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Common Vaccines and the Risk of Incident Dementia: A Population-based Cohort Study

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(See the Editorial Commentary by Salmon et al on pages 1224–6.)

Background. Observational studies suggesting that immunizations strongly decrease the risk of dementia had several methodological limitations. We assessed whether common vaccines are associated with the risk of dementia.

Methods. We assembled a population-based cohort of dementia-free individuals aged ≥50 years in the United Kingdom's Clinical Practice Research Datalink between 1988 and 2018. Using a nested case-control approach, we matched each patient with dementia with 4 controls. Conditional logistic regression yielded confounder-adjusted odds ratios (ORs) with 95% confidence intervals (CIs) of dementia associated with common vaccines >2 years before the index date compared with no exposure during the study period. Moreover, we applied a 10-year lag period and used active comparators (participation in breast or prostate cancer screening) to account for detection bias.

Results. Common vaccines were associated with an increased risk of dementia (OR, 1.38 [95% CI, 1.36–1.40]), compared with no exposure. Applying a 10-year lag period (OR, 1.20 [95% CI, 1.18–1.23]) and comparing versus prostate cancer screening (1.19 [1.11–1.27]) but not breast cancer screening (1.37 [1.30–1.45]) attenuated the risk increase.

Conclusions. Common vaccines were not associated with a decreased risk of dementia. Unmeasured confounding and detection bias likely accounted for the observed increased risk.

Keywords. epidemiology; immunization; public health; real-world evidence.

Dementia currently affects 50 million people globally, and its prevalence is expected to triple in the next decades owing to the aging population [1]. Given the scarcity of effective treatments and the poor prognosis of dementia, a major research focus has been the understanding of its pathology, with the ultimate aim being the development of novel therapeutic and prevention strategies. Based on numerous preclinical, serological, and pathological studies suggesting a link between a wide range of infectious pathogens and the development of dementia, the infectious hypothesis was postulated [2–8]. More recently, population-based observational studies corroborated this hypothesis by showing that infectious disease burden is associated with an increased risk of dementia [9–11].

Considering this growing body of evidence, a role for vaccines as preventive intervention for dementia was proposed. Indeed, subsequent observational studies uniformly reported strongly decreased risks of dementia (up to 80%) associated with several routinely administered vaccines, including those for influenza [12–14], shingles [15–17], or tetanus, diphtheria, and pertussis [17–19]. However, these studies had several potential methodological limitations, such as protopathic bias and detection bias due to the absence of a lag period [12–18] and immortal time bias [14, 15, 17, 18]. Moreover, healthy vaccinee bias poses an additional challenge for observational studies that aim to assess potentially beneficial effects of vaccines [20]. Of note, several of the aforementioned biases could lead to decreased effect estimates and spurious associations [21, 22]. Therefore, the interpretation of these impressive findings is challenging, and their potential translation in clinical practice unclear.

Given the limitations of available evidence, more research is urgently needed to address this clinically important question. To this end, we conducted a large, population-based cohort study to assess whether exposure to commonly administrated vaccines is indeed associated with a decreased risk of dementia.

METHODS

Data Source

We conducted a cohort study with a nested case-control analysis using the GOLD and Aurum data sets from the United

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Kingdom Clinical Practice Research Datalink (CPRD). The CPRD is a large primary care database enrolling >50 million patients across 1900 publicly funded UK practices, and it is broadly representative of the general population for critical variables such as age, sex, and ethnicity [23]. Medical diagnoses and procedures are coded using the Read code (GOLD) and SNOMED (Aurum) classification systems, and drugs prescribed by general practitioners are coded using the UK Prescription Pricing Authority Dictionary [23]. General practitioners in the United Kingdom serve as the first point of contact for nonemergency health-related issues. Thus, information on routinely recorded immunization, symptoms, laboratory tests, diagnoses, therapies, health-related behaviors, and referrals to secondary care is recorded in the database [23].

The CPRD undergoes routine quality control assessments, and recorded diagnoses are valid and of high quality [24]. To obtain proxies of socioeconomic status, the CPRD was linked to the Index of Multiple Deprivation (IMD), an area-level measure of deprivation comprising 7 domains (income, employment, education, health, crime, barriers to housing and services, and living environment) [25]. The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol 21_000550) and the Research Ethics Board of the Jewish General Hospital in Montreal, Quebec, Canada. Written consent from participants was not required owing to the use of anonymized data.

Study Cohort

The study cohort included all individuals aged ≥50 years who were enrolled in the CPRD between 1 January 1988 and 31 December 2018. Cohort entry was defined as the date of the study participant's 50th birthday or 1 year after their date of enrollment in the database, whichever occurred later. All participants were required to be dementia free at cohort entry; thus, we excluded those with a prior diagnosis of any dementia, including mild cognitive impairment, and those with early signs or symptoms suggestive of dementia (eg, memory impairment, aphasia, apraxia, and agnosia) at any time before cohort entry. Moreover, we excluded persons with prescriptions for medications indicated for the treatment of dementia, including acetylcholinesterase inhibitors (eg, donepezil, rivastigmine, and galantamine) and *N*-methyl-D-aspartate receptor antagonists (memantine) at any time before cohort entry. All eligible participants were then followed up from the date of cohort entry until the date of the first outcome event, the end of registration with the general practice, death from any cause, or the end of the study period (31 March 2021), whichever came first.

Case Definition

Within the study cohort, we identified all patients with a first-time diagnosis of dementia at any time after cohort entry. The diagnosis of dementia was based on Read codes (CPRD GOLD) and SNOMED codes (CPRD Aurum). The index date was set as the date corresponding to the date of the diagnostic code. Codes for dementia diagnoses have previously been confirmed to be reliable in the CPRD [26].

