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Herpes Zoster Vaccination and Dementia Occurrence

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IMPORTANCE Recent evidence from a quasi-experiment in Wales showed that herpes zoster (HZ) vaccination appears to prevent or delay dementia. Exploiting a similar quasi-experiment in Australia, this study investigated the effect of HZ vaccination on dementia occurrence in a different population and health system setting.

OBJECTIVE To determine the effect of HZ vaccination on the probability of receiving a new diagnosis of dementia.

DESIGN, SETTING, AND PARTICIPANTS In Australia, starting November 1, 2016, live attenuated HZ vaccination was provided free to individuals aged 70 to 79 years through primary care clinicians. Thus, individuals whose 80th birthday was just a few weeks before November 1, 2016, never became eligible, whereas those whose 80th birthday was just a few weeks later were eligible. The key strength of this quasi-experiment is that one would not expect that these comparison groups who differ in age only minutely would, on average, differ in any health characteristics and behaviors. Primary health care records were analyzed with week-of-birth information from 65 general practices across Australia, using a regression discontinuity design.

EXPOSURE Eligibility for HZ vaccination based on date of birth.

MAIN OUTCOME New diagnoses of dementia as recorded in primary care electronic health record data.

RESULTS In this sample of 101 219 patients, 52.7% were women and mean age was 62.6 years (SD, 9.3 years) as of November 1, 2016. Individuals born just before vs just after the date-of-birth eligibility threshold (November 2, 1936) for HZ vaccination were well balanced in their past preventive health services uptake and past chronic disease diagnoses. There was an abrupt increase of 16.4 percentage points (95% CI, 13.2-19.5; $P < .001$) in the probability of ever receiving HZ vaccination between patients born shortly before vs shortly after the date-of-birth eligibility threshold. The eligibility rules of the HZ vaccination program thus created comparison groups born just on either side of the date-of-birth eligibility threshold who were likely similar to each other, except for a large difference in their probability of receiving the intervention (HZ vaccination) of interest. This study found that eligibility for HZ vaccination (ie, being born shortly after vs shortly before November 2, 1936) decreased the probability of receiving a new dementia diagnosis during 7.4 years by 1.8 percentage points (95% CI, 0.4-3.3 percentage points; $P = .01$). Being eligible for HZ vaccination did not affect the probability of taking up other preventive health services (including other vaccinations) or the probability of receiving a diagnosis of common chronic conditions other than dementia.

CONCLUSIONS AND RELEVANCE By taking advantage of a quasi-experiment and corroborating findings from Wales in a different population, this study provides evidence of the potential benefits of HZ vaccination for dementia that is more likely to be causal than that of more commonly conducted associational studies.

Supplemental content

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Neurotropic herpesviruses have long been thought to potentially play a causative role in the development of dementia.[1-5] Herpes zoster (HZ) vaccination may therefore have a protective effect on the development of dementia. A second reason HZ vaccination could have benefits for dementia is that there is evidence, especially in the case of live attenuated vaccines, that vaccines have important off-target health effects induced by broader immune mechanisms.[6-8]

Recently, a study in electronic health record data from Wales has shown that HZ vaccination significantly reduced the probability of receiving a new dementia diagnosis during the subsequent 7 years.[9] By taking advantage of a quasi-experiment, the study in Wales overcame the fundamental limitation of the existing exclusively associational[10-20] evidence on HZ vaccination and dementia that individuals who opt to be vaccinated differ from those who do not in a variety of characteristics that are difficult to measure and that could thus confound the findings.[21] For instance, detailed information on health behaviors that are likely related to both dementia and vaccination, such as physical activity and diet,[22,23] is virtually never available in electronic health record data.

This study exploits a quasi-experiment similar to that in Wales to investigate the effect of HZ vaccination on the occurrence of dementia in a different population and health system setting. Specifically, only individuals aged 70 to 79 years on November 1, 2016, when the Australian National Immunisation Programme started its HZ vaccination program, were eligible for free live attenuated HZ vaccination (Zostavax [Merck]).[24-26] Thus, individuals who had their 80th birthday just before or on November 1, 2016 (ie, born before November 2, 1936), were ineligible for HZ vaccination, whereas those who had their 80th birthday just after November 1, 2016, were eligible. This eligibility rule resulted in an abrupt increase in the probability of ever receiving the HZ vaccine between individuals who differed in their age by merely a week across the date of birth-based eligibility threshold for the vaccination program. By comparing these groups born immediately on either side of the date of birth-based eligibility threshold, the Australian setting allows for a comparison of dementia incidence between eligible and ineligible groups of individuals who are not expected to differ in their characteristics (including health behaviors for which information is not available in electronic health record data) other than a minute difference in age and a large difference in the probability of ever receiving the HZ vaccine.

