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Dementia and Influenza Vaccination

A nationwide registry-based study

PhD thesis - Andreas Moses Appel

DANISH DEMENTIA RESEARCH CENTRE

REGION H Rigshospitalet

This thesis was submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen on September 30, 2024

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Preface and acknowledgments

This PhD project was carried out at the Danish Dementia Research Centre (DDRC), Department of Neurology, Copenhagen University Hospital - Rigshospitalet from 2021 to 2024. The Danish Dementia Research Centre is financially supported by the Danish Ministry of Health. This specific project was supported by the Danish Alzheimer Research Foundation.

The project began in October 2020 when I started as a research assistant at DDRC, where I was fortunate to have time to define and develop a scientific foundation for a PhD project. The project was developed in collaboration with a research group at DDRC that investigates links between dementia, medicine use, morbidity, and mortality in the Danish national registries. I had previously conducted registry-based dementia research and was excited to continue this path at DDRC. Thank you, Kirsten Nabe-Nielsen, for setting me on this path.

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Studies

This thesis is based on three original studies:

Study I **Appel AM**, Janbek J, Laursen TM, Gasse C, Waldemar G, Jensen-Dahm C. Dementia and influenza vaccination: Time trends and predictors of vaccine uptake among older adults. *(Submitted)*

Study II **Appel AM**, Janbek J, Jensen-Dahm C, Laursen TM, Waldemar G. The effect of influenza vaccination on hospitalization and mortality among people with dementia. *(Submitted)*

Study III **Appel AM**, Laursen TM, Jensen-Dahm C, Waldemar G, Janbek J. The effect of influenza vaccination on the rate of dementia among older adults. European Journal of Neurology *(In press)*

Abbreviations

AD	Alzheimer's Disease
ATC	Anatomical Therapeutic Chemical
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CRS	Civil Registration System
DNPR	Danish National Prescription Registry
GISRS	Global Influenza Surveillance and Response System
HR	Hazard Ratio
ICD-8	International Classification of Disease 8th revision
ICD-10	International Classification of Disease 10th revision
IRR	Incidence Rate Ratio
LTCF	Long-term Care Facility
NHSR	National Health Service Registry
NPR	National Patient Register
OR	Odds ratio
PCRR	Psychiatric Central Research Register
PPV	Positive Predictive Value
PY	Person-year
RR	Risk Ratio
VE	Vaccine Effectiveness
WHO	World Health Organization

Abstract

As people age, their risk of both dementia and severe infection increases. People with dementia are particularly vulnerable to infections and infection-related adverse outcomes. Therefore, preventive measures such as vaccination may be particularly important for people with dementia. Despite this, common dementia symptoms may act as barriers to vaccination and potentially create harmful healthcare gaps. Influenza vaccination is the most common form of immunization among older adults, preventing infections, infection-related hospital admissions, and deaths. However, knowledge of the coverage and effectiveness of influenza vaccines specifically for people with dementia is sparse. Furthermore, influenza vaccination has been suggested as a potential preventive measure for dementia, however, this topic is understudied with conflicting findings.

In this thesis, I will present three studies investigating links between influenza vaccination and dementia. The source population for all three studies was the entire population of older adults in Denmark aged 65 and above, identified and followed for several years in the Danish national registries with information on influenza vaccinations, dementia diagnosis, and relevant sociodemographic and health-related information.

Dementia among home-living older adults was associated with a considerably lower likelihood of receiving an influenza vaccine. Nursing home residents had a higher vaccination likelihood regardless of whether they had dementia. From the introduction of nationwide free influenza vaccines for older adults in Denmark in 2002 until 2019, the vaccine coverage for people with and without dementia was considerably lower than the World Health Organizations goal of 75%. Among people with dementia, vaccination was associated with reduced rates of hospitalizations and death, by a magnitude similar to the effect among people without dementia. Contrary to what has been reported in most other studies, in this project influenza vaccination was associated with a slightly increased risk of dementia. Additional analyses questioned the causality of this finding.

This project contributes valuable evidence of potential issues with access to vital health services for people with dementia, even in a setting of tax-supported healthcare with universal coverage. It also adds to the discussion of the potential for repurposing common vaccines as preventive measures for dementia. Further research is needed to accommodate issues of residual confounding due to health differences between vaccinated and unvaccinated people.

Resume (Danish)

I takt med at mennesket ældes, øges risikoen for både demens og alvorlige infektioner. Personer med demens er særligt sårbare over for infektioner og infektionsrelaterede sundhedsfølger. Derfor kan forebyggende tiltag som vaccination være særligt vigtige for personer med demens. Demenssymptomer kan dog samtidig fungere som barrierer for vaccination og føre til unødige risici for alvorlig sygdom. Influenzavaccination er den mest almindelige form for immunisering blandt ældre og forebygger infektioner såvel som infektionsrelaterede hospitalsindlæggelser og dødsfald. Der mangler dog viden om tilslutning til og virkning af influenzavacciner blandt personer med demens. Studier har desuden indikeret, at influenzavaccination muligvis kan nedsætte risikoen for demens. Her er evidensen ligeledes mangelfuld og resultaterne modstridende.

I denne afhandling vil jeg præsentere tre studier, der undersøger sammenhænge mellem influenzavaccination og demens. Kildepopulationen for alle tre studier var hele den ældre befolkning i Danmark på 65 år og derover, identificeret og fulgt i en længere årrække i de danske nationale registre med information om influenzavaccinationer, demensdiagnose og relevante sociodemografiske og sundhedsrelaterede data.

Demens blandt hjemmeboende ældre var forbundet med en markant lavere sandsynlighed for at blive vaccineret mod influenza. Beboere på plejehjem havde en højere sandsynlighed for vaccination, uagtet om de havde demens eller ej. Fra introduktionen af landsdækkende gratis influenzavacciner til alle ældre i Danmark i 2002 og frem til 2019 var vaccinedækningen for personer med og uden demens betydeligt lavere end Verdenssundhedsorganisationens mål på 75%. Blandt personer med demens var vaccination forbundet med et reduceret antal indlæggelser og dødsfald i en størrelsesorden svarende til effekten blandt mennesker uden demens. I modsætning til fund i andre studier, var influenzavaccination i dette projekt forbundet med en let øget risiko for demens. Yderligere analyser satte spørgsmålstegn ved kausaliteten af dette fund.

Dette projekt bidrager med værdifuld viden om potentielle problemer med adgang til vitale sundhedsydelser for personer med demens, selv i et sundhedssystem med tilsyneladende universel dækning. Projektet bidrager også til diskussionen om potentialet for almindelige vacciner som forebyggende middel mod demens. Yderligere forskning er nødvendig for at imødekomme spørgsmål om sundhedsforskelle mellem vaccinerede og ikke-vaccinerede personer.

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BACKGROUND

Dementia

Dementia is an age-related disorder that impairs cognition and the daily life abilities of those affected.[1] It is a highly debilitating disorder, often with far-reaching consequences for the affected individual, next of kin, and society at large.[2,3] The prevalence of dementia is increasing globally along with average lifespans,[4,5] posing a major public health challenge.[1,3] Around 50 million people were estimated to have dementia in 2015 and this number is projected to be over 150 million by 2050.[6,7]

Dementia is a set of symptoms, or syndrome, rather than a single disease, with many causes and subtypes.[2] Specific symptoms often vary across subtypes, causes, and stages of dementia, but some of the most common signs are memory problems, lack of concentration, impaired executive function, and emotional disturbances.[2,8] Common to all forms of dementia is a decline in cognitive function that decreases the ability to perform activities of daily living,[2] such as self-care management, remembering appointments, and managing personal finances. The most common subtypes of dementia are Alzheimer's Disease (AD), vascular dementia, dementia with Lewy bodies, and frontotemporal dementia.[2] These subtypes are delineated by the presence of specific pathologies in the brain. However, they are not mutually exclusive, meaning that pathologies can often coexist, even when a single diagnosis has been given.[2,6]

Diagnosis can be guided by both neuropathology and clinical observation. In most countries, the clinical diagnosis of dementia is standardized by the Diagnostic and Statistical Manual for Mental Disorders (DSM) developed by the American Psychiatric Association,[9] or the International Classification of Diseases (ICD) created by the World Health Organization.[10] According to these guidelines, a diagnosis of dementia requires a notable functional decline in more than one cognitive domain, including memory, along with a decline in emotional control.

The current treatment for dementia widely available to patients is primarily symptomatic with moderate and short-term effects.[11] There have been recent breakthroughs in the development of drugs that slow the disease progression of AD, some of which are approved in the United States for the treatment of early AD,[12] however, no cure currently exists for dementia. Increased attention

is therefore needed on preventing new dementia cases and providing the necessary care for those who develop the disorder.[3]

Infections, influenza, and dementia

One challenge of aging populations is the increased risk of severe infections and adverse outcomes in older age.[13–18] Underlying mechanisms include a decline in immune system function,[13–15] sometimes called immunosenescence, more time spent in high-transmission environments such as healthcare facilities,[19] and showing atypical signs and symptoms of infection, complicating timely diagnosis.[18] The infection risk at higher ages is likely exacerbated by the presence of dementia owing to additional risk factors for severe infections associated with cognitive decline.[20,21] First, the ability to maintain personal care and hygiene can be affected.[22] Second, impairment of the ability to self-manage existing infections or related comorbidities.[23,24] Third, an impaired blood-brain barrier may increase the vulnerability to infection.[25,26] That people with dementia have a higher risk of severe infections is supported by research showing higher rates of mortality and hospitalizations following infections in this group.[27–29]

Influenza is one of the most prevalent causes of infections globally.[30] Symptoms are in general mild but can progress to severe illness, particularly among high-risk groups such as older adults.[31–33] For older people with dementia, the risk of severe infection following influenza is even higher.[34] A viral respiratory disease caused by the viruses influenza A, B, and C, it often spreads through coughing and sneezing, however, contact transmission can occur.[35,36] Influenza is predominantly active during the colder months of the year in temperate regions,[37] but occasionally develops into local outbreaks and, in rare cases, global pandemics.[35] WHO estimates that 3-5 million cases of severe illness and 290,000-650,000 respiratory deaths can be attributed to seasonal influenza every year.[37] Most of these cases are older adults aged ≥65 years.[31,33] Influenza not only causes respiratory issues but can have many other adverse consequences including cardiovascular disease, functional decline, increased vulnerability to other infections, and exacerbation of comorbidities.[38] The burden of influenza-related disease is thus considerable, as are the economic consequences of the disease. Considering both the direct medically related costs and indirect costs related to productivity losses, the total economic burden of seasonal influenza was estimated at 87.1 billion dollars in 2003 in the United States alone.[39] Accounting for increasing prices and longer lifespans, this number is likely considerably higher in 2024.

Infections, including those caused by influenza, may not only be relevant as important comorbidities of dementia. They have also gained attention as potentially increasing the risk of cognitive impairment and dementia, particularly AD.[40–56] Some researchers have suggested that the relationship between cognition and the immune system is bi-directional with infection increasing the risk or progression of cognitive impairment, and cognitive decline in turn increasing the risk of severe infections.[57] The recent interest in the "infection hypothesis" began with a focus on the herpes simplex virus, however, other causes of infections, both viral, bacterial, and fungal, have been linked to a higher dementia risk.[40–46,48–51,53] While influenza has not been given the same attention as some other pathological agents, a few studies did find associations between influenza and neurodegenerative diseases, including AD.[53,58]

Influenza vaccination

The burden of influenza among older adults with dementia highlights the importance of preventive measures. The most effective prevention against severe influenza infection is immunization.

The influenza vaccine is one of the most common vaccines among older people. Development of an influenza vaccine began in the 1930s and was first licensed in 1945 in the United States.[59] Investigators soon realized that changes in the surface proteins, called antigenic drift, from mutations in the viral RNA, decreased the effectiveness of vaccines over time, even from one influenza season to the next.[59,60] To maintain high protection, WHO therefore established the Global Influenza Surveillance and Response System (GISRS) to monitor and flag active virus strains for vaccine production.[61] With the progression of technology and production methods, influenza vaccines now fall into two main classes. First, inactivated vaccines contain killed whole-virus particles or isolated surface proteins called antigens. Second, live-attenuated vaccines are composed of still-active but weakened virus particles, posing little risk of severe infection.[59] The effectiveness of vaccines can vary considerably based on strain match, active vs. inactive virus, and the presence and type of adjuvants which are auxiliary substances designed to boost the immune response.

Today, annual influenza vaccination is recommended for high-risk groups.[62] The high risk of severe infection among older adults prompted WHO to set a goal of 75% coverage for influenza vaccines in this particular risk group.[63] In countries with free-of-charge immunization programs

such as Denmark, the high-risk group of older adults has been defined as those aged ≥65.[64] Many chronic disorders are also highlighted in vaccination programs. However, dementia is not among these disorders even though immunization against influenza may be particularly relevant for people with dementia due to the increased risk of severe illness compared to cognitively intact older adults[34].

Despite the higher infection risk, dementia may decrease the likelihood of being vaccinated against influenza. Previous research has shown conflicting results regarding the impact of dementia on vaccination likelihood.[65–71] These studies were limited by uncertain exposure to vaccines due to self-reported vaccination history, the omission of potentially important confounders, or small or selected study populations. A large study in the United Kingdom did report a lower likelihood of vaccination among people with dementia, but only when they lived at home, not in a long-term care facility (LTCF) such as a nursing home.[69] This finding is consistent with impaired self-care management in dementia.[24] Studies mitigating the limitations of previous studies are needed to elucidate whether home-living people with dementia have a decreased likelihood of being immunized against influenza. Identifying such a healthcare gap could be valuable knowledge to prevent unnecessary infection-related adverse outcomes.

Even when people with dementia are vaccinated, the effectiveness of how well it prevents adverse outcomes could be different compared to those without cognitive problems. The higher infection risk may translate to a greater effect of the vaccine, emphasizing even further the necessity of focusing on dementia as a relevant chronic disorder in influenza vaccination programs. However, a smaller vaccine effectiveness (VE) is also possible due to a reduced immune response after vaccination.[72] VE literature has generally reported high vaccine effectiveness among other high-risk groups and older adults in general, but no study has focused on people with dementia.[73–79] Research in this area is important for elucidating the preventive potential of immunizing older people with dementia.

Finally, the emergence of the “infection hypothesis” has increased the interest in vaccines as a potential tool for the prevention of dementia.[80] This is an appealing proposition, as many vaccines would offer an affordable and widely available measure to mitigate the continuously increasing burden of dementia. Besides decreasing the risk of severe infection, non-specific effects of vaccines have been suggested as mechanisms that could reduce dementia risk or slow

progression.[81,82] Many common vaccines have been studied, including influenza, herpes, diphtheria, and tetanus vaccine.[80,83–89] While most studies have found considerably lower dementia risk associated with influenza vaccination, the evidence is inconsistent, and conflicting results have been reported.[87,90–97] The studies were limited by uncertain vaccination and dementia status or by being based on selected subpopulations, questioning the validity and generalizability of the findings. The few studies within the area combined with the conflicting results call for further research on the preventive potential of influenza vaccines on the risk and progression of dementia.[98]

The Danish national registers provide an opportunity to study dementia and influenza vaccination in an entire population of older adults. Individual data on dementia diagnosis and administered influenza vaccines enables the estimation of links between dementia and influenza vaccination over several years. Extensive information on demographic and health-related factors allows for the control of potential confounders and examining subgroup differences. Utilizing this data source could help to elucidate possible gaps and untapped resources in the care and prevention of dementia.

AIMS

The overall aim of the project was to investigate links between dementia and influenza vaccination among older people in Denmark aged 65 years and above. The specific aims of the project were:

1. To investigate whether prevalent dementia may influence the likelihood of receiving an influenza vaccination. We hypothesized that dementia decreases the likelihood of immunization, particularly for those living at home.

1. To investigate whether influenza vaccination prevents hospitalization and mortality among older adults with dementia.

2. To investigate the impact of influenza vaccination on the risk of dementia. We hypothesized that vaccination may decrease the risk of dementia.

MATERIALS AND METHODS

All three studies in this thesis are entirely based on Danish national register data, and the process of identifying people with dementia, influenza vaccination, and the covariate status of the study population was identical or similar across the studies. Therefore, I will first describe the data on dementia, influenza vaccination, and the covariates used in all studies. I will then briefly describe the methods specific to each of the studies to provide a basis for understanding the findings and the discussion of these. Detailed descriptions of the methods used in each study can be found in the manuscripts and supplementary material of the corresponding study.

Setting and data sources

The Danish national registries contain individual-level information on all Danish citizens in various domains including health, education, marital status, and addresses. The main datasets used in this thesis are the Civil Registration System (CRS),[99] the Danish National Patient Registry (NPR),[100] the Psychiatric Central Research Registry (PCRR),[101] the Danish National Prescription Registry (DNPR),[102] and the Danish National Health Service Register (NHSR).[103]

The central dataset in the Danish registry structure is the CRS. Established in 1968 and continuously updated since then, it contains the civil registration numbers (PNR) for every Danish citizen. As the PNR is available in all other individual-level national registries in Denmark, this unique personal identifier allows for the linkage of information across all registries. Apart from the PNR itself, the registry contains demographic information on each citizen including date of birth, sex, marital status, and migration in and out of Denmark.

Health-related data in this thesis was derived from the NPR, the PCRR, the DPNR, and the NHSR. The NPR contains information on all inpatient admissions to somatic wards in Denmark since 1977, and all outpatient and emergency contacts since 1995.[100] The PCRR contains information on all inpatient admissions to psychiatric wards in Denmark since 1969 and all outpatient and emergency contacts since 1995.[101] In the NPR and PCRR, all diagnoses are recorded upon discharge from the clinic using the International Classification of Disease (ICD) developed by the World Health Organization (WHO). In both registers, version 8 (ICD-8) was used until 1994 when the current version 10 (ICD-10) was introduced. The DNPR contains information on all drug prescriptions redeemed at Danish pharmacies since 1995.[102] The drugs are registered with a code

according to the WHO Anatomical Therapeutical Chemical (ATC) Classification System along with other information including the date of sale. The NHSR contains information on all services provided in primary care, including by general practitioners (GP), since 1990. For any free service provided, the GP must apply for reimbursement from the government, and all reimbursed services are then recorded in the NHSR.[103] The NHSR is therefore considered highly valid and complete regarding which services are performed in primary care. Each service is recorded with a unique number, identifying the specific service and the medical specialty in which it was performed. Instead of the exact date a service was provided, the week that the GP applied for reimbursement (i.e., week of billing) is recorded.

Identifying people with dementia

In all three studies, dementia was defined as a recorded diagnosis of dementia in the NPR or PCRR (ICD-8 or 10 code), or a redeemed prescription for anti-dementia medication (ATC code) in the DNPR (Table 1). We excluded people registered with dementia before the age of 65 years based on research reporting an overdiagnosis of dementia at younger ages.[104] The date of dementia was defined as the first registered diagnosis or redemption of prescribed anti-dementia medication.

Table 1: Dementia diagnoses in the International Classification of Disease (ICD) codes and anti-dementia medication in the Anatomical Therapeutic Chemical Classification (ATC) codes

Dementia type	**ICD-8 code**	**ICD-10 code**
Alzheimer's Disease	290.10	F00.0-00.9, G30.0-G30.9
Vascular dementia	293.09-19	F01.0-01.9
Frontotemporal dementia	290.11	F02.0, G31.0A, G31.0B
Dementia without specification	290.09-19	F03.9, G31.9
Other dementias	-	G31.8, G31.8E, F02.1-F02.8
Medication	**ATC code**	
Cholinesterase inhibitors		
Donepezil	N06DA02, N06DA52, N06DA53	
Rivastigmine	N06DA03	
Galantamine	N06DA04	
Glutamate-receptor antagonists		
Memantine	N06DX01, N06DA52, N06DA53	

Identifying people receiving an influenza vaccine

In all three studies, influenza vaccinations were defined as recorded vaccination in the NHSR or the DNPR. The vast majority of influenza vaccinations were identified through the NHSR. During the study periods of all three studies in this thesis, all free-of-charge influenza vaccinations to high-

risk groups in the national vaccine program, including people aged 65 years and above, were administered by their GP.

As mentioned above, the NHSR contains the week of billing rather than the date of administration. The service is likely provided shortly before the week of billing, and we therefore considered the first day of that week an appropriate approximation for the date of vaccination. We also included data on redeemed prescriptions of vaccinations from the DNPR, as these will likely reflect a free vaccination at the GP, even though it is not recorded in the NHSR.

The definition of being vaccinated or unvaccinated varied across the studies, guided by the various study aims. See the section on study-specific methods or the manuscripts for details of these definitions.

Covariates

Covariates were chosen based on their potential for being confounders in each study. Most covariates were similar across studies, however, the definition and selection of some covariates varied slightly. All covariates were identified through the Danish national registers, and in all studies included age, sex, educational attainment, and comorbidities. In study I, additional covariates were nursing home residency, marital status, urbanization of residence, and health resource use, defined as the number of general practitioner visits and the number of different medications used in the past 12 months. In study II, the number of general practitioner visits and an influenza or pneumonia hospitalization in the past 12 months was included. In study III nursing home residency was included in a sensitivity analyses. In the survival models of studies II and III, the calendar year was included as a covariate.

Information on age, calendar year, sex, and marital status were derived from the Danish Civil Registration System.[99] Data on completed education was drawn from the Danish education register.[105] In study I, age was assessed at inclusion, and in studies II and III it was the underlying time scale of the statistical models. For details on these models, see the section on study-specific methods below or the corresponding manuscripts at the end of the thesis. In all studies, sex and educational attainment were assessed at the age of 65. Education was divided into low (primary school; ≤9 years), medium (upper secondary, business high school, vocational internship; 10-12 years), and high (short-term further education, bachelor's degree, research degree; ≥12). Marital

status was defined as married or unmarried, with the latter including divorced or widowed. The number of general practitioner visits in the past 12 months was drawn from the NHSR and divided into three groups (≤6, 7-12, and >12). The number of medications used in the past 12 months was drawn from the DNPR and divided into three groups (≤4, 5-9, and ≥10) based on findings of a higher risk of adverse outcomes when using approximately ≥5 medications.[106] Nursing home residents were identified using the Care Home Data (CHD), which contains the addresses of all Danish care home facilities from 2014 onwards.[107] Comorbidities were identified as the first date of an ICD-8 or 10 diagnosis in the NPR or PCCR, or the first prescription in the DNPR, whichever came first. In study I, comorbidities were defined using the Charlson Comorbidity Index (CCI). The CCI provides a measure of disease burden for an individual by assigning a cumulative score based on the presence of 19 disorders, including dementia, each contributing between one and six points depending on severity and related mortality risk.[108] As dementia was the exposure in study I, we did not include it when calculating the CCI score. In Studies II and III, individual comorbidities were selected based on clinical expertise and previous literature.

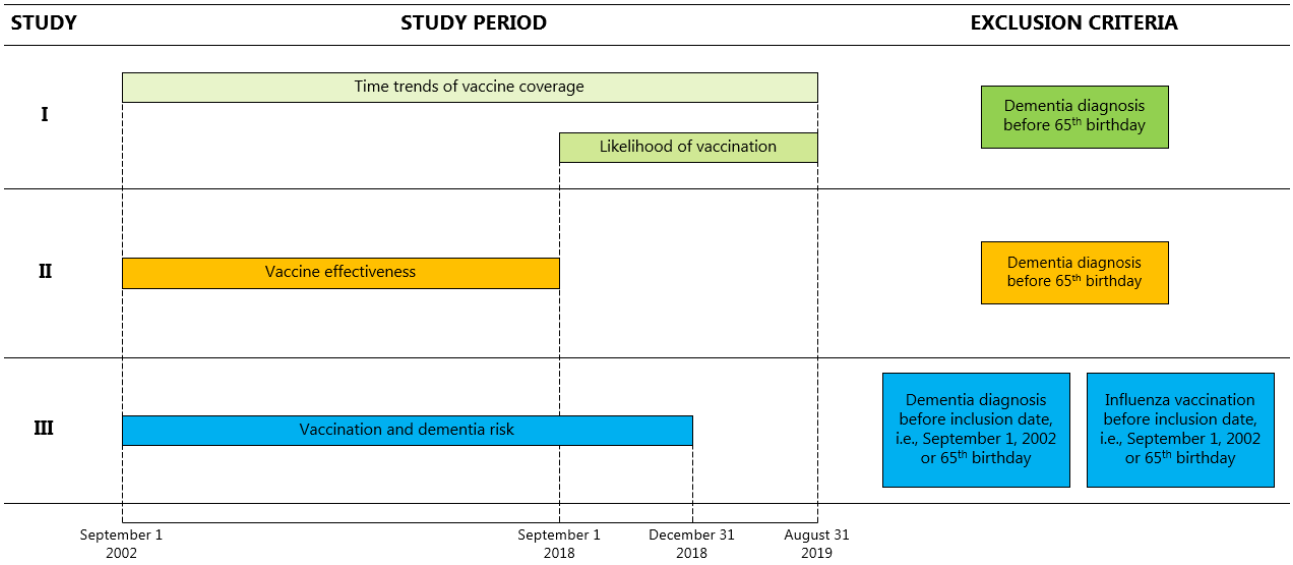
Ethics and approval

This PhD is part of a larger epidemiological research project approved by approved by Statistics Denmark (project no: 703702, authorization no: 325), the Danish Data Protection Agency (ID no: P-2021-250), and The Danish Health Data Authority. Neither approval from an ethics committee nor informed patient consent is required for register-based studies in Denmark.[109] Furthermore, data was only accessed in an anonymized form through Statistics Denmark's servers and all regulations were followed regarding the handling of potentially sensitive information.

Source population

The populations in all three studies consisted of all Danish residents aged 65 years or above from September 1, 2002, to the end of each study period. Figure 1 shows the study period and exclusion criteria for each study.

Figure 1: Study period and exclusion criteria for each of the three studies



Study-specific methods

Table 2: Overview of methods in the studies of this thesis

	Study I	Study II	Study III
Study unit	Individuals	Person years	Person years
Exposure	Prevalent dementia	Influenza vaccination	Influenza vaccination
Exposure groups	No dementia/home-living (ref) Dementia/home-living No dementia/nursing home Dementia/nursing home	Dementia/unvaccinated (ref) Dementia/vaccinated	Unvaccinated (ref) Vaccinated
Primary outcomes	Influenza vaccination	Hospitalization with influenza/pneumonia, hospitalization with respiratory infection, all-cause hospitalization, and all-cause mortality	Dementia
Covariates	Age, sex, educational level, marital status, urbanization, health resource use, CCI score	Age, calendar year, sex, educational level, comorbidities	Age, calendar year, sex, educational level, comorbidities
Statistical method	Logistic regression	Cox regression	Poisson regression
Statistical unit	Odds ratio (OR)	Hazard ratio (HR)	Incidence rate ratio (IRR)

Study I

The aim of this study was two-fold, First, we wanted to investigate the association between prevalent dementia and influenza vaccination among older adults aged ≥65. Second, we wanted to investigate time trends in the coverage of influenza vaccination among older adults with and without dementia. The study period was from September 1, 2002, the year when the offer of free influenza vaccines became available nationally in Denmark, until August 31, 2019. We stratified the study population into people with and without dementia on September 1 of each year of the study period, excluding people with dementia before age 65.