Control Selection

We used risk-set sampling to select appropriate controls. Each patient with dementia was matched with up to 4 dementia-free controls randomly selected from the risk set defined by the patient with dementia (ie, those still being followed up and event free at the date of the dementia event). Matching criteria included sex, age, year of cohort entry, duration of follow-up, and CPRD data set. Sex, age, year of cohort entry, and CPRD data set were included to minimize the potential confounding effect of these covariates, while duration of follow-up was included to ensure that patients with dementia and controls have an equal time-window to get exposed to vaccines and thus to avoid time-window bias [27]. The date corresponding to the same duration of follow-up for the case patients and controls was set as the index date for the controls. To avoid selection bias, controls could contribute to different risk sets and eventually become a case patient.

Exposure Definition

For all case patients and controls, we assessed the exposure to any of the common vaccines with a potential link to the risk of dementia that were received for the first time after cohort entry: immunization for influenza, pneumonia, shingles, tetanus, diphtheria, or pertussis. To account for the nonacute nature of dementia and potential diagnostic delays and to control for protopathic bias and early detection bias, we implemented a 2-year lag period [28, 29]. Thus, immunizations within 2 years before the dementia diagnosis for case patients or the corresponding index date for controls were considered unrelated to dementia, and these patients and controls were considered unexposed.

Covariates

We adjusted for the following potential confounders measured at cohort entry: body mass index category (<18.5, 18.5–24.9, 25–29, ≥30, or unknown [calculated as weight in kilograms divided by height in meters squared] in the last measurement before cohort entry), smoking history (ever, never, or unknown), socioeconomic status (IMD quintiles 1–5), and ethnicity. We also adjusted for a wide range of comorbid conditions, including alcohol-related disorders, arterial hypertension, atrial fibrillation, congestive heart failure, coronary artery disease, stroke or transient ischemic attack, peripheral vascular disease, dyslipidemia, diabetes mellitus, chronic kidney disease, liver disease, depression, epilepsy, Parkinson disease, traumatic brain injury, osteoporosis, hypothyroidism, and cancer, all diagnosed before cohort entry. Moreover, we adjusted for the use of the following drugs in the year before cohort entry: treatment for varicella

zoster virus infection, antibiotics, oral anticoagulants, antiplatelet agents, lipid-lowering drugs, β-blockers, thiazides, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, proton pump inhibitors, nonsteroidal anti-inflammatory drugs, opioids, immunosuppressants and biologics, antipsychotics, and antidepressants.

Primary Analysis

We used conditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for dementia associated with exposure to any of the common vaccines, compared with no exposure to these vaccines. To maximize the validity and completeness of the underlying data, we did not consider in the analyses case patients and matched controls who entered the study cohort in CPRD Aurum before 1 January 1996 [30]. We also excluded case patients and matched control with <2 years of follow-up, owing to the use of a 2-year lag period.

Secondary Analyses

We conducted 8 exploratory secondary analyses. First, we assessed the effect of each vaccine (influenza, pneumonia, shingles, tetanus, diphtheria, and pertussis) separately. Exposure to the tetanus vaccine was defined as exposure to the diphtheria-tetanus-pertussis (combined), diphtheria-tetanus (combined), or tetanus-only vaccine. Exposure to the diphtheria vaccine was defined as exposure to the diphtheria-tetanus-pertussis (combined), diphtheria-tetanus (combined), or diphtheria-only vaccine. Exposure to the pertussis vaccine was defined as exposure to the diphtheria-tetanus-pertussis (combined) or pertussis-only vaccine. Second, to assess potential effect modification by demographic characteristics, we stratified by age at cohort entry (<65 vs ≥65 years) and sex. Third, to examine a potential dose-response relation, we analyzed the risk of dementia in relation to the overall number of administered common vaccines (1, 2–3, ≥ 4). This analysis was also conducted for individual vaccines with statistically significant results.

Fourth, in a post hoc secondary analysis, we repeated the dose-response relation analysis using different cutoffs based on the distribution of the number of vaccines among exposed case patients and controls (1–3, 4–7, 8–12, or ≥ 13). Fifth, in another post hoc secondary analysis, we modeled the number of vaccines as a continuous variable, using restricted cubic splines with 5 interior knots to account for potential nonlinear associations with the outcome [31]. Sixth, to examine a potential time-response relation, we assessed the association of different time intervals since first immunization (for any and for individual vaccines) and dementia diagnosis. The intervals were based on the distribution of durations among the controls. To account for a potential nonlinear association with the outcome, we also modeled the time since first immunization as a continuous variable using the same approach mentioned above [31]. Finally, to assess potential effect modification by socioeconomic status and infectious disease burden, we stratified the cohort by IMD quintiles, immunization with any of the common vaccines before cohort entry, and the number of prior infections targeted by the vaccines of interest (0 or ≥ 1).

Sensitivity Analyses

We also performed 2 sensitivity analyses to assess the robustness of our findings. First, to account for the uncertainty regarding the delay between symptom onset and the diagnosis of dementia and the length of the time window between vaccine administration and dementia development, as well as to control for late detection bias, we repeated the primary analysis after extending the 2-year lag period to 3, 5, and 10 years. For these analyses, we considered only case patients and controls with a duration of follow-up at least equal to the lag period. Second, to account for residual detection bias and unmeasured confounding, we changed the reference group from "no exposure to common vaccines"' to "participation in breast cancer screening" among female patients and "participation in prostate cancer screening" among male patients. The rationale for using "active comparators," an approach initially developed by pharmacoepidemiologists for confounding control [32], was that the probability of disease detection and also the clinical characteristics should be comparable among patients who participate in different preventive healthcare programs, such as routine immunizations or cancer screening. For the analysis comparing exposure to common vaccines with participation in breast cancer screening, we restricted the study period from 1996 onward, given the absence of national coverage for the latter procedure in the United Kingdom before that date [33].