Key Points

Question What is the effect of herpes zoster vaccination on the probability of receiving a new diagnosis of dementia?

Findings In this quasi-experimental study using electronic health record data from Australia, being eligible for herpes zoster vaccination based solely on date of birth significantly decreased the probability of receiving a new dementia diagnosis during 7.4 years by 1.8 percentage points.

Meaning By taking advantage of a quasi-experiment, this study provides evidence for a beneficial effect of herpes zoster vaccination for preventing or delaying dementia that is more likely to be causal than the associations reported in the existing correlational evidence.

Methods

The HZ Vaccine Rollout in Australia

Australia's National Immunisation Programme, first introduced in 1997, is a collaborative program between the Australian state and territory governments that provides free vaccines to eligible individuals, with the goal of preventing diseases.[27] The National Immunisation Programme for HZ vaccination started on November 1, 2016.[24] As of that date, the live attenuated single-dose HZ vaccine (Zostavax) was provided free of charge nationwide in Australian primary care practices for individuals aged 70 to 79 years. Thus, individuals born on or after November 2, 1936 (ie, those who had their 80th birthday after November 1, 2016), were eligible for free HZ vaccination, whereas those born before November 2, 1936 (ie, those who had their 80th birthday before or on November 1, 2016), were ineligible and remained ineligible permanently. Further information on the HZ vaccination rollout in Australia is available elsewhere.[24-26]

Data Source

In this quasi-experimental study, we used data from PenCS,[28] an Australian-owned health informatics company, which provides detailed primary care electronic health records to researchers. The data included diagnoses, immunizations and other health care procedures, and prescribed medications from 65 general practitioner practices across each of Australia's 6 states and the Australian Capital Territory. These are practices that used PenCS software and agreed for their data to be used for research. More detail on these practices is available in eText 1 in Supplement 1.

For the purposes of our analysis, PenCS provided us with patients' dates of birth in weeks. As is customary in Australia's primary care records, diagnoses were coded by PenCS using open-ended text fields provided by the general practitioner. The text fields used to define each diagnosis in our analysis are listed in the eTable in Supplement 1. PenCS does not link any of its primary care records to hospital records or mortality registers.

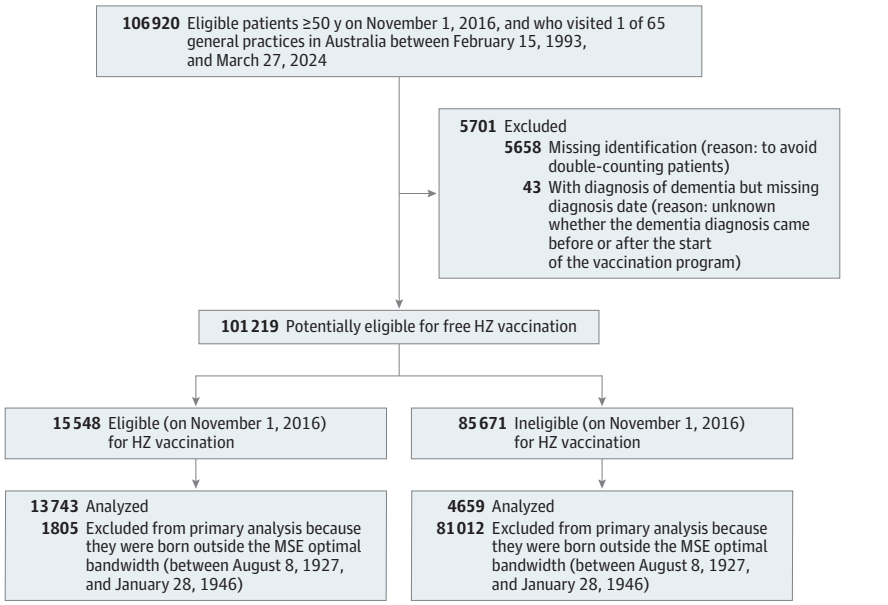
Selection and Exclusion Criteria for Patients

Our analysis was limited to patients aged 50 years or older on November 1, 2016, and who had visited 1 of 65 general practitioner practices in Australia between February 15, 1993, and March 27, 2024. **Figure 1** presents a flowchart describing the cohort development and the selection and exclusion criteria for the primary analyses.