Based on previous studies suggesting a different association between dementia and vaccination among older people in nursing homes compared to their home-living counterparts, we decided to create four exposure groups: 1) Home-living/no dementia, 2) Home-living/dementia, 3) Nursing home/no dementia, 4) Nursing home/dementia. We calculated the odds ratios (OR) of influenza vaccination for the study year 2018/19 with prevalent dementia and nursing home residency assessed at baseline, September 1, 2018. Home-living without dementia was the reference group, and ORs were estimated in three models with an increasing number of potential confounders included. We also performed sensitivity analyses to test the robustness of the main findings.

Time trends of vaccine coverage from 2002/03 to 2018/19 were estimated by descriptive analyses, calculating the proportion of vaccinated among people with and without dementia in a 12-month period from September 1 to August 31 the following year. For those with dementia, we estimated the crude vaccination coverage and a standardized coverage based on the age- and sex distribution among people without dementia.

Study II

The aim of this study was to investigate the association between influenza vaccination and the rate of hospitalization and mortality among older adults with dementia aged ≥65. We followed people from September 1, 2002, until August 31, 2018, until death, emigration, or end of follow-up. The population was stratified into people with and without dementia each year on September 1 and included all Danish citizens aged ≥65 years without a registered dementia diagnosis before the age of 65. Vaccination was time-dependent, and vaccination status was reset on September 1 of each year. The status of comorbidities was also updated on September 1 of each year. We estimated the hazard ratios (HR) of four study outcomes using a Cox proportional hazards model: 1)

Hospitalization with influenza or pneumonia; 2) Hospitalization with any respiratory infection; 3) All-cause hospitalization; 4) All-cause mortality. For the hospitalization outcomes, we included all inpatient and emergency contacts with the Danish healthcare systems for each individual and accounted for correlated risk times in the statistical model. We identified a hospitalization as new if it occurred more than one day after the previous admission.

We also estimated the association between influenza vaccination and outcome rates among people without dementia to examine whether vaccination had a greater preventive effect among people with dementia.

We performed several sensitivity analyses to test the robustness of our results. One of the main sensitivity analyses was the estimation of outcome HRs for periods before, during, and after influenza season from 2010/11 to 2017/18. Several studies have pointed out that dividing the risk time into these three periods can elucidate whether differences in the risk of severe outcomes between vaccinated and unvaccinated are due to disparities in health status between the two exposure groups.[110,111] A causal preventive effect of vaccination on the study outcomes should primarily be present during, and to some extent after, the influenza season. Conversely, a notably lower outcome rate before the season could indicate residual healthy vaccinee bias. The "before-period" was defined as the time from September 1 until that season's start date, the "during-period" was between the start and end dates of the season, and the "after-period" ran from the end date of the season to August 31 the following year. The start and end dates of the influenza season varied across the study years as they were defined by the first and last day of at least 15% positive influenza virus tests in The Danish Microbiology Database (MiBa).[112] The specific start and end dates for each study year can be found in the manuscript appendix of study II.

While nursing home residence was a potential confounder in Study II, we did not include nursing home status in the main analyses as in Study I. The reason for this was that validated information on nursing home addresses was only available for part of the study period (2014 onwards). Instead, we performed a sensitivity analysis, stratifying the study population into nursing home residents and home-living people. We performed several additional sensitivity analyses to test the robustness of our findings.

Study III

The aim of this study was to investigate the association between influenza vaccination and incident dementia among older adults aged 65+ years. The study population was followed from September 1, 2002, or their subsequent 65th birthday, until death, emigration, or December 31, 2018, whichever came first. We excluded people with a registered influenza vaccination or a dementia diagnosis before inclusion.

We estimated incidence rate ratios (IRR) of dementia using a Poisson regression model and compared rates in exposure groups according to three distinct definitions of influenza vaccine exposure: 1) Never vaccinated (ref) vs ever vaccinated; 2) Number of vaccinations (0 (ref),1,2,3-5,6+); and 3) Vaccination within 5 years before a dementia diagnosis (ref) vs. more than 5 years before diagnosis. IRRs were estimated in three models with an increasing number of covariates. Vaccination, along with relevant covariates, was time-dependent in the models, meaning that individuals could contribute risk time as unvaccinated before vaccination and as vaccinated after vaccination.

Several sensitivity analyses were performed. First, we tested for indications of residual confounding by using negative control outcomes. This method involves estimating the association between exposure and outcomes assumed to be causally unrelated to the exposure and comparing this estimate to the association between exposure and the outcome of interest [113]. In the present study, we chose the negative control outcomes of cancer and hip fracture. Second, we estimated the association between vaccination and mortality to explore the potential impact of competing risk of death. Third, we estimated the association between influenza vaccination and dementia stratified by sex, age groups, and calendar periods.

RESULTS SUMMARY

In this section, I will present the key findings of the three studies in this thesis. Additional results can be found in the manuscripts and corresponding supplemental material at the end of this thesis.

Study populations

Table 3 presents the number of people and person-years included in each study. In Study I, 1,096,051 people in 2018, 34,283 with dementia, were included in the analysis estimating the association between dementia and influenza vaccination. The time trend analysis consisted of 141,360 people with dementia and 1,687,216 people without dementia. In Study III, 134,002 people with dementia were followed for 454,844 PYs. The comparison population in Study III consisted of 1,620,162 people without dementia followed through 13,929,479 PYs. In Study II, 1,673,421 people were followed for 14,065,154 PYs.

Table 3: Summary of the number of people and person-years included in the three studies

	Study I		Study II		Study III
	Likelihood	Time trends	Dementia	No dementia	Entire population
Total, N	1,096,051	1,828,576	-	1,620,162	1,673,421
Total, PY*	-	-	-	13,929,479	14,065,154
Dementia, N	34,283	141,360	134,002	-	135,399
Dementia, PY*	-	-	454,844	-	-
Vaccinated, N	534,487	1,167,224	-	-	991,729
Vaccinated, PY*	-	-	187,860	4,817,910	6,549,905
Hospitalizations	-	-	378,940	3,790,169	-
Deaths	-	-	105,208	570,094	-

*Person years

Study I: Dementia related to lower vaccination odds among home-living people

Likelihood of vaccination

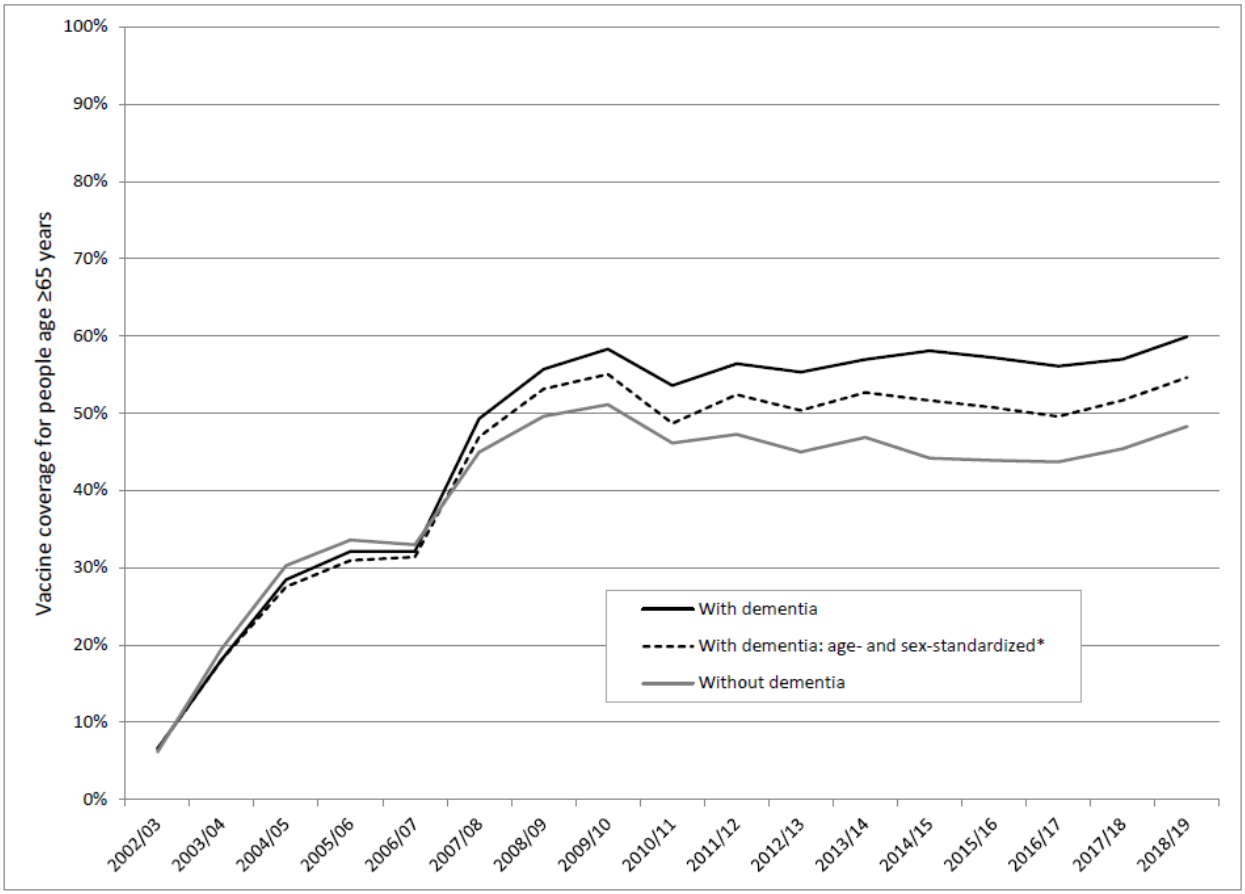
The likelihood of receiving an influenza vaccine during the period from September 1, 2018, to August 31, 2019, was different for people with and without dementia. Adjusting only for age and sex revealed a slightly lower vaccination likelihood according to dementia status, however, further

adjustment for CCI and health resource use decreased the OR for all exposure groups. Compared to the reference group of home-living people without dementia, home-living people with dementia had a 24% lower likelihood of vaccination (OR: 0.76; 95 CI: 0.74-0.78), while nursing home residents had a higher likelihood of vaccination in both those with (OR: 1.18; 95 CI: 1.14-1.22) and without dementia (OR: 1.28; 95 CI: 1.24-1.33).

Time trends of vaccination coverage

From the introduction of the national influenza vaccination program in 2002 until the end of the study period in 2019, the number of recorded vaccinations administered as part of the program increased from 49,329 to 546,287. During the same period, the number of people in the study population increased from 800,387 to 1,122,319. This resulted in an overall vaccination coverage of 6.2% in 2002/03 to 48.7% in 2018/19. Coverage increased substantially from 2002/2003, peaking in 2009/10 at 52.4% and since plateaued, at least until 2018/19. Vaccination trends were similar for people with and without dementia but started to diverge in 2007/08. From 2008/09 onwards, the coverage was notably higher for those with dementia. Age and sex-standardization decreased the coverage among people with dementia, however, it remained higher than for people without dementia. The coverage did not surpass 60% in any of the two groups (Figure 2).

Figure 2: Time trends of influenza vaccine coverage for people aged ≥65 years with and without dementia from 2002/03 to 2018/19.



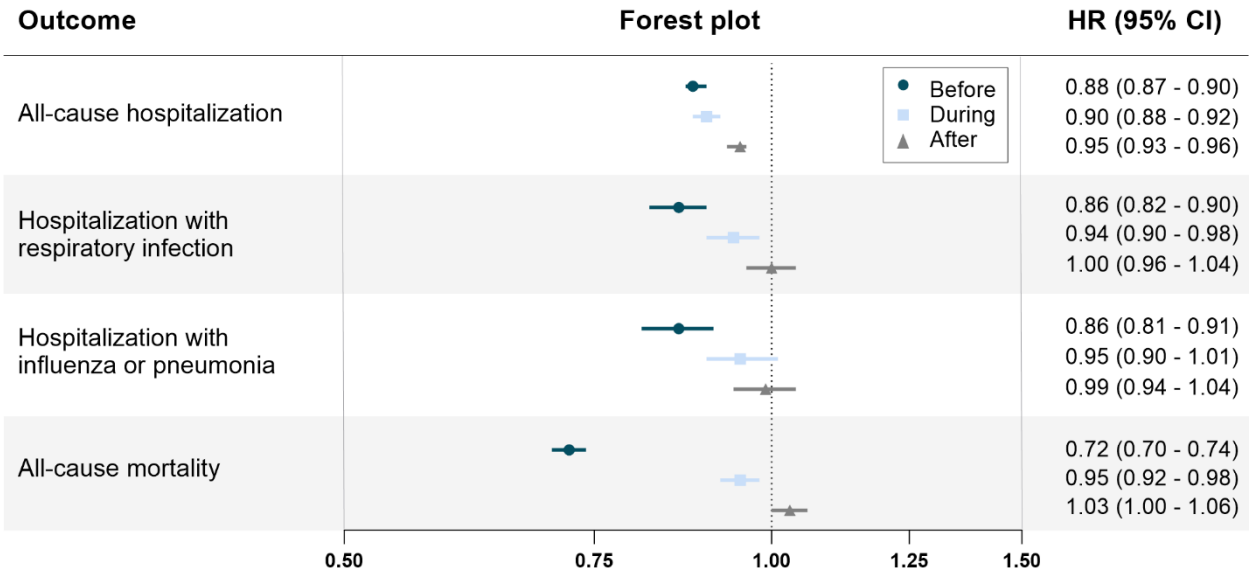
*Standardized to age- and sex-distribution of those without dementia

Study II: Influenza vaccination associated with a lower rate of hospitalization and mortality among people with dementia

Throughout the study period, 1,038,999 people were vaccinated, corresponding to 59.2% of the study population. Among people with dementia, vaccinated people were older, had a higher comorbidity burden, and had more visits to their general practitioner in the past 12 months, compared to unvaccinated. The number of hospitalizations during the study period among people with dementia was 378,940 for any cause, 46,726 with respiratory infections, and 31,872 with influenza or pneumonia. 105,208 people with dementia died during follow-up.

In a fully adjusted model, influenza vaccination among people with dementia was associated with a 9-10% lower hospitalization rate and a 9% lower mortality rate. The lower outcome rates among vaccinated were most pronounced before the influenza season while after the season they were similar to, or in some cases slightly higher than, unvaccinated (Figure 4).

Figure 4: Hazard ratios (HR) and 95% confidence intervals (CI) of outcomes for vaccinated compared to unvaccinated individuals before, during, and after the influenza season – among people with dementia.



HRs were adjusted for age, calendar year, sex, educational attainment, comorbidities, and number of general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

For home-living people with dementia, vaccination was associated with lower rates of all-cause hospitalization and mortality while only the mortality rate was lower among nursing home residents with dementia. Vaccinated people had lower outcome rates throughout the study period, but slightly more pronounced in the first half.

The outcome rates associated with influenza vaccination were similar among people without dementia, however, they did show a lower mortality rate (HR 0.72 95% CI: 0.72-0.73) and slightly higher hospitalization rates. The rates were again lowest before the influenza season and highest after the season.

Study III: Dementia rate following influenza vaccination

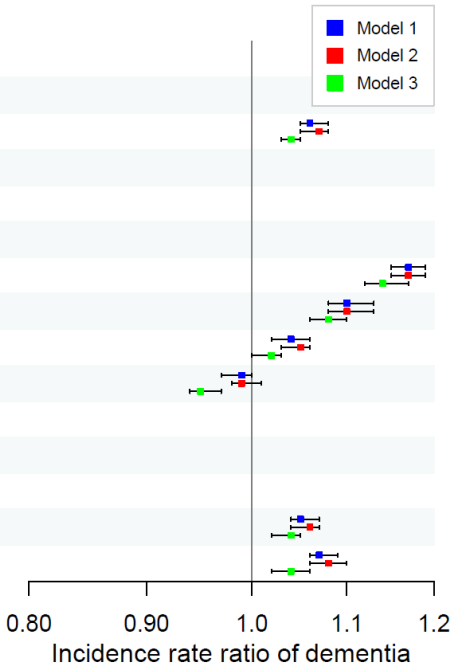
During the follow-up period, 135,399 people were diagnosed with dementia. The crude dementia rate was higher among vaccinated compared to unvaccinated people and increased with increasing number of vaccinations. The rate was also higher after five years from the first vaccination.

The association between vaccination and dementia changed considerably when comparing dementia rates in the exposure groups by estimating covariate-adjusted incidence rate ratios (IRR).

We found that at least one vaccination during the study period was associated with a 4% higher incidence rate of dementia compared to those not vaccinated. Furthermore, we found an inverse relationship between the number of vaccinations and the rate of dementia. Compared to unvaccinated, those with only one vaccination during follow-up had the highest dementia rate (IRR: 1.14; 95% CI: 1.12-1.17). The IRR gradually decreased with an increasing number of vaccinations and was 5% lower than for unvaccinated among people with six or more vaccinations (95% CI: 0.93-0.97). The dementia rate within and after five years from the first vaccination was identical (Figure 3).

Figure 3: Incidence rate ratios of dementia according to different influenza vaccine exposures. Identical to figure included in study II (in press)

Vaccination Exposure	No. of Dementia Cases	Dementia Rate*
Vaccination status		
Not vaccinated (ref)	56,387	7.5
Vaccinated	79,012	12.1
Number of vaccinations		
0 (ref)	56,387	7.5
1	15,178	10.4
2	10,217	10.5
3-5	22,407	11.3
≥6	31,210	14.6
Timing of dementia		
No vaccinations (ref)	56,387	7.5
Within five years of first vaccination	36,126	9.9
After five years of first vaccination	42,886	14.9



The x-axis in the graph has been log-transformed. *Crude incidence rate of dementia per 1,000 person-years. Model 1: Adjustment for age, calendar year, and sex. Model 2: Model 1 + adjustment for marital status and educational attainment. Model 3: Model 2 + adjustment for comorbidities.

In the stratified sensitivity analyses, the higher dementia rate among vaccinated was most pronounced in the youngest age group (65-74) and during the last third of the study period (2014-2018). Conversely, vaccination was associated with a lower dementia rate in the highest age group (≥85) and in the first third of the study period (2002-2007). Associations between influenza vaccination and the negative control outcomes were similar to the association between vaccination and dementia. The rate of cancer was 7% higher, 6% higher for hip fractures, and 10% higher for death among vaccinated We found no differences between men and women.

Discussion

In this section, I will present the key findings of this project in four themes relating to each of the studies: 1) Dementia and vaccination likelihood, 2) dementia and time trends of vaccination, 3) dementia and vaccine effectiveness, and 4) vaccination and dementia risk. I will discuss potential explanations for our findings and compare and contrast these to similar studies. Then, I will discuss strengths and limitations, both for the project as a whole and specifically for each study, as well as some of the many methodological considerations made during this project. Finally, based on the discussion of findings, I will present my conclusions in response to the overall and specific aims presented earlier in this thesis.

Dementia and vaccination likelihood

From September 1, 2018, to August 31, 2019, we found a considerably lower likelihood of vaccination for home-living older adults with dementia compared to home-living older people without dementia. As mentioned in the background section, dementia can impair self-care and treatment of existing comorbidities.[24] Cognitive deficits might be even more impairing regarding the uptake of preventive measures such as vaccination.[114] Sources of reduced self-care ability include diminished insight into one's health status, refusal of care, and loss of independence.[24]

We only found one other study investigating the association between dementia and vaccination separately for home-living older adults and nursing home residents.[69] The study by Shah et al. was based on primary care data from the United Kingdom and reported a lower likelihood of vaccination associated with dementia for home-living people, however, only 4% compared to 24% in the present study. The smaller difference in vaccination likelihood in the UK study could partly be due to the use of different statistical models. In the present study, we estimated the odds ratio of vaccination by applying a logistic regression model while Shah et al. estimated relative risks by applying a log binomial regression model. The more common an outcome is the higher the odds ratio will be compared to the risk ratio (relative risk).[115] Another potential source of the different findings is a higher degree of misclassification of dementia in primary care data compared to secondary care.[69,116] If this misclassification was similar for vaccinated and unvaccinated (i.e., non-differential), it may have biased the true difference towards the null. Finally, the general coverage of influenza vaccines has historically been higher in the UK compared to Denmark,

making the relative difference in the likelihood of vaccination smaller, even if the absolute difference is similar.[117]

Compared to home-living without dementia, we found a considerably higher likelihood of vaccination among nursing home residents both with and without dementia. A highly vulnerable group of people combined with an elevated transmission risk incentivizes nursing homes to focus on vaccinating their residents.[19] That nursing home residents with dementia had the highest likelihood of vaccination is in line with other research on nursing home data alone. These studies reported an association between dementia or cognitive deficits and a higher vaccination likelihood.[66,118] The high vulnerability to infections related to dementia could increase vaccination likelihood even further in nursing homes where reduced self-care abilities may be less of a barrier. Conversely, one study of nursing home data in the United States did not find an effect of dementia on the likelihood of vaccination.[68]

Two studies have reported a 71% and 77% higher likelihood of vaccination among people with dementia when not accounting for living situation (i.e., nursing home vs. home-living).[65,70] The generalizability of these findings is questionable as they were based on smaller populations of patients with Chron's Disease and questionnaire respondents, respectively. They also had limited or no adjustment for potentially confounding factors.[65,70]

While outside the scope of this project, time since diagnosis may be important for the impact of dementia on vaccination likelihood. A French study investigated the trends of vaccination since dementia diagnosis among older adults. Despite a small sample size, the results indicated a lower likelihood of vaccination in the period immediately after dementia diagnosis, followed by a higher likelihood four years after diagnosis.[67] Part of this pattern may be explained by more people with dementia moving into nursing homes during the study period or selective attrition of the most vulnerable people with dementia. It could also reflect a natural focus on the newly diagnosed disease and delaying seemingly less relevant preventive measures.[67,114,119] Dementia may also reduce adherence to vaccination, as a Spanish study found a 15% lower likelihood of influenza vaccination among people with dementia vaccinated in the year prior.[71]

Time trends of vaccination

We investigated associations between dementia and influenza vaccination among all Danish people aged ≥65 from 2002 to 2018. During this period, we found that time trends of vaccine coverage followed a similar pattern for people with and without dementia. The coverage was lowest at the beginning of the study period, around 6% in 2002/03, increasing considerably until 2009/10 when it plateaued. From 2007/08 the coverage was noticeably higher for people with dementia, however, neither those with nor without dementia surpassed a coverage of 60%, considerably lower than the WHO goal of 75% among older people.

The low coverage in the first years after introducing the free vaccination offer could have multiple explanations. A systematic review of factors related to influenza vaccination pointed to knowledge of preventive measures as well as advice from family or health professionals to be some of the most impactful for the decision of whether to get vaccinated.[119] An initially low awareness in the general population and among health professionals could therefore have affected the uptake of the vaccine considerably. Even when aware of the free vaccination, negative attitudes towards the need for the vaccine could have affected the uptake, such as expectations of low efficacy, low likelihood of catching the virus, or not considering influenza a serious enough condition to take preventive action.[114,119] Finally, a large number of older adults in Copenhagen were vaccinated free of charge in a municipal program and not recorded in the national registries.[120] Inhabitants of Copenhagen may have preferred the municipal offer at first but slowly transitioned to the national program once they became familiar with it. The municipal program likely only explains part of the trend, as excluding inhabitants of Copenhagen did not alter the patterns found in the entire population.

The sharp increase in coverage until 2008/09 may then be explained by an increase in the awareness and attitude towards vaccines. These changes could come about partly because of a concurrent pandemic of Influenza A which caused a large spike in severe influenza cases from March 2009 to July 2010.[121] The plateau in Danish influenza vaccine coverage since 2010 could suggest a saturation in the influenza vaccine uptake in the Danish population using the current strategies. The higher coverage among people with dementia during the last half of the study period may in part be due to the higher age, higher comorbidity burden, and more GP contacts, all of which were strongly associated with vaccination in 2018/19 in our study. A considerably larger

proportion of nursing home residents among people with dementia likely also contributed to the higher coverage.[19]

To our knowledge, no previous study has investigated time trends of influenza vaccination among people with dementia in a similar fashion. A study from Israel reported a considerable increase in the general vaccine coverage from 2002 onward, however with a more linear trend than in Denmark.[122] The trends in this study for people both with and without dementia are aligned with the entire population of older adults in Denmark reported with surveillance data from Statens Serum Institut [123] as well as in WHO surveys.[117] As in Denmark, most countries experienced a plateau or a slight decrease in coverage from 2008/09 to 2014/15, however, with considerable differences in coverage levels.[117,124]

Vaccine effectiveness (VE)

Our findings in Study II indicate that influenza vaccination was effective in decreasing the risk of hospitalization and death among people with dementia. Vaccinated with dementia had a 9-10% lower rate of hospitalizations and a 9% lower mortality rate compared to unvaccinated with dementia.