Supplementary Analyses

Some studies assessing the role of vaccines in the risk of dementia also looked specifically at Alzheimer disease (AD) [16]. Hence, we repeated the analyses after narrowing our case definition to include only diagnoses of AD. The diagnosis of AD was based on a modified algorithm initially developed and validated by Imfeld et al [34] and previously used by our group (Supplementary Methods) [9, 35]. All analyses were conducted using SAS software, version 9.4 (SAS Institute).

RESULTS

Our study cohort included 13 383 431 dementia-free individuals aged ≥50 years (Figure 1). The mean (standard deviation) age at cohort entry was 70 (10) years, and 62% of the cohort members were female. During 140 721 533 person-years of follow-up, 443 484 individuals in the cohort developed dementia, generating a crude incidence rate of 3.2 per 1000 person-years. As expected, the prevalence of risk factors for dementia —such as cardiovascular disease, diabetes mellitus, and

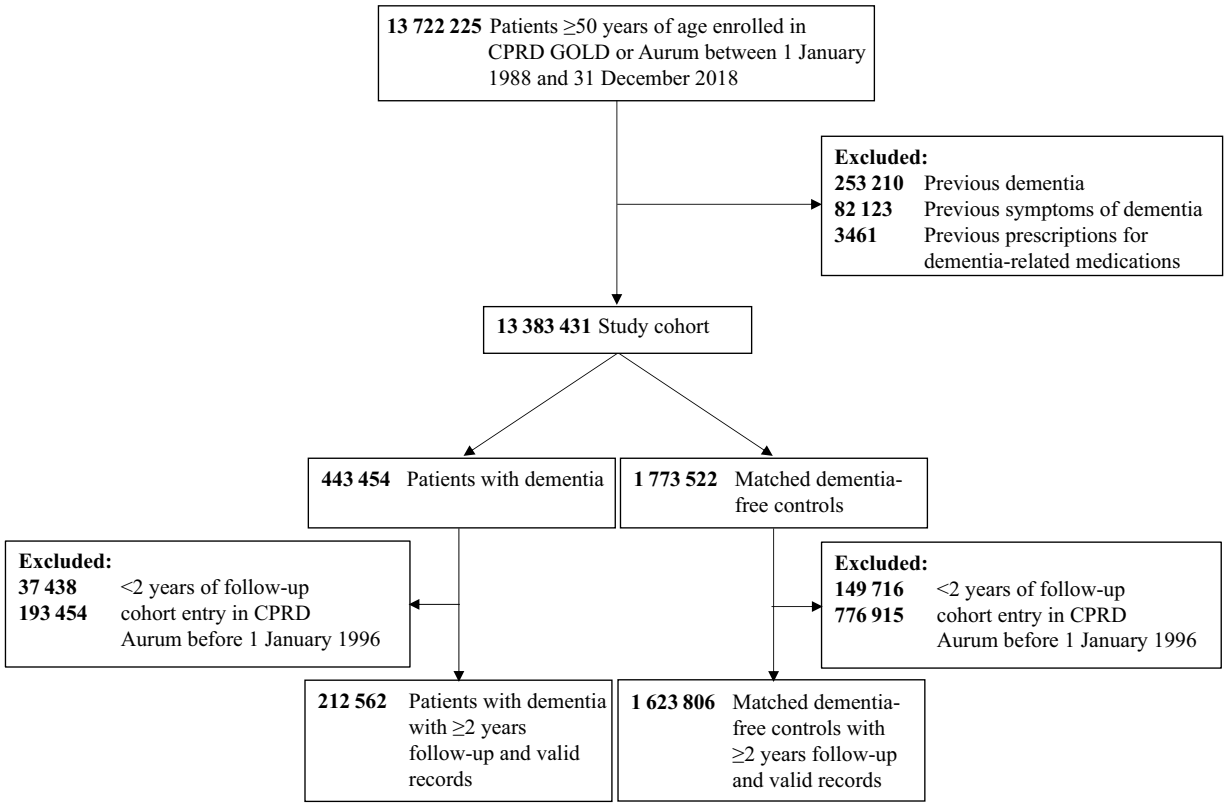

Figure 1. Flowchart illustrating the construction of the study cohort and the selection of patients with dementia and dementia-free controls. Patients with dementia and matched controls entering the cohort in Clinical Practice Research Datalink (CPRD) Aurum before 1 January 1996 were excluded to maximize the validity and completeness of the underlying data [30].

depression—was higher among patients with dementia than among dementia-free controls (Table 1). Exposed case patients and controls were, on average, sicker than unexposed case patients and controls (Supplementary Table 1).

Exposure to common vaccines, when compared with no exposure, was associated with an increased risk of dementia (OR, 1.38 [95% CI, 1.36–1.40]), (Table 2). This increase in the risk was driven by the immunizations for influenza (OR, 1.39 [95% CI, 1.37–1.41]) and pneumococcus (1.12 [1.11–1.13]). The immunizations for shingles (OR, 0.95 [95% CI, .92–.98]) and diphtheria (0.94 [.92–.96]) were associated with small decreases in the risk of dementia, while no such associations were observed for the immunizations for tetanus (0.99 [.97–1.00]) or pertussis (1.00 [.89–1.11]). There was no major effect modification by age or sex.