Outcome and Exposure Definitions

In our primary analysis, the follow-up period began on the start date (November 1, 2016) of the HZ vaccination program. Our dataset ended on March 27, 2024, which marked the end of the follow-up period.

Figure 1. Flowchart of Development of Analysis Sample



HZ indicates herpes zoster; MSE, mean squared error.

The outcome of interest was new diagnoses of dementia made during the follow-up period. If more than 1 diagnosis for dementia was recorded for a patient, we used the date of the first diagnosis. This approach of using the date of the first diagnosis was also used for defining the date of all other diagnoses in our analyses. Given the neuropathologic overlap between dementia types and the difficulty in distinguishing dementia types clinically,[29-31] as well as the reduced statistical power when studying less common outcomes, we defined dementia as dementia of any type or cause. The codes used to define dementia (as well as all other diagnoses used in our analyses) are listed in the eTable in Supplement 1.

The exposure was eligibility for free HZ vaccination as determined by an individual's date of birth. Week of birth in our data was coded such that each week started on a Monday. Because November 2, 1936, was also a Monday, we were able to determine the eligibility status of each patient in the data.

Statistical Analysis

We used 3 methodological approaches, which are described in more detail (along with all robustness checks and tests for confounding) in eText 2 in Supplement 1. First, we used a regression discontinuity (RD) design, which exploits the discontinuity in eligibility for a free HZ vaccination at the date-of-birth eligibility threshold (ie, November 2, 1936). This analysis is based on the rationale that individuals born very close to either side of the November 2, 1936, threshold are expected to be similar to one another in observed and unobserved characteristics except for their eligibility status for HZ vaccination. In addition to restricting the analysis to a bandwidth around the threshold, the RD design assigns the highest weights (by using triangular kernel weighting) to individuals born nearest the November 2, 1936, threshold. The key strength of RD is that it provides an unbiased effect estimate as long as any confounding variables do not abruptly change at the November 2, 1936, date-of-birth threshold.[32,33]

The RD design provides unbiased effect estimates even in the presence of censoring as long as the degree of censoring does not abruptly change between individuals at the November 2, 1936, date-of-birth threshold. Nonetheless, in secondary analyses, we accounted for the different amounts of follow-up time across patients by modeling dementia as a time-to-event outcome. The first time-to-event approach was a cause-specific accelerated failure time model, using the approach by Adeleke et al,[34] who specifically adapted this model to RD settings. In the second time-to-event approach, we used an alternative approach to RD, termed the local randomization approach,[32,35] to determine a narrow bandwidth around the November 2, 1936, eligibility threshold in which patients could be expected to be similar in observed and unobserved characteristics. For the sample of patients within this narrow bandwidth, we then created Kaplan-Meier plots for the vaccine-eligible group and vaccine-ineligible group and used Gray's test to compare cumulative incidence curves between eligible and ineligible patients.

Finally, we used a variant of the RD design, called comparative RD, in secondary analyses by using an additional cohort of vaccine-ineligible individuals in our data. The additional cohort was born between May 13, 1918, and August 1, 1927, whereas the cohort of vaccine-ineligible patients in our primary RD analysis was born between August 8, 1927, and January 28, 1946. By adding these data, comparative RD tends to provide increased statistical power relative to standard RD.[36] All *P* values were 2-sided, with $\alpha = .05$ as the significance level. All analyses were run in R version 4.3.2 (R Foundation for Statistical Computing), and all RD analyses used the rdrobust package unless otherwise noted.