To our knowledge, no previous study has estimated the association between influenza vaccination and rates of hospitalization and mortality specifically among older adults with dementia, complicating the comparison with previous studies. When looking at research on risk groups that include dementia as one of several qualifying conditions, they generally report considerably higher estimates of VE than what we found in the present project. Nichol et al. estimated a pooled VE across six study years from 1990/91 to 1995/96 based on insurance data from the United States. They found a 32% lower hospitalization rate and a 64% lower mortality rate associated with vaccination in an 'intermediate risk group' which included people with a diagnosis of dementia, diabetes, renal disease, or rheumatologic disease.[73] Shapiro et al. estimated VE in a single season (2000/2001) in Israel based on national health insurance data. In a 'high-risk group' including those with dementia, heart disease, lung disease, diabetes or endocrine disorders, renal disease, or stroke, they found a 30% lower hospitalization rate and a 70% lower mortality rate among vaccinated.[125] A meta-analysis from 2018 of six studies with high-risk groups, not all of them including dementia, reported a 61% lower mortality rate among vaccinated. They did not find sufficient evidence to perform a similar estimation of hospitalization rates.[76]

The comparatively modest VE in our study could have multiple explanations. First, people with dementia may have a different effect of vaccination compared to the broader risk groups mentioned above. Dementia is associated with a high hospitalization and mortality risk, independently of comorbidities[126–128] and this high baseline risk may have reduced the effect of the vaccine in comparison to other health conditions.[16] Second, the effectiveness may also have been hampered by a low immune response to the vaccine due to the immunosenescence associated with dementia.[15]

Factors not directly related to the vaccine should also be considered as explanations for the relatively low VE among people with dementia. One of the most discussed topics in VE literature is the influence of confounding by indication and healthy vaccinee bias.[110,111,129–135] These are two types of confounding where health differences unrelated to the biological mechanism of a vaccine can bias the estimated VE, however, they act in opposite directions. Confounding by indication describes a situation where people with pre-existing chronic illnesses are more likely to be vaccinated. Conversely, healthy vaccinee bias is defined by a higher likelihood of vaccination among the healthier individuals in a population.[135] In the absence of proper confounder adjustment, confounding by indication will lead to an underestimation of VE while healthy vaccinee bias will lead to an overestimation. It can be difficult to ascertain the extent of confounding by indication and healthy vaccinee bias and both mechanisms are often present in the same study.[135]

In our study, the higher baseline proportion of comorbidities and more GP visits in the past 12 months among vaccinated could indicate a generally lower health status beyond what we adjusted for in the study and thus confounding by indication. This hypothesis is supported by another Danish study from Hellfritzsch et al. based on influenza vaccine data from the national registries. In this study, vaccination was associated with a higher self-reported frailty and a higher degree of functional impairment and comorbidity burden, but not with lifestyle factors.[70]

There were, however, also signals of healthy vaccinee bias in our data. Several VE studies have attempted to elucidate the impact of this bias in the general population of older adults by comparing VE in periods of higher viral circulation with VE in periods with lower circulation.[110,129,136] A similar or seemingly higher VE in periods with low circulation could indicate healthy vaccinee bias. This was the case in the present study, where the reduced outcome rates among vaccinated were most pronounced before the influenza season and gradually increased during and after the

season. Another potential source of healthy vaccinee bias is that those with higher adherence to the vaccine program will have contributed with more person-years as vaccinated compared to those with lower adherence throughout the study period. Higher adherence has been linked to healthy vaccinee bias while lack of adherence has been associated with recent hospitalization and diagnosis of a major chronic disorder.[71]

It has been noted in the VE literature that bias due to health differences between vaccinated and unvaccinated people has a greater impact on studies with unspecific outcomes.[129,135] Much of the discussion has focused on all-cause mortality, partly due to the large discrepancy between a high estimated effectiveness of influenza vaccines of around 50% and a comparatively low estimated proportion of winter deaths attributable to influenza of about 5%.[129] Thus in the present study, we not only compared rates of mortality and hospitalization from all causes, but also rates of hospitalization with any respiratory infection and hospitalization with influenza/pneumonia. Influenza vaccination was associated with similar VE regardless of the endpoint, indicating that bias from health status differences may not have impacted our results to a large degree. Hellfritzsch et al. also suggest that confounding by indication and healthy vaccinee bias may be less influential in the Danish healthcare system with universal coverage compared to countries such as the United States where most of the high VE estimates have been reported.[70]

Compared to studies including low-risk groups or the general population from other countries we found a considerably lower VE among people without dementia, more aligned with estimates of influenza-attributable mortality.[73,76,125] This could also indicate a smaller impact of bias due to health differences in Denmark compared to other countries.[70]

Living in a nursing home increases the likelihood of being immunized against influenza and may decrease the likelihood of being admitted to the hospital.[126,137,138] This may be part of the reason why vaccination was only associated with lower hospitalization rates among home-living people with dementia and not nursing home residents in study II.

Vaccination and dementia risk

In study III, being vaccinated at least once during the study period was associated with a slightly higher incidence rate of dementia. While this increase persisted after 5 years from the first vaccination, the dose-response relation between the number of vaccinations and dementia rate did

not align well with a casual mechanism as the highest rate was found among those with one vaccination during follow-up and the lowest rate among those with six vaccinations.

Evidence of the potential biological connection between influenza vaccination and dementia remains sparse. From the existing literature, it is difficult to imagine a plausible biological mechanism linking influenza vaccination with higher dementia risk. This has also been pointed out by a study reporting notably higher odds of dementia among people who had received an influenza vaccine (OR: 1.39; 95% CI; 1.37–1.41).[95] Conversely, several mechanisms have been proposed to explain how common vaccines, including influenza, reduce the risk of dementia. These can be divided into direct and indirect effects of vaccines on dementia risk.[98] Evidence of a direct protective effect has been suggested in mouse models where influenza and Bacillus Calmette-Guérin vaccines improved memory and alleviated neuropathology related to AD.[81,82] Vaccines may indirectly reduce dementia risk by preventing severe infection, based on evidence that specific infections can trigger neuroinflammation and subsequent neurodegeneration.[40–56,88] Another potential indirect effect is the prevention of other risk factors of dementia. In support of this, influenza vaccination has been associated with a lower risk of cardio- and cerebrovascular disease,[79,139] however, it should be noted that this may at least in part be due to healthy vaccinee bias.

The majority of studies on this topic have reported a lower risk of dementia among vaccinated.[87,90–94,96,97] Among these, studies focusing on influenza vaccines have reported a 40% to 4% lower risk of dementia among vaccinated. If vaccination is associated with the risk of developing dementia, a protective effect seems most probable, however, the current evidence of such an effect has several potential sources of bias. As pointed out by Douros et al., the internal validity of these studies is limited by the absence of a sufficient lag period between influenza vaccination and dementia diagnosis. Without proper time separation of vaccination and dementia, estimates could be influenced by protopathic bias. This bias can occur if the outcome of interest affects the likelihood of exposure. As outlined in the background section, undiagnosed or prodromal dementia may reduce vaccine uptake, at least for a time, causing a downward bias of the true vaccine effect.[95] It should be noted that, while likely less probable, detection bias could act in the opposite direction by increasing the likelihood of being diagnosed with dementia when visiting the doctor for vaccination.[95] The only study applying a lag period reported that the 4% lower dementia among vaccinated in the main analysis increased to a 6% higher dementia rate when vaccination and

dementia diagnosis were separated by at least two years. This could indicate that protopathic bias is a concern in similar studies without a lag period. We did not find indications of protopathic bias in the present study, as the hazard rate of dementia was similar within and after 5 years from vaccination. Due to the cohort design, we were not able to apply a lag period.

Part of the difference in results could be due to differences in the impact of confounding by indication and healthy vaccinee bias. A lower risk in three studies from Taiwan may be caused by healthy vaccinee bias being more pronounced in high-risk groups such as chronic patients.[91,92,97] As mentioned above, healthy vaccinee bias may also be more prominent in countries without universal healthcare, such as the United States.[70] The only two previous studies that reported a higher dementia risk among vaccinated were from the United Kingdom.[89,95] In countries with more equal access to healthcare such as Denmark and the United Kingdom, confounding by indication may be more likely than healthy vaccinee bias.[70] A lower health status/higher frailty among vaccinated in the Danish registry data is supported by the similarity of the associations between vaccination and dementia and the associations between vaccination and the negative control outcomes of cancer and hip fracture.[113]

Underlying health differences between vaccinated and unvaccinated may also explain our findings of large differences in the association between influenza vaccination and dementia rate between the first, second, and third periods of study follow-up. The notably reduced dementia rate associated with vaccination from 2002-2007 could reflect an initial healthy vaccinee bias during a period with relatively low vaccine coverage. The slightly increased and considerably increased dementia rates in the periods 2008-2013 and 2014-2018, respectively, could indicate a gradual change towards confounding by indication.

Finally, influenza vaccination may have a particular preventive effect in certain groups with a high baseline risk of both severe infections and dementia. This was the hypothesis of two studies reporting 32% and 36% lower hazard rates of dementia associated with influenza vaccination in patients with chronic obstructive pulmonary disease and chronic kidney disease, respectively.[91,92]

Strengths and limitations

This project has several strengths and certain limitations when considering the aim of the project and the existing research within the area. Some of these have already been discussed above, and

detailed discussions of strengths and limitations can be found in each of the three papers. In the following paragraph, I will present the main strengths and limitations.

Because this project was entirely based on the Danish national registries, the source population for each study was the entire group of older adults in Denmark. This ensured a high degree of external validity, i.e., generalizability of the findings, compared to many other studies within the research area. The registers included information on all free-of-charge vaccines administered in the national vaccination program since its beginning in 2002, which provided a study period between 16 and 19 years in the three studies. The wide availability and universal coverage of the influenza vaccine for older adults aged 65 and above decreased the likelihood of confounding due to socioeconomic differences as well as healthy vaccinee bias as outlined above.[70] Dementia diagnosis in the Danish registries has been validated and found to be of a high positive predictive value, meaning that the vast majority of people diagnosed with dementia did in fact have the disorder.[140] We also had valid information on a long list of potential confounders including age, sex, marital status, educational attainment, health care use, and comorbidity. All information was continuously recorded in the registers, either annually or by a specific date, allowing us to adjust for time-varying confounding in studies II and III. The large source population and high completeness of data provided sufficient statistical power to perform several sensitivity and subgroup analyses to test the robustness of our findings and investigate signals of potential bias in our estimates. The big sample sizes also allowed the estimation of effects with high precision, i.e., small confidence intervals. As this increases the risk of clinically irrelevant associations being statistically significant, the findings are discussed and contextualized throughout this thesis.

In the following, I will present limitations regarding the assessment of the main concepts studied in the project: dementia and influenza vaccination. I will also consider the extent to which confounding and other limitations may have impacted the results.

Information on dementia

As mentioned above, dementia diagnosis in the Danish hospital registries is estimated to have a high positive predictive value. In a validation study from 2007, 86% of those with an ICD-10 diagnosis of dementia were considered to have the disorder upon individual assessment by experts.[140] However, there are other caveats related to register-diagnoses which increase the likelihood of information bias. Underdiagnosis of dementia in administrative data has been a

concern in many observational studies, and the Danish hospital registries are no exception. A study from 2014 estimated that diagnoses recorded in secondary care constituted approximately 46% of all dementia cases in Denmark at the time.[141] Most of the missing cases likely stem from people with prodromal dementia, unrecognized dementia, or advanced dementia where diagnosis is considered unhelpful, and those not seeking a diagnosis for other reasons, such as the expectation of stigma. Finally, some cases may only be diagnosed in primary care for which we did not have data access. The misclassification of dementia is most likely non-differential and may therefore have attenuated differences in vaccination likelihood and vaccine effectiveness when comparing people with and without dementia. Prodromal dementia could have introduced reverse causations in study III, however, as the dementia risk was similar within and after five years since vaccination, we do not consider this bias to have a substantial impact. Some cases in primary care may be identified through prescriptions for anti-dementia medication, as these ordinarily require a diagnosis. Thus, to mitigate the misclassification we included redeemed prescriptions for anti-dementia drugs in our definition of dementia.

Identifying people with dementia based on anti-dementia drugs itself introduces a smaller risk of misclassification. According to our definition of dementia, people with dementia in Parkinson's Disease (PD) were not applicable, however, they are sometimes prescribed anti-dementia medication. While the misclassification is likely limited, we tried to mitigate it in studies II and III by not counting people with an ICD diagnosis of PD or who received specific medication to treat PD.

Information on diagnosed subtypes of dementia where available in the Danish hospital registries, however, the low validity precluded their inclusion in this project.[140,142] It could have been relevant to estimate vaccine effectiveness by the specific subtype as some types may be related to higher baseline mortality rates.[143–146] AD may be more relevant in study III as the infection hypothesis has focused on AD. We also lacked information on dementia severity, which could have been of interest to the uptake of influenza vaccination in study I.

Information on influenza vaccinations

Information on influenza vaccination in the National Health Service Register (NHSR) has not been validated. As mentioned above, the NHSR contains all the services reported by health professionals in primary care.[103] The sensitivity of vaccine data is likely high, as the general

practitioners who usually administer the vaccines do not receive reimbursement for services if they do not report them. The specificity is likely also high, as the study population in all three studies were older adults eligible for free-of-charge vaccinations, and thus had little incentive to pay for a vaccine at a private clinic or pharmacy.

Certain drawbacks of the vaccine data should be noted. The influenza vaccines in the NHSR only cover the free-of-charge vaccines so misclassification of people being vaccinated outside the national program is possible. This source of misclassification may have been particularly relevant before the national vaccination offer became available and could have had a small impact on the analyses in study II. Self-paid vaccination might of course also have occurred in our study population during the first few years after free vaccines were introduced and could partly explain the low initial coverage we found when mapping vaccination trends in study I.

A source of misclassification that may have affected all three studies is the influenza vaccination program in the Municipality of Copenhagen. This program, starting in 1996, vaccinated older inhabitants for free at pop-up clinics, and vaccinations were not recorded on an individual level in the national registers, preventing us from identifying them in this project. The extent of the potential misclassification is therefore difficult to accurately assess. According to a survey at the time, a little more than half of the target group was vaccinated through this program before the national offer was introduced,[120] and Copenhagen Municipality reported high adherence to the program even in the few years after the national offer was introduced. To examine the potential influence of this misclassification, we performed subgroup analyses in all three studies by excluding eligible inhabitants of Copenhagen in the relevant periods. None of these analyses resulted in notable differences compared to our main findings.

Confounding

As outlined throughout this discussion, literature on the links between vaccines and health has pointed to healthy vaccinee bias and confounding by indication as some of the main concerns. We tried to limit these confounding mechanisms as much as possible by controlling for healthcare use and comorbidity burden in all three studies. The specific health-related covariates differed in the studies, based on methods in previous studies and expert knowledge among the co-authors and collaborators. However, residual confounding due to health differences between vaccinated people may have influenced our findings.

The concept of frailty has been used in some studies to mitigate confounding.[147,148] The Danish registries lack much of the information often included in frailty definitions such as weight loss, physical condition (e.g., grip strength, walking pace), or impaired ability to perform activities of daily living.[149–151] Conversely, including frailty could have complicated interpretations of our findings, as dementia or cognitive impairment is often a part of frailty definitions or very closely related to the factors included in frailty definitions.

Lifestyle may be related to the likelihood of vaccination, the risk of dementia, the risk of severe infections, and the effectiveness of influenza vaccines.[152–155] Lifestyle factors may therefore have been relevant as confounders in this project, even though Hellfritzsch et al. did not find an association between lifestyle and influenza vaccination among a group of older people in Denmark.[70] If lifestyle was different for vaccinated and unvaccinated people in our data, it would likely have been in the form of a healthy vaccinee effect and biased the associations in study II towards a greater VE and in study III towards a lower dementia risk. To mitigate potential confounding due to alcohol use in study II we also included ICD diagnosis of alcohol disorder, however, this likely only accounts for those with severe alcohol problems. We did include educational attainment in all three studies, which is linked to lifestyle.[156] It should be noted, however, that educational information was missing for a considerable proportion of the oldest people in the source population. Including income information may have reduced the potential residual confounding from socioeconomic position.[157]

Finally, nursing home data before 2014 is of low validity and was therefore only applied in a subgroup analysis in study II.[158]

Other

We did not have access to genetic data, which may have been relevant as an effect moderator in study II and III. A variant, or allele, of the apolipoprotein E gene (APOE4) has been identified as one of the main genetic risk factors for dementia,[159] and may also increase vulnerability to infections.[160] Furthermore, recent research indicates that certain genotypes may increase the risk of both neuroinflammation and AD.[161,162]

As pointed out by multiple studies, healthy vaccinee bias may have inflated our estimated VE for all-cause mortality.[129,135] It could therefore have been relevant to investigate the association between influenza vaccination and specific infection-related causes of death. We chose not to

include the cause of death, however, as the Cause of Death register has not been validated and data on all-cause mortality is nearly complete.[99,163] Further research may consider more specific mortality outcomes when investigating the effectiveness of influenzas vaccination among people with and without dementia.

Methodological considerations

Carrying out this register-based project involved many difficult decisions, such as which data to include and what methods to apply. In this section, I will describe some of these decisions and the reasoning behind them.

We included data on the study population up until August 31, 2019, however, we had access to complete registry data until December 31, 2021. However, we chose the specific endpoint of follow-up due to the COVID-19 pandemic, which started in the spring of 2020. The increased focus on viral diseases and vaccinations might have distorted the associations and hampered the interpretation and generalizability of our findings. To that end, the governmental organization responsible for tracking tax-supported influenza vaccinations in Denmark, Statens Serum Insititut, reported markedly higher vaccine coverage in the years 2020/21 and 2021/2022.[164,165]

In study II, hospitalization was defined as the admission date, and information on the discharge date was not included. Thus, we did not account for time spent at the hospital, which technically was "immortal time" when hospitalization was the outcome, as people could not be admitted while already at the hospital. However, people could still die during this time, so accounting for it may have introduced other bias issues and complicated interpretations even further.

To our knowledge, no consensus exists about how to define an "influenza season". Thus, to examine the presence of residual confounding, we created our own definition, inspired by Jackson et al.[110] Like Jackson et al., the influenza season in study II was delineated by the proportion of positive influenza tests and thus varied from year to year during the study period. This method may have introduced information bias if the number of positive tests in The Danish Microbiology Database (MiBa) did not accurately reflect the circulation of influenza in Denmark at the time. However, we thought an influenza season based on positive tests preferable to the alternative with a somewhat arbitrarily fixed, uniform period for each study year, which has also been pointed out in the literature.[129]

To study the preventive effect of influenza vaccinations on dementia risk, we considered either a cohort design or a case-control design with matching, both of which have been used in similar studies.[87,90–94,96,97] In the end, in study II we chose the cohort design to account for time-varying confounding.[166] This precluded the application of a lag period to estimate the potential impact of protopathic or detection bias, which we tried to accommodate by stratifying the follow-up time for vaccinated people into periods within or after five years since vaccination.

Conclusion

This project aimed to investigate specific links between dementia and influenza vaccination among older adults through three research questions.

Consistent with the existing literature, we found that home-living older adults with dementia may be less likely to be vaccinated against the seasonal influenza virus, compared to cognitively intact older adults. This potential healthcare gap deserves increased attention among health professionals and policymakers. Nursing home residents had a higher likelihood of vaccination regardless of dementia. The estimated coverage of influenza vaccines in the present project, and most other studies, has been below the level recommended by the World Health Organization, pointing to suboptimal conditions for avoiding potentially preventable adverse outcomes following infection.

Influenza vaccination seems to be just as, or even more, effective in preventing hospitalizations and deaths for people with dementia compared to those without dementia. Residual confounding should be considered., however, it may have impacted our results to a lower degree than much of the previous research. While it is difficult to ascertain how much the true vaccine effect was impacted by bias, people with dementia should continue to be offered influenza vaccines, and potentially in a more proactive manner than previously.

Based on our findings and the findings of other studies, we cannot convincingly conclude whether influenza vaccination reduces or increases the risk of dementia. The findings of the present study may be less influenced by residual health-related confounding and more generalizable to the general population of older adults compared to previous research. Thus, this project adds valuable knowledge and questions the preventive potential of influenza vaccination on the risk of dementia.

Perspectives

In this section, I will suggest the potential public health implications of the project findings and suggest future directions for research on the links between dementia and influenza vaccination.

Public health

This thesis highlights associations between influenza vaccination and dementia among older adults which may have important implications for public health policy.

Past efforts to protect older people from severe infections through immunization against influenza have generally come up short.[117] Our findings show that among people with dementia, coverage of influenza vaccines up until the winter of 2019 did not meet the minimum goal of 75% among high-risk groups set by the World Health Organization in 2003.[63] This is despite a large proportion of people with dementia living in nursing homes, which often have a higher vaccine coverage as compared with other settings. Having dementia and living at home may be a particular barrier to influenza vaccination. This potential healthcare gap deserves more attention from health professionals and policymakers to ensure equity of care for people with dementia. The high vaccine coverage during the COVID-19 pandemic could act as an inspiration for authorities in this regard.[164,165]

While modest, we did find lower rates of hospitalization and mortality associated with influenza vaccination among people with dementia. Thus, even small improvements in the uptake of influenza vaccines could have a substantial benefit on a societal level, considering the increasing prevalence of dementia and the high burden of infections.[3,6,27–29] High-dose vaccines are currently offered free of charge to certain high-risk groups in Denmark and in other countries, and they could also be considered for people with dementia.[167] As could adjuvanted vaccines, which have been linked to a greater immune response among people with suspected immunosenescence.[168–170]

Future research

Most of the research on the impact of dementia on vaccination likelihood has been based on data from a single year or influenza season.[66,68–70] As mentioned above, time since diagnosis may influence the uptake and adherence of influenza vaccines.[67,71] These associations can only be

studied further in a cohort design. Following people across multiple seasons could also improve the generalizability of future studies and elucidate the impact of variations in viral activity, uptake patterns, and vaccination policies.[67]

As this was the first study on vaccine effectiveness (VE) specifically among people with dementia, more research is needed to substantiate the findings. Optimal ways of estimating vaccine effectiveness have been debated for many years.[110,111,129,135,148,171–177] The discussion has mainly focused on how to appropriately account for the suspected health differences between those who receive influenza vaccines and those who don't, i.e., confounding by indication and healthy vaccinee bias. A popular method to mitigate this potential bias in VE studies is to include information on laboratory-confirmed influenza as the outcome of interest in a cohort study or to define cases and controls in a test-negative design.[171,172] Another strategy to reduce confounding of VE estimates is to include only vaccinated and compare those receiving high-dose vaccines with those receiving standard-dose vaccines.[178] However, confounding by indication should still be considered, as those receiving high-dose vaccines may be frailer.

The present project has added important knowledge on the potential for influenza vaccines to decrease the risk of dementia. However, further research is needed to accommodate limitations and examine unanswered questions. Similar to VE studies, the main limitation is the potential confounding effect of pre-existing health differences between vaccinated and unvaccinated people. Thus, similar methods may be used to mitigate confounding by indication and healthy vaccinee bias, such as comparing different types of vaccination among vaccinated people only e.g., higher dose versus standard dose vaccines.[162] The existence and type of adjuvants has also been suggested to influence the effect of influenza vaccines on dementia risk.[162] Because dementia pathology is often present for years, even decades, before symptom onset, vaccination may have a greater preventive effect at earlier ages than what has previously been researched.[162,179] Healthy vaccinee bias may be even more prevalent in younger age groups, however, so studying vaccine effects in a younger population requires careful consideration. Finally, a recent study reported lower odds of AD associated with pneumococcus vaccination for certain genotypes.[161] Influenza vaccination was not associated with lower AD risk in that particular study; however, further research is needed to examine whether the preventive potential of common vaccines can vary according to genotype.[161,162] Additional in vivo and in vitro studies are also needed to elucidate the underlying immunological and neurological effects of common vaccines.

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STUDY I

Dementia and influenza vaccination: Time trends and predictors of vaccine uptake among older adults

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Abstract

PURPOSE: Older adults with dementia are at an increased risk of hospitalizations with respiratory infections and death, emphasizing the need for increased focus on preventive measures. In this study, we investigated the uptake of influenza vaccination among older adults with and without dementia.

METHODS: We conducted a cross-sectional study with data from national registries on the entire Danish population aged ≥65 years. We mapped time trends of vaccination for each vaccination season (September to August) from 2002/03 to 2018/19. Using multivariable logistic regression, we estimated the odds of vaccination in 2018/19 in nursing home residents and home-living older adults with and without dementia.

RESULTS: We included 800,387 individuals in 2002/03 and 1,122,319 in 2018/19. After a period of similar and increasing uptake of influenza vaccines among people with and without dementia, the uptake plateaued from 2007/08 to 2018/19 and was consistently higher in those with dementia during this period. The odds of vaccination in 2018/19 were lower for home-living people with dementia compared to home-living people without dementia (OR: 0.76; 95% CI: 0.74-0.78). The highest odds were among nursing home residents both with (OR: 1.28; 95% CI:1.24-1.33) and without dementia (1.18; 95% CI: 1.14-1.22).

CONCLUSION: Between 2002/03 and 2018/19 vaccine coverage among older adults in Denmark was <60%, regardless of dementia status, not reaching the WHO target of 75%. Home-living older adults with dementia were 24% less likely to receive an influenza vaccine, representing an important target group for future vaccination programs.

Keywords: Dementia, Influenza, Vaccination, Prevention, Aging

Introduction

The seasonal influenza virus is one of the most prevalent infections globally.[1] Serious infections often occur among older adults, and those with underlying chronic illness, with an estimated 90% of all influenza-related deaths occurring in people aged ≥65.[2] Thus, influenza vaccination in the general population of older adults is important and has been shown to reduce morbidity and mortality.[3] Older adults with dementia are at an increased risk of serious infections and related morbidity and mortality compared to those without dementia.[4,5] Immunization can therefore be particularly beneficial for people with dementia. However, many national influenza vaccination programs do not highlight people with dementia as a high-risk group. Due to cognitive problems such as memory difficulties and reduced insight, older adults with dementia may be less likely to get vaccinated.[6]

Previous studies investigating how dementia affects the uptake of influenza vaccines among older adults have reported inconsistent findings. The majority reported a higher likelihood of vaccination among people with dementia or cognitive impairment compared to those without,[7–9] while others reported null findings or a lower likelihood of vaccination among people with dementia.[10–12] Most studies were based on small study populations, selective patient groups with chronic diseases [8] or nursing home residents,[7,9,11] or used self-reported vaccination data. One larger study indicates a different effect of dementia on vaccination uptake for home-living older adults compared with nursing home residents.[13] No published study has included information on potentially important confounders such as educational level and marital status.[7–13] Thus, studies with large unselected populations that account for nursing home residency and other confounders are needed. Using the nationwide Danish registries, our study aimed to investigate the uptake of influenza vaccination in home-living people and nursing home residents with and without dementia. A secondary aim was to estimate time trends of vaccination coverage in Denmark for people with and without dementia since the offer of free influenza vaccination for older adults was introduced in 2002.

Methods

Study design

In this repeated cross-sectional study, we used population-based data with information from Danish nationwide registries.

Population

All Danish residents aged ≥65 years on September 1 in each year were included from 2002 to 2018. September 1 was chosen based on the defined influenza vaccination period (see definition below). Individuals who were diagnosed with dementia before the age of 65 were excluded to focus on late-onset dementia where studies have reported low validity of dementia diagnosed at younger ages.[14]

Data sources

All residents in Denmark are assigned a personal identification number at birth or immigration. This enables the linkage of healthcare and sociodemographic data from nationwide registries at an individual level.[15] The Danish National Health Service Register for primary care contains information about all reimbursed services carried out in general practices in Denmark, including the vast majority of the free influenza given to older adults aged ≥65 years from 2002 to 2022.[16] Together, the Danish National Patient Register [17] and the Danish Psychiatric Central Research Register [18] contain information on all somatic and psychiatric in- and outpatients, including date of admission and discharge, procedures performed, as well as primary and, optionally, secondary diagnoses according to the International Classification of Disease 8th edition (ICD-8) from 1977 to 1993 and 10th edition (ICD-10) from 1994 onwards. The Danish National Prescription Registry contains individual-level information on all prescription drugs dispensed at Danish pharmacies since 1995.[15] The Danish Civil Registration System contains information on a number of sociodemographic factors such as date of birth, sex, residency in a nursing home, marital status, and vital status. The Population's Education Register contains information on the highest attained education.[15]

Dementia

Dementia status was evaluated on September 1 each year. Dementia was defined as a first diagnosis of dementia, or a first redeemed prescription for an anti-dementia drug (Table 1).