The risk of dementia increased further with increasing number of administered vaccines (up to an OR of 1.55 with ≥13 vaccines; Supplementary Table 2), although the risk curve was less steep and became flatter for larger numbers of vaccines (Supplementary Figure 1). Moreover, the greatest increase in the risk was observed in the first 2 years after the end of the imposed lag period (Supplementary Table 2 and Figure 2). Socioeconomic status did not modify the association between exposure to common vaccines and risk of dementia, and study participants with vaccines or infections before cohort entry showed smaller increases in risk than those without (Supplementary Table 3). The application of longer lag periods led to a gradual attenuation of the increased risk (down to an OR of 1.20 with a 10-year lag period; Table 3). This attenuation was also observed among male study participants when prostate cancer screening was used as the active comparator (OR, 1.17 [95% CI, 1.09–1.25]) but not among female participants when breast cancer screening was used (1.39 [95% CI, 1.31–1.47]).

Focusing on AD led to findings that were consistent with those derived from the dementia analyses. The flowchart illustrating the construction of the study cohort and the selection of case patients and controls is shown in Supplementary Figure 2. The baseline characteristics of patients with AD and AD-free controls and of exposed and unexposed case patients and controls are shown in Supplementary Tables 4 and 5. Finally, the results of the primary, secondary, and sensitivity analyses are shown in Supplementary Tables 6–9 and Supplementary Figure 3.

DISCUSSION

Our large population-based cohort study showed no decreased risk of dementia associated with exposure to common vaccines

Table 1. Baseline Characteristics of Patients With Dementia and Dementia-Free Controls

Characteristic	Patients With Dementia, No. (%)[a] (n = 212 562)	Controls, No. (%)[a] (n = 846 891)
Age, mean (SD), y	70.4 (10.0)	70.5 (10.0)
Follow-up, mean (SD), y	10.3 (5.6)	10.3 (5.6)
Male sex	80 904 (38.1)	322 183 (38.0)
Race		
White	99 079 (46.6)	400 339 (47.3)
Black	2741 (1.3)	8990 (1.1)
Asian	3877 (1.8)	16 105 (1.9)
Other	363 (0.2)	1603 (0.2)
Mixed	568 (0.3)	2273 (0.3)
Unknown	105 934 (49.8)	417 581 (49.3)
Socioeconomic status		
IMD 1 (least deprived)	22 782 (10.7)	97 968 (11.6)
IMD 2	24 521 (11.5)	104 592 (12.4)
IMD 3	27 064 (12.7)	111 329 (13.1)
IMD 4	32 576 (15.3)	124 010 (14.6)
IMD 5 (most deprived)	30 724 (14.5)	111 870 (13.2)
Unknown	74 895 (35.2)	297 122 (35.1)
BMI[b,c]		
18.5–24.9	58 842 (27.7)	217 833 (25.7)
<18.5	2921 (1.4)	8848 (1.0)
25–29.9	58 847 (27.7)	238 519 (28.2)
≥30	30 070 (14.1)	118 855 (14.0)
Unknown	61 882 (29.1)	262 836 (31.0)
Smoking[b]		
Never	81 176 (38.2)	328 409 (38.8)
Ever	86 073 (40.5)	318 333 (37.6)
Unknown	45 313 (21.3)	200 149 (23.6)
Comorbid conditions		
Alcohol-related disorders	11 431 (5.4)	37 494 (4.4)
Arterial hypertension	73 255 (34.5)	278 977 (32.9)
Atrial fibrillation	9045 (4.3)	30 590 (3.6)
Congestive heart failure	6233 (2.9)	22 058 (2.6)
Coronary artery disease	28 356 (13.3)	96 151 (11.4)
Stroke or transient ischemic attack	13 578 (6.4)	38 074 (4.5)
Peripheral vascular disease	5744 (2.7)	18 653 (2.2)
Cancer	17 911 (8.4)	70 586 (8.3)
Chronic kidney disease	7058 (3.3)	25 807 (3.0)
Liver disease	1686 (0.8)	5911 (0.7)
Hypothyroidism	13 632 (6.4)	50 120 (5.9)
Dyslipidemia	23 169 (10.9)	82 328 (9.7)
Diabetes mellitus	19 864 (9.3)	59 497 (7.0)
Osteoporosis	8656 (4.1)	29 186 (3.4)
Traumatic brain injury	44 (0.0)	44 (0.0)
Epilepsy	4385 (2.1)	10 296 (1.2)
Parkinson disease	2140 (1.0)	3390 (0.4)
Depression	30 616 (14.4)	92 838 (11.0)
Medications[d]		
VZV treatment	1322 (0.6)	4836 (0.6)
Antibiotics	40 449 (19.0)	147 744 (17.4)
Oral anticoagulants	6696 (3.2)	23 384 (2.8)
Antiplatelet agents	46 343 (21.8)	154 781 (18.3)
Opioids	51 312 (24.1)	173 630 (20.5)
Lipid-lowering drugs	41 469 (19.5)	141 255 (16.7)
β-Blockers	36 467 (17.2)	135 029 (15.9)
Thiazides	33 986 (16.0)	133 378 (15.7)
Angiotensin-converting enzyme inhibitors	31 451 (14.8)	115 980 (13.7)
Angiotensin II receptor blockers	12 044 (5.7)	46 554 (5.5)
Calcium channel blockers	34 207 (16.1)	125 957 (14.9)
Nonsteroidal anti-inflammatory drugs	43 094 (20.3)	158 829 (18.8)
Immunosuppressants or biologics	14 811 (7.0)	54 303 (6.4)
Proton pump inhibitors	31 445 (14.8)	113 158 (13.4)
Antidepressants	30 044 (14.1)	81 115 (9.6)
Antipsychotic drugs	12 602 (5.9)	35 171 (4.2)

Abbreviations: BMI, body mass index; IMD, Index of Multiple Deprivation; SD, standard deviation; VZV, varicella zoster virus.

[a]Data represent no. (%) of case patients or controls, unless otherwise specified.

[b]Measured at the earliest time before cohort entry.

[c]BMI calculated as weight in kilograms divided by height in meters squared.