Table. Baseline Characteristics of the Analysis Sample and Eligible and Ineligible Patients at the Date-of-Birth Eligibility Threshold[a]

	Sample within MSE optimal bandwidth, No. (%) (n = 18 402)	Patients at the threshold, %[b]		Discontinuity at the threshold, percentage points	*P* value (discontinuity at the threshold)
		Eligible	Ineligible		
Sociodemographic characteristics					
Male	8176 (44.4)	46.5	44.2	2.3	.19
Female	9992 (54.3)	53.5	55.8	−2.3	.19
Married	5402 (29.4)	28.5	26.6	1.9	.21
Aboriginal or Torres Strait Islander[c]	128 (0.7)	0.7	0.9	−0.1	.69
Clinical diagnoses					
Hypertension	2931 (15.9)	18.2	17.8	0.4	.76
Hyperlipidemia	1948 (10.6)	11.5	11.9	−0.4	.69
Respiratory conditions	1305 (7.1)	6.4	8.0	−1.5	.09
Osteoarthritis	1538 (8.4)	9.7	9.9	−0.2	.84
Nonhematologic cancers	1464 (8.0)	10.3	9.5	0.8	.44
Heart conditions	1681 (9.1)	11.0	10.8	0.2	.87
Diabetes mellitus	1120 (6.1)	6.2	5.6	0.6	.48
Depression	472 (2.6)	2.2	2.2	−0.1	.90
Osteoporosis	871 (4.7)	5.2	6.5	−1.3	.11
Back pain	365 (2.0)	2.7	1.9	0.8	.11
Gout	444 (2.4)	2.7	2.9	−0.2	.72
Stroke or TIA	468 (2.5)	3.0	2.8	0.2	.74
Hematologic conditions	300 (1.6)	1.9	1.7	0.2	.67
Chronic kidney disease	232 (1.3)	1.9	1.7	0.2	.73
Uptake of preventive health services					
HZ vaccination	176 (1.0)	1.1	1.1	0.0	.99
Statin use	1332 (7.2)	7.9	7.1	0.8	.41
Antihypertensive use	1086 (5.9)	7.0	5.6	1.4	.09
PPV	3442 (18.7)	21.1	19.4	1.7	.22
Influenza vaccination	4675 (25.4)	27.5	27.3	0.2	.89
DPT vaccination	1098 (6.0)	4.4	5.3	−0.9	.21
Cancer screening	491 (2.7)	1.0	1.6	−0.6	.15

Abbreviations: DPT, diphtheria, tetanus, and pertussis; HZ, herpes zoster; MSE, mean squared error; PPV, pneumococcal polysaccharide vaccine; TIA, transient ischemic attack.

[a] The MSE optimal bandwidth used in our primary analysis for the effect of eligibility for HZ vaccination on new diagnoses of dementia was 482 weeks. A total of 1620 of the 101 219 patients (1.6%) in the entire sample and 234 of 18 402 patients (1.3%) in the MSE optimal bandwidth had missing information on sex. The clinical diagnoses shown are the 15 most common diagnoses in the data whereby COVID-19 was excluded from this table because there was no diagnosis of COVID-19 before November 1, 2016. The codes used to define each condition are shown in the eTable in Supplement 1. All diagnoses are defined as being recorded before November 1, 2016. The codes used to define each indicator of preventive health services uptake are shown in the eTable in Supplement 1. All indicators were defined as being recorded before November 1, 2016. Cancer screening refers to the uptake of colorectal or breast cancer screening, which, in accordance with Australian cancer screening guidelines, was defined as uptake of fecal occult blood testing (for colorectal cancer screening) and mammography (for breast cancer screening).[37,38]

[b] The values for eligible and ineligible patients at the threshold were estimated using the same regression discontinuity design as in our primary analysis (with a bandwidth of 482 weeks).

[c] The only information available on race and ethnicity was a variable called "ethnicity," which has 5 categories: Aboriginal, Torres Strait Islander, Aboriginal and Torres Strait Islander, non-Indigenous, and not recorded. Because there is little effective variation between the categories, the first 3 are grouped.

Ethics

This research was approved by the Stanford University institutional review board and considered minimal risk. Informed consent was waived by the institutional review board because it was not feasible to obtain it.