Table 1: Dementia diagnoses in the International Classification of Disease (ICD) codes and anti-dementia medication in the Anatomical Therapeutic Chemical Classification (ATC) codes

Dementia type	**ICD-8 code**	**ICD-10 code**
Alzheimer's Disease	290.10	F00.0-00.9, G30.0-G30.9
Vascular dementia	293.09-19	F01.0-01.9
Frontotemporal dementia	290.11	F02.0, G31.0A, G31.0B
Dementia without specification	290.09-19	F03.9, G31.9
Other dementias	-	G31.8, G31.8E, F02.1-F02.8
Medication	**ATC code**	
Cholinesterase inhibitors		
Donepezil	N06DA02, N06DA52, N06DA53	
Rivastigmine	N06DA03	
Galantamine	N06DA04	
Glutamate-receptor antagonists		
Memantine	N06DX01, N06DA52, N06DA53	

Living status

We defined living status as either living in one's own home or in a nursing home. Living status was assessed on August 31 in each year. Nursing home residents were identified through the Care Home Data developed by the Danish Health Data Authority.[19]

Influenza vaccination

We defined influenza vaccination as a registered vaccination in the Danish National Health Service Register [16] or a redeemed prescription for an influenza vaccine in the Danish National Prescription Registry.[15] We derived our definition of the vaccination period from Statens Serum Institut (SSI), a branch of the Danish Ministry of Health responsible for the supply and surveillance of the Danish influenza vaccination program.[20] SSI divides the uptake of influenza vaccines into seasons instead of calendar years, based on the "influenza season" in Denmark, i.e. the period approximately from September to January in which influenza prevalence is typically higher than the remaining months of the year.[21] This is also in line with previous research on influenza vaccine uptake.[9,10,12,22,23] However, some people may be registered before or after this period due to early vaccination or late registration. Therefore, we decided to consider cases registered from September to August to have occurred in a single vaccination period or season.

Covariates

We included the following covariates, based on evidence indicating their potential for confounding the association between dementia and influenza vaccination: age (i.e. date of birth), sex, marital status, educational level, level of urbanization, health resource use, and comorbidity. Age was divided into seven five-year intervals (65-69, 70-74, 75-79, 80-84, 85-89, 90-94, and ≥95). Marital

status was dichotomized (married and unmarried). Urbanization of residence was divided into three levels (High, Intermediate, and Low) based on the classification by Statistics Denmark. This classification classifies the residential municipalities according to population density following the Degree of Urbanization developed by Eurostat.[24] Education was categorized into three levels of years of education (≤9 years: Low, 10-12 years: Medium, and ≥13 years: High). All sociodemographic factors were assessed at the closest possible time before the start of the vaccination season of each year (August 31 in the corresponding year for age and urbanization of residence and the annual status in the previous year for the remaining covariates). We defined health resource use as the number of contacts with the general practitioner (GP) and the number of concomitant medications, both factors assessed during the year before the start of the vaccination season. Information on GP contacts was divided into three groups (≤6, 7-12, and >12). Number of concomitant medications was drawn from redeemed prescriptions and divided into three groups (≤4, 5-9, and ≥10) according to previously described cutoff values related to adverse outcomes (i.e., polypharmacy).[25] We defined comorbidities based on the Charlson Comorbidity Index (CCI) [26]. We calculated a cumulative CCI score based on diagnoses of 19 chronic diseases excluding dementia, weighted according to their health burden, and divided the score into five groups (0, 1, 2, 3, and ≥4).

Statistical analysis

To examine time trends, we performed repeated cross-sectional analyses on the number of registered influenza vaccinations in each influenza season. We estimated the vaccine coverage in each year from 2002/03 to 2018/19. To compare the coverage between people with and without dementia, we estimated the crude vaccine coverage for the two groups, as well as standardizing the coverage for those with dementia according to the age- and sex distribution for people without dementia.

The association between dementia and influenza vaccination uptake was explored in two steps. First, we calculated the distribution of vaccination and covariates in 2018/19 according to dementia status. Second, we performed multivariate logistic regression analyses to estimate the odds ratio (OR) of influenza vaccination. As previous studies have indicated a different effect of dementia on the likelihood of influenza vaccination for home-living people compared to nursing home residents, we combined dementia status and living status and examined four exposure groups: 1) Home-living people without dementia, 2) home-living people with dementia, 3) nursing home residents without dementia, 4) nursing home residents with dementia. In all analyses, home-living

people with dementia were chosen as the reference group. In model one, we adjusted for age and sex. In model two, we included the remaining covariates.

Sensitivity analyses

From 1996, older inhabitants of the Municipality of Copenhagen were offered a free vaccine at pop-up vaccination clinics, in hospitals, or at nursing homes. These vaccinations were not registered on an individual level and it is therefore not possible to identify individuals who utilized this offer in the national registries. The vaccine coverage from 1996 through 1998 was 56% of the approximately 63,000 people in the target group,[27] and after the national vaccination offer was introduced, the majority of the older inhabitants of Copenhagen continued to use the municipal offer. To examine the impact of the assumed misclassification of influenza vaccination among inhabitants of the Municipality of Copenhagen, we estimated the time trend and association between dementia and influenza vaccination, excluding those living in the Municipality of Copenhagen on September 1 of each year. We performed all analyses in SAS version 9.4.

Results

We included 800,387 individuals in 2002/03, 23,589 of whom had a dementia diagnosis. In 2018/19, this number had increased to 1,122,319; 35,549 with dementia (Figure 1).

Figure 1. Study population in 2002 (A) and 2018 (B).

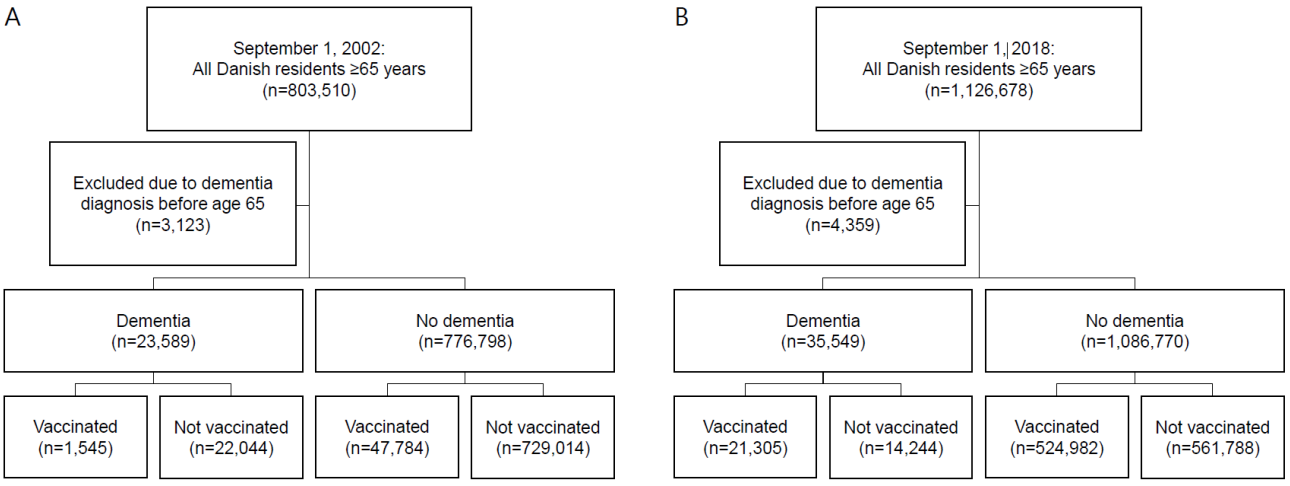


Table 2 shows the characteristics of the study population in 2018/19 stratified by dementia status. A notable difference was that 45.9% of those with dementia were living in nursing homes compared to only 1.9% of those without dementia. People with dementia were also considerably

older, more often female and unmarried, had a lower educational level, more GP contacts, a higher number of drugs, a higher CCI score, and slightly higher residential urbanization.

We found similar trends for influenza vaccine coverage in people with and without dementia, with an increase in coverage until 2008/09 and a subsequent plateau until the end of the study period. However, there were noticeable differences between the groups. The coverage among those with dementia peaked at 59.9% in 2018/19 while the highest coverage among those without dementia was 51.1% in 2009/10. After 2006/07, the coverage was consistently higher in those with dementia (difference between 4.3 and 13.9 percentage points). When standardized to the age and sex distribution of those without dementia, the vaccine coverage for people with dementia attenuated but remained between 2.0 and 7.5 percentage points higher from 2007/08 to 2018/19 (Figure 2).

Table 3 shows the number of vaccinated and odds ratios (ORs) of vaccination for combinations of living status and dementia status. Adjusted for all covariates, home-living people with dementia were 24% less likely to be vaccinated compared to home-living people without dementia (OR: 0.76; 95% CI: 0.74-0.78). Nursing home residents both with (OR: 1.28; 95% CI:1.24-1.33) and without dementia (OR: 1.18; 95% CI: 1.14-1.22) were more likely to be vaccinated than home-living people. In the fully adjusted model, higher age, more GP contacts, higher number of drugs, and higher CCI score were all associated with higher odds of vaccination while lower educational level, lower urbanization, and being unmarried were associated with lower odds of getting vaccinated (Table 3).

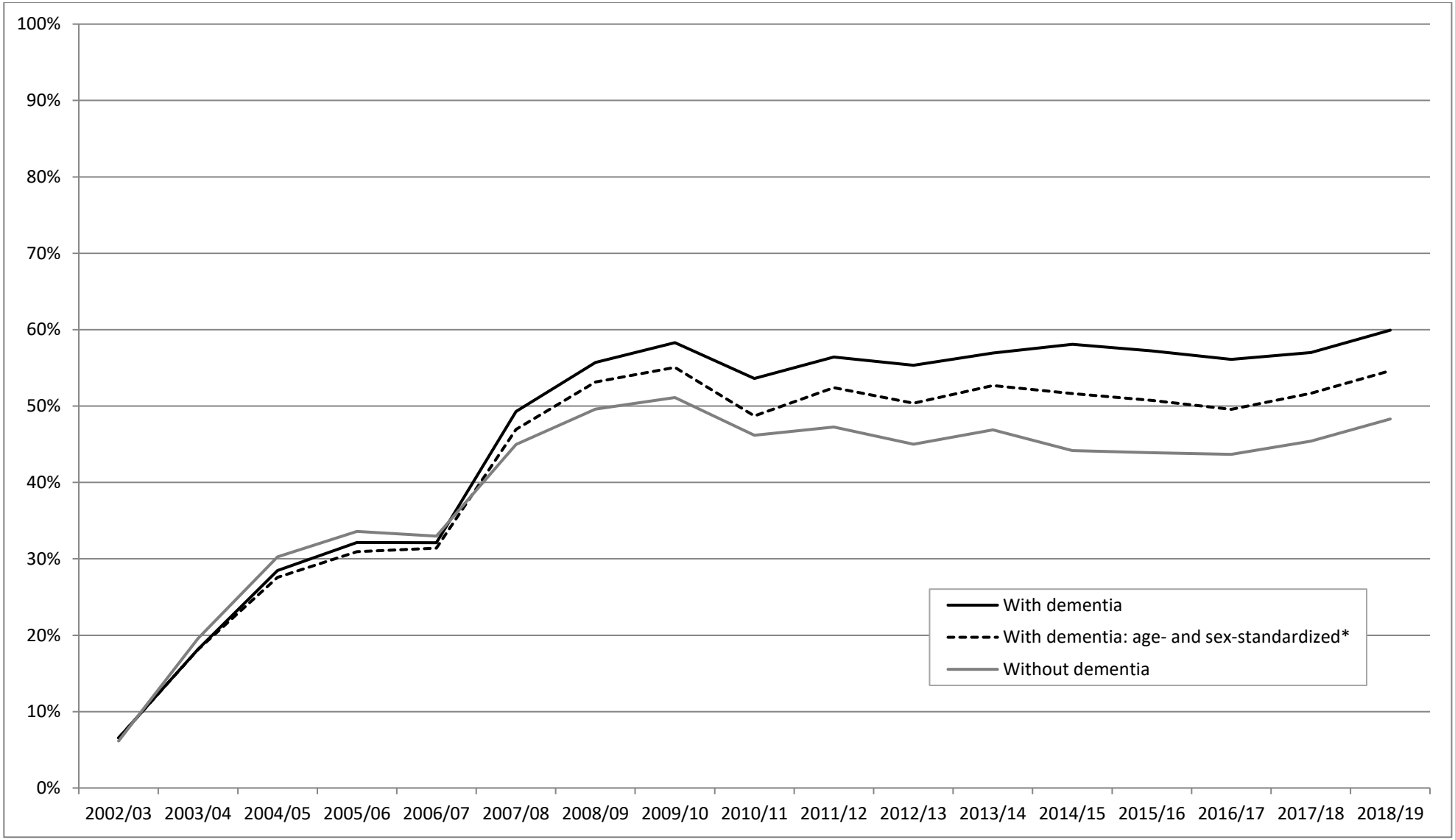
Excluding inhabitants of the Municipality of Copenhagen decreased the study population from 5.6% to 7.6% for each study year, corresponding to approximately 58,000 individuals on average. Figure A1 shows the population numbers in 2002 and 2018 after exclusion (Figure A1 in the appendix). In this subsample, there was a marginally higher coverage of vaccination for both people with and without dementia, particularly from 2004/05 through 2013/15 (Figure A2 in the appendix). The difference in study characteristics between people with and without dementia on September 1, 2018, was almost identical to that of the entire population, as were the ORs in the minimally and fully adjusted models (Table A1 and A2 in the appendix)

Table 2. Characteristics of the study population by dementia status in 2018/19

	Dementia (N: 35,549)	No dementia (N: 1,086,770)
	N (%)	N (%)
Age in years		
65-69	947 (2.7)	317,355 (29.2)
70-74	4,210 (11.9)	321,068 (29.5)
75-79	7,024 (19.8)	211,274 (19.4)
80-84	9,223 (25.9)	130,424 (12.0)
85-89	8,216 (23.1)	68,073 (6.3)
90-94	4,708 (13.2)	29,755 (2.8)
≥95	1,221 (3.4)	8,821 (0.8)
Sex		
Female	21,867 (61.5)	585,099 (53.8)
Marital status		
Unmarried[a]	21,362 (60.1)	447,228 (41.2)
Educational attainment		
High	5,838 (16.9)	252,449 (23.7)
Medium	11,771 (34.2)	435,960 (41.0)
Low	16,831 (48.9)	375,570 (35.3)
Living status		
Nursing home	16,329 (45.9)	20,898 (1.9)
Residential urbanization		
High	10,800 (30.5)	290,936 (26.8)
Intermediate	12,466 (35.3)	375,669 (34.7)
Low	12,111 (34.2)	416,801 (38.5)
General practitioner contacts[b]		
≤6	4,437 (12.5)	421,982 (38.8)
7-12	6,961 (19.6)	297,402 (27.4)
>12	24,151 (67.9)	367,386 (33.8)
Number of drugs[b]		
≤4	6,208 (17.5)	468,181 (43.1)
5-9	12,901 (36.3)	362,703 (33.4)
≥10	16,440 (46.2)	255,886 (23.5)
CCI[c] score		
0	11,743 (33.0)	529,306 (48.7)
1	7,215 (20.3)	175,972 (16.2)
2	6,680 (18.8)	186,858 (17.2)
3	3,929 (11.1)	78,050 (7.2)
≥4	5,982 (16.8)	116,584 (10.7)
Vaccination status		
Vaccinated	21,305 (59.9)	524,982 (48.3)

[a]Including divorced and widowed. [b]Assessed during the 12 months prior to the assessment of influenza vaccination. [c]Charlson Comorbidity Index.

Figure 2. Time trends of influenza vaccination rates among people aged ≥65 years with and without dementia from 2002/03 to 2018/19.



*Standardized to age- and sex-distribution of those without dementia

Table 3. Number of vaccinated against influenza virus and odds ratios (OR) of influenza vaccination for combinations of living- and dementia status and covariates

	Vaccinated (N)	Model 1[a] OR (95% CI)	Model 2[b] OR (95% CI)
Living status/dementia			
Home-living/no dementia (ref)	511,241	1	1
Home-living/dementia	10,185	0.91 (0.88-0.94)	0.76 (0.74-0.78)
Nursing home/no dementia	13,741	1.58 (1.53-1.63)	1.18 (1.14-1.22)
Nursing home/dementia	11,120	1.64 (1.59-1.70)	1.28 (1.24-1.33)
Age in years			
65-69 (ref)	116,257	1	1
70-74	154,682	1.58 (1.56-1.59)	1.50 (1.48-1.51)
75-79	119,787	2.12 (2.09-2.14)	1.90 (1.88-1.93)
80-84	82,897	2.55 (2.51-2.58)	2.20 (2.17-2.23)
85-89	46,266	2.69 (2.65-2.74)	2.26 (2.23-2.31)
90-94	20,644	2.72 (2.56-2.68)	2.20 (2.21-2.25)
≥95	5,754	2.36 (2.27-2.46)	2.07 (1.97-2.18)
Sex			
Male (ref)	251,086	1	1
Female	295,201	0.95 (0.95-0.96)	0.98 (0.98-0.99)
Marital status			
Married (ref)	324,566	1	1
Unmarried[c]	221,609	0.78 (0.77-0.78)	0.73 (0.72-0.73)
Educational attainment			
High (ref)	132,105	1	1
Medium	213,101	0.83 (0.82-0.84)	0.79 (0.78-0.80)
Low	190,200	0.75 (0.74-0.76)	0.70 (0.69-0.71)
Urbanization level			
High (ref)	158,598	1	1
Intermediate	191,404	0.87 (0.86-0.88)	0.86 (0.85-0.87)
Low	195,330	0.75 (0.74-0.75)	0.76 (0.75-0.76)
General practitioner contacts[d]			
≤6 (ref)	151,648	1	1
7-12	155,686	1.81 (1.79-1.82)	1.49 (1.48-1.51)
>12	238,953	2.53 (2.51-2.56)	1.72 (1.70-1.74)
Number of drugs[d]			
≤4 (ref)	172,144	1	1
5-9	200,396	1.86 (1.85-1.88)	1.50 (1.48-1.51)
≥10	173,747	2.73 (2.71-2.76)	1.92 (1.89-1.94)
CCI[e] score			
0 (ref)	222,723	1	1
1	96,864	1.49 (1.47-1.50)	1.20 (1.19-1.21)
2	103,324	1.50 (1.48-1.51)	1.24 (1.22-1.25)
3	48,698	1.82 (1.79-1.85)	1.30 (1.27-1.32)
≥4	74,678	1.95 (1.93-1.98)	1.29 (1.27-1.31)

[a]Adjusted for age and sex. [b]Model including all variables in the table. [c]Including divorced and widowed.
[d]Assessed in the year prior to assessment of influenza vaccination. [e]Charlson Comorbidity Index.

Discussion

In this study based on the entire Danish population of older adults, we found that elderly people with dementia living at home had lower odds of obtaining an influenza vaccination compared with home-living older adults without dementia. Nursing home residents both with and without dementia were more likely to be vaccinated than those living at home. Our study was unique in including an entire nationwide population of older adults with the possibility to stratify by dementia and living status. Furthermore, our findings highlight that although uptake of influenza vaccines has improved since the introduction of the Danish vaccination program, coverage has remained below 60% among older adults regardless of dementia status.

Our findings of lower vaccination odds among home-living people with dementia is in line with a large study from the UK reporting an influenza vaccination likelihood of 4% lower in home-living older adults with dementia compared with those without dementia. The smaller difference in vaccination likelihood between home-living with and without dementia in the UK study may be due to a higher misclassification of dementia. The UK study was entirely based on primary care data, and while dementia is underreported in the Danish secondary care registers, the issue is likely even bigger in primary care.[13,28] Furthermore, there is generally a higher uptake of influenza vaccines in the UK compared to Denmark, which could also partly explain the smaller differences between older adults with and without dementia.[29] Similar to our study, a cross-sectional study on non-institutionalized older adults in Spain reported a lower likelihood of revaccination for those with dementia.[12]

Our finding of the highest odds of vaccination being among nursing home residents with dementia was in line with the above-mentioned study from the UK. However, the differences in vaccination likelihood between home-living without dementia and nursing home residents both with and without dementia were considerably lower in the UK study than in the present study.[13] Studies only including nursing home residents have shown inconsistent results. In a study of 4,076 French nursing home residents, dementia was associated with a higher likelihood of vaccination (OR: 1.53; 95% CI: 1.17-2.00).[9] Having cognitive deficits in general has also been related to a higher likelihood of vaccination in a large sample of nursing home residents in the US.[7] However, another

large-scale study from the US did not find an effect of dementia on vaccine uptake among nursing home residents.[11]

In line with previous studies, we found that higher age, more GP contacts, and higher number of drugs were associated with higher odds of vaccination, while lower education, lower urbanization, and being unmarried were associated with lower odds of receiving a vaccine.[10–13,22,23,30]

The time trends of influenza vaccination we identified in this study were similar for both people with and without dementia, showing an initial increase and a plateau from 2008/09 to 2018/19. No published study has explored the time trends of influenza vaccination among people with dementia; however, our results are in line with surveillance data from Statens Serum Institut [20] as well as WHO surveys.[29] These surveys reported considerable differences among the countries from the WHO European Region in both trends and magnitude of influenza vaccine uptake, ranging from 0.03% in Ukraine in 2014/15 to 83% in the Netherlands in 2008/09.[29] In Denmark, as well as in most countries in the European Region, there was a plateau or a slight decrease in uptake from 2008/09 to 2014/15, with similar trends having been reported in other studies.[31]

Our finding that dementia among home-living older adults was associated with 24% lower odds of vaccination could reflect several mechanisms. One source of this difference may be that cognitive impairment has been associated with poorer disease management, including a lack of insight into one's health status, lower adherence to treatment and preventive measures, and reduced ability to manage and meet healthcare appointments.[6] Due to these problems, GPs and home care staff should have a strong focus on offering vaccination to home-living older adults with dementia. In nursing homes, with high availability of healthcare staff and vaccination policies due to increased transmission risk, the above-mentioned barriers may be less important and explain our findings of higher vaccination odds in nursing home residents.

As mentioned previously, influenza vaccination has been free of charge for people aged 65 years and older in Denmark since the fall of 2002. The initially low vaccine uptake and subsequent increase could have multiple explanations. In the main analyses based on the entire population of older adults, those living in Copenhagen may have preferred the municipal vaccination offer at first but then slowly started using the national offer instead. The similar trend when excluding inhabitants of Copenhagen may point to low initial awareness of the national offer among older adults in the remaining part of the country. The plateau in vaccination rate since 2009/10 could

suggest a saturation in the influenza vaccine uptake in the Danish population. However, data from SSI show that, after being around 50% for many years, the vaccine uptake among all Danish residents age 65 or older in season 2020/21 and 2021/22 met the goal set by WHO of a minimum of 75% immunization among older adults.[20,32] The increased uptake may be the result of a greater awareness of viral infections and vaccine possibilties due the COVID pandemic. Interventions targeting home-living older adults with dementia could potentially help sustain the higher uptake in the future. Furthermore, even a small improvement in the uptake among home-living with dementia could have great societal benefits as people with dementia have a higher risk of serious infections and subsequent adverse outcomes compared to cognitively intact older people.[4,5]

The main strength of our study is the use of nationwide registries, enabling us to follow the rates of influenza vaccination in an entire elderly population from the inception of the Danish vaccination program in 2002 until 2019. The registries also included highly valid information on nursing home status [19] which has not been accounted for in most previous studies. There are, however, several limitations related to the use of Danish registries. First, even though the registered dementia diagnoses have a high positive predictive value, the registries only contain dementia diagnoses from secondary care, which include approximately 46% of the estimated dementia cases in Denmark.[33] We tried reducing the misclassification of dementia by also identifying cases through redeemed prescriptions of anti-dementia medication. Second, another potential source of misclassification was the fact that the Danish National Health Service Register does not include information on vaccinations administered outside primary care. As previously mentioned, this was the case for an unknown number of older inhabitants of the Municipality of Copenhagen during the study period. However, excluding those living in Copenhagen on September 1 for each study year had only a negligible impact on the time trends and did not change the association between dementia and vaccination. Some employers may also provide free vaccination to their staff, but given that our study population was near or above the average retirement age in Denmark we regarded this a smaller concern. Third, the registries did not include information on several potentially important confounders of the association between dementia and influenza vaccination such as lifestyle factors.[23]

In conclusion, in this nationwide study, the rate of free-of-charge influenza vaccinations among older adults increased from 2002/03 until 2009/10 and has since plateaued, both for people with and without dementia. Home-living older adults with dementia had the lowest odds of vaccination,

when accounting for potential confounders, and could be an important target group for future vaccination campaigns. By taking advantage of the current awareness regarding viral infections due to COVID-19, it may be possible to create a sustainably higher uptake and regularly reach the WHO target of 75% influenza immunization among older people. This could be of particular benefit for groups at high risk of adverse outcomes of infections such as people with dementia.

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Competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Christiane Gasse reports a relationship with Novo Nordisk Foundation and Alfred Benzon Foundation that includes funding/grants.

Ethical approval

Danish law does not require ethics committee approval or informed patient consent for registry-based studies.[34] 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.