[d]Measured in the year before entry into the cohort.

among adults ≥ 50 years of age. Instead, we observed an increased risk of dementia, which was driven by immunizations for influenza and pneumococcus. The strongest increase in the risk was observed in the first years after immunization. In sensitivity analyses addressing the potential impact of detection bias and unmeasured confounding, the results were not always consistent, generally showing an attenuation of the increased risk.

The rationale for our study was based on the infectious hypothesis for the development of dementia [36]. This hypothesis, according to which neurotoxic inflammation and oxidative stress in the brain caused by different microorganisms may play a pivotal role in the pathophysiology of dementia, is >100 years old but was recently rediscovered and corroborated by preclinical and population-based observational studies [9–11, 36]. Building on that, it was further proposed that vaccines could decrease the risk of dementia by preventing infections [19].

To date, observational studies in the area have shown that different vaccines are associated with strongly decreased risks of dementia [19]. However, flaws in the design of these studies may have introduced major biases. First, the studies did not apply a lag period between the vaccination and the diagnosis of dementia or used a short (90-day) time interval that is probably insufficient to account for the insidious, nonacute nature of the outcome dementia and the known associated diagnostic delays [12–18]. On one hand, the lack of a lag period can lead to protopathic bias, if initial symptoms of an underlying but yet undiagnosed disease alter the probability of exposure. Indeed,

Table 2. Association Between Common Vaccines and the Risk of Incident Dementia: Primary Analysis and Stratified by Individual Vaccines and Demographic Characteristics

Exposure	Patients With Dementia (n = 212 562)	Controls (n = 846 891)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Primary analysis				
Any vaccine	174 253 (82.0)	652 704 (77.1)	1.48 (1.46–1.50)	1.38 (1.36–1.40)
Unexposed	38 309 (18.0)	194 187 (22.9)	Reference	Reference
Individual vaccines				
Influenza vaccine	169 628 (79.8)	630 359 (74.4)	1.48 (1.46–1.50)	1.39 (1.37–1.41)
Unexposed	42 934 (20.2)	216 532 (25.6)	Reference	Reference
Pneumococcal vaccine	89 638 (42.2)	340 426 (40.2)	1.13 (1.12–1.14)	1.12 (1.11–1.13)
Unexposed	122 924 (57.8)	506 465 (59.8)	Reference	Reference
Shingle vaccine	11 768 (5.5)	47 784 (5.6)	0.96 (.93–.98)	0.95 (.92–.98)
Unexposed	200 794 (94.5)	799 107 (94.4)	Reference	Reference
Diphtheria vaccine[b]	13 873 (6.5)	58 521 (6.9)	0.94 (.92–.96)	0.94 (.92–.96)
Unexposed	198 689 (93.5)	788 370 (93.1)	Reference	Reference
Tetanus vaccine[c]	27 432 (12.9)	110 313 (13.0)	0.99 (.97–1.00)	0.99 (.97–1.00)
Unexposed	185 130 (87.1)	736 578 (87.0)	Reference	Reference
Pertussis vaccine[d]	405 (0.2)	1603 (0.2)	1.01 (.90–1.12)	1.00 (.89–1.11)
Unexposed	212 157 (99.8)	845 288 (99.8)	Reference	Reference
Age at cohort entry				
50-64 y	44 809 (21.1)	164 248 (19.4)	1.65 (1.61–1.70)	1.41 (1.37–1.45)
≥65 y	129 444 (60.9)	488 456 (57.7)	1.42 (1.40–1.45)	1.35 (1.33–1.38)
Sex				
Female	106 941 (50.3)	403 068 (47.6)	1.41 (1.38–1.43)	1.32 (1.30–1.35)
Male	67 312 (31.7)	249 636 (29.5)	1.63 (1.59–1.66)	1.50 (1.46–1.54)

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]We adjusted for the following potential confounders measured at cohort entry: body mass index, smoking, socioeconomic status, ethnicity, alcohol-related disorders, arterial hypertension, atrial fibrillation, congestive heart failure, coronary artery disease, stroke or transient ischemic attack, peripheral vascular disease, dyslipidemia, diabetes mellitus, chronic kidney disease, liver disease, depression, epilepsy, Parkinson disease, traumatic brain injury, osteoporosis, hypothyroidism, cancer, treatment for varicella zoster virus infection, antibiotics, oral anticoagulants, antiplatelet agents, lipid-lowering drugs, β-blockers, thiazides, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, proton pump inhibitors, nonsteroidal anti-inflammatory drugs, opioids, immunosuppressants and biologics, antipsychotics, and antidepressants.

[b]Diphtheria-tetanus-pertussis (combined), diphtheria-tetanus (combined), or diphtheria vaccine.

[c]Diphtheria-tetanus-pertussis (combined), diphtheria-tetanus (combined), or tetanus vaccine.

[d]Diphtheria-tetanus-pertussis (combined) or pertussis vaccine.

early signs of dementia may result in avoiding or postponing vaccinations, especially in older adults, which would then produce artificially decreased estimates. On the other hand, the lack of a lag period can introduce early detection bias, if physician visits for the purpose of vaccination alter the probability of a subsequent diagnosis of dementia. Of note, it also weakens the biological rationale, since a decrease in the risk of dementia immediately after vaccination does not seem plausible.

Second, several studies required a minimum number of physician visits during the study period [14, 15, 17, 18]. This approach can introduce immortal time bias because study subjects are not allowed to experience the outcome (are "immortal") until the required number of physician visits is reached. Importantly, immortal time bias has been shown to artificially decrease point estimates and lead to spurious associations with strongly "protective" effects [21]. Finally, another bias that can decrease point estimates and that possibly contributed to previous findings is healthy vaccinee bias, which occurs when individuals with better overall health and inclined toward health-seeking behaviors are more likely to participate in preventive programs such as vaccinations [22].