Results

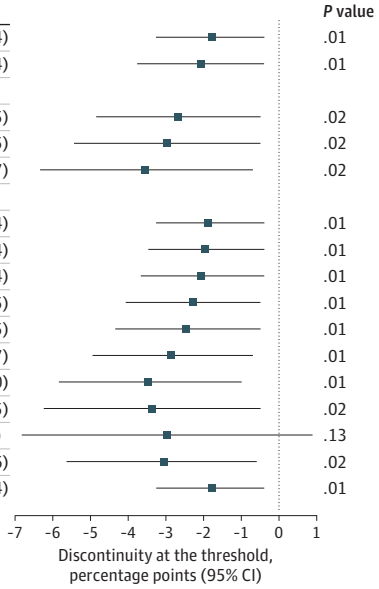
Characteristics of the Study Population

Our dataset contained data on 101 219 unique patients. The **Table** shows the sociodemographic and clinical characteristics of the 18 402 patients in the mean squared error optimal bandwidth (used for our primary analysis on the effect of eligibility for HZ vaccination on new diagnoses of dementia) of 482 weeks around the November 2, 1936, date-of-birth eligibility threshold. Within this bandwidth, 54.3% were women and 44.3% were men (approximately 1.3% of the data had missing values for the sex variable); mean age was 77 years (SD, 4.7 years). The follow-up period for our primary analysis was from November 1, 2016, to March 27, 2024.

We estimated that adults born 1 week after the November 2, 1936, date-of-birth eligibility cutoff had a 16.4 percentage point (95% CI, 13.2-19.5; $P < .001$) higher probability of ever

Figure 2. Effect of Being Eligible for Herpes Zoster Vaccination on New Diagnoses of Dementia

Model	Percentage of patients with a new diagnosis of dementia: Eligible patients at the threshold	Percentage of patients with a new diagnosis of dementia: Ineligible patients at the threshold	Discontinuity at the threshold, percentage points (95% CI)	*P* value
Main specification	3.7	5.5	-1.8 (-3.3 to -0.4)	.01
Uniform kernel	3.4	5.5	-2.1 (-3.8 to -0.4)	.01
Polynomial order				
2	3.3	6.1	-2.7 (-4.9 to -0.5)	.02
3	3.2	6.2	-3.0 (-5.5 to -0.5)	.02
4	3.0	6.5	-3.6 (-6.4 to -0.7)	.02
Bandwidth, y				
9	3.7	5.6	-1.9 (-3.3 to -0.4)	.01
8	3.7	5.6	-2.0 (-3.5 to -0.4)	.01
7	3.6	5.7	-2.1 (-3.7 to -0.4)	.01
6	3.5	5.8	-2.3 (-4.1 to -0.5)	.01
5	3.5	5.9	-2.5 (-4.4 to -0.5)	.01
4	3.2	6.1	-2.9 (-5.0 to -0.7)	.01
3	3.0	6.5	-3.5 (-5.9 to -1.0)	.01
2	2.7	6.1	-3.4 (-6.3 to -0.5)	.02
1	1.7	4.7	-3.0 (-6.9 to 0.9)	.13
Active patients	4.8	8.0	-3.1 (-5.7 to -0.6)	.02
Excluded patients with baseline dementia	3.7	5.6	-1.8 (-3.3 to -0.4)	.01



Squares show the point estimate; horizontal bars, the 95% CI. The main specification used triangular kernels, a local linear polynomial, and observations within the mean squared error optimal bandwidth of 482 weeks.

receiving the HZ vaccine than those born just 1 week earlier (eFigure 1 in Supplement 1). Measured in the mean squared error optimal bandwidth of 255 weeks around the November 2, 1936, threshold, the mean HZ vaccination probability was 6.5% (95% CI, 5.6%-7.3%) vs 30.2% (95% CI, 29.0%-31.4%) among individuals ineligible vs those eligible for the vaccine, respectively.

In contrast to HZ vaccination uptake, we found no discontinuities across the November 2, 1936, date-of-birth eligibility threshold in any of the following measures as assessed before the start date of the HZ vaccination program on November 1, 2016: (1) the probability of having received a diagnosis of any of the 15 most common diagnoses in our data; (2) uptake of preventive health services other than HZ vaccination; (3) diagnoses of dementia; and (4) risk factors for dementia on which we had information in our data (obesity, hyperlipidemia, hypertension, diabetes, current smoking, use of antihypertensive medications, and use of statins) (eFigures 2 and 12 in Supplement 1). These tests therefore support the expectation that individuals born just on either side of the November 2, 1936, date-of-birth threshold were similar to each other in observed and unobserved characteristics except for a large difference in HZ vaccination uptake.

Effect of Eligibility for HZ Vaccination on New Diagnoses of Dementia

Using our RD approach, we found that eligibility for free HZ vaccination decreased the probability of receiving a new dementia diagnosis during the 7.4-year follow-up period by 1.8 percentage points (95% CI, 0.4-3.3; $P = .01$) (**Figure 2**). The effect was similar across follow-up periods ranging from 4 to 7 years and grace periods ranging from zero to 156 weeks (**Figure 3**). There was no evidence of a significant treatment effect heterogeneity by sex (eFigure 3, eFigure 4, and eText 3 in Supplement 1).

