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Shingles and risk of developing dementia: results from the UK Biobank cohort.

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Abstract

Objectives: To investigate association between shingles and dementia, and to examine how any association is affected by Zostavax vaccination.

Design: Nested case-control study.

Settings: Data were from the UKbiobank cohort study with a total of 502,650 participants (both males and females).

Participants: The analysis included 3,658 incident dementia cases and 497,992 controls. Inclusion criteria for incident cases was dementia diagnosis 3 years or more after the first assessment date from all sources including ICD10, 9, self-reported and primary care linkage record. Subjects with no dementia code from all sources were coded as controls. Shingles and Zostavax vaccination were investigated for their association with dementia risk.

Results: Subjects with shingles diagnosed 3 years or more prior to dementia diagnosis were at 60% increased risk of developing dementia. In those subjects who had not had Zostavax vaccination, shingles increased the risk of dementia (OR 1.35 with 95%CI. 1.16 to 1.58) however a non-significant decrease in risk was found for subjects who had been vaccinated against VZV (OR 0.76 with 95% CI. 0.42 to 1.36).

Conclusion: A history of shingles was associated with an increased risk of dementia, indicating that VZV may play-a role in the development of dementia. In subjects who were eligible for the immunisation and vaccinated with Zostavax we saw no increased risk of developing dementia.

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Article summary

Strengths and limitations of this study

1. This study used data available for the entire cohort of the UK Biobank and disease outcomes were ascertained through robust sources including the Hospital Episodes Statistics (HES) and through primary care data linkage.

2. Recent studies investigated the possible role of varicella zoster virus (VZV) – and dementia. We reported an association between shingles (the major disease in older people caused by VZV) and the risk of developing dementia in this UK cohort.

3. As VZV is the only herpesvirus for which an effective vaccine (Zostavax) is approved, we have also been able, for the first time, to establish whether vaccination against a herpesvirus influences any association seen with dementia**.**

4. This study inherits some weakness in that the UKBiobank study participants are not fully representative of the UK population, as suggested by low prevalence of dementia compared to the general population. Our findings however suggest the true effect of this particular virus on dementia may in fact be higher in the general population.

5. We did not investigate other type of herpes viruses that may also play role in dementia aetiology.

Introduction

The number of people worldwide afflicted with Alzheimer's disease (AD) or dementia of other types is high – the AD number being estimated to be currently at least 30 million, and by 2150 predicted to exceed 152 million. The recent Lancet Commission on dementia has highlighted potentially reversible causes[1]. Despite many years of research into the role of beta amyloid, the main component of the characteristic plaques seen in AD brains, no significant advances confirming a role for beta amyloid in causing the disease, or in the treatment of AD have yet been made. One unrelated possibility gaining increasing attention is whether viruses may have a role in initiating or aiding the development of dementia. For example, we previously proposed that herpes simplex virus type 1 (HSV1) is present in latent form in the post mortem brains of elderly people, causing both direct viral damage and inflammation on reactivation, and that this damage accumulates over time, leading eventually to the development of AD[2 3].

The possibility of involvement of other herpesviruses in the disease and in dementia has also been investigated, albeit to a very much lesser extent. Cytomegalovirus has been suggested to cause immune dysregulation, thereby leading to reactivation of latent HSV1[4 5]. The potential role of Varicella-zoster virus (VZV), another herpesvirus, in dementia has rarely been considered. However, it is very common, infecting most people in childhood with the primary infection resulting in chicken pox. The virus, remains latent in the body lifelong, in the case of VZV, it persists in the cranial nerves and dorsal root ganglia. Reactivation causes herpes zoster, known more commonly as shingles, which appears as a painful rash usually on one side of the torso.

The main risk factor for shingles, as with dementia, is increasing age. The reactivated virus can enter the brain, causing a productive infection, inflammation and cell death, as well as long-term effects in some cases such as cognitive decline. An early investigation of brain from AD patients and age-matched controls was unable to detect VZV DNA in brain of either group[3], but this result has not since been confirmed or disproved by PCR searches of greater sensitivity. However, even if VZV is not present in brain, this does not preclude its having a role in AD, as VZV reactivation in the periphery can an effect on the central nervous system (CNS).

In a study aiming to investigate any links between shingles and three amyloid-associated diseases of aging including AD, Bubak et al (2020)[6] found that herpes zoster plasma has significantly higher levels of beta amyloid and amylin than have controls, and that addition of exogenous beta amyloid or amylin causes increases amyloid aggregation. The authors concluded that shingles might accelerate progression of these diseases via aggregation of beta amyloid.

In this study, we investigated whether there was an association between shingles and risk of developing dementia in the UK Biobank cohort. Zostavax vaccination, which is used to prevent shingles (zoster) and zoster-related post-herpetic neuralgia, has been offered routinely by the NHS from 2013 for people aged 70-80. The uptake was initially 61.8% although it has declined more recently (42.8% in 2016/17)[7]. VZV is the only herpesvirus for which an effective vaccine is currently approved, and so for the first time the possible impact on dementia risk of vaccination against a herpesvirus was investigated also.

Methodology

Study design

A nested case-control study.

Cohort description

The UK Biobank (UKB) is a national cohort with 502,650 participants (both males and females) aged between 39 to 71 years. Participants were recruited in 2006-2010, aged 40-69 years at the time and continue to be longitudinally followed to capture subsequent health events. More details can be found at http://www.ukbiobank.ac.uk/. Participants consented to the UK Biobank for their data and /or samples to be used for health-related research purposes. Ethics approved for UK Biobank was obtained from the North West- Haydock research ethics committee (REC reference: 16/NW/0274). All findings were deposited within the UKBiobank website as a way of dissemination to all participants and other researchers.

Dementia case identification

ICD 10 and 9

The ICD 10 and 9 codes for dementia were obtained from the publication by Wilkinson et al[8].

The ICD 10 has 212 data fields (follow-up data) and the ICD 9 has 46 data fields (follow-up data). Our analysis used data available up to 31st January 2020. Information on the date when the codes were recorded was available for each follow-up. For subjects with any of the dementia codes appearing more than once, the earliest diagnosis date was used.

Primary Care record linkage

Data from Primary Care linkage was available in 45% of the UK Biobank participants at the time of this analysis. There are two versions of medical Read codes available in the UKB: version 2 (v2) and version 3 (ctV3 or v3). Both versions provide a standard vocabulary for clinicians to record patient findings and procedures, in health and social care IT systems across primary and secondary care within the National Health Service (NHS) in the UK.

First, we applied the dementia medical Read code version 2 listed in the article by Wilkinson[8]. We further mapped read code version 2 with version 3 using the mapping file. This mapping file was provided by the UKB. The mapping file allows the specific code to be mapped across different platforms. We then generated Structured Query Language (SQL) to extract data from the UKB portal. The date on when dementia was recorded was also extracted. This enabled us to define if the case was an incident or prevalent case. For individuals where dementia codes appeared more than once, the record with the earliest date was kept (first time of diagnosis).

All dementia cases across all data sources were then further classified into one of the following: incident or prevalent cases and controls.

Criteria for case and control identification

For incident cases, subjects had to fulfil both of the following criteria 1) dementia diagnosis occurred 3 years or more after the first assessment date and 2) subjects with a dementia code from any sources. For controls, subjects with no dementia code from all sources were coded as controls.