Our results do not support a role for vaccinations in the prevention of dementia. Indeed, we did not observe a decreased risk of dementia with common vaccines overall or with individual vaccines (apart from marginal effects with shingles and diphtheria vaccines). Design-specific aspects, such as the application of a nested case-control analysis that eliminated immortal time bias and the use of a 2-year lag period that minimized protopathic and early detection bias, may have accounted for the discrepancy between our results and those from previous studies.

The observed increase in the risk was unexpected. Given the lack of any biological rationale linking vaccinations to an increased risk of dementia, and considering the totality of our findings, we deem unmeasured confounding and late detection bias to be the most plausible explanations. First, unmeasured confounding—that is, confounding bias due to covariates that are not recorded in the underlying data source—is an inherent challenge in observational studies. The fact that case patients and controls exposed to common vaccines were, on average, sicker than unexposed patients and controls supports this notion. Second, late detection bias is also possible. In line with this hypothesis, the

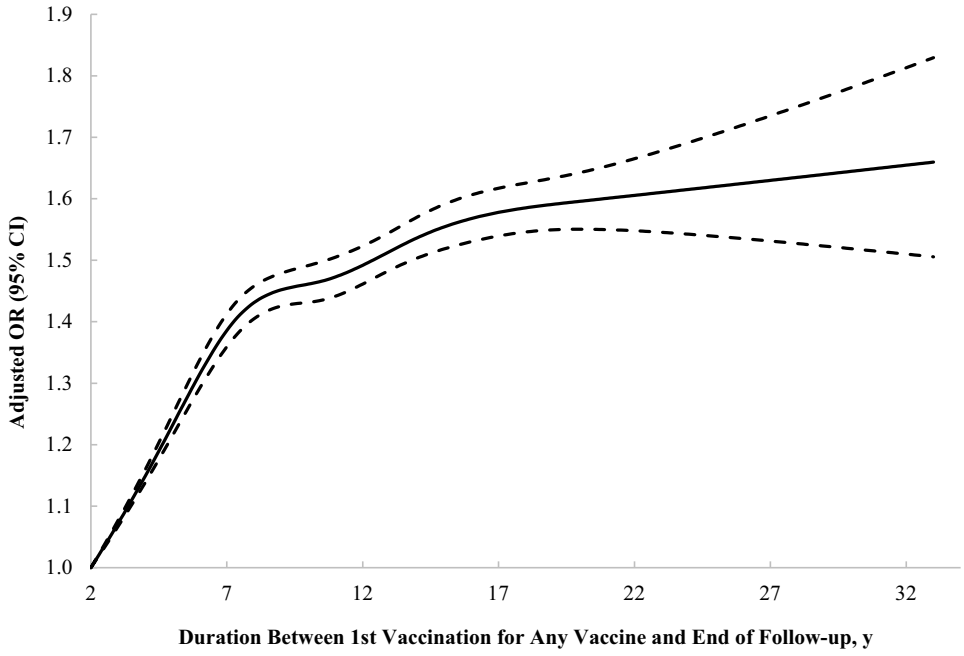

Figure 2. Association between time since first immunization and risk of incident dementia. Abbreviations: CI, confidence interval; OR, odds ratio.

Table 3. Association Between Common Vaccines and the Risk of Incident Dementia: Sensitivity Analyses

Exposure	Patients With Dementia, No. (%)	Controls, No. (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Lag period: 3-y	n = 196 331	n = 782 174		
Any vaccine	159 390 (81.2)	596 179 (76.2)	1.47 (1.45–1.49)	1.37 (1.35–1.39)
Influenza	154 819 (78.9)	574 193 (73.4)	1.48 (1.46–1.50)	1.38 (1.36–1.40)
Pneumococcus	82 282 (41.9)	311 491 (39.8)	1.14 (1.12–1.15)	1.12 (1.11–1.14)
Shingles	8250 (4.2)	32 746 (4.2)	1.00 (.97–1.03)	0.99 (.96–1.03)
Diphtheria[b]	12 802 (6.5)	53 588 (6.9)	0.95 (.93–.96)	0.95 (.93–.97)
Tetanus[c]	25 885 (13.2)	103 510 (13.2)	1.00 (.98–1.01)	1.00 (.98–1.01)
Pertussis[d]	359 (0.2)	1395 (0.2)	1.02 (.91–1.15)	1.00 (.89–1.13)
Lag period: 5 y	n = 166 684	n = 663 978		
Any vaccine	131 486 (78.9)	490 598 (73.9)	1.44 (1.42–1.47)	1.34 (1.32–1.36)
Influenza	126 957 (76.2)	469 282 (70.7)	1.45 (1.43–1.48)	1.35 (1.33–1.37)
Pneumococcus	67 366 (40.4)	253 218 (38.1)	1.15 (1.14–1.17)	1.13 (1.12–1.15)
Shingles	2790 (1.7)	10 860 (1.6)	1.03 (.98–1.09)	1.02 (.96–1.07)
Diphtheria[b]	10 497 (6.3)	43 574 (6.6)	0.95 (.93–.98)	0.96 (.94–.98)
Tetanus[c]	22 473 (13.5)	89 307 (13.5)	1.00 (.99–1.02)	1.00 (.99–1.02)
Pertussis[d]	266 (0.2)	1047 (0.2)	1.01 (.88–1.16)	1.00 (.87–1.14)
Lag period: 10 y	n = 101 496	n = 404 100		
Any vaccine	69 505 (68.5)	259 500 (64.2)	1.30 (1.28–1.32)	1.20 (1.18–1.23)
Influenza	65 382 (64.4)	240 815 (59.6)	1.34 (1.31–1.36)	1.23 (1.21–1.25)
Pneumococcus	30 510 (30.1)	113 653 (28.1)	1.15 (1.13–1.17)	1.11 (1.09–1.13)
Shingles	…[e]	…[e]	2.00 (.18–22.06)	1.00 (.06–15.50)
Diphtheria[b]	4872 (4.8)	20 167 (5.0)	0.96 (.93–.99)	0.96 (.93–1.00)
Tetanus[c]	13 462 (13.3)	53 203 (13.2)	1.01 (.99–1.03)	1.01 (.99–1.03)
Pertussis[d]	104 (0.1)	411 (0.1)	1.01 (.81–1.25)	1.00 (.80–1.24)
Active comparator for female patients	n = 119 422	n = 475 824		
Any vaccine	87 306 (73.1)	326 650 (68.6)	1.50 (1.41–1.58)	1.39 (1.31–1.47)
Breast cancer screening	1618 (1.4)	8261 (1.7)	Reference	Reference