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 from 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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Dementia and influenza vaccination:
Time trends and predictors of vaccine uptake among older adults

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Appendix

Figure A1. Study population in 2002 (A) and 2018 (B) – without inhabitants of the Municipality of Copenhagen

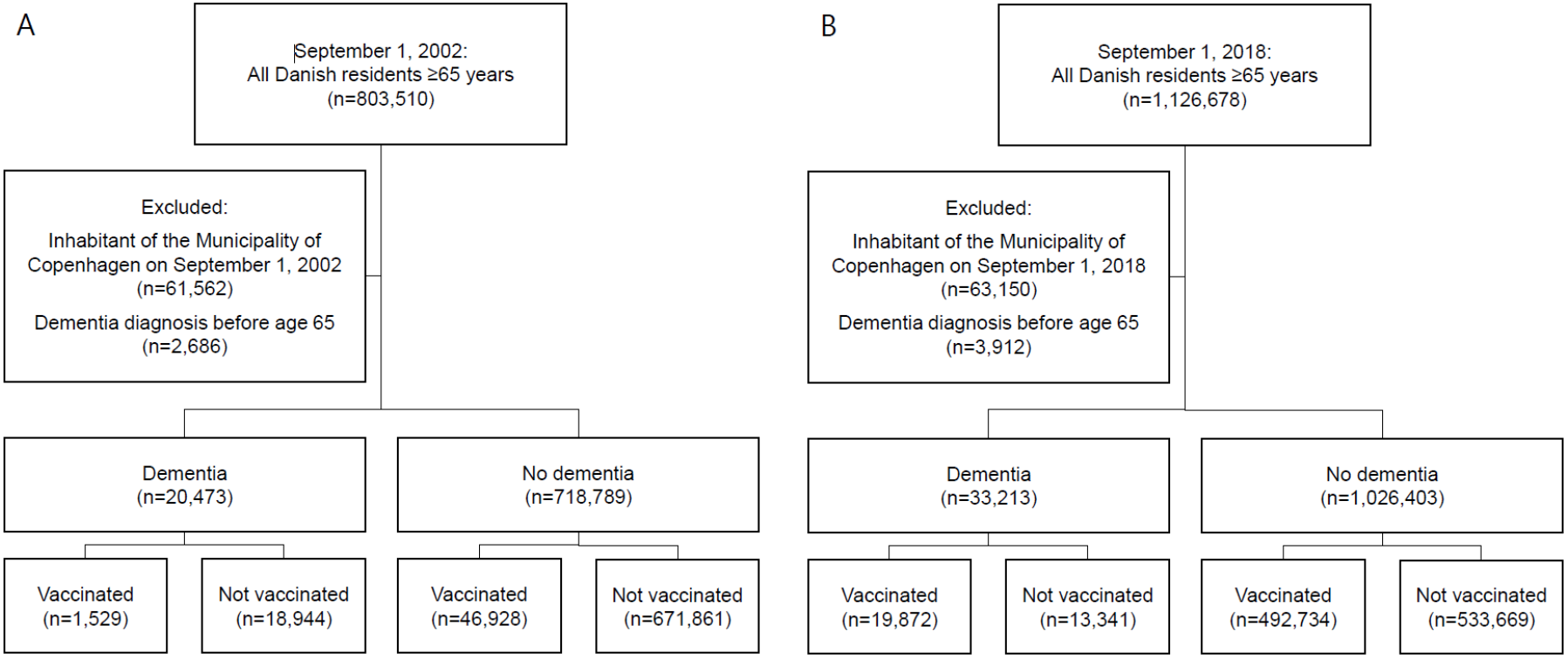
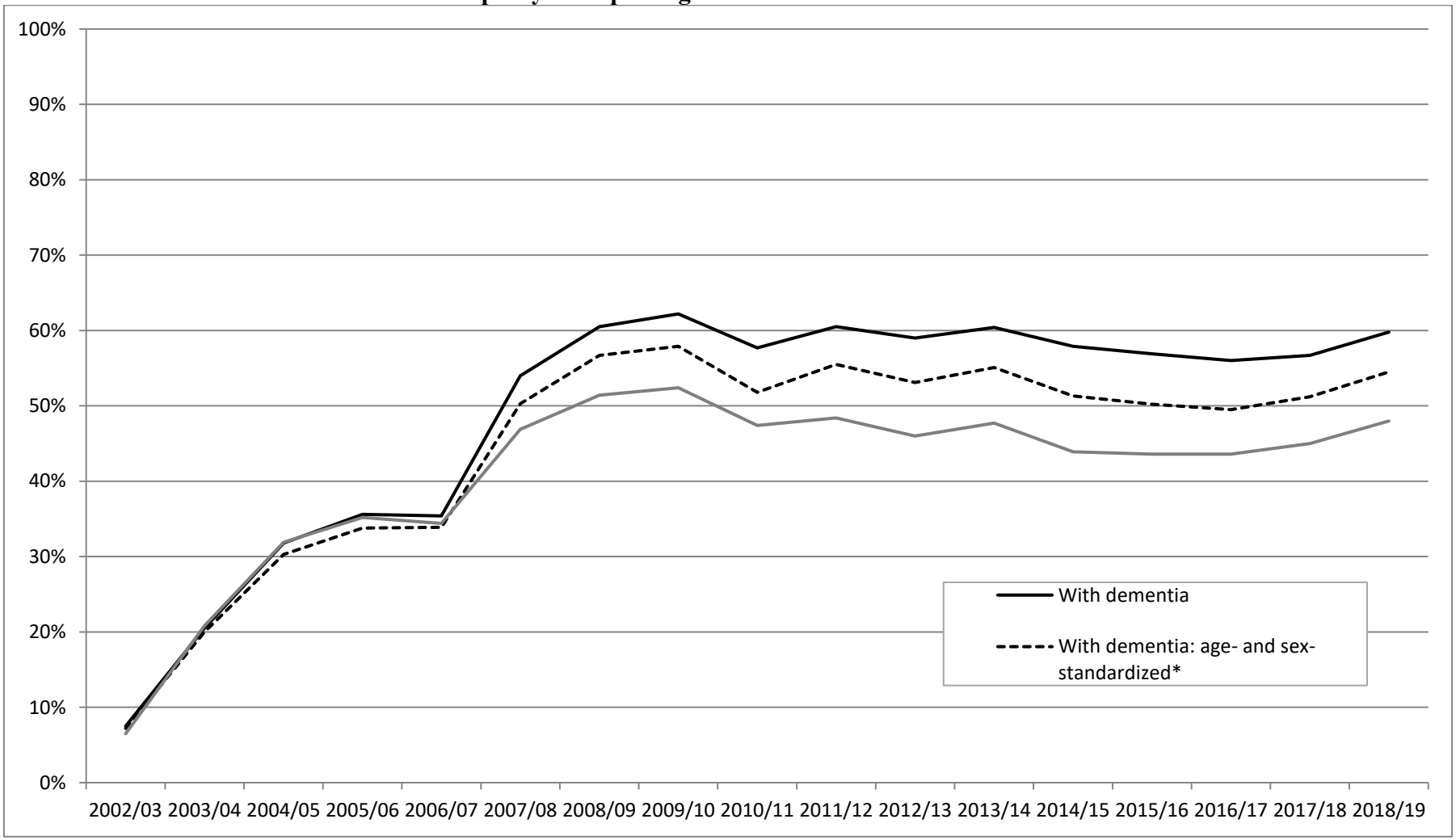


Figure A2. Time trends of influenza vaccination rates among people aged ≥65 years with and without dementia from 2002/03 to 2018/19 - without inhabitants of the Municipality of Copenhagen



*Standardized to age- and sex-distribution of those without dementia

Table A1. Characteristics of the study population by dementia status in 2018/19 - without inhabitants of the Municipality of Copenhagen

	Dementia (N: 33,213) N (%)	No dementia (N: 1,026,403) N (%)
Age in years		
65-69	861 (2.6)	297,379 (29.0)
70-74	3,910 (11.8)	302,798 (29.5)
75-79	6,559 (19.7)	200,356 (19.5)
80-84	8,687 (26.2)	124,600 (12.1)
85-89	7,690 (23.1)	64,864 (6.3)
90-94	4,387 (13.2)	28,185 (2.8)
≥95	1,119 (3.4)	8,221 (0.8)
Sex		
Female	20,300 (61.1)	551,257 (53.7)
Marital status		
Unmarried[a]	19,656 (59.2)	412,465 (40.2)
Educational attainment		
High	5,404 (16.7)	233,084 (23.2)
Medium	10,991 (34.1)	414,382 (41.2)
Low	15,854 (49.2)	358,380 (35.6)
Living status		
Nursing home	15,166 (45.7)	19,279 (1.9)
Residential urbanization		
High	8,464 (25.6)	230,569 (22.6)
Intermediate	12,466 (37.7)	375,669 (36.7)
Low	12,111 (36.7)	416,801 (40.7)
General practitioner contacts[b]		
≤6	4,141 (12.5)	397,566 (38.7)
7-12	6,542 (19.7)	280,986 (27.4)
>12	22,530 (67.8)	347,851 (33.9)
Number of drugs[b]		
≤4	5,768 (17.4)	441,290 (43.0)
5-9	12,037 (36.2)	343,301 (33.4)
≥10	15,408 (46.4)	241,812 (23.6)
CCI[c] *score*		
0	11,084 (33.4)	501,083 (48.8)
1	6,750 (20.3)	166,386 (16.2)
2	6,231 (18.8)	176,619 (17.2)
3	3,661 (11.0)	73,497 (7.2)
≥4	5,487 (16.5)	108,818 (10.6)
Vaccination status		
Vaccinated	19,872 (59.8)	492,734 (48.0)

[a]Including divorced and widowed. [b]Assessed during the 12 months prior to the assessment of influenza vaccination. [c]Charlson Comorbidity Index.

Table A2. Number of vaccinated against influenza virus and odds ratios (OR) of influenza vaccination for combinations of living- and dementia status and covariates - without inhabitants of the Municipality of Copenhagen

	Vaccinated (N)	Model 1[a] OR (95% CI)	Model 2[b] OR (95% CI)
Living status/dementia			
Home-living/no dementia (ref)	480,098	1	1
Home-living/dementia	9,563	0.92 (0.90-0.95)	0.77 (0.74-0.79)
Nursing home/no dementia	12,636	1.58 (1.53-1.63)	1.19 (1.15-1.23)
Nursing home/dementia	10,309	1.65 (1.59-1.71)	1.29 (1.24-1.34)
Age in years			
65-69 (ref)	107,636	1	1
70-74	144,533	1.58 (1.56-1.60)	1.50 (1.48-1.51)
75-79	112,998	2.13 (2.11-2.16)	1.91 (1.89-1.94)
80-84	78,876	2.57 (2.54-2.61)	2.21 (2.18-2.24)
85-89	43,864	2.72 (2.68-2.77)	2.28 (2.24-2.32)
90-94	19,411	2.64 (2.58-2.70)	2.20 (2.14-2.25)
≥95	5,288	2.34 (2.25-2.44)	2.05 (1.94-2.16)
Sex			
Male (ref)	236,411	1	1
Female	276,195	0.95 (0.95-0.96)	0.99 (0.98-0.99)
Marital status			
Married (ref)	309,489	1	1
Unmarried[c]	203,013	0.77 (0.77-0.78)	0.73 (0.72-0.73)
Educational attainment			
High (ref)	121,171	1	1
Medium	201,211	0.84 (0.83-0.85)	0.79 (0.78-0.80)
Low	180,553	0.75 (0.75-0.76)	0.70 (0.70-0.71)
Urbanization level			
High (ref)	124,917	1	1
Intermediate	191,404	0.89 (0.88-0.90)	0.89 (0.88-0.90)
Low	195,330	0.76 (0.76-0.77)	0.78 (0.77-0.79)
General practitioner contacts[d]			
≤6 (ref)	141,219	1	1
7-12	146,010	1.81 (1.79-1.83)	1.49 (1.48-1.51)
>12	225,377	2.56 (2.53-2.58)	1.72 (1.70-1.74)
Number of drugs[d]			
≤4 (ref)	160,463	1	1
5-9	188,446	1.87 (1.85-1.89)	1.50 (1.48-1.51)
≥10	163,697	2.76 (2.73-2.79)	1.92 (1.90-1.95)
CCI[e] score			
0 (ref)	209,038	1	1
1	91,197	1.50 (1.48-1.51)	1.20 (1.19-1.22)
2	97,088	1.50 (1.49-1.52)	1.24 (1.22-1.25)
3	45,791	1.84 (1.81-1.87)	1.30 (1.28-1.33)
≥4	69,492	1.97 (1.94-2.00)	1.30 (1.28-1.32)

[a]Adjusted for age and sex. [b]Model including all variables in the table. [c]Including divorced and widowed. [d]Assessed in the year prior to assessment of influenza vaccination. [e]Charlson Comorbidity Index.

STUDY II

The effect of influenza vaccination on hospitalization and mortality among people with dementia

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Abstract

INTRODUCTION: People with dementia have an increased risk for infection-related complications, which may be mitigated by common vaccinations. The aim was to investigate the association between influenza vaccination and the rates of all-cause and influenza-related hospitalizations and deaths among older adults with dementia.

METHODS: We followed all Danish residents aged 65 and above from September 1, 2002, to August 31, 2018. Residents turning 65 years old or receiving a dementia diagnosis during the study period were included in the study from the first following September 1. Vaccination status was reset, and covariates assessed, on September 1 each year. We used proportional hazard Cox regression to compare rates of all-cause hospitalization, hospitalization with a respiratory infection, hospitalization with influenza or pneumonia, and all-cause mortality for vaccinated and unvaccinated.

RESULTS: Across the entire study period, we included 1,754,164 individuals, 134,002 with dementia. Rates of hospitalization were 9-10% lower, and the mortality rate 9% lower, for vaccinated compared to unvaccinated among people with dementia.

DISCUSSION: Influenza vaccination was associated with lower rates of hospitalization and mortality among people with dementia. Further exploration of the preventive potential of influenza vaccination among people with dementia is important for shaping interventions in this vulnerable group.

Keywords: Dementia, Vaccination, Prevention, Infection, Effectiveness

Introduction

Respiratory infections are one of the leading causes of hospitalizations and deaths among older adults.[1] Among older people with dementia, studies have found a higher rate of hospitalization and mortality related to respiratory infections,[2–5] as well as a higher influenza-related mortality.[6,7] There are many potential reasons why people with dementia have a high burden of infection. Patient-specific factors include generally reduced immunity, reduced ability to communicate infection symptoms, and often presenting with atypical signs of infections.[8–10] Structural factors include living situations with a high risk of infection such as nursing homes.[11] and a reduced likelihood of receiving common vaccinations such as the influenza vaccine.[12]

An increased risk of infection-related complications among people with dementia[8–10] may translate to a greater effect of preventive measures such as influenza vaccination compared to the general population. While there have been multiple reports of the beneficial effects of influenza vaccinations on infection-related hospitalizations and mortality among high-risk groups and older adults in general,[6,13–18] no study has investigated how influenza vaccination could impact such outcomes specifically for people with dementia. Documenting a preventive effect in this vulnerable group would be important for promoting influenza vaccination. This study aimed to investigate the association between influenza vaccination and the rates of all-cause and influenza-related hospitalizations and deaths among older adults with dementia.

Methods

Population and design

The study was based on a dynamic cohort drawn from the Danish national registries. The study population was defined on September 1, 2002, as all Danish residents aged 65 years or older, without a dementia diagnosis before age 65, and followed until August 31, 2018, emigration, or death, whichever came first. Residents in Denmark turning 65 years old during the study period were included in the study from the following 1st of September.

Dementia

Dementia was defined as a first diagnosis of dementia in the National Patient Register[19] or Psychiatric Central Research Register,[20] according to the International Classification of Disease (ICD), or the first redeemed prescription of anti-dementia drugs in the National Prescription

Registry,[21] according to the Anatomical Therapeutic Chemical Classification System (ATC) (see Table A1 for specific codes).

Influenza vaccination

We identified influenza vaccinations through the National Health Service Register.[22] In Denmark, free-of-charge influenza vaccinations were offered to people aged ≥65 years during the study period and were administered by their general practitioner (GP). The GPs are reimbursed when reporting the provided services to the health authorities, and these services are recorded in the National Health Service Register.[22] To increase the completeness of influenza vaccination information in our study, we also included data from the National Prescription Registry.[21]

Outcomes

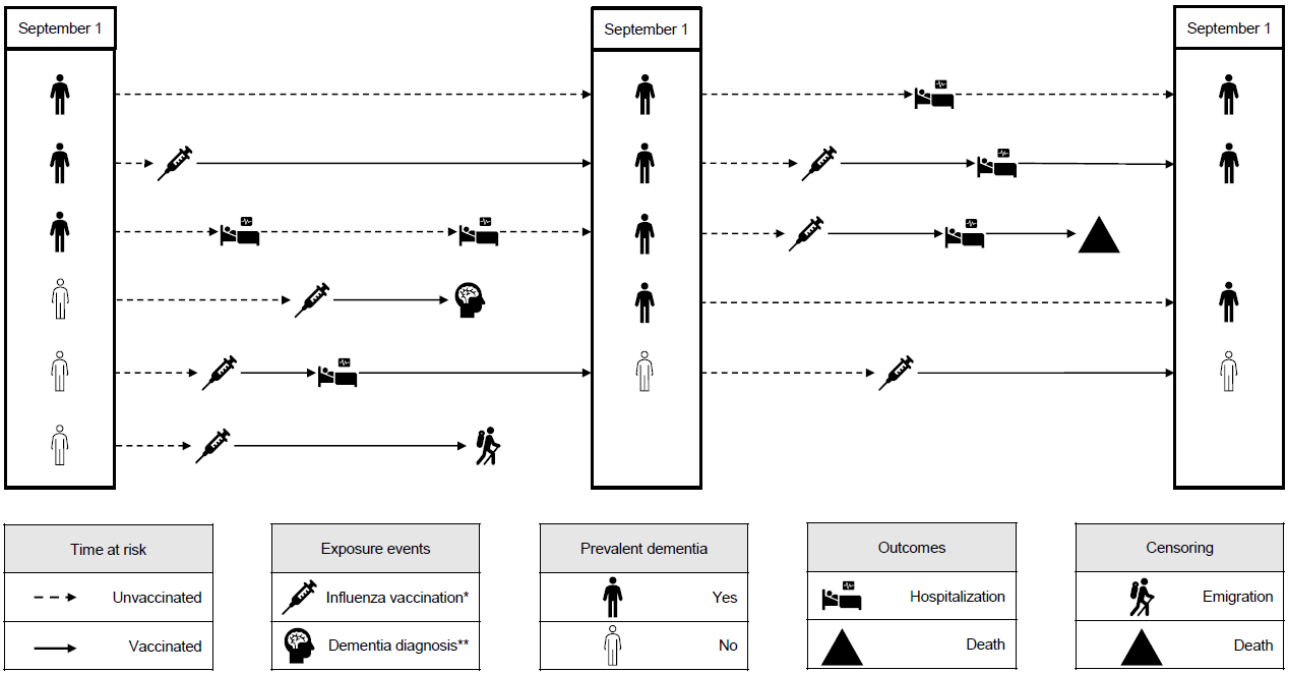
Three outcomes were investigated: All-cause hospitalization, hospitalization with a respiratory infection, hospitalization with influenza or pneumonia, and all-cause mortality. Hospitalizations were defined as primary and secondary diagnoses during an inpatient or emergency contact, as recorded in the National Patient Register.[19] The specific codes defining hospitalization with respiratory infection, and influenza or pneumonia, are listed in the appendix (Table A1). To avoid counting relocations of patients within or between hospital departments and administrative registrations of diagnoses as separate admissions, we collapsed all records that occurred on the same day or within one day into a single hospitalization (detailed in Janbek et al. 2021).[4] All-cause mortality was defined as having a death date in the Civil Registration System.[23]

Covariates

The following covariates were selected based on their potential for confounding the association between influenza vaccination and hospitalizations or death: Age, sex, highest attained educational level at age 65 years, selected comorbidities, number of visits to their general practitioner (GP), and hospitalization with influenza or pneumonia in the past 12 months. Information on age and sex was drawn from the Civil Registration System[23] and educational data came from the Population Education Register.[24] Comorbidities were identified in the National Patient Register and the Prescription Registry as the first disease diagnosis or the first medication (a proxy for disease diagnosis in the primary care setting where no diagnostic codes are directly registered). Selected comorbidities were the disease groups of pulmonary, cardiovascular, liver, renal, and metabolic diseases as well as diabetes and cancer (see table A1 in the appendix). The selection of comorbidities was guided by the list of chronic illnesses that have qualified individuals for free

influenza vaccination under the Danish vaccination program since 2007, and further guided by previous literature.[25] Visits to a GP were identified in the National Health Service Register and divided into three groups (≤6, 7-12, and >12). Previous influenza or pneumonia hospitalizations were identified in the National Patient Register.

Figure 1. Illustration of study design with examples of individual trajectories across two study years



*Vaccination status was reset on September 1. **An individual was censored at the dementia date and no longer followed in that study period but entered the next period as a person with dementia.

Data analyses

Main analyses

The study was designed as a survival analysis partly inspired by Jackson et al.[26] Figure 1 illustrates the study design with examples of individual trajectories across two study years. We used proportional hazard Cox regression to compare rates of all-cause hospitalization, hospitalization with a respiratory infection, hospitalization with influenza or pneumonia, and all-cause mortality for vaccinated and unvaccinated. We estimated hazard ratios (HRs) and 95% confidence intervals (CI) corresponding to a 5% significance level, with calendar time as the underlying time scale. All individuals were considered unvaccinated from September 1 of every year until the date of vaccination and then vaccinated from that point onward until August 31 of that year. We stratified the analyses into people with and without dementia, assessed on September 1 of each year. People

diagnosed with dementia during the study period were censored on the date of diagnosis and subsequently included in the dementia group from the following September 1, provided they survived and did not emigrate in the interim.

In the main analyses, we combined data from all study years and adjusted for age, sex, educational attainment, comorbidities, and number of GP visits and hospitalization with influenza/pneumonia in the past 12 months. Sex and educational attainment were assessed at age 65, while age, comorbidities, GP visits, and previous influenza/pneumonia hospitalization were assessed on September 1. We used a version of Cox regression that allowed us to model hospitalizations as recurrent events,[27] such that all hospitalizations were included in the analyses, provided they were separate admissions according to our definition above. The Breslow method accounted for correlated person-time within the same individual.

Sensitivity analyses

First, we estimated the HR of the outcomes before, during, and after the influenza season for each year from 2010 to 2018. We defined a period before, during, and after the influenza season to distinguish between a potential true vaccine effect from an effect biased by unmeasured health differences between the vaccinated and unvaccinated. Jackson et al. applied this method and showed that reported reductions in outcome risk during influenza season were attributed to bias as the largest reduction of risk was observed in the period before influenza season, where it was deemed unlikely to be a true vaccine effect.[26] The start and end of the influenza season in our study were based on National influenza surveillance data from the Danish Microbiology Database (MiBa)[28] and defined as the first and last week with at least 15% positive specimens (see start and end dates of influenza season in Table A2 in the appendix). The information was available as summary data through the WHO's FluNet from 2010 onwards.[29]

Second, we performed analyses stratified on nursing home residency from 2014 to 2018. Nursing home residents were identified through the Care Home Data developed by the Danish Health Data Authority,[30] available from 2014. People were considered nursing home residents from the day of moving into a nursing home onwards.

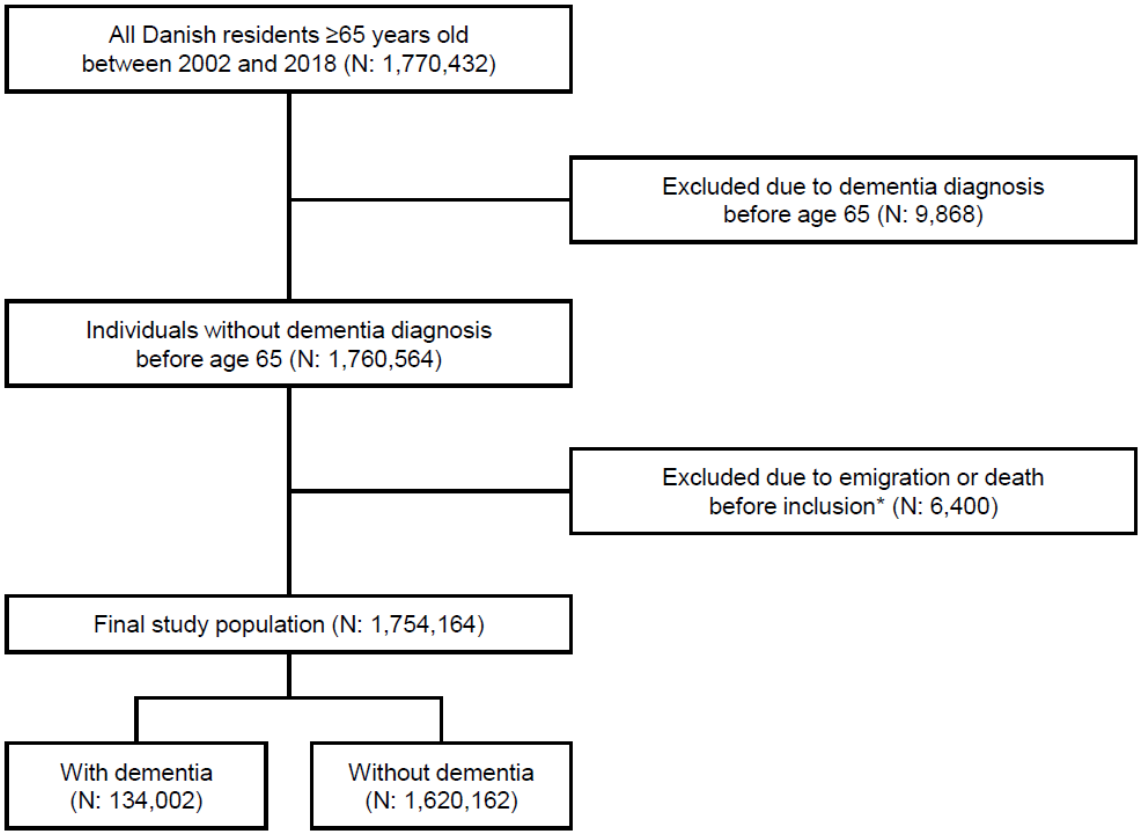
Third, we estimated the association between vaccination and the outcomes separately for the two periods from 2002/03 to 2009/10 and from 2010/2011 to 2017/2018. In a previous study, we found that the former period was characterized by a low initial vaccine coverage which increased considerably up until 2009/10, when it effectively plateaued.[31]

Fourth, we estimated the associations between vaccination and outcomes separately for men and women. Finally, we repeated all analyses, including the other sensitivity analyses, without people living in Copenhagen on September 1. We did this to examine the impact of unregistered vaccinations due to a municipal program of free influenza vaccinations not recorded in our data source. For details of the vaccination program in the Municipal of Copenhagen see Christensen et al. 1998.[32] All analyses were conducted using SAS 9.4 and R 4.3.1.

Results

The study population included 1,754,164 individuals, 134,002 with dementia (Figure 2).

Figure 2. Selection of study population



*Inclusion was defined as the first September 1 after turning 65 years old, from 2002 to 2017.

Table 1 shows the study population characteristics for vaccinated and unvaccinated people with dementia (Table 1). Vaccinated were slightly older, had a higher educational level and comorbidity burden, more visits to their general practitioner in the past 12 months.