Shingles identification

We used three sources to derive shingles variable including ICD10, 9 and Primary Care record

linkage. We used the same approach to identify shingles cases and further applied a 3-year window prior to age at dementia diagnosis for cases and age at last follow up for controls. In subjects who had shingles diagnosis more than once, the first diagnosis was used. Shingles variable was coded as binary (yes/no).

Zostavax vaccination

We investigated also the association of shingles and dementia in sub-cohort of subjects who were eligible for Zostavax vaccination (vaccine used to prevent shingles and zoster-related post-herpetic neuralgia). Data were extracted from the Primary Care linkage record only. The code provided by the UKB was used to identify Zostavax vaccination including date of event. Zostavax vaccine was available within the NHS from 2013 onwards for people age 70 and over. We therefore computed the age of subjects in 2013 and included only those with age 70+ in this sub-analysis. Zostavax vaccination variable was coded as binary (yes/no). Of those who were vaccinated, 13.6% had had shingles before vaccination.

Patient and Public Involvement

There is no patient and public involvement in this study as we analysed dataset obtained from the UKbiobank.

Statistical analysis

Logistic regression analysis was performed using Stata version 15.0 [9]. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. A significant odds ratio is considered when 95% CI does not include 1. For shingles and Zostavax vaccination variable, "no" category was used as reference category. We tested if age (at diagnosis for cases and until last follow up in 2017 for controls) and gender were a confounding factor for shingles and a dementia outcome. Each potential confounder was tested and had to satisfy two criteria if they were to be defined as a confounder.

Criterion 1: among the unexposed (subjects with no shingles code), there should be an association between the confounder and the dementia outcome.

Criterion 2: the potential confounder must be associated with the main exposure (shingles), but not as a result of the exposure. To achieve this, we tested the association between the confounder and shingles in the control population.

Our analysis suggested that only age is a confounding factor. We therefore fitted the model adjusted for age.

Results

There were 3,658 incident cases and 497,992 controls, with dementia cases on average being older than controls (see Table 1). The Student t-test suggested this difference was significant (P-value<0.05). The number of female participants was slightly higher than males (54.41% female and 45.59% male - see Table 2). There were however more males than females in the incident group. The total number of participants who had shingles was 35,781 (or 7.14%) (Table 3). There were almost 12% of dementia cases with shingles as compared to 7% of controls. Results from Chi-square test suggested a significant difference in distribution of shingles between dementia cases and controls (P-value <0.05).

Table 1 Summary statistics showing age of control and incident (dementia) cases

Group	N	Mean	SD	Min	Max
Incident dementia cases	3658	69.55	6.24	44.00	79.00
Controls (No dementia)	497992	65.40	8.11	46.00	83.00

Student-t test p-value 0.0000

Table 2 Distribution of gender in the control and incident (dementia) groups

Sex	Incident dementia Cases (%)	Controls (No dementia) (%)	Total
Female	1778 (48.61)	271164 (54.45)	272942 (54.41)
Male	1880 (51.39)	226828 (45.55)	228708 (45.59)
Total	3658 (100)	497992 (100)	501650 (100)

Table 3 Distribution of shingles for the case control and incident (dementia) case groups.

Shingles	Incident dementia cases (%)	Controls (No dementia) (%)	Total (%)
No	3217 (88.21)	462460 (92.90)	465677 (92.86)
Yes	430 (11.79)	35351 (7.10)	35781 (7.14)
Total	3647 (100)	497811 (100)	501458 (100)

Pearson chi-square = 120.1433 P-value <0.05

After adjusting for age, subjects with shingles diagnosed 3 years or more prior to dementia diagnosis were at 60% increased risk of developing dementia (95% C.I 1.45 to 1.78) (Table 4).

Table 4 Estimated risk of dementia with or without > 3 year prior shingles diagnosis.

Shingles	Odds ratio[#]	St.Err.	P-value	[95% Confident Interval]	
No	1.000				
Yes	1.607	0.083	<0.001	1.452	1.779

[#] *adjusted for age*

To examine the effect of Zostavax vaccination on dementia, first, we included any subjects who reported had had shingles before and after Zostavax vaccine (Table 5a). Results show that in subjects who had had dementia. An inverse association suggesting decreased risk was observed for subjects who had been vaccinated (OR 0.761 with 95%CI.C 0.424 to 1.364); however, this did not reach statistical significance.

As it appears that there is a higher incidence of shingles in the group that have vaccination, we removed from our calculations those subjects who had had shingles *before* they were vaccinated (13.6%). This then demonstrated that vaccination against shingles decreased, as expected, the subsequent incidence of shingles (1.33%). Importantly, there is no dementia case in shingles group who had Zostavax vaccine (Table 5b).

Table 5a Estimated risk of dementia with or without > 3 year prior shingles diagnosis, in subjects with and without vaccination.

Zostavax vaccination	Shingles	Dementia			Odds ratio	95% Confident Interval	
		Controls (No dementia) (%)	Incident dementia cases (%)	Total (%)			
Yes	No	4969 (84.75)	95 (87.96)	5064 (84.81)	1.000		
	Yes	894 (15.25)	13 (12.04)	907 (15.19)	0.761	0.424	1.364
	Total	5863 (100)	108 (100)	5971 (100)			
No	No	78258 (92.10)	1589 (89.57)	79847(92.04)	1.000		
	Yes	6717 (7.90)	185 (10.43)	6902 (7.96)	1.356	1.163	1.583
	Total	84975 (100)	1774 (100)	86749 (100)			

Table 5b distribution of shingles and dementia in subjects who had shingles after Zostavax vaccine

Shingles	Dementia		
	Controls (No dementia) (%)	Incident dementia cases (%)	Total (%)
No	4969 (98.65)	95 (100.00)	5064 (98.67)
Yes	68 (1.35)	0 (0.00)	68 (1.33)
Total	5037 (100.00)	95 (100.00)	5132 (100)

Discussion

In this study, we found a significant difference in distribution of shingles between dementia incident cases and controls in a cohort with large sample sizes. Our main finding is that shingles increases the risk of incident case dementia. A possible explanation is that VZV is a direct cause of dementia or that shingles causes inflammation in the periphery that leads to brain inflammation and possible reactivation of HSV1 and/or that VZV, like CMV, causes immune dysregulation as suggested for the role of CMV in AD, by Stowe et al. (2012)[4] and Westman et al. (2014)[5].

In our analysis, we opted to restrict the date of shingles diagnosis to those who were diagnosed 3 years prior to dementia diagnosis, to minimise possible detection bias from too short an exposure time prior to study outcome. Similarly, for dementia incident cases, we used a diagnosis date of 3 years after their first attendance date. This was done to minimise likelihood of including prevalent cases of dementia. This approach has been used previously for dementia outcomes in the UKB dataset[10].

In the United Kingdom (UK) the incidence of HZ increases from 7.1 per 1000 person-years among 60–64 year olds to 12.2 per 1000 among individuals aged ≥85[11]. The lifetime risk of HZ is around 10–30%[12]. Although rare, it is possible to have shingles more than once. In our study, overall shingles incidence rate was 8.01 per 1000 person-years. We further examined incidence in the sub-cohort aged 60-64, and found that shingles incidence rate was 7.56 per 1000 person-years, which is close to the reported national figure.