Table 3. Continued

Exposure	Patients With Dementia, No. (%)	Controls, No. (%)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Active comparator for male patients	n = 80 904	n = 322 183		
Any vaccine	52 054 (64.3)	193 272 (60)	1.24 (1.16–1.33)	1.17 (1.09–1.25)
Prostate cancer screening	1103 (1.4)	4995 (1.6)	Reference	Reference

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]We adjusted for the following potential confounders measured at cohort entry: body mass index, smoking, socioeconomic status, ethnicity, alcohol-related disorders, arterial hypertension, atrial fibrillation, congestive heart failure, coronary artery disease, stroke or transient ischemic attack, peripheral vascular disease, dyslipidemia, diabetes mellitus, chronic kidney disease, liver disease, depression, epilepsy, Parkinson disease, traumatic brain injury, osteoporosis, hypothyroidism, cancer, treatment for varicella zoster virus infection, antibiotics, oral anticoagulants, antiplatelet agents, lipid-lowering drugs, β-blockers, thiazides, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, proton pump inhibitors, nonsteroidal anti-inflammatory drugs, opioids, immunosuppressants and biologics, antipsychotics, and antidepressants.

[b]Diphtheria-tetanus-pertussis (combined), diphtheria-tetanus (combined), or diphtheria vaccine.

[c]Diphtheria-tetanus-pertussis (combined), diphtheria-tetanus (combined), or tetanus vaccine.

[d]Diphtheria-tetanus-pertussis (combined) or pertussis vaccine.

[e]Numbers <5 were suppressed based on data protection regulations of the Clinical Practice Research Datalink.

strongest increase in the risk was observed immediately after the end of the imposed 2-year lag period, and the use of longer lag periods led to the attenuation of increased risk. Moreover, the increase in risk was driven by regularly recurring vaccinations (influenza and pneumococcus for those at higher risk)—that is, vaccinations leading to more frequent physician visits and potentially to elevated chances of disease detection—and not by vaccinations more likely to be administered in an one-off fashion.

Our study has strengths. First, the application of nonrestrictive inclusion criteria likely maximized the generalizability of our findings. Second, the large sample size, including >200 000 patients with dementia, allowed the calculation of precise effect estimates for the primary analysis but also for secondary analyses including individual vaccines and demographic or other clinically relevant subgroups. Finally, the use of a nested case-control analysis and a lag period minimized biases, such as immortal time and protopathic bias.

Our study also has limitations. First, despite extensive statistical adjustments, residual confounding possibly affected our findings, leading to the observed increased risk. For example, while we matched for age, chronological age does not necessarily reflect biological age. Therefore, residual confounding due to frailty, for example, cannot be excluded. Moreover, time-dependent confounding is also possible, especially given the long duration of follow-up. Second, given that the mean age at cohort entry was high (70 years), potentially protective effects of vaccination in nonelderly populations may have been "masked." However, the OR did not change in the subgroup of study participants who entered the cohort at 50–64 years of age. That being said, the effects of early vaccination need to be specifically assessed in future studies. Third, exposure was assessed based on records from public healthcare providers, which could introduce some underreporting and misclassification. However, we expect the majority of study cohort members to be vaccinated at their primary care practice, as vaccines are free under the routine immunization program [37]. Finally, misclassification of the outcome is also possible. That being said, the recording of dementia in the CPRD has been shown to be accurate [26].

Overall, our large population-based study showed no decreased risk of dementia associated with routinely administered vaccines. Thus, our findings do not support a role for immunizations in the prevention of this neurodegenerative disease. The observed increased risk is likely a result of unmeasured confounding and detection bias.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. S. S. attended scientific advisory committee meetings or consulted for AstraZeneca, Atara, Bristol-Myers-Squibb, Merck, Novartis, Panalgo, Pfizer, and Seqirus and received speaking fees from Boehringer-Ingelheim and Novartis. P. B. received consulting fees from Becton Dickinson on topics unrelated to the current work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. World Health Organization. Dementia 2020. https://www.who.int/news-room/fact-sheets/detail/dementia. Accessed 8 June 2021.

