions of people without dementia. The fully adjusted model was for age, sex, calendar year, civil status, highest attained educational level, length of stay and CCI. Each cell in the two heat maps represents RR estimates and colors increase in intensity with increasing RR. Numbers inside each cell are the RRs as presented in the adjacent tables to each of the heat maps where 95% confidence intervals are also presented. Numbers in cells that are in red represent those with insignificant RRs. Index admissions that were eligible for more than one of the follow-up periods were represented in multiple periods in our analyses. Abbreviations: RR=Risk Ratio; CI= confidence interval.

Online Resource references

1. Janbek J, Taudorf L, Musaeus CS, Frimodt-Møller N, Laursen TM, Waldemar G. Increased short- and long-term mortality following infections in dementia: a nationwide registry-based cohort study. Eur J Neurol [Internet]. 2020 Nov 9;ene.14595. Available from: https://onlinelibrary.wiley.com/doi/10.1111/ene.14595

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