People with a weakened immune system are at higher risk of shingles. Neurological sequelae in shingles sufferers range from mild to severe in immunocompetent patients to extremely severe

and even fatal, in immunocompromised people. Several studies have evaluated changes in cognition after the very rare disease herpes zoster encephalitis (HZE), and/or other neuropsychiatric sequelae[13-15]. Antiviral treatment with acyclovir or valacyclovir was used in every study apart from that of Appelbaum et al.[13], who used "no specific therapy". The results were variable, Wetzel et al. (2002)[15] detecting no change (apart from possible impairment of "visuo-constructive abilities"), whereas the others found appreciable deterioration; however, all these studies used only very small numbers of patients, of variable ages, and variable periods of assessment after the acute disease. More recently, Grahn et al (2013)[16] investigated 14 patients, age range 19 to 83, three years after the acute disease, and found that the patients showed signs of long-term cognitive impairment in the domains of speed and attention, memory and learning and executive function; also, a greater proportion of VZV patients was classified with mild cognitive impairment (MCI) , compared with 28 controls , matched for age and gender.

Two recent population epidemiological studies in Taiwan on VZV and dementia/AD implicated VZV in the disease[17 18]. Investigations were made using the Taiwan National Health Insurance Research Database, which operated from 1995 and to which 99.9% of the population subscribed (by 2014). The first study[17] investigated 846 patients with herpes zoster ophthalmicus (HZO), mean age 61.6 years, and 2538 age-matched comparison patients. The patients were identified by first-time principal diagnosis in clinics or in hospitals, and the comparison patients were selected by matching them with a given HZO patient in their usage of medical services in the same index year. The incidences rates of senile dementia were investigated within the 5-year period after their index dates. The covariate-adjusted HR of dementia was found to be 2.97 (95% CI, 1.90-4.67), revealing that the risk of developing dementia was high in HZO patients (no details of any antiviral treatment were provided).

In the second study[18], Chen et al compared almost 40,000 patients diagnosed with herpes zoster with the same number of controls, aged 50-90 years in the period 1997-2013, the mean follow-up period being 6 years. The definition of herpes zoster was based on at least one inpatient and/or outpatient diagnosis. The incidence of senile dementia was found to be slightly higher than that of controls (HR 1.11, 95% CI: 1.04-1.17). However, comparing VZV patients treated with antivirals with untreated patients, the risk of SD was greatly diminished (adjusted relative risk,

0.55, 95% CI 0.34-0.65). Thus, in contrast to the HZO result, the increased risk of SD was low in HZ patients, yet antiviral treatment was highly protective.

Direct comparisons cannot be made between our results and those of Chen et al because all the patients in the UK shingles group would almost certainly have been treated with antivirals, whereas only about 5% of the Taiwanese shingles patients were treated thus. Chen et al. were therefore able to compare not only risk of dementia for shingles patients - mostly untreated - with matched controls, but also risk for antiviral-treated shingles patients compared with untreated shingles patients. Surprisingly though, in our study the risk of dementia for shingles patients is higher rather than lower than in the Taiwan study. Whether this results from differences in ethnicity is unknown. A further possible explanation is that the difference relates to adjustment for additional variables in in the Chen analyses.

We also sought to look at the possible modifying effects of vaccination with Zostavax. In our study the non-vaccinated subjects, subjects were at 35% increased risk, with this reaching statistical significance (P value<0.0001). Subjects who had been vaccinated showed the inverse effect, with a decreased dementia risk of around 24%, although this did not reach statistical significance Table 5a. What is perhaps unsurprising, in view of the severity of shingles' symptoms, is that in our cohort, a high proportion of people who had had shingles then decided to be vaccinated. Thus in Table 5b, we have removed the data on this group when calculating the effect of vaccination against shingles on incidence of dementia, and when calculating the effect of vaccination on shingles incidence, as obviously, the subjects had not been vaccinated *before* they had shingles.

Our findings thus show that people at older age who have not had Zostavax vaccination are at increased risk of dementia, and indicate that this vaccination may protect against subsequent dementia.

The protective effect of vaccination against shingles on subsequent incidence of dementia is presumably attributable to the reduced likelihood of the subjects suffering from shingles, and could be explained by a decreased occurrence of reactivation of HSV1 in brain, caused by indirect or possibly direct action of VZV. We suggested this explanation in a previous comment[19] on the observed protective effect against AD of vaccines against diphtheria, tetanus, poliomyelitis and influenza [20]. In fact, a further example has been noted very recently, namely,

vaccination against BCG, which showed that neuropsychiatric symptoms can occur even if a putative pathogen is not present in brain[21 22].

Our study has inherent strengths and weaknesses. The UKB is a national cohort of half a million people with an average follow up of almost 12 years (up until 2020). Disease outcome was ascertained by robust sources including the Hospital Episodes Statistics (HES) and through primary care data linkage. Although the primary care data linkage covered 45% of participants at the time of data analysis, this source of data has the benefit of capturing mild symptom shingles cases. Most people suffering from shingles seeks medical advice/treatment first from their GP prior to referral to hospital for further treatments, particularly with some severe cases, hence these data have enabled us to capture shingles cases in the community. We were able to demonstrate also the effect of shingles immunisation on shingles and dementia risk. The weaknesses include the fact that the UKB entire cohort consists of only 1.12% of all dementia cases with age of 65 and over, which is far less than the national figure prevalence of dementia - 7.1% for the total age-standardised 65+ population (based on 2013 data)[23]. The diagnoses are also based on records rather than direct patient contact (although the validity seems satisfactory).

It is to be noted that the UKB participants are in general healthier, less obese and smoke less than people in the general population. It was also reported that UKB participants suffered less heart and kidney disease and cancer as compared to the national figures[24]. This has led to a non-representative of the sampling population, a so-called a “healthy volunteer” selection bias. The fact that we have seen the dementia risk increase with shingles within this healthy cohort suggests that the effect of shingles on the general public might well be higher.

We did not take any anti-herpetic treatments into account which could potentially have an effect on dementia risk if shingles occurred long before dementia diagnosis. Also, we did not include other types of herpesvirus in our analysis.

Conclusion

Our study suggests a potential role of VZV in dementia, particularly in subjects who have not been vaccinated for VZV. Further studies should further investigate the role of Zostavax vaccination in reducing this excess risk of dementia and examine the possible causal pathway between HZ and dementia.

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Role of sponsor

Sponsor has no role in study design, data acquisition or involve in any process of data analysis.

Conflict of Interest

There is no competing of interest.

Author contributions

RI, CD and KM were involved in study conception, idea and design. KM, AL, AB and KM were involved in data acquisition and data quality check. AL carried out data analysis. AL, KM, RC, RI, CD carried out result interpretation. All authors involved in drafting and approved the final version of the manuscript. KM is the study guarantor.

Data Availability

Upon publishing this article, we have fulfilled our proposed work agreement with the UK Biobank and have returned our data that we used for these analyses to the UKBiobank as part of the agreement. However, the data from the UK Biobank (www.ukbiobank.ac.uk) are third party and their legal agreement means that we do not have permission to share the data. The UK

Biobank data used in this study can however be accessed by applying through the UK Biobank Access Management System (www.ukbiobank.ac.uk/register-apply).