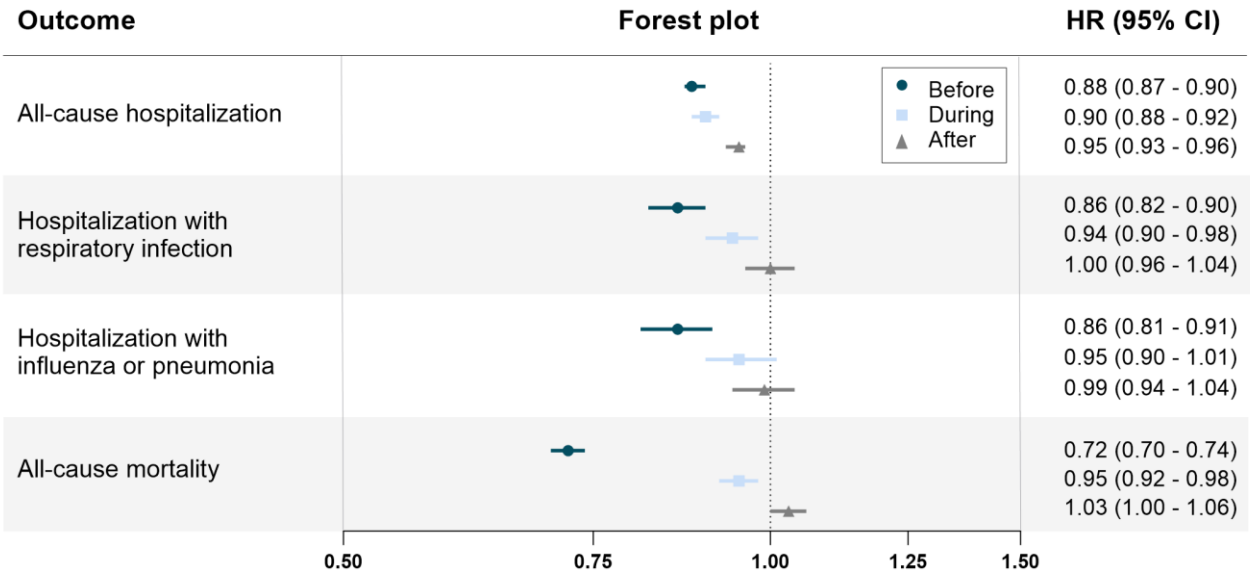
Table 1. Study population characteristics among people with dementia

Characteristics	Number of people on September 1, 2009		Person years during the entire study period	
	Vaccinated N: 19,007 (%)	Unvaccinated N: 13,659 (%)	Vaccinated % (187,860)	Unvaccinated % (266,984)
Age in years				
65-74	2,432 (12.8)	1,951 (14.3)	12.5	15.3
75-84	8,783 (46.2)	5,919 (43.3)	46.1	46.1
≥85	7,792 (41.0)	5,789 (42.4)	41.4	38.6
Sex				
Female	12,420 (65.3)	9,307 (68.1)	64.5	66.9
Educational attainment				
High	471 (2.5)	287 (2.1)	2.8	2.3
Medium	1,453 (7.6)	922 (6.8)	9.2	7.5
Low	13,206 (69.5)	9,264 (67.8)	72.6	66.4
Unknown	3,877 (20.4)	3,186 (23.3)	15.3	23.8
Comorbidities				
Pulmonary	2,228 (11.7)	1,246 (9.1)	12.1	9.7
Cardiovascular	11,050 (58.1)	7,506 (55.0)	60.3	54.4
Diabetes	2,801 (14.7)	1,603 (11.7)	15.2	13.0
Cancer	3,245 (17.1)	2,225 (16.3)	18.5	16.4
Liver	12 (0.1)	20 (0.2)	0.1	0.1
Renal	351 (1.9)	236 (1.7)	2.4	2.0
Hypercholesterolemia	5,666 (25.5)	3,478 (29.8)	37.4	26.8
General practitioner visits in the past 12 months				
≤6	2,261 (11.9)	2,565 (18.8)	10.8	16.1
7-12	3,766 19.8)	3,228 (23.6)	19.3	21.7
>12	12,980 (68.3)	7,866 (57.6)	69.9	62.2
Influenza/pneumonia hospitalization in the past 12 months				
Yes	643 (3.4)	483 (3.5)	3.5	3.2

Table 2 presents the HRs between vaccination and the study outcomes for people with dementia. The fully adjusted HR for vaccinated was 0.90 (95% CI: 0.89-0.91) for all-cause hospitalization when compared to unvaccinated. We found an almost identical estimate for hospitalization with respiratory infection (HR: 0.91; 95% CI: 0.89-0.93), for hospitalization with influenza or pneumonia (HR: 0.91; 95% CI: 0.89-0.93), and for all-cause mortality (HR: 0.91; 95% CI: 0.90-0.92) (Table 2).

In a fully adjusted model, the rate of all-cause hospitalization for vaccinated was 12% lower before the influenza season, 10% lower during the season and 5% lower after the season. For hospitalization with respiratory infections, the rate for vaccinated people was 16% lower before the season, and 6% lower during the season, but no different from unvaccinated after the season. For hospitalization with influenza or pneumonia, the rate for vaccinated people was also 16% lower before the season, however, not different from unvaccinated during or after the season. The all-cause mortality rate was 28% lower before the season, 5% lower during the season, and 3% higher after the season (Figure 3 and Tables A3-6).

Figure 3. Figure 3: Hazard ratios (HR) and 95% confidence intervals (CI) of outcomes for vaccinated compared to unvaccinated individuals before, during, and after the influenza season – among people with dementia



HRs were adjusted for age, calendar year, sex, educational attainment, comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table 2. Hazard ratios for vaccinated compared to unvaccinated among people with dementia

		Model 1*		Model 2†		Model 3‡	
	Number of events	HR	95% CI	HR	95% CI	HR	95% CI
All-cause hospitalization							
Unvaccinated (ref)	224,644	1		1		1	
Vaccinated	154,296	0.95	0.95-0.96	0.95	0.94-0.96	0.90	0.89-0.91
Hospitalization with respiratory infection							
Unvaccinated (ref)	26,287	1		1		1	
Vaccinated	20,439	1.00	0.98-1.02	1.00	0.98-1.02	0.91	0.89-0.93
Hospitalization with influenza or pneumonia							
Unvaccinated (ref)	18,080	1		1		1	
Vaccinated	13,792	0.98	0.95-1.00	0.98	0.95-1.00	0.91	0.89-0.93
All-cause mortality							
Unvaccinated (ref)	61,747	1		1		1	
Vaccinated	43,461	0.95	0.94-0.96	0.95	0.94-0.96	0.91	0.90-0.92

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Stratifying analyses by nursing home residence in people with dementia showed decreased all-cause mortality HRs in both nursing home residents (HR: 0.85; 95% CI: 0.82-0.87) and home-living persons (HR: 0.76; 95% CI: 0.73-0.80). Vaccinated nursing home residents with dementia had rates of all-cause hospitalization similar to unvaccinated (HR: 0.98; 95% CI: 0.96-1.00), while those living at home had lower rates compared to unvaccinated (HR: 0.91; 95% CI: 0.90-0.93). Vaccination was related to decreased rates of hospitalizations and mortality in the entire study period but slightly more so during the first half of the 16-year period (Table A8). Outcome rates among vaccinated were also decreased for both men and women, however, the mortality rate was slightly lower among men (Table A9). Excluding inhabitants of the municipality of Copenhagen showed similar results as in the main analyses, with slightly increased HRs of hospitalizations (Table A10).

When repeating the main analyses for people without dementia, vaccination was associated with a HR for all-cause hospitalization of 0.95 (95% CI: 0.95-0.96), a HR for hospitalization with respiratory infection 0.95 (95% CI: 0.93-0.97), a HR for hospitalization with influenza or pneumonia of 0.92 (95% CI: 0.91-0.93), and a HR for all-cause mortality of 0.72 (95% CI: 0.72-0.73) (Table A12). Similar to people with dementia, the HR among people without dementia for any outcome was lowest before, and highest after, the influenza season. For hospitalizations, the HR associated with vaccination was only lower before and during the influenza season, between 2% and 16%, while mortality was considerably lower in all three periods (Figure A1 and Tables A13-16). Outcome rates were similar to the entire population when stratifying by nursing home residence, except for hospitalization with respiratory infection and influenza/pneumonia, which was no longer different for vaccinated and unvaccinated (Table A17). The associations between vaccination and outcomes were similar in the early and later years and for men and women among people without dementia. Excluding inhabitants of the Municipality of Copenhagen slightly increased the estimated rate but did not change the direction of the associations (Tables A18-19).

Discussion

In this nationwide cohort study, influenza vaccination was associated with moderately reduced hospitalization and mortality rates among people with dementia. Among people without dementia, vaccination was associated with a similar, though slightly higher, rate of hospitalization, and a considerably lower mortality rate.

To our knowledge, this is the first study investigating the effectiveness of influenza vaccines for preventing hospitalizations and death specifically among older adults with dementia. This complicates a comparison of our findings to the existing literature. However, two studies have estimated the association between influenza vaccination and the rate of hospitalization in broader groups at risk of influenza-related complications which included dementia as one of several qualifying conditions. Within these risk groups, studies reported a 30-32% lower hospitalization rate and a 64-70% lower mortality rate associated with influenza vaccinations[13,33]. A meta-analysis from 2018 reported a significantly lower mortality rate among vaccinated in high-risk groups in general of 61%, while there was insufficient evidence for an effect on admission rates[15]. In contrast, we found only 9-10% lower hospitalization rates and a 9% lower mortality rate among people with dementia. The comparatively small effect of vaccination in the present study among people with dementia may be partly attributed to differences in this patient group compared to other risk groups and those without dementia. First, dementia is associated with a higher baseline risk of hospitalization and death compared to many other patient groups [34–37]. Second, the immune response from vaccination for people with dementia may also be lower compared to other patient groups due to a higher degree of immunosenescence[10]. Moreover, confounders may affect the estimated risks differently among people with dementia and other patient groups, e.g., healthy vaccine bias may be more pronounced in the general population without dementia. Finally, although not directly comparable, the lower mortality rate among vaccinated persons without dementia in our study was not as pronounced as in previous studies with low-risk older adults or the general population of older people[13,15,33]. These differences may be due to differences in data sources, settings, and time periods across studies.

The reduced rate of hospitalization and mortality among vaccinated may reflect a true protective effect of the vaccine. However, other explanations should be considered. The lower outcome rates were more pronounced in the period before the start of the influenza season and increased during and after the season. Thus, our findings could be interpreted as being due to people vaccinated before the influenza season having a better overall health status, referred to as healthy vaccinee effect[26,38]. This potential healthy vaccinee bias may be particularly pronounced in a study like the present, where those who are vaccinated regularly likely contribute with more person-years than those with few vaccinations[39]. The fact that the estimated differences diminished in the period during and after may have been due to vulnerable unvaccinated people dying during each study year[26,40]. It is important to note that no generally accepted definition of an influenza season exists,

and that peak influenza periods are difficult to delineate with certainty. However, the start and end dates of the influenza season applied in this study were based on the most comprehensive data available regarding influenza activity in Denmark from 2010 to 2018. In contrast to the healthy vaccinee hypothesis, a higher comorbidity burden and more GP visits in the past 12 months may indicate a generally lower health status among vaccinated. It is possible that adjustment for these factors did not completely remove confounding due to health differences between vaccinated and unvaccinated. Such residual confounding could mean that the vaccine effect in our study is underestimated. Conversely, these baseline differences may also reflect an increased healthcare-seeking behavior among vaccinated. Healthcare use could thus have affected our findings if better treatment of comorbidities among vaccinated leads to a more favorable prognosis and thus lower hospitalization and mortality rates.

The main strengths of this study are the nationwide nature of the data and the long study period spanning 16 years. This allowed us to further examine rates in subgroups of interest and periods before, during, and after the influenza season. As is the case for most studies investigating the effect of influenza vaccination in high-risk groups, our study is limited by the potential for misclassification of influenza vaccination due to self- or employer-paid vaccines that were not recorded in the registers we had access to. However, due to vaccination being free for everyone in our study population and their age being close to, or over, the average retirement age in Denmark, we do not consider this an important source of misclassification. Inhabitants of Copenhagen could also have unregistered vaccinations due to a municipal program offering free vaccines for older adults which were not recorded in the national registries. Excluding those living in Copenhagen from the data increased the estimates by a few percentage points. Still, it did not change the direction or the magnitude of associations between vaccination and outcomes to a meaningful degree. Several studies have reported a likely underdiagnosing of dementia in administrative health records, including the Danish health registers[41]. To accommodate this, we used all available data to identify dementia cases, including prescriptions for dementia medication. Finally, as mentioned above our method of identifying influenza seasons is not based on a generally accepted definition.

In conclusion, while considering several possible explanations, our finding of a 9-10% decreased rate of adverse outcomes for the vaccinated persons with dementia is relevant for informing interventions aimed at promoting influenza vaccinations in this vulnerable group. As this was the first study focusing on people with dementia, more studies are needed to build on our findings and

further explore potential residual confounding. Exploring this topic further is crucial as a protective effect of influenza vaccination on mortality and hospitalization calls for increasing vaccination rate among people with dementia.

Conflict of interest

None.

Data availability statement

This study is based entirely on anonymized personal data in the Danish national registries. This data is only accessible with authorization from the Danish Data Protection Agency, the Danish Health Authority, the Danish Health Data Authority, the Danish Medicines Authority, and Statistics Denmark.

Ethics statement

Danish law does not require informed patient consent or ethics committee approval for registry-based studies.[42] This study is part of a project that has been approved by the Danish Data Protection Agency, Statistics Denmark and the Danish Health Data Authority.

Author contributions

Andreas Moses Appel: Conceptualization (equal); writing – original draft (lead); formal analysis (lead); writing – review and editing (equal). Thomas Munk Laursen: Formal analysis (supporting); writing – review and editing (equal). Christina Jensen-Dahm: writing – review and editing (equal). Gunhild Waldemar: Conceptualization (equal); writing – review and editing (equal). Janet Janbek: Conceptualization (equal); formal analysis (supporting); writing – review and editing (equal).

Sponsor's role

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The effect of influenza vaccination on hospitalization and mortality among people with dementia

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Appendix

Table A1. Codes in the International Classification of Disease (ICD) and Anatomical Therapeutic Chemical Classification System (ATC) for identifications of dementia, hospitalizations and comorbidities

	ICD-8	ICD-10	ATC codes
Dementia type			
Alzheimer's disease	290.10	F00.0-00.9, G30.0-G30.9	N06DA02-N06DA04, N06DA52, N06DA53, N06DX01
Vascular dementia	293.09-19	F01.0-01.9	
Frontotemporal dementia	290.11	F02.0, G31.0A, G31.0B	
Dementia, unspecified	290.09-19	F03.9, G31.9	
Other dementias		G31.8, G31.8E, F02.1-F02.8	
Hospitalization			
Respiratory infections		A150, A159, A169, A310, A319, A481, B440, B441, J00-06, J09-18, J20-22, J31, J32, J340A-D, J350, J36, J37, J383C, J383D, J387G, J387F, J390, J391, J40, J41, J429A, J429B, J440, J441, J659, J985D, J986D, J85, J86	
Influenza or pneumonia		J09-11, J18	
*Comorbidities**			
Pulmonary	490-492, 493.00, 493.02, 493.08, 493.09	J40-45	
Cardiovascular disease	400-404, 410.09, 411.09, 412, 413.09, 414.09, 426, 427, 428, 431, 432-434, 435.09, 437, 438, 782.29	I10-15, I23, I25, I27, I28, I47-49, I50, 161-164, I69	C02-C04, C07-C09
Diabetes	249, 250	E10-14	A10
Cancer	140-149, 150-159, 160-163, 170-172, 174, 180-189, 190-193, 196-199, 200-207	C00-26, C30-41, C43-58, C60-97	
Liver disease		K72	
Renal disease		N18	
Metabolic disease		E78.0	C10

*ATC codes were registered at least twice within 12 months

Table A2. Start and end dates of influenza season for each study period

Year	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17	2017/18
Start	December 20	February 20	December 10	February 3	February 9	January 18	December 26	December 25
End	April 24	May 13	March 7	March 9	April 12	April 3	March 5	April 15

Table A3. All-cause hospitalization for vaccinated compared to unvaccinated among people with dementia

	Model 1*		Model 2†		Model 3‡	
	HR	95% CI	HR	95% CI	HR	95% CI
Before influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	0.93	0.92-0.95	0.93	0.92-0.95	0.88	0.87-0.90
During influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	0.96	0.94-0.97	0.96	0.94-0.97	0.90	0.88-0.92
After influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	0.99	0.98-1.01	0.99	0.98-1.01	0.95	0.93-0.96

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A4. Hospitalization with respiratory infection for vaccinated compared to unvaccinated among people with dementia

	Model 1*		Model 2†		Model 3‡	
	HR	95% CI	HR	95% CI	HR	95% CI
Before influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	0.94	0.90-0.98	0.94	0.90-0.98	0.86	0.82-0.90
During influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	1.02	0.98-1.07	1.02	0.98-1.07	0.94	0.90-0.98
After influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	1.09	1.05-1.14	1.09	1.05-1.14	1.00	0.96-1.04

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A5. Hospitalization with influenza or pneumonia for vaccinated compared to unvaccinated among people with dementia

	Model 1*		Model 2†		Model 3‡	
	HR	95% CI	HR	95% CI	HR	95% CI
Before influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	0.92	0.88-0.98	0.92	0.87-0.98	0.86	0.81-0.91
During influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	1.03	0.97-1.08	1.03	0.97-1.08	0.95	0.90-1.01
After influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	1.07	1.02-1.12	1.07	1.02-1.12	0.99	0.94-1.04

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A6. All-cause mortality for vaccinated compared to unvaccinated among people with dementia

	Model 1*		Model 2†		Model 3‡	
	HR	95% CI	HR	95% CI	HR	95% CI
Before influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	0.76	0.73-0.78	0.76	0.73-0.78	0.72	0.70-0.74
During influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	1.00	0.96-1.03	1.00	0.96-1.03	0.95	0.92-0.98
After influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	1.07	1.04-1.10	1.07	1.04-1.10	1.03	1.00-1.06

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A7. Hazard ratios for vaccinated compared to unvaccinated stratified by nursing home residence among people with dementia

	Nursing home residents						Home-living people					
	Model 1*		Model 2†		Model 3‡		Model 1*		Model 2†		Model 3‡	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All-cause hospitalization												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	1.02	1.00-1.04	1.01	1.00-1.03	0.98	0.96-1.00	0.99	0.97-1.00	0.99	0.97-1.00	0.91	0.90-0.93
Hospitalization with a respiratory infection												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	1.10	1.04-1.15	1.10	1.04-1.15	1.03	0.98-1.08	1.09	1.04-1.14	1.09	1.04-1.14	0.96	0.91-1.00
Hospitalization with influenza or pneumonia												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	1.10	1.04-1.17	1.10	1.04-1.17	1.04	0.98-1.11	1.05	0.99-1.11	1.05	1.00-1.11	0.94	0.89-1.00
All-cause mortality												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	0.86	0.84-0.89	0.87	0.84-0.89	0.85	0.82-0.87	0.82	0.78-0.86	0.82	0.78-0.86	0.76	0.73-0.80

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A8. Hazard ratios for vaccinated compared to unvaccinated stratified by study period among people with dementia

	2002/03 to 2009/10						2010/11 to 2018/19					
	Model 1*		Model 2†		Model 3‡		Model 1*		Model 2†		Model 3‡	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All-cause hospitalization												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	0.93	0.92-0.95	0.93	0.92-0.95	0.89	0.88-0.90	0.96	0.95-0.97	0.96	0.95-0.97	0.91	0.90-0.92
Hospitalization with a respiratory infection												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	0.95	0.92-0.98	0.95	0.92-0.98	0.88	0.85-0.91	1.02	0.99-1.05	1.02	0.99-1.04	0.93	0.91-0.95
Hospitalization with influenza or pneumonia												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	0.91	0.88-0.95	0.91	0.88-0.95	0.86	0.82-0.89	1.01	0.98-1.04	1.01	0.98-1.04	0.93	0.90-0.96
All-cause mortality												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	0.96	0.94-0.98	0.96	0.94-0.98	0.92	0.90-0.94	0.94	0.92-0.95	0.94	0.92-0.95	0.89	0.88-0.91

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A9. Hazard ratios for vaccinated compared to unvaccinated stratified by sex among people with dementia

	Men						Women					
	Model 1*		Model 2†		Model 3‡		Model 1*		Model 2†		Model 3‡	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All-cause hospitalization												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	0.97	0.96-0.98	0.97	0.96-0.98	0.91	0.89-0.92	0.94	0.93-0.95	0.94	0.93-0.95	0.90	0.89-0.91
Hospitalization with a respiratory infection												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	1.01	0.98-1.04	1.01	0.98-1.04	0.92	0.89-0.95	0.98	0.96-1.01	0.98	0.95-1.01	0.91	0.88-0.93
Hospitalization with influenza or pneumonia												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	1.00	0.96-1.03	1.00	0.96-1.03	0.92	0.89-0.95	0.95	0.92-0.99	0.95	0.92-0.99	0.90	0.87-0.93
All-cause mortality												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	0.92	0.90-0.95	0.93	0.91-0.95	0.87	0.85-0.89	0.96	0.95-0.98	0.96	0.95-0.98	0.92	0.91-0.94

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A10. Hazard ratios for vaccinated compared to unvaccinated among people with dementia - without inhabitants of the Municipality of Copenhagen

		Model 1*		Model 2†		Model 3‡	
	Events	HR	95% CI	HR	95% CI	HR	95% CI
All-cause hospitalization							
Unvaccinated (ref)	187,277	1		1		1	
Vaccinated	145,443	0.98	0.98-0.99	0.98	0.98-0.99	0.93	0.92-0.93
Hospitalization with respiratory infection							
Unvaccinated (ref)	21,369	1		1		1	
Vaccinated	19,144	1.06	1.03-1.08	1.05	1.03-1.08	0.95	0.93-0.97
Hospitalization with influenza or pneumonia							
Unvaccinated (ref)	14,693	1		1		1	
Vaccinated	12,909	1.03	1.01-1.06	1.03	1.00-1.06	0.95	0.92-0.97
All-cause mortality							
Unvaccinated (ref)	53,092	1		1		1	
Vaccinated	41,908	0.95	0.94-0.97	0.95	0.94-0.97	0.91	0.90-0.92

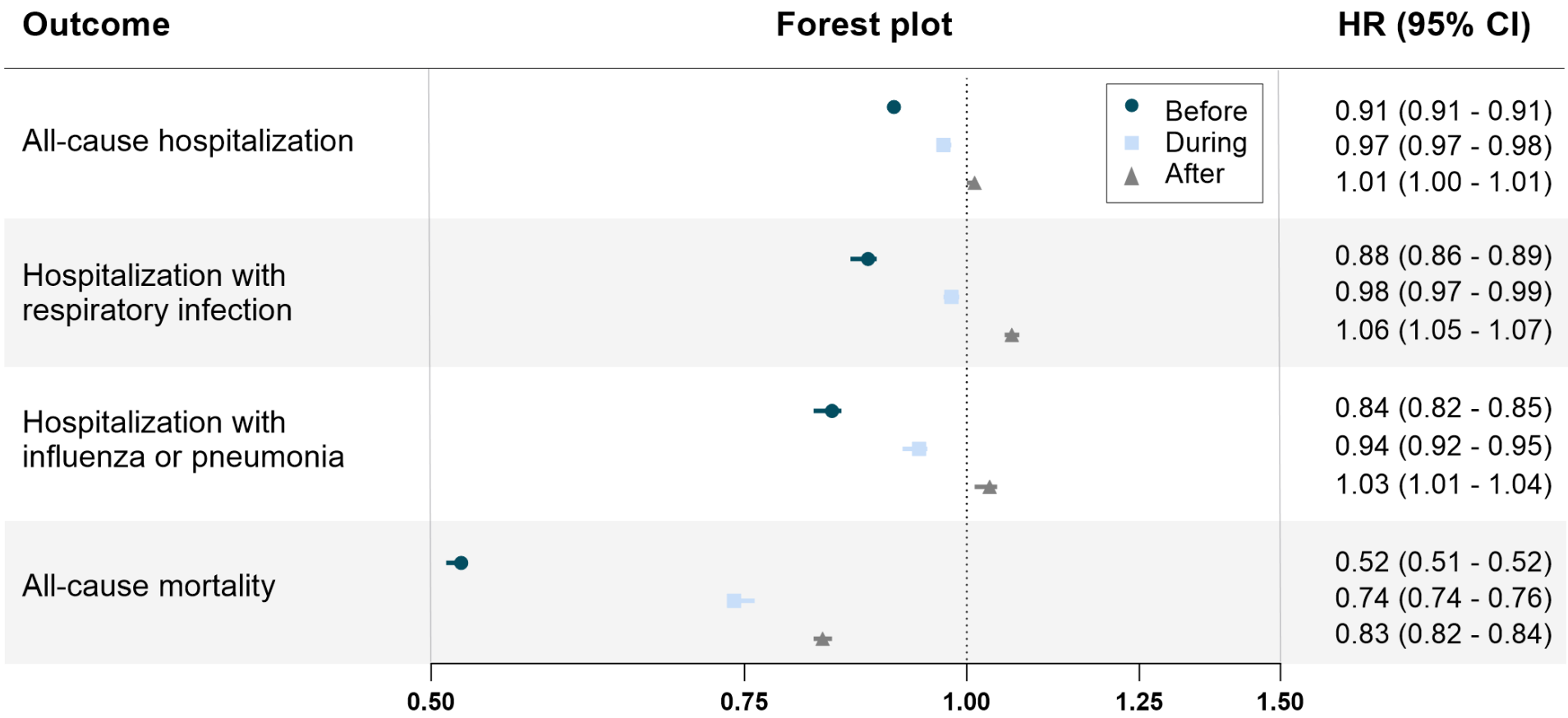
*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A11. Study population characteristics among people without dementia