Robustness Checks

Our results were robust to a series of additional checks (Figure 2). First, the effect estimates remained similar in magnitude when using uniform kernel weights instead of triangular kernel weights, local quadratic instead of local linear regression, and bandwidths between 1 and 9 years. We conducted similar robustness checks (eFigures 5 and 6 in Supplement 1) for the effect of HZ vaccination eligibility on HZ vaccine uptake.

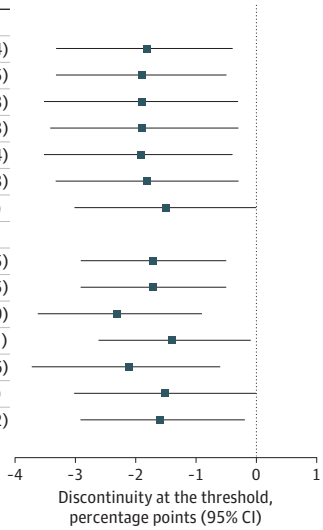
Second, we also found a significant reduction in new diagnoses of dementia from HZ vaccination eligibility (−3.1 percentage points; 95% CI, −5.7 to −0.6; $P = .02$) when restricting our study cohort to the 61 903 frequent primary care visitors ("active" patients) in our data.

Third, our results remained similar when excluding patients with a diagnosis of dementia recorded before the start date of the HZ vaccination program.

Fourth, we found that the acceleration factor was significantly larger than 1 (ie, a protective effect from HZ vaccination eligibility) for all but the very shortest bandwidths (for which the 95% CIs are wide due to the smaller sample size) (eFigure 7 in Supplement 1). Similarly, our Kaplan-Meier plots within a 12-, 9-, and 6-month bandwidth around the threshold, in which eligible and ineligible patients were balanced on covariates (eFigure 10 in Supplement 1), showed that eligible patients take longer to receive a diagnosis of dementia than ineligible patients (eFigure 8 in Supplement 1). Cumulative incidence curves with accompanying Gray's tests for the same

Figure 3. Effect of Being Eligible for Herpes Zoster Vaccination on New Diagnoses of Dementia Across Different Grace and Follow-Up Periods

Period	Percentage of patients with a new diagnosis of dementia		Discontinuity at the threshold, percentage points (95% CI)	*P* value
	Eligible patients at the threshold	Ineligible patients at the threshold		
Grace period, wk				
0	3.7	5.5	-1.8 (-3.3 to -0.4)	.01
26	3.6	5.5	-1.9 (-3.3 to -0.5)	.01
52	3.5	5.4	-1.9 (-3.5 to -0.3)	.02
78	3.4	5.2	-1.9 (-3.4 to -0.3)	.02
104	3.3	5.2	-1.9 (-3.5 to -0.4)	.02
130	3.1	4.9	-1.8 (-3.3 to -0.3)	.02
156	2.9	4.4	-1.5 (-3.0 to 0.0)	.04
Follow-up period, y				
4	0.9	2.5	-1.7 (-2.9 to -0.5)	.01
4.5	1.0	2.7	-1.7 (-2.9 to -0.5)	.01
5	1.0	3.2	-2.3 (-3.6 to -0.9)	.001
5.5	1.8	3.2	-1.4 (-2.6 to -0 1)	.03
6	2.2	4.3	-2.1 (-3.7 to -0.6)	.01
6.5	2.8	4.3	-1.5 (-3.0 to 0.0)	.06
7	3.5	5.1	-1.6 (-2.9 to -0.2)	.02



Grace periods are amounts of time since November 1, 2016, after which follow-up time was considered to begin. Horizontal bars depict 95% CIs. The main specification used a grace period of 0 weeks and follow-up period of 7.4 years.

bandwidths (12, 9, and 6 months) also confirmed these findings (*P* = .01, *P* = .01, and *P* = .005, respectively) (eFigure 9 in Supplement 1).

Fifth, consistent with the findings from our primary approach, our comparative RD approach found that HZ vaccination eligibility reduced the probability of a new diagnosis of dementia by 1.5 percentage points (95% CI, 0.2-2.7; *P* = .02) during the 7.4-year follow-up period (eFigure 11 in Supplement 1).

