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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 Episodes Statistics and primary care linkage health records.

Participants The analyses included 2378 incident dementia cases and 225 845 controls. Inclusion criteria for incident cases were a dementia diagnosis 3 years or more after the first assessment date derived from all sources including International Classification of Diseases (ICD)-10, ICD-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% CI: 0.978 to 1.211). In those subjects who had had Zostavax vaccination, the risk of dementia significantly decreased (OR: 0.808 with 95% CI: 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.

Strengths and limitations of this study

- This study used a subset of UK Biobank cohort, and disease outcomes and exposures were ascertained through sources including the Hospital Episodes Statistics primary care data linkage.
- As varicella-zoster virus is the only herpes virus for which an effective vaccine (Zostavax) is approved, we have also been able to establish whether vaccination against a herpes virus influences dementia.
- The analysis of vaccination was based only on eligible subjects.
- 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 with the general population.
- We did not investigate other types of herpes viruses that may also play a 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 2050 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 postmortem 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 herpes viruses in the disease and in dementia has also been investigated, although to a much lesser extent. Cytomegalovirus (CMV) 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 herpes virus, 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 patients with AD 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.

In a study aiming to investigate any links between shingles and three amyloid-associated diseases of ageing including AD, Bubak *et al*[6] found that herpes zoster (HZ) 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 (UKB) cohort. Zostavax vaccination, which is used to prevent shingles (zoster) and zoster-related post-herpetic neuralgia, has been offered routinely by the National Health Service (NHS) from 2013 for people aged 70–80 years. The uptake was initially 61.8% although it has declined more recently (42.8% in 2016/2017).[7] VZV is the only herpes virus for which an effective vaccine is currently approved, and so for the first time the possible impact on dementia risk of vaccination against a herpes virus was investigated also.

METHODOLOGY

Study design

A nested case–control study.

Cohort description

The UKB is a national cohort with half a million participants (both male and female) aged between 39 and 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 UKB for their data and/or samples to be used for health-related research purposes. All findings were deposited within the UKB 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 assembling our final dataset. The dataset contained 228 930 eligible participants.

Dementia case identification

ICD-10 and 9

The International Classification of Diseases (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 31 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 were available in 45% of the UKB 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 information technology (IT) systems across primary and secondary care within the NHS in the UK.

First, we applied the dementia medical Read code version 2 listed in the article by Wilkinson *et al*.[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 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 were 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 ICD-10, ICD-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 subcohort 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 aged 70 years and over. We therefore computed the age of subjects in 2013 and included only those aged 70+ years 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 UKB.

Statistical analysis

Logistic regression analysis was performed using Stata V.15.0.[9] ORs and 95% CIs were estimated. A significant OR 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 Comorbidity 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's t-test. To explore the distribution of sex, shingles between non-dementia and dementia group, we used X^2 test. P value of <0.05 is considered as statistical significance.

RESULTS

There were 2378 incident cases and 225 845 controls, with dementia cases on average being older than controls (see table 1). The Student's t-test suggested this difference was significant (p<0.05). The number of female participants was slightly higher than male participants (54.41% female and 45.59% male; see table 2). There were however more male than female 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 with 15% of controls. Results from X^2 test suggested a significant difference in distribution of shingles between dementia cases and controls (p<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% CI: 0.978 to 1.211) (table 4).

To examine the effect of Zostavax vaccination on dementia, we included eligible subjects for Zostavax vaccine (table 5). Age at vaccination and CCI 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% CI: 0.657 to 0.993).

DISCUSSION

In this study, we found a significant difference in distribution of shingles between dementia incident cases and controls in a subcohort where medical record was available from both Hospital Episodes Statistics (HES) 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 adjusting 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*[4] and Westman *et al*.[5] Indeed, results from a large cohort study using data from the Korean National Health Insurance Service of about 1.14 million participants suggested similar findings to our study (OR: 0.90 with 95% CI: 0.84 to 0.97).[11]

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)	225 845	65.35	8.07	46.00	81.00

Student's t-test p=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)	123 685 (54.77)	124 872 (54.71)
Male	1191 (50.08)	102 160 (45.55)	103 351 (45.29)
Total	2378 (100.00)	225 845 (100.00)	228 223 (100.00)

Pearson X^2=22.36, p<0.05.

We analysed a subcohort 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 UK, the incidence of HZ increases from 7.1 per 1000 person-years among those aged 60–64 years old to 12.2 per 1000 among individuals aged ≥85 years.[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 HZ encephalitis, 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*[17] detecting no change (apart from possible impairment of 'visuoconstructive 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*[18] investigated 14 patients, age range 19–83 years, 3 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 patients with VZV was classified with mild cognitive impairment, 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 HZ 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 patient with HZO in their usage of medical services in the same index year. The incidence 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 to 4.67), revealing that the risk of developing dementia was high in patients with HZO (no details of any antiviral treatment were provided).

In the second study,[20] Chen *et al*[20] compared almost 40 000 patients diagnosed with HZ 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 HZ 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 to 1.17). However, comparing patients with VZV treated with antivirals with untreated patients, the risk of developing dementia was greatly diminished (adjusted relative risk: 0.55, 95% CI: 0.34 to 0.65). Thus, in contrast to the HZO result, the increased risk of SD was low in patients with HZ, yet antiviral treatment was highly protective.

Direct comparisons cannot be made between our results and those of Chen *et al*[20] because all the patients in the UK shingles group would almost certainly have been treated with antivirals, whereas only about 5% of the Taiwanese

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)	191 066 (84.63)	193 020 (84.61)
Yes	417 (17.59)	34 699 (15.37)	35 116 (15.39)
Total	2371 (100.00)	225 765 (100.00)	228 136 (100.00)

Pearson X^2=8.863, p<0.05.

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

Shingles	OR*	95% CI	OR†	95% CI
No	1.000			
Yes	1.175	1.057 to 1.307	1.088	0.978 to 1.211

*Unadjusted.
†Adjusted for age and sex.

patients with shingles were treated thus. Chen *et al*[20] were therefore able to compare not only risk of dementia for patients with shingles—mostly untreated—with matched controls, but also risk for antiviral-treated patients with shingles compared with untreated patients with shingles. Surprisingly though, in our study, the risk of dementia for patients with shingles 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 the Chen *et al* 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 CCI.

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 underestimate, 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 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 seek medical advice/treatment first from their General practitioner 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 years 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 with the national figures.[26] This has led to a non-representative of the sampling population, a so-called 'healthy volunteer' selection bias.

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

Variables	OR	95% CI
Age at vaccination	1.182	1.137 to 1.228
Female	Reference	
Male	1.044	0.925 to 1.177
Not affected by shingles	Reference	
Affected by shingles	0.886	0.755 to 1.04
Charlson Comorbidity Index	1.489	1.446 to 1.534
Zostavax vaccination, no	Reference	
Yes	0.808	0.657 to 0.993

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 herpes virus 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.

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Competing interests None declared.

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Patient consent for publication Not required.

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

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Data availability statement Data may be obtained from a third party and are not publicly available. 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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