Characteristics	Number of people on September 1, 2009		Person years during the entire study period	
	Vaccinated N: 438,282 (%)	Unvaccinated N: 419,427 (%)	Vaccinated % (4,817,910)	Unvaccinated % (9,111,569)
Age in years				
65-74	224,783 (51.3)	277,132 (66.1)	50.3	63.3
75-84	157,653 (36.0)	103,038 (24.6)	36.9	27.6
≥85	55,846 (12.7)	39,257 (9.3)	12.8	9.0
Sex				
Female	242,884 (55.4)	232,435 (55.4)	55.3	55.3
*Educational attainment**				
High	15,873 (3.6)	15,326 (3.7)	4.1	3.9
Medium	53,339 (12.2)	51,081 (12.2)	13.6	12.8
Low	338,679 (77.3)	325,534 (77.8)	76.1	75.6
Unknown	30,390 (7.0)	26,724 (6.4)	6.2	7.8
Comorbidities				
Pulmonary	52,369 (12.0)	22,402 (5.3)	12.0	6.7
Cardiovascular	184,995 (42.2)	119,092 (28.4)	43.4	31.1
Diabetes	58,277 (13.3)	33,939 (8.1)	13.9	9.5
Cancer	75,698 (17.3)	54,590 (13.0)	18.3	14.0
Liver	307 (0.1)	254 (0.1)	0.1	0.1
Renal	7,125 (1.6)	3,913 (0.9)	1.9	1.1
Hypercholesterolemia	178,102 (40.6)	117,085 (27.9)	42.0	28.0
General practitioner visits in the past 12 months				
≤6	111,804 (25.5)	198,495 (47.3)	26.5	44.4
7-12	120,742 (27.6)	107,014 (25.5)	27.4	24.8
>12	205,736 (46.9)	113,918 (27.2)	46.1	30.8
Influenza/pneumonia hospitalization in the past 12 months				
Yes	7,328 (1.7)	4,072 (1.0)	1.6	1.0

*763 individuals with missing educational attainment on September 1, 2009

Figure A1. Hazard ratios (HR) and 95% confidence intervals (CI) of outcomes for vaccinated compared to unvaccinated individuals before, during, and after the influenza season – among people without dementia



HRs were adjusted for age, calendar year, sex, educational attainment, comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A12. Hazard ratios for vaccinated compared to unvaccinated among people without dementia

		Model 1*		Model 2†		Model 3‡	
	Number of events	HR	95% CI	HR	95% CI	HR	95% CI
All-cause hospitalization							
Unvaccinated (ref)	4,104,812	1		1		1	
Vaccinated	2,685,357	1.16	1.16-1.17	1.16	1.16-1.16	0.95	0.95-0.96
Hospitalization with respiratory infection							
Unvaccinated (ref)	348,718	1		1		1	
Vaccinated	286,352	1.34	1.34-1.35	1.34	1.33-1.35	0.95	0.93-0.97
Hospitalization with influenza or pneumonia							
Unvaccinated (ref)	198,349	1		1		1	
Vaccinated	151,849	1.20	1.19-1.21	1.20	1.19-1.20	0.92	0.91-0.93
All-cause mortality							
Unvaccinated (ref)	363,368	1		1		1	
Vaccinated	206,726	0.87	0.87-0.88	0.88	0.87-0.88	0.72	0.72-0.73

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A13. All-cause hospitalization for vaccinated compared to unvaccinated among people without dementia

	Model 1*		Model 2†		Model 3‡	
	HR	95% CI	HR	95% CI	HR	95% CI
Before influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	1.12	1.11-1.12	1.12	1.11-1.12	0.91	0.91-0.91
During influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	1.20	1.19-1.20	1.20	1.20-1.21	0.97	0.97-0.98
After influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	1.21	1.20-1.21	1.21	1.20-1.21	1.01	1.00-1.01

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A14. Hospitalization with respiratory infection for vaccinated compared to unvaccinated among people without dementia

	Model 1*		Model 2†		Model 3‡	
	HR	95% CI	HR	95% CI	HR	95% CI
Before influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	1.21	1.20-1.23	1.22	1.20-1.23	0.88	0.86-0.89
During influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	1.38	1.36-1.39	1.38	1.37-1.40	0.98	0.97-0.99
After influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	1.52	1.50-1.53	1.52	1.51-1.54	1.06	1.05-1.07

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A15. Hospitalization with influenza or pneumonia for vaccinated compared to unvaccinated among people without dementia

	Model 1*		Model 2†		Model 3‡	
	HR	95% CI	HR	95% CI	HR	95% CI
Before influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	1.09	1.07-1.11	1.09	1.07-1.11	0.84	0.82-0.85
During influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	1.23	1.21-1.25	1.23	1.21-1.26	0.94	0.92-0.95
After influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	1.36	1.34-1.38	1.36	1.34-1.39	1.03	1.01-1.04

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A16. All-cause mortality for vaccinated compared to unvaccinated among people without dementia

	Model 1*		Model 2†		Model 3‡	
	HR	95% CI	HR	95% CI	HR	95% CI
Before influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	0.63	0.62-0.64	0.64	0.63-0.65	0.52	0.51-0.52
During influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	0.91	0.90-0.93	0.92	0.91-0.93	0.74	0.74-0.76
After influenza season						
Unvaccinated (ref)	1		1		1	
Vaccinated	0.99	0.98-1.00	1.00	0.99-1.01	0.83	0.82-0.84

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A17. Hazard ratios for vaccinated compared to unvaccinated stratified by nursing home residence among people without dementia

	Nursing home residents						Home-living people					
	Model 1*		Model 2†		Model 3‡		Model 1*		Model 2†		Model 3‡	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All-cause hospitalization												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	0.99	0.97-1.00	0.99	0.97-1.00	0.93	0.91-0.94	1.19	1.18-1.19	1.19	1.18-1.19	0.96	0.96-0.97
Hospitalization with a respiratory infection												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	1.13	1.10-1.17	1.13	1.10-1.17	1.01	0.97-1.05	1.37	1.36-1.39	1.39	1.37-1.40	0.97	0.96.98
Hospitalization with influenza or pneumonia												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	1.08	1.04-1.13	1.08	1.04-1.13	0.99	0.95-1.03	1.23	1.21-1.25	1.24	1.22-1.26	0.93	0.92-0.94
All-cause mortality												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	0.83	0.81-0.85	0.83	0.81-0.85	0.79	0.77-0.81	0.81	0.80-0.82	0.82	0.81-0.83	0.65	0.65-0.66

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A18. Hazard ratios for vaccinated compared to unvaccinated stratified by study period among people without dementia

	2002/03 to 2009/10						2010/11 to 2018/19					
	Model 1*		Model 2†		Model 3‡		Model 1*		Model 2†		Model 3‡	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All-cause hospitalization												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	1.14	1.14-1.14	1.14	1.14-1.14	0.95	0.94-0.95	1.18	1.17-1.18	1.18	1.18-1.18	0.96	0.96-0.96
Hospitalization with a respiratory infection												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	1.30	1.29-1.31	1.30	1.28-1.31	0.95	0.94-0.96	1.37	1.36-1.38	1.37	1.36-1.38	0.97	0.96-0.98
Hospitalization with influenza or pneumonia												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	1.15	1.14-1.16	1.15	1.13-1.16	0.90	0.89-0.91	1.22	1.21-1.24	1.23	1.22-1.24	0.93	0.92-0.94
All-cause mortality												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	0.90	0.89-0.90	0.90	0.89-0.91	0.76	0.75-0.76	0.84	0.84-0.85	0.85	0.84-0.86	0.69	0.69-0.70

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A19. Hazard ratios for vaccinated compared to unvaccinated stratified by sex among people without dementia

	Men						Women					
	Model 1*		Model 2†		Model 3‡		Model 1*		Model 2†		Model 3‡	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
All-cause hospitalization												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	1.18	1.17-1.18	1.18	1.17-1.18	0.95	0.95-0.96	1.15	1.15-1.15	1.15	1.14-1.15	0.96	0.95-0.96
Hospitalization with a respiratory infection												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	1.32	1.31-1.33	1.32	1.31-1.33	0.95	0.94-0.96	1.35	1.34-1.36	1.35	1.34-1.36	0.97	0.96-0.98
Hospitalization with influenza or pneumonia												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	1.18	1.17-1.20	1.19	1.17-1.20	0.91	0.90-0.92	1.20	1.19-1.21	1.20	1.18-1.21	0.93	0.92-0.94
All-cause mortality												
Unvaccinated (ref)	1		1		1		1		1		1	
Vaccinated	0.88	0.87-0.89	0.89	0.88-0.89	0.72	0.71-0.72	0.87	0.86-0.87	0.87	0.86-0.88	0.73	0.73-0.74

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

Table A20. Hazard ratios for vaccinated compared to unvaccinated among people without dementia - without inhabitants of the Municipality of Copenhagen

		Model 1*		Model 2†		Model 3‡	
	Events	HR	95% CI	HR	95% CI	HR	95% CI
All-cause hospitalization							
Unvaccinated (ref)	3,707,171	1		1		1	
Vaccinated	2,551,765	1.18	1.18-1.19	1.18	1.18-1.18	0.97	0.96-0.97
Hospitalization with respiratory infection							
Unvaccinated (ref)	307,081	1		1		1	
Vaccinated	271,422	1.40	1.39-1.41	1.39	1.39-1.40	0.98	0.98-0.99
Hospitalization with influenza or pneumonia							
Unvaccinated (ref)	174,361	1		1		1	
Vaccinated	143,878	1.24	1.23-1.25	1.24	1.23-1.25	0.94	0.94-0.95
All-cause mortality							
Unvaccinated (ref)	328,053	1		1		1	
Vaccinated	199,245	0.88	0.88-0.89	0.88	0.88-0.89	0.73	0.72-0.73

*Adjusted for age, calendar year, and sex. †Model 1 + adjusted for educational attainment. ‡Model 2 + adjusted for comorbidities, and general practitioner visits and hospitalization with influenza or pneumonia in the past 12 months.

STUDY III

The effect of influenza vaccination on the rate of dementia among older adults

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Abstract

BACKGROUND AND PURPOSE: Previous studies have reported conflicting results regarding the association between influenza vaccination and dementia. This association was investigated in a nationwide register-based cohort study.

METHODS: Using nationwide registries, dementia-free adults aged ≥65 years in Denmark from 2002 to 2018 without previous influenza vaccinations were included. Poisson regression facilitated confounder-adjusted comparisons of dementia rates for ever versus never vaccinated, number of vaccinations and within/after 5 years from first vaccination. Sensitivity analyses included stratification on age and sex.

RESULTS: Vaccination during follow-up was associated with a slightly higher rate of dementia when adjusted for sociodemographic factors and comorbidities, both within and after the first 5 years from first vaccination (incidence rate ratio [IRR] 1.04; 95% confidence interval [CI] 1.03–1.05). The rate of dementia decreased with increasing number of vaccinations. The highest rate was amongst those with only one vaccination (IRR 1.14; 95% CI 1.12–1.17) and the rate of dementia was only decreased amongst those with six or more vaccinations (IRR 0.95; 95% CI 0.93–0.97). Applying the same models to control outcomes of hip fracture and cancer resulted in higher rates amongst vaccinated people of 6% and 7%, respectively. Vaccinated people also had a 10% higher mortality rate.

DISCUSSION: Our results do not support the case for a preventive effect of influenza vaccination on the risk of dementia in the general population, as reported by some previous studies. However, the higher dementia rate amongst vaccinated people found in this study is probably due to residual confounding, indicated by a higher rate for control outcomes and mortality.

Keywords: Vaccination; Influenza; Dementia; Public health; Prevention

Introduction

Dementia is a major public health challenge that globally affects an increasing number of people because of ageing populations.[1] Identifying factors that can potentially mitigate the risk of dementia is therefore of high priority.[1]

It has been proposed that common adult vaccines, including the influenza vaccine, may reduce the risk of dementia.[2] Several biological mechanisms may underlie a potential protective effect of influenza vaccination. First, vaccination reduces the risk of infections in general, which have been linked to the progression of cognitive impairment and incident dementia through neuroinflammation.[3,4] Second, influenza vaccination may reduce the risk of cardiovascular and cerebrovascular disease, which are risk factors for dementia.[5,6] Third, in an Alzheimer's disease mouse model influenza vaccination led to an increased clearance of amyloid-beta through microglial activation and improved performance on a memory test.[7]

Six observational studies found a lower risk of dementia amongst older adults receiving influenza vaccines compared to unvaccinated persons.[8–13] However, these studies have several limitations that may reduce their results' validity. One smaller study assessed vaccination status by self-administered questionnaires with low reporting rates, increasing the risk of misclassification.[8] Two studies were based on selected samples of patients with chronic kidney disease[9] or chronic obstructive pulmonary disease,[10] limiting the generalizability of the results. Two studies from the United States were based on large nationwide samples but restricted to veterans or selective insurance data;[11,12] thus their results may not be generalizable to the entire population of older adults. Finally, a study from the UK was based on primary care data[13] with a questionable validity of dementia diagnosis. Furthermore, another study based on the same data found considerably higher odds of dementia amongst those vaccinated against influenza.[14] Although the latter study included a larger age span and followed the population for longer, the opposite direction of association with an almost identical data source is worrying. Thus, whether influenza vaccination is associated with the risk of dementia is still controversial and more research is needed.[15]

Since 2002, all Danish citizens aged ≥65 have been offered an influenza vaccination free of charge. Therefore, the Danish registers provide a unique opportunity to investigate the association between influenza vaccination and the risk of dementia amongst older adults.

This nationwide registry-based study investigated whether late-life influenza vaccination, including the number and timing of vaccinations, is associated with a reduced risk of dementia.

Methods

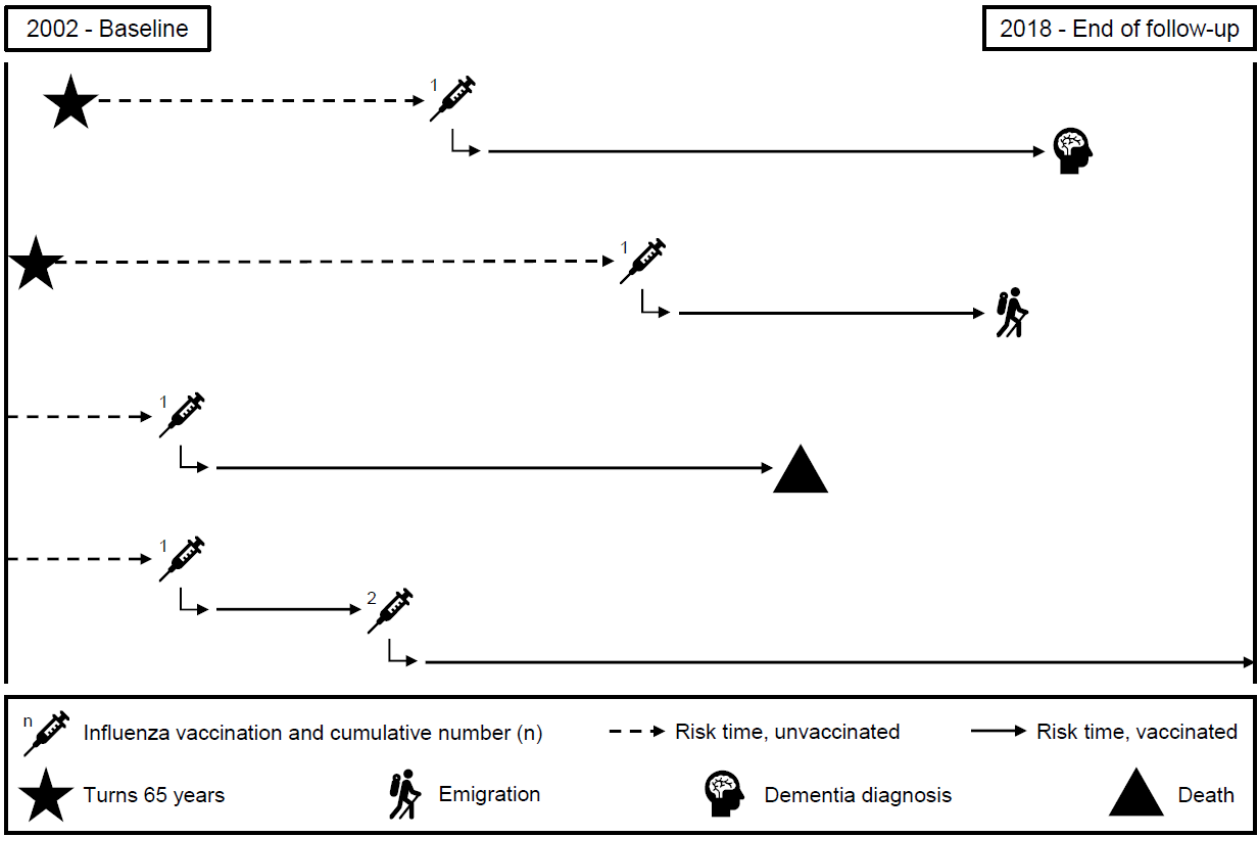
Data sources

The study is based entirely on Danish nationwide registries, enabled through linkage with a personal identifier given to all legal residents in Denmark.[16]

Population

From the start of the Danish influenza vaccination programme in 2002 to 2018, all Danish residents were followed from age ≥65 until dementia diagnosis, emigration or death (Figure 1). Individuals were included from 1 September 2002, or, if younger than 65 years at this time, on their 65th birthday through rolling entry. Individuals were excluded if they had been diagnosed with dementia or received an influenza vaccine before inclusion. People with mild cognitive impairment were not excluded.

Figure 1. Simplified graphical representation of the study design



Influenza vaccinations

Since 2002, influenza vaccination has been offered free of charge to all Danish citizens ≥65 years of age, mainly in primary care. Influenza vaccination in this study was defined as a registered receipt of influenza vaccination in the Danish National Health Service Register[17] or a redeemed prescription for an influenza vaccine in the Danish National Prescription Register,[18] both assessed from 2002 onwards. Available data on prescriptions redeemed before 2002 in the prescription register (from 1995) were very few and were used to exclude people with vaccinations before inclusion. Influenza vaccination was assessed in three ways: (1) ever versus never vaccinated during follow-up; (2) number of vaccinations during follow-up in five categories (0, 1, 2, 3–5, ≥6); and (3) the time between first influenza vaccination and dementia diagnosis defined as within or after 1, 2 and 5 years since vaccination. Individuals could contribute risk time as both unvaccinated and vaccinated depending on if/when they received their first influenza vaccination (time-dependent variable).

Dementia

All-cause dementia was defined as the first registered inpatient or outpatient diagnosis of any type in the Danish National Patient Register[19] or Danish Psychiatric Central Research Register[20] or the first redeemed prescription for anti-dementia medication in the Danish National Prescription Registry (see Table A1 for details). Anti-dementia medication included donepezil, galantamine, rivastigmine, and memantine.

Covariates

The covariates in this study were selected based on their potential for confounding the association between influenza vaccination and dementia, that is, factors associated with receiving an influenza vaccination and independent risk factors of dementia. Age, sex, and marital status were identified through the Civil Registration System,[21] educational attainment through the Danish education registers,[22] and comorbidities through the hospital and prescription registries mentioned above. Age and calendar year were the underlying time scales in our statistical model and were included as time-dependent covariates. Sex and educational attainment were assessed at the start of follow-up. Educational attainment was divided into four categories: high (short-term further education, bachelor's degree, research degree; ≥12 years), medium (upper secondary, business high school, vocational internship; 10–12 years), low (primary school; ≤9 years) and unknown. Marital status was included as a time-dependent covariate, allowing for multiple changes throughout the study period. Information on marital status was available at the end of each year without exact marriage

dates. Therefore, the status date was approximated as 1 January of the following year. The following comorbidities were chosen based on their biological plausibility of being risk factors for dementia: stroke, cardiac arrhythmia, peripheral vascular disease, hypertension, diabetes, hyperlipidaemia, depression, alcohol use and Parkinson's disease. Comorbidities were identified through the first instance of an inpatient or outpatient diagnosis in the hospital registers or the first redeemed prescription in the prescription register if followed by a second redeemed prescription within the following year. Medication was only used to identify comorbidities if the drugs were specific to treating those comorbidities (See Table A1 for the specific diagnostic and medication codes used in this study). Comorbidities were included as time-dependent variables, persisting from first identification onwards during the remaining follow-up period.

Statistical analyses

In the main analyses, the incidence rate ratios (IRRs) by vaccine status for all-cause dementia were estimated by log-linear Poisson regression with the logarithm of the person-years at risk as an offset variable. The Poisson model requires rates to be piecewise constant within each time interval. In this study, the underlying time scales were age and calendar time, both in 1-year groups. This method is equivalent to a Cox regression survival model.[23,24] Compared with no vaccination during the study period, the effect of any vaccination at age ≥65, the number of vaccinations and the time between the first vaccination and dementia diagnosis were estimated in the following models. In model 1, adjustments were made for age, sex and calendar year. In model 2, marital status and educational attainment were additionally adjusted for. In model 3, further adjustments were made for the comorbidities mentioned above.

Several sensitivity analyses were performed to explore the validity of our main results. First, whether the results could have been influenced by confounding was explored. This was done by testing whether the rates of cancer and hip fractures, that is, negative control outcomes[25] assumed to be causally unrelated to the exposure, were different for vaccinated and unvaccinated individuals. Second, whether the competing risk of death could impact our results was explored by estimating the mortality rate ratio for vaccinated compared to unvaccinated. Third, the main association was analysed in subgroups stratified by 10-year age intervals (65–74, 75–84 and ≥85), by three calendar periods (2002–2007, 2008–2013 and 2014–2018) and by sex. Fourth, older adults living in the municipality of Copenhagen have been offered free influenza vaccines since 1996 outside the national programme that were not registered in any of our available data sources. Thus, an unknown number of inhabitants of Copenhagen may be misclassified as unvaccinated

during our study period. To examine the impact of this misclassification, IRRs were estimated in a subpopulation without individuals living in Copenhagen who were eligible to receive the free influenza vaccination offer. Of those, individuals living in Copenhagen at any time between 1996 and inclusion into our study were excluded. After inclusion individuals were censored on the date they moved to Copenhagen. SAS version 9.4 was used for all statistical analyses. Figure 3 was created using R version 4.2.2.

Results

During the total follow-up of 14,065,154 person-years, 135,399 were diagnosed with dementia, resulting in a crude incidence rate of 9.6 per 1000 person-years. Figure 2 shows how the study population was selected.

Figure 2. Selection of study population. Inclusion was September 1st, 2002, or when subsequently turning 65 years old

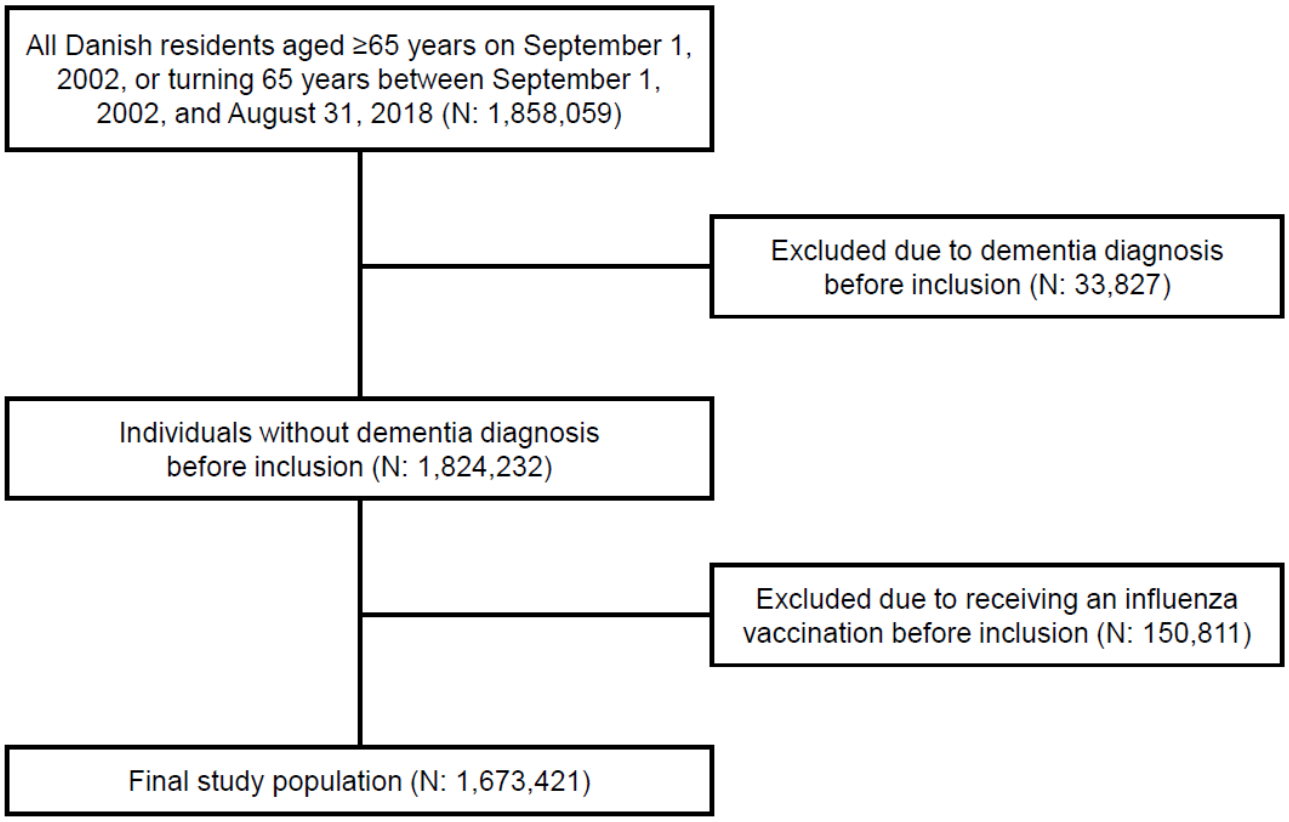


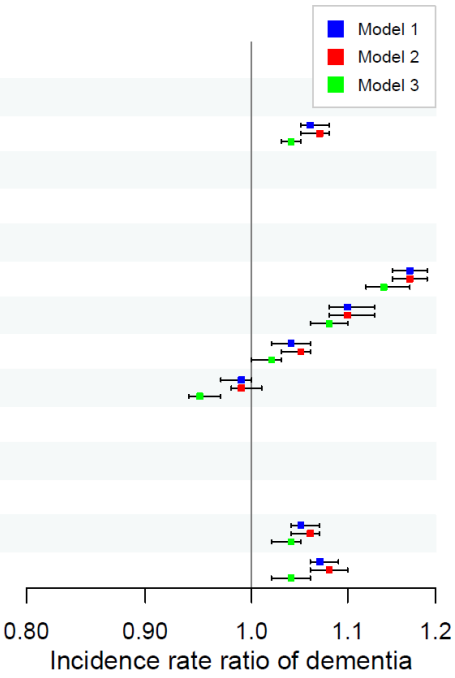
Table 1 shows the distribution of covariates in the study population stratified by vaccination status, presented both as number of individuals at inclusion and as person-years during the study period. At inclusion, people vaccinated during follow-up had higher educational attainment and were more often diagnosed with hypertension and hyperlipidaemia, but less often diagnosed with alcohol

abuse and Parkinson's disease. In contrast, vaccinated people had a slightly higher contribution of person time from females compared to unvaccinated and vaccinated people also had considerably more person time recorded with hypertension, hyperlipidaemia, cardiac arrhythmia and diabetes. Finally, vaccinated people were slightly older at dementia diagnosis.

shows the IRRs of dementia and related 95% confidence intervals (CIs), number of dementia cases during follow-up, and crude incidence rate of dementia for ever versus never vaccinated, number of vaccinations, and within or after 5 years from the first vaccination. A 4% higher incidence rate of dementia was found amongst ever vaccinated compared with never vaccinated in a fully adjusted model (IRR 1.04; 95% CI 1.02–1.05) (see Table 2). Compared to no vaccination, one, two or three to five vaccinations were associated with a slightly higher dementia rate whilst those with six or more vaccinations had the only lower rate. The incidence rate was 4% higher within and after 5 years since the first vaccination compared to no vaccinations (Table A2). The rate was similarly increased within and after 1 year since the first vaccination, 6% and 3% respectively. The rate was also similar within and after 2 years since the first vaccination, 5% and 3% respectively (data not shown).