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2	This study used a nested case-control study design.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	What was done: Shingles exposure and Zostavax vaccination were investigated with dementia risk. What was found: Subjects with shingles diagnosed 3 years or more prior to dementia diagnosis were at 60% increased risk of developing dementia. For subjects who had not had Zostavax vaccination, shingles increased the risk of dementia (OR 1.356 with 95%CI.C 1.163 to 1.583). A decreased risk was found for subjects who had been vaccinated against VZV (OR 0.761 with 95%CI.C 0.424 to 1.364), but it did not quite reach statistical significance.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4	
Objectives	3	State specific objectives, including any prespecified hypotheses	4	In this study, we investigated whether there was an association between shingles

	Item No.	Recommendation	Page No.	Relevant text from manuscript
				and risk of developing dementia in the UK Biobank cohort. VZV is the only herpesvirus for which an effective vaccine is currently approved, and so for the first time the possible impact on dementia risk of vaccination against a herpesvirus was investigated also.
Methods				
Study design	4	Present key elements of study design early in the paper	4	A nested case-control study.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4	The UK Biobank (UKB) is a national cohort with 502,650 participants (both males and females) aged between 39 to 71 years. Participants were recruited in 2006-2010, aged 40-69 years at the time and continue to be longitudinally followed to capture subsequent health events.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5	Criteria for case and control identification For incident cases, subjects had to fulfil both of the following criteria 1) dementia diagnosis occurred 3 years or more after the first assessment date and 2) subjects with a dementia code

	Item No.	Recommendation	Page No.	Relevant text from manuscript
				from any sources. For controls, subjects with no dementia code from all sources were coded as controls.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6	Outcome: All dementia cases across all data sources were then further classified into one of the following: incident or prevalent cases and controls. Exposures: Shingles identification We used the same approach to identify shingles cases and further applied a 3-year window prior to age at dementia diagnosis for cases and age at last follow up for controls. Zostavax vaccination We investigated also the association of shingles and dementia in sub-cohort of subjects who were eligible for Zostavax vaccination- Zostavax vaccine was available within the NHS from 2013 onwards for

	Item No.	Recommendation	Page No.	Relevant text from manuscript
				people age 70 and over. We therefore computed the age of subjects in 2013 and included only those with age 70+ in this sub-analysis. Confounders: Our analysis suggested that only age is a confounding factor. We therefore fitted the model adjusted for age.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		Shingles: We used three sources to derive shingles variable including ICD10, 9 and Primary Care record linkage. Zostavax vaccination: Data were extracted from the Primary Care linkage record only. The code provided by the UKB was used to identify Zostavax vaccination including date of event.
Bias	9	Describe any efforts to address potential sources of bias	6	We tested if age (at diagnosis for cases and until last follow up in 2017 for controls) and gender were a confounding factor for shingles and a dementia outcome. Each potential confounder was tested and had to satisfy two criteria if they

	Item No.	Recommendation	Page No.	Relevant text from manuscript
				were to be defined as a confounder. Criterion 1: among the unexposed (subjects with no shingles code), there should be an association between the confounder and the dementia outcome. Criterion 2: the potential confounder must be associated with the main exposure (shingles), but not as a result of the exposure. To achieve this, we tested the association between the confounder and shingles in the control population.
Study size	10	Explain how the study size was arrived at	6	Criteria for case and control identification For incident cases, subjects had to fulfil both of the following criteria 1) dementia diagnosis occurred 3 years or more after the first assessment date and 2) subjects with a dementia code from any sources. For controls, subjects with no dementia code from all sources were coded as controls.

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6	Shingles variable was coded as binary (yes/no). Zostavax vaccination variable was coded as binary (yes/no). For shingles and Zostavax vaccination variable, "no" category was used as reference category.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6	Logistic regression analysis was performed using Stata version 15.0 9. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. A significant odds ratio is considered when 95% CI does not include 1. For shingles and Zostavax vaccination variable, "no" category was used as reference category. We tested if age (at diagnosis for cases and until last follow up in 2017 for controls) and gender were a confounding factor for shingles and a dementia outcome. Each potential confounder was tested and had to satisfy two criteria if they were to be defined as a confounder.
		(*b*) Describe any methods used to examine subgroups and interactions	6	Zostavax vaccine was available within the NHS from 2013 onwards for people age 70 and over. We therefore computed the age of subjects in 2013 and included only those with age 70+ in this sub-analysis.

		(*c*) Explain how missing data were addressed		
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A	
		(*e*) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6	There were 3,658 incident cases and 497,992 controls, with dementia cases.
		(b) Give reasons for non-participation at each stage	N/A	
		(c) Consider use of a flow diagram	N/A	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7	The number of female participants was slightly higher than males (54.41% female and 45.59% male - see Table 2). There were however more males than females in the incident group.
		(b) Indicate number of participants with missing data for each variable of interest	N/A	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	7-8	The total number of participants who had shingles was 35781 (or 7.14%) (Table 3). There were almost 12% of dementia cases with shingles as compared to 7% of controls. Table 5 report number of Zostavax vaccination.
		Cross-sectional study—Report numbers of outcome events or summary measures		

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7	After adjusting for age, subjects with shingles diagnosed 3 years or more prior to dementia diagnosis were at 60% increased risk of developing dementia (95% C.I 1.45 to 1.78) (Table 4).
		(*b*) Report category boundaries when continuous variables were categorized	N/A	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7-8	Shingles increased risk of dementia in subjects who had not had Zostavax vaccination (OR 1.356 with 95%CI.C 1.163 to 1.583). An inverse association suggesting decreased risk was observed for subjects who had been vaccinated (OR 0.761 with 95%CI.C 0.424 to 1.364); however, this did not reach statistical significance (Table 5).
Discussion				
Key results	18	Summarise key results with reference to study objectives	8	In this study, we found a significant difference in distribution of shingles between dementia incident cases and controls in a cohort with large sample sizes.
			10	Our findings suggest that Zostavax vaccination modifies dementia risk associated with shingles.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11	Our study has inherent strengths and weaknesses. The UKB is a national cohort of half a million people with an average follow up of almost 12 years (up until 2020). Disease outcome was ascertained by robust sources including the Hospital Episodes Statistics (HES) and through primary care data linkage. Although the primary care data linkage covered 45% of participants at the time of data

analysis, this source of data has the benefit of capturing mild symptom shingles cases. Most people suffering from shingles seeks medical advice/treatment first from their GP prior to referral to hospital for further treatments, particularly with some severe cases, hence these data have enabled us to capture shingles cases in the community. We were able to demonstrate also the effect of shingles immunisation on shingles and dementia risk. The weaknesses include the fact that the UKB entire cohort consists of only 1.12% of all dementia cases with age of 65 and over, which is far less than the national figure prevalence of dementia - 7.1% for the total age-standardised 65+ population (based on 2013 data)23. The diagnoses are also based on records rather than direct patient contact (although the validity seems satisfactory).

It is to be noted that the UKB participants are in general healthier, less obese and smoke less than people in the general population. It was also reported that UKB participants suffered less heart and kidney disease and cancer as compared to the national figures24.

				This has led to a non-representative of the sampling population, a so-called a “healthy volunteer” selection bias. The fact that we have seen the dementia risk increase with shingles within this healthy cohort suggests that the effect of shingles on the general public might well be higher.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12	It is to be noted that the UKB participants are in general healthier, less obese and smoke less than people in the general population. It was also reported that UKB participants suffered less heart and kidney disease and cancer as compared to the national figures24. This has led to a non-representative of the sampling population, a so-called a “healthy volunteer” selection bias. We did not take any anti-herpetic treatments into account which could potentially have an effect on dementia risk if shingles occurred long before dementia diagnosis. Also, we did not include other types of herpesvirus in our analysis.
Generalisability	21	Discuss the generalisability (external validity) of the study results	11	The fact that we have seen the dementia risk increase with shingles within this healthy cohort suggests

				that the effect of shingles on the general public might well be higher.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12	Funding We would like to thank the Advantage Foundation for funding this work. Role of sponsor Sponsor has no role in study design, data acquisition or involve in any process of data analysis.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Shingles, Zostavax vaccination and risk of developing dementia: a nested case-control study - results from the UK Biobank cohort.