2. Alonso R, Pisa D, Aguado B, Carrasco L. Identification of fungal species in brain tissue from Alzheimer's disease by next-generation sequencing. J Alzheimers Dis **2017**; 58: 55–67.
3. Balin BJ, Hammond CJ, Little CS, et al. *Chlamydia pneumoniae*: an etiologic agent for late-onset dementia. Front Aging Neurosci **2018**; 10:302.
4. Beydoun MA, Beydoun HA, Elbejjani M, Dore GA, Zonderman AB. *Helicobacter pylori* seropositivity and its association with incident all-cause and Alzheimer's disease dementia in large national surveys. Alzheimers Dement **2018**; 14:1148–58.
5. Lovheim H, Olsson J, Weidung B, et al. Interaction between cytomegalovirus and herpes simplex virus type 1 associated with the risk of Alzheimer's disease development. J Alzheimers Dis **2018**; 61:939–45.
6. Itzhaki RF. Herpes simplex virus type 1 and Alzheimer's disease: possible mechanisms and signposts. FASEB J **2017**; 31:3216–26.
7. Singhrao SK, Harding A, Poole S, Kesavalu L, Crean S. *Porphyromonas gingivalis* periodontal infection and its putative links with Alzheimer's disease. Mediators Inflamm **2015**; 2015:137357.
8. Zhan X, Stamova B, Jin LW, DeCarli C, Phinney B, Sharp FR. Gram-negative bacterial molecules associate with Alzheimer disease pathology. Neurology **2016**; 87: 2324–32.
9. Douros A, Santella C, Dell'Aniello S, et al. Infectious disease burden and the risk of Alzheimer's disease: a population-based study. J Alzheimers Dis **2021**; 81: 329–38.
10. Mawanda F, Wallace RB, McCoy K, Abrams TE. Systemic and localized extra-central nervous system bacterial infections and the risk of dementia among US veterans: a retrospective cohort study. Alzheimers Dement **2016**; 4:109–17.
11. Sipilä PN, Heikkilä N, Lindbohm JV, et al. Hospital-treated infectious diseases and the risk of dementia: a large, multicohort, observational study with a replication cohort. Lancet Infect Dis **2021**; 21:1557–67.
12. Liu JC, Hsu YP, Kao PF, et al. Influenza vaccination reduces dementia risk in chronic kidney disease patients: a population-based cohort study. Medicine **2016**; 95:e2868.
13. Luo CS, Chi CC, Fang YA, Liu JC, Lee KY. Influenza vaccination reduces dementia in patients with chronic obstructive pulmonary disease: a nationwide cohort study. J Investig Med **2020**; 68:838–45.
14. Wiemken TL, Salas J, Hoft DF, Jacobs C, Morley JE, Scherrer JF. Dementia risk following influenza vaccination in a large veteran cohort. Vaccine **2021**; 39:5524–31.
15. Scherrer JF, Salas J, Wiemken TL, Hoft DF, Jacobs C, Morley JE. Impact of herpes zoster vaccination on incident dementia: a retrospective study in two patient cohorts. PLoS One **2021**; 16:e0257405.
16. Schnier C, Janbek J, Lathe R, Haas J. Reduced dementia incidence after varicella zoster vaccination in Wales 2013–2020. Alzheimers Dement **2022**; 8:e12293.
17. Wiemken TL, Salas J, Morley JE, Hoft DF, Jacobs C, Scherrer JF. Comparison of rates of dementia among older adult recipients of two, one, or no vaccinations. J Am Geriatr Soc **2022**; 70:1157–68.
18. Scherrer JF, Salas J, Wiemken TL, Jacobs C, Morley JE, Hoft DF. Lower risk for dementia following adult tetanus, diphtheria, and pertussis (Tdap) vaccination. J Gerontol A Biol Sci Med Sci **2021**; 76:1436–43.
19. Wu X, Yang H, He S, et al. Adult vaccination as a protective factor for dementia: a meta-analysis and systematic review of population-based observational studies. Front Immunol **2022**; 13:872542.
20. Remschmidt C, Wichmann O, Harder T. Frequency and impact of confounding by indication and healthy vaccinee bias in observational studies assessing influenza vaccine effectiveness: a systematic review. BMC Infect Dis **2015**; 15: 429.
21. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care **2012**; 35:2665–73.
22. Nelson JC, Jackson ML, Weiss NS, Jackson LA. New strategies are needed to improve the accuracy of influenza vaccine effectiveness estimates among seniors. J Clin Epidemiol **2009**; 62:687–94.
23. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol **2015**; 44:827–36.
24. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the general practice research database: a systematic review. Br J Clin Pharmacol **2010**; 69:4–14.
25. Noble S, McLennan D, Noble M, et al. The English indices of deprivation 2019. London, UK: Ministry of Housing, Communities and Local Government, **2019**.
26. McGuinness LA, Warren-Gash C, Moorhouse LR, Thomas SL. The validity of dementia diagnoses in routinely collected electronic health records in the United Kingdom: a systematic review. Pharmacoepidemiol Drug Saf **2019**; 28: 244–55.
27. Suissa S, Dell'aniello S, Vahey S, Renoux C. Time-window bias in case-control studies: statins and lung cancer. Epidemiology **2011**; 22:228–31.
28. Rothman KJ. Induction and latent periods. Am J Epidemiol **1981**; 114:253–9.
29. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. Lancet **2017**; 390: 2673–734.

30. Wolf A, Dedman D, Campbell J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. Int J Epidemiol **2019**; 48:1740.
31. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med **1989**; 8:551–61.
32. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Curr Epidemiol Rep **2015**; 2:221–8.
33. Moser K, Sellars S, Wheaton M, et al. Extending the age range for breast screening in England: pilot study to assess the feasibility and acceptability of randomization. J Med Screen **2011**; 18:96–102.
34. Imfeld P, Brauchli Pernus YB, Jick SS, Meier CR. Epidemiology, co-morbidities, and medication use of patients with Alzheimer's disease or vascular dementia in the UK. J Alzheimers Dis **2013**; 35:565–73.
35. Sinyavskaya L, Gauthier S, Renoux C, et al. Comparative effect of statins on the risk of incident Alzheimer disease. Neurology **2018**; 90:e179.
36. Fulop T, Witkowski JM, Bourgade K, et al. Can an infection hypothesis explain the beta amyloid hypothesis of Alzheimer's disease? Front Aging Neurosci **2018**; 10:224.
37. NHS. NHS vaccinations and when to have them. https://www.nhs.uk/conditions/vaccinations/nhs-vaccinations-and-when-to-have-them. Accessed 12 May 2022.