Figure 3. Incidence rate ratios of dementia according to different influenza vaccine exposures

Vaccination Exposure	No. of Dementia Cases	Dementia Rate*
Vaccination status		
Not vaccinated (ref)	56,387	7.5
Vaccinated	79,012	12.1
Number of vaccinations		
0 (ref)	56,387	7.5
1	15,178	10.4
2	10,217	10.5
3-5	22,407	11.3
≥6	31,210	14.6
Timing of dementia		
No vaccinations (ref)	56,387	7.5
Within five years of first vaccination	36,126	9.9
After five years of first vaccination	42,886	14.9



The x-axis in the graph has been log-transformed. *Crude incidence rate of dementia per 1,000 person-years. Model 1: Adjustment for age, calendar year, and sex. Model 2: Model 1 + adjustment for marital status and educational attainment. Model 3: Model 2 + adjustment for comorbidities.

Table 1. Study population characteristics stratified by vaccination status

	Vaccinated		Not vaccinated	
Characteristics	N[a]: 991,729	PY[b]: 6,549,905	N[a]: 681,692	PY[b]: 7,515,249
Sex (N (%))				
Female	531,928 (53.6)	3,647,297 (55.7)	366,725 (53.8)	4,123,719 (54.9)
Educational attainment (N (%))[c]				
High	46,443 (4.7)	271,197 (4.1)	25,559 (3.7)	294,269 (3.9)
Medium	142,030 (14.3)	875,476 (13.4)	87,518 (12.8)	983,649 (13.1)
Low	716,772 (72.3)	4,968,884 (75,9)	476,994 (70.0)	5,659,738 (75.3)
Unknown	86,484 (8.7)	434,348 (6.6)	91,621 (13.4)	577,593 (7.7)
Marital status (N (%))[c]				
Married	645,012 (65.0)	3,589,316 (54.8)	380,909 (55.9)	4,267,797 (56.8)
Unmarried	343,720 (34.7)	2,960,337 (45.2)	296,090 (43.4)	3,217,893 (42.8)
Unknown	2,997 (0.3)	252 (0.0)	4,693 (0.7)	29,559 (0.4)
Comorbidities (N (%))[c]				
Hypertension	451,693 (45.5)	4,473,372 (68.3)	280,922 (41.2)	3,751,639 (49.9)
Hyperlipidemia	161,933 (16.3)	2,640,546 (40.3)	96,670 (14.2)	1,778,205 (23.7)
Peripheral vascular disease	6,397 (0.6)	37,380 (0.6)	4,646 (0.7)	35,640 (0.5)
Stroke	8,070 (0.8)	49,677 (0.8)	6,426 (0.9)	50,521 (0.7)
Cardiac arrhythmia	12,903 (1.3)	149,175 (2.3)	7,586 (1.1)	86,333 (1.1)
Diabetes	59,617 (6.0)	768,863 (11.7)	40,517 (5.9)	531,831 (7.1)
Parkinson's Disease	10,053 (1.0)	177,460 (2.7)	9,306 (1.4)	111,491 (1.5)
Depression	17,384 (1.8)	115,987 (1.8)	11,487 (1.7)	117,803 (1.6)
Alcohol abuse	14,456 (1.5)	102,598 (1.6)	13,924 (2.0)	119,726 (1.6)
Age at dementia diagnosis (Median, Q1, Q2)	82.9 (78.1, 87.4)	-	81.6 (75.7, 86.6)	-

[a] Number and percentages in column denote distribution at inclusion. [b] Person-years during follow-up. [c] At inclusion i.e., September 1st, 2002, or when subsequently turning 65 years old.

Table 2. Incidence rate ratio for vaccinated compared to those not vaccinated

	Model 1[a]		Model 2[b]		Model 3[c]	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Dementia as the outcome						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.06	1.05-1.08	1.07	1.05-1.08	1.04	1.03-1.05
Death as the outcome						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.14	1.13-1.14	1.16	1.16-1.17	1.10	1.09-1.10
Cancer as the outcome						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.08	1.07-1.09	1.08	1.07-1.09	1.07	1.06-1.07
Hip fracture as the outcome						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.07	1.04-1.11	1.08	1.05-1.12	1.06	1.03-1.10

[a] Adjustment for age, calendar year, and sex. [b] Model 1 + adjustment for marital status and educational attainment.

[c] Model 2 + adjustment for comorbidities.

The negative control outcome analyses showed almost identical results to the main analyses, with a 7% higher cancer rate and a 6% higher hip fracture rate amongst those with a recorded influenza vaccination. Vaccinated people also had a 10% higher mortality rate compared with unvaccinated in the fully adjusted model (see Table 2 and Tables A3-5).

There was an inverse relation between age group and dementia rate amongst vaccinated versus unvaccinated people: in ages 65–74, the dementia rate was 11% higher for vaccinated, 5% higher in ages 75–84 and 3% lower in ages ≥85 (see Table A6). The dementia rate was 10% lower for vaccinated people during the early calendar period from 2002 to 2007, 7% higher for 2008–2013 and 18% higher for 2014–2018 (see Table A7). No considerable differences were found between the sex-stratified and main analyses (data not shown).

Excluding inhabitants of Copenhagen decreased the total person-years at risk and the number of dementia cases by approximately 6% and 10%, respectively (data not shown). The IRRs of dementia, mortality and control outcomes were similar or identical in this subpopulation to those of the entire study population (see Tables A8-13).

Discussion

In this nationwide retrospective cohort study, a 4% higher dementia rate associated with influenza vaccination amongst older adults was found when adjusting for relevant demographic and health-related confounders. The causality of this finding, however, is questioned by the results of several of our additional analyses. First, it aligns poorly with the complex dose–response relationship between number of vaccinations and dementia rate, with a 14% higher dementia rate after one vaccination and gradually decreasing until it was 5% lower after six vaccinations. Second, the similarity of the main analyses and associations with the control outcomes of hip fracture and cancer, as well as the higher mortality rate amongst vaccinated people, indicate considerable residual confounding due to differences in health status and health-seeking behaviour. Third, the difference in the association between vaccination and dementia across age groups and time period may suggest bias due to difference in uptake patterns across age and since the start of the Danish vaccination programme.

Our findings did not align with any previous study in this area. In all but one of the previous studies, influenza vaccination was associated with a reduction of the dementia risk of between 40%[12] and 4%.[13] The 39% higher odds of dementia among vaccinated in one study[14] far exceeded

the rate differences in the present study. The estimated associations in both the present and previous studies may have been influenced by bias to an extent that it affected the interpretation and perspectives of the findings. Whilst it can be challenging to predict the direction and magnitude of bias in all observational research, some sources of potential bias in the present and previous studies can be identified. As Douros et al. remark, prodromal dementia symptoms may lower the likelihood of vaccination, potentially introducing protopathic bias (i.e., reverse causality) which could mask a higher dementia rate amongst vaccinated people.[14] Conversely, detection bias may have increased the dementia rate amongst vaccinated people if general practitioner visits for vaccination lead to a higher likelihood of being diagnosed with dementia. No strong indications of the presence of these bias mechanisms were found in the present study, as there was no difference in dementia rate within or after the first year, first 2 years or first 5 years after the first vaccination. None of the studies finding a lower dementia rate amongst vaccinated people examined the presence of reverse causality or detection bias in their data.

Our study has several strengths. First, the Danish national registries contain highly valid information on influenza vaccination,[17] dementia diagnosis,[26] comorbidities,[19] and sociodemographic factors[21,22] for the entire Danish population of older adults. Second, the registries allowed for a long follow-up period with a lower mean age at cohort entry (65 years) compared with many of the previous studies. Third, the large sample facilitated precise estimation of associations in relevant subgroups and exploration of whether uncontrolled confounding[25] or competing risk of death could have influenced our findings. Finally, the cohort design allowed us to account for time-dependent confounding. There are also several limitations to our study. As mentioned above, the results of our negative control outcome analyses suggest that uncontrolled differences in health and behaviour may have biased our findings.[25] Furthermore, there is also a risk of information bias when using data from administrative registers to investigate potential health effects, and the present study is no different. First, underdiagnosis of dementia in healthcare registries is a common issue across European populations, including the Danish.[27] To mitigate the potential issue of misclassification of dementia, cases from all available sources in the Danish registries, that is, data on secondary care diagnoses and prescription medication, were identified. Despite these efforts, misclassification of dementia, especially if differential, may still have impacted our results. Second, misclassification of exposure to influenza vaccines is also possible. It is known that older adults living in Copenhagen were offered free vaccines that were not registered in the national registers for primary care services or redeemed prescriptions. However,

excluding inhabitants of Copenhagen from our study population had minor to no impact on the crude and adjusted associations between vaccination and dementia, death or the control outcomes. Furthermore, vaccinations through self-payment or place of employment could not be identified through available national registers. However, as the entire study population was eligible for free vaccinations during the study period, combined with the widespread availability of influenza vaccines across Denmark, self-paid vaccination is not expected to be common enough to have affected the overall findings. Third, for a considerable proportion of the study population, educational attainment could not be assessed, and for a very small proportion marital status was missing. The proportion with an unknown educational level (and marital status) was higher amongst unvaccinated than vaccinated people, potentially biasing the adjusted effect estimates. However, the bias is probably negligible, as adjusting for the two variables had no meaningful impact on the estimates. Fourth, as exact marriage dates were not available, marital status may have been misclassified for a limited period in a few individuals. However, it is not likely that this potential misclassification has affected the results. Finally, identifying comorbidities using registry data may also include a risk of misclassification. Validation studies exist for the majority of, but not all, codes used in the identification of comorbidities in the present study[28–33] generally showing moderate to high validity (see the Appendix for details of the specific codes). As mentioned above, differences in the average health status for vaccinated compared to unvaccinated people may persist despite adjustment for relevant comorbidities. On the one hand, vaccinated people may be frailer than those without any vaccinations during the study period, in ways that could not be adjusted for in the present study.[34] This may have contributed to the higher dementia and mortality rate when comparing ever versus never vaccinated. On the other hand, those vaccinated regularly each year may have a higher health status than those with few or no vaccinations.[35] This may explain why lower rates of dementia and death were found amongst those with six or more vaccinations compared with unvaccinated, but a higher rate amongst those with fewer than six vaccinations. Future studies should consider additional and valid measures for healthcare-seeking behavior and healthcare utilization to further explore the impact of residual confounding/healthy vaccinee effect. The cohort design did not allow for a lag period between vaccination and dementia diagnosis as there was no index date for those without dementia. Therefore, to investigate the potential impact of reverse causality (i.e., protopathic and detection bias), the dementia rates within 5 years and after 5 years of the first vaccination were estimated.[28–33]

The evidence taken together does not provide a convincing case for a protective effect of influenza vaccination on the risk of dementia. However, based on our study there is no obvious reason to warn against a potential increased risk of dementia related to influenza vaccination. Further observational studies should focus on minimizing confounding from health behaviour and health status as well as on investigating whether preventive effects could exist for specific subpopulations and vaccination at earlier ages than previously studied.[15] More research is also needed to elucidate the CNS and immune system effects of common adult vaccinations.

Author contributions

Andreas Moses Appel: Conceptualization (equal); writing – original draft (lead); formal analysis (lead); writing – review and editing (equal). Janet Janbek: Conceptualization (equal); formal analysis (supporting); writing – review and editing (equal). Christina Jensen-Dahm: Conceptualization (equal); writing – review and editing (equal). Thomas Munk Laursen: Formal analysis (supporting); writing – review and editing (equal). Gunhild Waldemar: Conceptualization (equal); writing – review and editing (equal).

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Conflict of interest statement

The authors declare no conflicts of interest.

Data availability statement

This study is based entirely on anonymized personal data in the Danish national registries. This data is only accessible with authorization from the Danish Data Protection Agency, the Danish Health Authority, the Danish Health Data Authority, the Danish Medicines Authority, and Statistics Denmark.

Ethics statement

Danish law does not require informed patient consent or ethics committee approval for registry-based studies[36]. This study is part of a project that has been approved by the Danish Data Protection Agency, Statistics Denmark and the Danish Health Data Authority.

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The effect of influenza vaccination on the rate of dementia among older adults

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Appendix

Table A1. Codes in the International Classification of Disease (ICD) and Anatomical Therapeutic Chemical Classification System (ATC) for identification of dementia and comorbidities

	ICD-8	ICD-10	ATC codes
Dementia type			
Alzheimer's disease	290.10	F00.0-00.9, G30.0-G30.9	N06DA02-N06DA04, N06DA52, N06DA53, N06DX01
Vascular dementia	293.09-19	F01.0-01.9	
Frontotemporal dementia	290.11	F02.0, G31.0A, G31.0B	
Dementia without specification	290.09-19	F03.9, G31.9	
Other dementias	-	G31.8, G31.8E, F02.1-F02.8	
Comorbidities[a,b]			
Hypertension	400-404, 410.09, 411.09, 412.09, 413.09, 414.09, 435.09, 437.00-437.09, 438.09	*I10-I13, I15*	*C02-C04, C07-C09*
Hyperlipidemia	279.00	*E78*	C10
Peripheral vascular disease	440-445	I70,*I71*,I72,I73,I74, I77	
Stroke	430, 431, 433, 434, 436	*I60-I64, I69*	
Cardiac arrhythmia	427.93, 427.94, 427.97	*I48, I49*	C01B
Diabetes	249, 250	*E10-E14*	A10A, A10B
Parkinson's Disease	66, 342.99	*G20*	N04
Depression	296.09, 296.29, 296.99, 298.09, 300.4, 300.19	*F32*	
Alcohol use	303.09, 303.19, 303.20, 303.28, 303.29, 303.99	F10.1	

[a] ATC codes were registered at least twice within a 12-month period. [b] ICD and ATC codes in italics are validated in the Danish registries (see references in the main text for validation studies).

Table A2. Incidence rate ratio of all-cause dementia by any vaccination, number, and timing of vaccination – entire study population

	Model 1[a]		Model 2[b]		Model 3[c]	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Ever vs. never vaccinated						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.06	1.05-1.08	1.07	1.05-1.08	1.04	1.03-1.05
No. of vaccinations						
0 (ref)	1		1		1	
1	1.17	1.15-1.19	1.17	1.15-1.19	1.14	1.12-1.17
2	1.10	1.08-1.13	1.10	1.08-1.13	1.08	1.06-1.10
3-5	1.04	1.02-1.06	1.05	1.03-1.06	1.02	1.00-1.03
≥6	0.99	0.97-1.00	0.99	0.98-1.01	0.95	0.94-0.97
Timing of dementia						
No vaccination (ref)	1		1		1	
Within five years	1.05	1.04-1.07	1.06	1.04-1.07	1.04	1.02-1.05
After five years	1.07	1.06-1.09	1.08	1.06-1.10	1.04	1.02-1.06

[a] Adjustment for age, calendar year, and sex. [b] Model 1 + adjustment for marital status and educational attainment. [c] Model 2 + adjustment for comorbidities.

Table A3. Incidence rate ratio of all-cause mortality by any vaccination, number, and timing of vaccination – entire study population

	Model 1[a]		Model 2[b]		Model 3[c]	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Ever vs. never vaccinated						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.14	1.13-1.14	1.16	1.16-1.17	1.10	1.09-1.10
No. of vaccinations						
0 (ref)	1		1		1	
1	1.20	1.19-1.21	1.22	1.21-1.23	1.16	1.15-1.17
2	1.14	1.13-1.16	1.17	1.16-1.18	1.11	1.10-1.12
3-5	1.11	1.10-1.12	1.14	1.13-1.15	1.08	1.07-1.08
≥6	1.10	1.09-1.11	1.13	1.12-1.14	1.05	1.05-1.06
Timing of dementia						
No vaccination (ref)	1		1		1	
Within five years	1.11	1.11-1.12	1.15	1.14-1.15	1.09	1.08-1.09
After five years	1.17	1.16-1.18	1.20	1.19-1.20	1.11	1.11-1.12

[a] Adjustment for age, calendar year, and sex. [b] Model 1 + adjustment for marital status and educational attainment. [c] Model 2 + adjustment for comorbidities.

Table A4. Incidence rate ratio of cancer by any vaccination, number, and timing of vaccination – entire study population

	Model 1[a]		Model 2[b]		Model 3[c]	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Ever vs. never vaccinated						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.08	1.07-1.09	1.08	1.07-1.09	1.07	1.06-1.07
No. of vaccinations						
0 (ref)	1		1		1	
1	1.08	1.07-1.09	1.08	1.07-1.09	1.07	1.05-1.08
2	1.07	1.06-1.09	1.07	1.06-1.09	1.06	1.04-1.07
3-5	1.07	1.06-1.09	1.07	1.06-1.08	1.06	1.04-1.07
≥6	1.10	1.09-1.12	1.10	1.09-1.11	1.08	1.07-1.10
Timing of dementia						
No vaccination (ref)	1		1		1	
Within five years	1.08	1.07-1.09	1.08	1.07-1.09	1.06	1.05-1.07
After five years	1.09	1.08-1.10	1.09	1.08-1.10	1.07	1.06-1.08

[a] Adjustment for age, calendar year, and sex. [b] Model 1 + adjustment for marital status and educational attainment. [c] Model 2 + adjustment for comorbidities.

Table A5. Incidence rate ratio of hip fracture by any vaccination, number, and timing of vaccination – entire study population

	Model 1[a]		Model 2[b]		Model 3[c]	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Ever vs. never vaccinated						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.07	1.04-1.11	1.08	1.05-1.12	1.06	1.03-1.10
No. of vaccinations						
0 (ref)	1		1		1	
1	1.08	1.03-1.14	1.09	1.03-1.14	1.07	1.01-1.12
2	1.15	1.09-1.22	1.16	1.09-1.23	1.14	1.07-1.21
3-5	1.04	0.99-1.08	1.04	1.00-1.08	1.02	0.98-1.07
≥6	1.06	1.01-1.11	1.08	1.01-1.13	1.05	1.01-1.10
Timing of dementia						
No vaccination (ref)	1		1		1	
Within five years	1.06	1.02-1.10	1.06	1.02-1.11	1.05	1.01-1.09
After five years	1.09	1.05-1.14	1.11	1.06-1.16	1.08	1.04-1.13

[a] Adjustment for age, calendar year, and sex. [b] Model 1 + adjustment for marital status and educational attainment. [c] Model 2 + adjustment for comorbidities.

Table A6. Incidence rate ratio of dementia for vaccinated compared to those not vaccinated in 10-year age groups – entire study population

	Model 1[a]		Model 2[b]		Model 3[c]	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Age 65-74 years						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.20	1.16-1.23	1.22	1.18-1.25	1.11	1.08-1.14
Age 75-84 years						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.08	1.06-1.10	1.08	1.07-1.10	1.05	1.03-1.07
Age 85+ years						
Not vaccinated (ref)	1		1		1	
Vaccinated	0.97	0.95-0.99	0.97	0.95-0.99	0.97	0.95-0.99

[a] Adjustment for age, calendar year, and sex. [b] Model 1 + adjustment for marital status and educational attainment. [c] Model 2 + adjustment for comorbidities.

Table A7. Incidence rate ratio of dementia for vaccinated compared to those not vaccinated in calendar periods – entire study population

	Model 1[a]		Model 2[b]		Model 3[c]	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
2002-2007						
Not vaccinated (ref)	1		1		1	
Vaccinated	0.90	0.89-0.92	0.91	0.89-0.93	0.90	0.88-0.92
2008-2013						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.09	1.07-1.11	1.10	1.08-1.12	1.07	1.05-1.09
2014-2018						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.23	1.20-1.26	1.24	1.21-1.27	1.18	1.16-1.21

[a] Adjustment for age, calendar year, and sex. [b] Model 1 + adjustment for marital status and educational attainment. [c] Model 2 + adjustment for comorbidities.

Table A8. Incidence rate ratio of all-cause dementia by any vaccination, number, and timing of vaccination – without inhabitants of the Municipality of Copenhagen

	Model 1[a]		Model 2[b]		Model 3[c]	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Ever vs. never vaccinated						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.10	1.09-1.12	1.10	1.09-1.12	1.07	1.06-1.09
No. of vaccinations						
0 (ref)	1		1		1	
1	1.20	1.17-1.22	1.20	1.18-1.22	1.17	1.15-1.20
2	1.14	1.12-1.17	1.15	1.12-1.17	1.12	1.09-1.14
3-5	1.08	1.06-1.10	1.08	1.06-1.10	1.05	1.03-1.07
≥6	1.03	1.01-1.05	1.04	1.02-1.05	0.99	0.98-1.01
Timing of dementia						
No vaccination (ref)	1		1		1	
Within five years	1.09	1.07-1.11	1.09	1.08-1.11	1.07	1.05-1.08
After five years	1.12	1.10-1.14	1.12	1.10-1.14	1.08	1.06-1.09

[a] Adjustment for age, calendar year, and sex. [b] Model 1 + adjustment for marital status and educational attainment. [c] Model 2 + adjustment for comorbidities.

Table A9. Incidence rate ratio of all-cause mortality by any vaccination, number, and timing of vaccination – without inhabitants of the Municipality of Copenhagen

	Model 1[a]		Model 2[b]		Model 3[c]	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Ever vs. never vaccinated						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.16	1.15-1.17	1.19	1.18-1.20	1.12	1.11-1.13
No. of vaccinations						
0 (ref)	1		1		1	
1	1.22	1.21-1.23	1.24	1.23-1.25	1.18	1.17-1.19
2	1.17	1.16-1.18	1.20	1.18-1.21	1.13	1.12-1.14
3-5	1.14	1.13-1.15	1.17	1.16-1.18	1.10	1.09-1.11
≥6	1.12	1.11-1.13	1.16	1.15-1.17	1.08	1.07-1.08
Timing of dementia						
No vaccination (ref)	1		1		1	
Within five years	1.14	1.13-1.15	1.17	1.16-1.18	1.11	1.10-1.12
After five years	1.19	1.28-1.20	1.22	1.21-1.23	1.13	1.13-1.14

[a] Adjustment for age, calendar year, and sex. [b] Model 1 + adjustment for marital status and educational attainment.
[c] Model 2 + adjustment for comorbidities.

Table A10. Incidence rate ratio of cancer by any vaccination, number, and timing of vaccination – without inhabitants of the Municipality of Copenhagen

	Model 1[a]		Model 2[b]		Model 3[c]	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Ever vs. never vaccinated						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.10	1.09-1.11	1.09	1.09-1.10	1.08	1.07-1.09
No. of vaccinations						
0 (ref)	1		1		1	
1	1.09	1.08-1.11	1.09	1.08-1.10	1.08	1.06-1.09
2	1.09	1.07-1.10	1.09	1.07-1.10	1.07	1.05-1.09
3-5	1.09	1.08-1.10	1.09	1.07-1.10	1.07	1.06-1.08
≥6	1.12	1.10-1.13	1.11	1.10-1.12	1.09	1.08-1.11
Timing of dementia						
No vaccination (ref)	1		1		1	
Within five years	1.09	1.08-1.10	1.09	1.08-1.10	1.07	1.06-1.08
After five years	1.11	1.09-1.12	1.10	1.09-1.12	1.08	1.07-1.10

[a] Adjustment for age, calendar year, and sex. [b] Model 1 + adjustment for marital status and educational attainment.
[c] Model 2 + adjustment for comorbidities.

Table A11. Incidence rate ratio of hip fracture by any vaccination, number, and timing of vaccination – without inhabitants of the Municipality of Copenhagen

	Model 1[a]		Model 2[b]		Model 3[c]	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Ever vs. never vaccinated						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.09	1.05-1.13	1.10	1.06-1.14	1.07	1.03-1.11
No. of vaccinations						
0 (ref)	1		1		1	
1	1.08	1.02-1.14	1.08	1.02-1.15	1.06	1.00-1.12
2	1.16	1.08-1.24	1.17	1.09-1.25	1.14	1.06-1.21
3-5	1.06	1.01-1.12	1.07	1.01-1.13	1.04	0.99-1.09
≥6	1.09	1.04-1.15	1.11	1.06-1.17	1.08	1.02-1.13
Timing of dementia						
No vaccination (ref)	1		1		1	
Within five years	1.07	1.02-1.12	1.08	1.03-1.13	1.05	1.01-1.10
After five years	1.12	1.07-1.17	1.13	1.08-1.18	1.09	1.04-1.14

[a] Adjustment for age, calendar year, and sex. [b] Model 1 + adjustment for marital status and educational attainment.
[c] Model 2 + adjustment for comorbidities.

Table A12. Incidence rate ratio of dementia for vaccinated compared to those not vaccinated in 10-year age groups – without inhabitants of the Municipality of Copenhagen

	Model 1[a]		Model 2[b]		Model 3[c]	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
Age 65-74 years						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.22	1.18-1.25	1.24	1.20-1.27	1.12	1.09-1.16
Age 75-84 years						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.11	1.08-1.13	1.11	1.09-1.13	1.08	1.06-1.10
Age 85+ years						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.02	1.00-1.05	1.02	1.00-1.04	1.02	1.00-1.04

[a] Adjustment for age, calendar year, and sex. [b] Model 1 + adjustment for marital status and educational attainment. [c] Model 2 + adjustment for comorbidities.

Table A13. Incidence rate ratio of dementia for vaccinated compared to those not vaccinated in calendar periods – without inhabitants of the Municipality of Copenhagen

	Model 1[a]		Model 2[b]		Model 3[c]	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
2002-2007						
Not vaccinated (ref)	1		1		1	
Vaccinated	0.94	0.92-0.97	0.95	0.92-0.97	0.94	0.91-0.96
2008-2013						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.15	1.12-1.17	1.16	1.13-1.18	1.12	1.10-1.14
2014-2018						
Not vaccinated (ref)	1		1		1	
Vaccinated	1.24	1.21-1.27	1.24	1.21-1.28	1.19	1.16-1.22

[a] Adjustment for age, calendar year, and sex. [b] Model 1 + adjustment for marital status and educational attainment. [c] Model 2 + adjustment for comorbidities.

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