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Abstract

Objectives: To investigate the association between shingles and dementia, and between Zostavax vaccination and dementia.

Design: Nested case-control study.

Settings: Data were drawn from the UK Biobank cohort study with a total of 228,223 participants with hospital episode statistics and primary care linkage health records.

Participants: The analyses included 2,378 incident dementia cases and 225,845 controls. Inclusion criteria for incident cases was a dementia diagnosis 3 years or more after the first assessment date derived from all sources including ICD10, 9, self-report and primary care linkage records. Subjects with no dementia code from all sources were coded as controls. Both shingles and Zostavax vaccination were investigated for their association with dementia risk.

Results: There was a small but non-significant increase in the risk of dementia in subjects with shingles diagnosed 3 years or more prior to dementia diagnosis (OR 1.088 with 95% C.I. 0.978-1.211). In those subjects who had had Zostavax vaccination, the risk of dementia was significant decreased (OR 0.808 with 95% C.I. 0.657 to 0.993).

Conclusion: A history of shingles was not associated with an increased risk of dementia. In subjects who were eligible for the immunisation and vaccinated with Zostavax we saw reduced risk of developing dementia.

Word count: 200

Article summary

Strengths and limitations of this study

1. This study used a subset of UKBiobank cohort and disease outcomes and exposures were ascertained through sources including the Hospital Episodes Statistics (HES) primary care data linkage.

2. As VZV is the only herpesvirus for which an effective vaccine (Zostavax) is approved, we have also been able, to establish whether vaccination against a herpesvirus influences dementia**.**

3. The analysis of vaccination was based only in eligible subjects.

4. This study inherits some weakness in that the UK Biobank study participants are not fully representative of the UK population, as suggested by low prevalence of dementia compared to the general population.

5. We did not investigate other type of herpes viruses that may also play role in dementia aetiology.

Introduction

The number of people worldwide afflicted with Alzheimer's disease (AD) or dementia of other types is high – AD being estimated to be currently at least 30 million, and by 2150 predicted to exceed 152 million. The recent Lancet Commission on dementia has highlighted potentially reversible causes[1]. Despite many years of research into the role of beta amyloid, the main component of the characteristic plaques seen in AD brains, no significant advances confirming a role for beta amyloid in causing the disease, or in the treatment of AD have yet been made. One unrelated possibility gaining increasing attention is whether viruses may have a role in initiating or aiding the development of dementia. For example, we previously proposed that herpes simplex virus type 1 (HSV1), which is present in latent form in the post mortem brains of elderly people, causes both direct viral damage and inflammation on reactivation, and that this damage accumulates over time, potentially leading to the development of AD[2 3].

The possibility of involvement of other herpesviruses in the disease and in dementia has also been investigated, albeit to a much lesser extent. Cytomegalovirus has been suggested to cause immune dysregulation, thereby leading to reactivation of latent HSV1[4 5]. The potential role of Varicella-zoster virus (VZV), another herpesvirus, in dementia has rarely been considered. However, it is very common, infecting most people in childhood, with the primary infection resulting in chicken pox. The virus, remains latent in the body lifelong, in the case of VZV, it persists in the cranial nerves and dorsal root ganglia. Reactivation causes herpes zoster, known more commonly as shingles, which appears as a painful rash usually on one side of the torso.

The main risk factor for shingles, as with dementia, is increasing age. The reactivated virus can enter the brain, causing a productive infection, inflammation and cell death, as well as long-term effects in some cases such as cognitive decline. An early investigation of brain from AD patients and age-matched controls was unable to detect VZV DNA in brain of either group[3], but this result has not since been confirmed or disproved by PCR searches of greater sensitivity. However, even if VZV is not present in brain, this does not preclude its having a role in AD, as VZV reactivation in the periphery could have an effect on the central nervous system (CNS).

In a study aiming to investigate any links between shingles and three amyloid-associated diseases of aging including AD, Bubak et al (2020)[6] found that herpes zoster plasma has significantly higher levels of beta amyloid and amylin than have controls, and that addition of exogenous beta amyloid or amylin causes increases amyloid aggregation. The authors concluded that shingles might accelerate progression of these diseases via aggregation of beta amyloid.

In this study, we investigated whether there was an association between shingles and risk of developing dementia in the UK Biobank cohort. Zostavax vaccination, which is used to prevent shingles (zoster) and zoster-related post-herpetic neuralgia, has been offered routinely by the NHS from 2013 for people aged 70-80. The uptake was initially 61.8% although it has declined more recently (42.8% in 2016/17)[7]. VZV is the only herpesvirus for which an effective vaccine is currently approved, and so for the first time the possible impact on dementia risk of vaccination against a herpesvirus was investigated also.

Methodology

Study design

A nested case-control study.

Cohort description

The UK Biobank (UKB) is a national cohort with half a million participants (both males and females) aged between 39 to 71 years. Participants were recruited in 2006-2010, aged 40-69 years at the time and continued to be longitudinally followed to capture subsequent health events. More details can be found at http://www.ukbiobank.ac.uk/. Participants consented to the UK Biobank for their data and /or samples to be used for health-related research purposes. Ethics approved for UK Biobank was obtained from the North West- Haydock research ethics committee (REC reference: 16/NW/0274). All findings were deposited within the UK Biobank website as a way of dissemination to all participants and other researchers. This study is based on a subset of the entire cohort for which primary care data linkage is available. We excluded any participants who informed the UKB of their withdrawal prior to assemble our final dataset. The dataset contained 228,930 eligible participants.

Dementia case identification

ICD 10 and 9

The ICD 10 and 9 codes for dementia were obtained from the publication by Wilkinson et al[8]. The ICD 10 has 212 data fields (follow-up data) and the ICD 9 has 46 data fields (follow-up data). Our analysis used data available up to 31st January 2020. Information on the date when the codes were recorded was available for each follow-up. For subjects with any of the dementia codes appearing more than once, the earliest diagnosis date was used.

Primary Care record linkage

Data from Primary Care linkage was available in 45% of the UK Biobank participants at the time of this analysis. There are two versions of medical Read codes available in the UKB: version 2 (v2) and version 3 (ctV3 or v3). Both versions provide a standard vocabulary for clinicians to record patient findings and procedures, in health and social care IT systems across primary and secondary care within the National Health Service (NHS) in the UK.

First, we applied the dementia medical Read code version 2 listed in the article by Wilkinson[8]. We further mapped read code version 2 with version 3 using the mapping file. This mapping file was provided by the UKB. The mapping file allows the specific code to be mapped across different platforms. We then generated Structured Query Language (SQL) to extract data from the UKB portal. The date on when dementia was recorded was also extracted. This enabled us to define if the case was an incident or prevalent case. For individuals where dementia codes appeared more than once, the record with the earliest date was kept (first time of diagnosis).

All dementia cases across all data sources were then further classified into one of the following: incident or prevalent cases and controls.

Criteria for case and control identification

For incident cases, subjects had to fulfil both of the following criteria 1) dementia diagnosis occurred 3 years or more after the first assessment date and 2) subjects with a dementia code from any sources. Prevalent cases that had already been diagnosed was excluded (707 prevalent cases). For controls, subjects with no dementia code from all sources were coded as controls.

Shingles identification

We used three sources to derive shingles variable including ICD10, 9 and Primary Care record linkage. We used the same approach to identify shingles cases and further applied a 3-year window prior to age at dementia diagnosis for cases and age at last follow up for controls. In subjects who had shingles diagnosis more than once, the first diagnosis was used. Shingles variable was coded as binary (yes/no).

Zostavax vaccination

We investigated the association of shingles and dementia in this sub-cohort of subjects who were eligible for Zostavax vaccination (vaccine used to prevent shingles and zoster-related post-herpetic neuralgia). Data were extracted from the Primary Care linkage record only. The code provided by the UKB was used to identify Zostavax vaccination including date of event. Zostavax vaccine was available within the NHS from 2013 onwards for people age 70 and over. We therefore computed the age of subjects in 2013 and included only those with age 70+ in this analysis. Zostavax vaccination variable was coded as binary (yes/no).

Patient and Public Involvement

There is no patient or public involvement in this study as we analysed dataset obtained from the UK Biobank.

Statistical analysis

Logistic regression analysis was performed using Stata version 15.0 [9]. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. A significant odds ratio is considered when 95% CI does not include 1. For shingles and Zostavax vaccination variable, "no" category was used as reference category. We fitted age (at diagnosis for cases and until last follow up in 2017 for controls) and gender as confounding factors for shingles and a dementia outcome. Each potential confounder was tested and had to satisfy two criteria if they were to be defined as a confounder.

Criterion 1: among the unexposed (subjects with no shingles code), there should be an association between the confounder and the dementia outcome.

Criterion 2: the potential confounder must be associated with the main exposure (shingles), but not as a result of the exposure. To achieve this, we tested the association between the confounder and shingles in the control population.

Our analysis suggested that both age and sex are confounding factors. For Zostavax vaccination, we added shingles and Charlson co-morbidity index (CCI), age at vaccination and sex in the model. The CCI was generated based on the code developed recently by Ludvigsson et al. [10] Both CCI and age at vaccination were also confirmed as confounding factors. To compare mean difference of age between non-dementia and dementia group, we used Student t-test. To explore the distribution of sex, shingles between non-dementia and dementia group, we used chi-square test. P-value <0.05 is considered as statistical significance.

Results

There were 2,378 incident cases and 225,845 controls, with dementia cases on average being older than controls (see Table 1). The Student t-test suggested this difference was significant (P-value<0.05). The number of female participants was slightly higher than males (54.41% female and 45.59% male - see Table 2). There were however more males than females in the incident group. The total number of participants who had shingles was 35,116 (or 15.39%) (Table 3). There were 18% of dementia cases with shingles as compared to 15% of controls. Results from Chi-square test suggested a significant difference in distribution of shingles between dementia cases and controls (P-value <0.05).

Table 1 Summary statistics showing age of control and incident (dementia) cases

Group	N	Mean	SD	Min	Max
Incident dementia cases	2378	68.91	6.51	44.00	79.00
Controls (No dementia)	225845	65.35	8.07	46.00	81.00

Student-t test p-value 0.0000

Table 2 Distribution of gender in the control and incident (dementia) groups

Sex	Incident dementia Cases (%)	Controls (No dementia) (%)	Total
Female	1187 (49.92)	123685 (54.77)	124872 (54.71)
Male	1191 (50.08)	102160 (45.55)	103351 (45.29)
Total	2378 (100.00)	225845 (100.00)	228223 (100.00)

Pearson chi-square = 22.36 P-value <0.05

Table 3 Distribution of shingles for the case control and incident (dementia) case groups.

Shingles	Incident dementia cases (%)	Controls (No dementia) (%)	Total (%)
No	1954 (82.41)	191066 (84.63)	193020 (84.61)
Yes	417 (17.59)	34699 (15.37)	35116 (15.39)
Total	2371 (100.00)	225765 (100.00)	228136 (100.00)

Pearson chi-square = 8.863 P-value <0.05

After adjusting for age and sex, there was a small but non-significant increase in the risk of dementia in subjects with shingles diagnosed 3 years or more prior to dementia diagnosis (OR 1.088 with 95%C.I. 0.978-1.211) (Table 4).

Table 4 Estimated risk of dementia with or without > 3 year prior shingles diagnosis.

Shingles	Odds ratio*	[95% Confident Interval]		Odds ratio#	[95% Confident Interval]	
No	1.000					
Yes	1.175	1.057	1.307	1.088	0.978	1.211

**Unadjusted # adjusted for age and sex*

To examine the effect of Zostavax vaccination on dementia, we included eligible subjects for Zostavax vaccine (Table 5). Age at vaccination and Charlson co-morbidity index as continuous variables showed an increased dementia risk by 18% and 49% respectively. Results show that in subjects who had had dementia, an inverse association suggesting decreased risk was observed for subjects who had been vaccinated (OR 0.808 with 95%C.I. 0.657 to 0.993).

Table 5 Estimated risk of dementia with or without > 3 year prior shingles diagnosis, in subjects with and without vaccination.

Variables	OR	95% Confident Interval	
Age at vaccination	1.182	1.137	1.228
Female	-Ref-		
Male	1.044	0.925	1.177
Not affected by shingles	-Ref-		
Affected by Shingles	0.886	0.755	1.04
Charlson co-morbidity index	1.489	1.446	1.534
Zostavax vaccination- No	-Ref-		
-Yes	0.808	0.657	0.993

Discussion

In this study, we found a significant difference in distribution of shingles between dementia incident cases and controls in a sub-cohort where medical record was available from both hospital episode statistics and primary care linkage. These data sources provided us with a more complete data for both dementia outcome and shingles exposure. Our finding suggests that there was a small but non-significant increase in the risk of dementia in subjects with shingles diagnosed 3 years or more prior to dementia diagnosis after adjust for age and sex. This is despite that fact that VZV has been suggested as a direct cause of dementia or that shingles causes inflammation in the periphery that might lead to brain inflammation and possible reactivation of HSV1 and/or that VZV, like CMV, causes immune dysregulation as suggested for the role of CMV in AD, by Stowe et al. (2012)[4] and Westman et al. (2014)[5]. Indeed, results from large cohort study using data from the Korean National Health Insurance Service of about 1.14M participants suggested similar findings to our study (OR 0.90 with 95% C.I. 0.84-0.97)[11].

We analysed a sub-cohort of the entire UKB from which health records from HES and primary care were available. These health records enabled us to capture shingles, Zostavax vaccination and dementia diagnosis.

In our analysis, we opted to restrict the date of shingles diagnosis to those who were diagnosed 3 years prior to dementia diagnosis, to minimise possible detection bias from too short an exposure time prior to study outcome. Similarly, for dementia incident cases, we used a diagnosis date of 3 years after their first attendance date. This was done to minimise likelihood of including prevalent cases of dementia. This approach has been used previously for dementia outcomes in the UKB dataset[12].

In the United Kingdom (UK) the incidence of HZ increases from 7.1 per 1000 person-years among 60–64 year olds to 12.2 per 1000 among individuals aged ≥85[13]. The lifetime risk of HZ is around 10–30%[14]. People with a weakened immune system are at higher risk of shingles. Neurological sequelae in shingles sufferers range from mild to severe in immunocompetent patients to extremely severe and even fatal, in immunocompromised people. Several studies have evaluated changes in cognition after the very rare disease herpes zoster encephalitis (HZE), and/or other neuropsychiatric sequelae[15-17]. Antiviral treatment with acyclovir or valacyclovir was used in every study apart from that of Appelbaum et al.[15], who used "no specific therapy". The results were variable, Wetzel et al. (2002)[17] detecting no change (apart from possible

impairment of "visuo-constructive abilities"), whereas the others found appreciable deterioration; however, all these studies used only very small numbers of patients, of variable ages, and variable periods of assessment after the acute disease. More recently, Grahn et al (2013)[18] investigated 14 patients, age range 19 to 83, three years after the acute disease, and found that the patients showed signs of long-term cognitive impairment in the domains of speed and attention, memory and learning and executive function; also, a greater proportion of VZV patients was classified with mild cognitive impairment (MCI) , compared with 28 controls , matched for age and gender.

Two recent population epidemiological studies in Taiwan on VZV and dementia/AD implicated VZV in the disease[19 20]. Investigations were made using the Taiwan National Health Insurance Research Database, which operated from 1995 and to which 99.9% of the population subscribed (by 2014). The first study[19] investigated 846 patients with herpes zoster ophthalmicus (HZO), mean age 61.6 years, and 2538 age-matched comparison patients. The patients were identified by first-time principal diagnosis in clinics or in hospitals, and the comparison patients were selected by matching them with a given HZO patient in their usage of medical services in the same index year. The incidences rates of senile dementia were investigated within the 5-year period after their index dates. The covariate-adjusted HR of dementia was found to be 2.97 (95% CI, 1.90-4.67), revealing that the risk of developing dementia was high in HZO patients (no details of any antiviral treatment were provided).

In the second study[20], Chen et al compared almost 40,000 patients diagnosed with herpes zoster with the same number of controls, aged 50-90 years in the period 1997-2013, the mean follow-up period being 6 years. The definition of herpes zoster was based on at least one inpatient and/or outpatient diagnosis. The incidence of senile dementia was found to be slightly higher than that of controls (HR 1.11, 95% CI: 1.04-1.17). However, comparing VZV patients treated with antivirals with untreated patients, the risk of SD was greatly diminished (adjusted relative risk, 0.55, 95% CI 0.34-0.65). Thus, in contrast to the HZO result, the increased risk of SD was low in HZ patients, yet antiviral treatment was highly protective.

Direct comparisons cannot be made between our results and those of Chen et al because all the patients in the UK shingles group would almost certainly have been treated with antivirals, whereas only about 5% of the Taiwanese shingles patients were treated thus. Chen et al. were

therefore able to compare not only risk of dementia for shingles patients - mostly untreated - with matched controls, but also risk for antiviral-treated shingles patients compared with untreated shingles patients. Surprisingly though, in our study the risk of dementia for shingles patients is higher rather than lower than in the Taiwan study. Whether this results from differences in ethnicity is unknown. A further possible explanation is that the difference relates to adjustment for additional variables in in the Chen analyses.

We sought possible effects of vaccination with Zostavax. In our study, subjects who had been vaccinated showed the inverse effect, with a decreased dementia risk of around 20%.

Our findings suggest that this group may be protected from dementia in the future. There is a possibility that healthy people tend to seek vaccination therefore in our analysis we adjusted for Charlson co-morbidity index.

VZV might have either a direct or an indirect involvement in dementia, indirect in causing neuroinflammation and subsequent reactivation of HSV1 in brain, with consequent damage, so that the protective effect of vaccination against shingles on subsequent incidence of dementia could be attributed to a decreased occurrence of HSV1 reactivation in brain. We suggested this explanation in a previous comment[21] on the observed protective effect against AD of vaccines against diphtheria, tetanus, poliomyelitis and influenza [22]. In fact, a further example has been noted very recently, namely, vaccination against BCG, which showed that neuropsychiatric symptoms can occur even if a putative pathogen is not present in brain[23 24].

The fact that shingles causes only a small, non-significant risk of dementia, yet vaccination against shingles is protective, seems at first sight to be paradoxical. Possibly the risk of shingles found here is an under-estimate, or else it might be that the reduced risk for those vaccinated is attributable to off-target effects, as found for several other vaccines - affecting the immune system and subsequently, reactivation of HSV1, as suggested.

Our study has inherent strengths and weaknesses. The UKB is a national cohort of half a million people with an average follow up of almost 12 years (up until 2020). Disease outcome was ascertained by robust sources including the Hospital Episodes Statistics (HES) and through primary care data linkage. Although the primary care data linkage covered 45% of participants at the time of data analysis, this source of data has the benefit of capturing mild symptom shingles

cases. Most people suffering from shingles seeks medical advice/treatment first from their GP prior to referral to hospital for further treatments, particularly with some severe cases, hence these data have enabled us to capture shingles cases in the community. We were able to demonstrate the effect of shingles immunisation and dementia risk. The weaknesses include the fact that the UKB entire cohort consists of only 1.12% of all dementia cases with age of 65 and over, which is far less than the national figure prevalence of dementia - 7.1% for the total age-standardised 65+ population (based on 2013 data)[25]. The diagnoses are also based on records rather than direct patient contact (although the validity seems satisfactory).

It is to be noted that the UKB participants are in general healthier, less obese and smoke less than people in the general population. It was also reported that UKB participants suffered less heart and kidney disease and cancer as compared to the national figures[26]. This has led to a non-representative of the sampling population, a so-called a "healthy volunteer" selection bias.

We did not take any anti-herpetic treatments into account which could potentially have an effect on dementia risk if shingles occurred long before dementia diagnosis. Also, we did not include other types of herpesvirus in our analysis.

Conclusion

Our study suggests a potential effect of Zostavax vaccination in reducing the risk of dementia. Future studies should examine the possible causal pathway between shingles vaccination and dementia.

Acknowledgment

We would like to thank all the UKB participants and staffs for making this study possible (Application number 5864).

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Role of sponsor

Sponsor has no role in study design, data acquisition or involve in any process of data analysis.

License

Conflict of Interest

There is no competing interest.

Author contributions

RI, CD and KM were involved in study conception, idea and design. KM, AL, AB and KM were involved in data acquisition and data quality check. AL carried out data analysis. AL, KM, RC, RI, CD carried out interpretation of the results. All authors involved in drafting and approved the final version of the manuscript. KM is the study guarantor.

Data Availability

Upon publishing this article, we have fulfilled our proposed work agreement with the UK Biobank and have returned our data that we used for these analyses to the UK Biobank as part of the agreement. However, the data from the UK Biobank (www.ukbiobank.ac.uk) are third party and their legal agreement means that we do not have permission to share the data. The UK Biobank data used in this study can however be accessed by applying through the UK Biobank Access Management System (www.ukbiobank.ac.uk/register-apply).

Ethics Statement

Ethics approved for UK Biobank was obtained from the North West- Haydock research ethics committee (REC reference: 16/NW/0274).

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2	This study used a nested case-control study design.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3	What was done: Shingles exposure and Zostavax vaccination were investigated with dementia risk. What was found: There was a small but non-significant increase in the risk of dementia in subjects with shingles diagnosed 3 years or more prior to dementia diagnosis (OR 1.088 with 95% C.I. 0.978-1.211). In those subjects who had had Zostavax vaccination, the risk of dementia was significant decreased (OR 0.808 with 95% C.I. 0.657 to 0.993).
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5	
Objectives	3	State specific objectives, including any prespecified hypotheses	5	In this study, we investigated whether there was an association between shingles and risk of developing dementia in the UK Biobank cohort. VZV is the only herpesvirus for which an effective vaccine is

	Item No.	Recommendation	Page No.	Relevant text from manuscript
				currently approved, and the possible association between Zostavax vaccination and dementia risk was investigated also.
Methods				
Study design	4	Present key elements of study design early in the paper	5	A nested case-control study.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	The UK Biobank (UKB) is a national cohort with 502,650 participants (both males and females) aged between 39 to 71 years. Participants were recruited in 2006-2010, aged 40-69 years at the time and continue to be longitudinally followed to capture subsequent health events. This study is based on a subset of the entire cohort for which primary care data linkage is available.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6	Criteria for case and control identification For incident cases, subjects had to fulfil both of the following criteria 1) dementia diagnosis occurred 3 years or more after the first assessment date and 2) subjects with a dementia code from any sources. For controls,

	Item No.	Recommendation	Page No.	Relevant text from manuscript
				subjects with no dementia code from all sources were coded as controls.
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7	Outcome: All dementia cases across all data sources were then further classified into one of the following: incident or prevalent cases and controls. Exposures: Shingles. For shingles identification, we used the same approach to identify shingles cases and further applied a 3-year window prior to age at dementia diagnosis for cases and age at last follow up for controls. :Zostavax vaccination We investigated also the association of shingles and dementia in sub-cohort of subjects who were eligible for Zostavax vaccination- Zostavax vaccine was available within the NHS from 2013 onwards for people age 70 and over. We

	Item No.	Recommendation	Page No.	Relevant text from manuscript
				therefore computed the age of subjects in 2013 and included only those with age 70+ in this sub-analysis. Confounders: Our analysis suggested that age, sex, age at vaccination and Charlson co-morbidity index (CCI) are confounding factors. We therefore fitted the model adjusted for age and sex for shingles exposure and for Zostavax vaccination, the model was adjusted for age at vaccination, sex and CCI .
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		Shingles: We used three sources to derive shingles variable including ICD10, 9 and Primary Care record linkage. Zostavax vaccination: Data were extracted from the Primary Care linkage record only. The code provided by the UKB was used to identify Zostavax vaccination including date of event.
Bias	9	Describe any efforts to address potential sources of bias	7	We tested if age (at diagnosis for cases and until last follow up in 2017 for controls), gender, age at vaccination and CCI were

Item No.	Recommendation	Page No.	Relevant text from manuscript
			a confounding factor. Each potential confounder was tested and had to satisfy two criteria if they were to be defined as a confounder. Criterion 1: among the unexposed (subjects with no shingles code), there should be an association between the confounder and the dementia outcome. Criterion 2: the potential confounder must be associated with the main exposure (shingles), but not as a result of the exposure. To achieve this, we tested the association between the confounder and shingles in the control population.
Study size	10 Explain how the study size was arrived at	7	Criteria for case and control identification For incident cases, subjects had to fulfil both of the following criteria 1) dementia diagnosis occurred 3 years or more after the first assessment date and 2) subjects with a dementia code from any sources. For controls, subjects with no dementia code

Item No.	Recommendation	Page No.	Relevant text from manuscript
			from all sources were coded as controls.

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7	Shingles variable was coded as binary (yes/no). Zostavax vaccination variable was coded as binary (yes/no). For shingles and Zostavax vaccination variable, "no" category was used as reference category.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7	Logistic regression analysis was performed using Stata version 15.0 9. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. A significant odds ratio is considered when 95% CI does not include 1. For shingles and Zostavax vaccination variable, "no" category was used as reference category. We tested if age (at diagnosis for cases and until last follow up in 2017 for controls) and gender were a confounding factor for shingles and a dementia outcome. For Zostavax vaccination, we further tested age at vaccination, CCI variables. Each potential confounder was tested and had to satisfy two criteria if they were to be defined as a confounder.
		(*b*) Describe any methods used to examine subgroups and interactions	7	Zostavax vaccine was available within the NHS from 2013 onwards for people age 70 and over. We therefore computed the age of subjects in 2013 and included only

				those with age 70+ in this sub-analysis.
		(*c*) Explain how missing data were addressed		
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A	
		(*e*) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7	There were 2,378 incident cases and 225,845 controls (subjects with no dementia).
		(b) Give reasons for non-participation at each stage	N/A	
		(c) Consider use of a flow diagram	N/A	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8	The number of female participants was slightly higher than males (54.71% female and 45.29% male - see Table 2). There were however slight more males than females in the incident group.
		(b) Indicate number of participants with missing data for each variable of interest	N/A	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	8-9	The total number of participants who had shingles was 35,116 (or 15.39%) (Table 3). There were 18% of dementia cases with shingles as compared to 15% of controls. Table 5 report number of Zostavax vaccination.
		Cross-sectional study—Report numbers of outcome events or summary measures		

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9	After adjusting for age and sex, there was a small but non-significant increase in the risk of dementia in subjects with shingles diagnosed 3 years or more prior to dementia diagnosis (OR 1.088 with 95%C.I. 0.978-1.211) (Table 4). Subjects who had had dementia, an inverse association suggesting decreased risk was observed for subjects who had been vaccinated (OR 0.808 with 95%C.I. 0.657 to 0.993) (Table5).
		(*b*) Report category boundaries when continuous variables were categorized	N/A	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A	
Discussion				
Key results	18	Summarise key results with reference to study objectives	10	Our finding suggests that there was a small but non-significant increase in the risk of dementia in subjects with shingles diagnosed 3 years or more prior to dementia diagnosis after adjust for age and sex.
			12	We sought possible effects of vaccination with Zostavax. In our study, subjects who had been vaccinated showed the inverse effect, with a decreased dementia risk of around 20%.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13	Our study has inherent strengths and weaknesses. The UKB is a national cohort of half a million people with an average follow up of almost 12 years (up until 2020). Disease outcome was ascertained by robust sources including the Hospital Episodes Statistics (HES) and through primary care data linkage. Although the primary care data linkage covered 45% of participants at the time of data analysis, this source of data has the benefit of capturing mild symptom shingles cases. Most people suffering from shingles seeks medical advice/treatment first from

				their GP prior to referral to hospital for further treatments, particularly with some severe cases, hence these data have enabled us to capture shingles cases in the community. We were able to demonstrate the effect of shingles immunisation and dementia risk. The weaknesses include the fact that the UKB entire cohort consists of only 1.12% of all dementia cases with age of 65 and over, which is far less than the national figure prevalence of dementia - 7.1% for the total age-standardised 65+ population (based on 2013 data)25. The diagnoses are also based on records rather than direct patient contact (although the validity seems satisfactory).
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13	It is to be noted that the UKB participants are in general healthier, less obese and smoke less than people in the general population. It was also reported that UKB participants suffered less heart and kidney disease and cancer as compared to the national figures24. This has led to a non-representative of the sampling population, a so-called a "healthy volunteer" selection bias.

				We did not take any anti-herpetic treatments into account which could potentially have an effect on dementia risk if shingles occurred long before dementia diagnosis. Also, we did not include other types of herpesvirus in our analysis.
Generalisability	21	Discuss the generalisability (external validity) of the study results	13	Our study suggests a potential effect of Zostavax vaccination in reducing the risk of dementia.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13	Funding We would like to thank the Advantage Foundation for funding this work. Role of sponsor Sponsor has no role in study design, data acquisition or involve in any process of data analysis.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.