Testing for Confounding

For our effect estimates to be unbiased, the key assumption that needs to be fulfilled is that no confounding variable changed abruptly at the November 2, 1936, date-of-birth eligibility threshold.[32,33] Such a discontinuity of a confounding variable at the threshold could occur if another intervention or policy used the same date-of-birth threshold for its eligibility criterion that the HZ vaccination program used. We investigated this possibility in 3 ways.

First, because another intervention that used a November 2, 1936, date-of-birth eligibility criterion and was not specific to dementia would be unlikely to affect only dementia diagnoses without also having an effect on other common diagnoses, we investigated whether being eligible for HZ vaccination based on date of birth had an effect on common disease diagnoses other than dementia. Using the same RD approach as in our primary analysis for dementia, we conducted this test for new diagnoses of each of the 15 most common diagnoses in the PenCS data. Unlike with dementia, being eligible for HZ vaccination according to date of birth had no significant effect on the incidence of any of these 15 conditions during the 7.4-year follow-up period (**Figure 4**).

Second, we conducted the same analysis as for common clinical diagnoses for indicators of preventive health services uptake. The rationale for these analyses was 2-fold: to investigate (1) whether another intervention aimed at improving preventive health service use (eg, another vaccination program) used a November 2, 1936, date-of-birth eligibility criterion; and (2) whether HZ vaccination itself may have led to increased uptake of other preventive health services. For each of our indicators (influenza vaccination; pneumococcal vaccination; diphtheria, tetanus, and pertussis vaccination; statin use; use of antihypertensive medications; and cancer screenings), we found no evidence that HZ vaccination eligibility affected preventive health services uptake (Figure 4).[37,38]

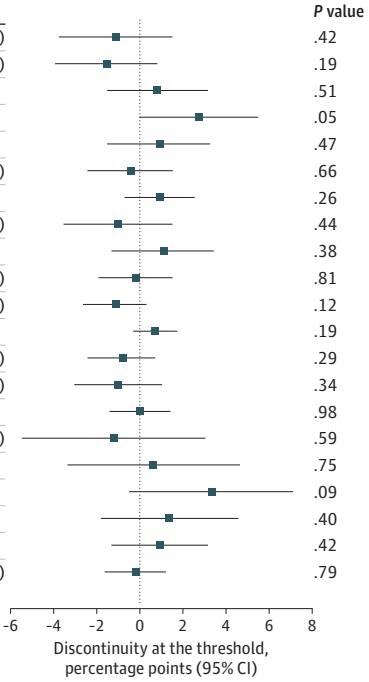
Third, if another intervention used a November 2 date-of-birth eligibility criterion, then we might expect to see differences in the effect of this threshold on new diagnoses of dementia for birth years other than 1936. We thus implemented the same analysis as for our primary analysis (shown in Figure 2), but shifted the date-of-birth eligibility threshold to each of the 3 years before and after 1936. We found that the only date-of-birth threshold that resulted in a significant effect on new diagnoses of dementia was the threshold used by the HZ vaccination program (ie, November 2, 1936) (eFigure 13 in Supplement 1).

Discussion

This study found that individuals born immediately on either side of the November 2, 1936, date-of-birth eligibility threshold for HZ vaccination had a large difference in their

Figure 4. Effect of Being Eligible for Herpes Zoster Vaccination on the 15 Most Common Clinical Diagnoses and Uptake of Other Preventive Health Services During the 7.4-Year Follow-Up Period

Outcome	Percentage of patients who received the diagnosis or preventive health service during the follow-up period		Discontinuity at the threshold, percentage points (95% CI)	*P* value
	Eligible patients at the threshold	Ineligible patients at the threshold		
Hypertension	12.5	13.6	-1.1 (-3.7 to 1.5)	.42
Hyperlipidemia	8.8	10.3	-1.5 (-3.9 to 0.8)	.19
Respiratory conditions	9.0	8.2	0.8 (-1.5 to 3.1)	.51
Heart disease	15.0	12.3	2.7 (0.0 to 5.4)	.05
Osteoarthritis	9.9	9.0	0.9 (-1.5 to 3.2)	.47
Nonhematologic conditions	7.8	8.3	-0.4 (-2.4 to 1.5)	.66
Diabetes mellitus	4.7	3.8	0.9 (-0.7 to 2.5)	.26
Osteoporosis	12.2	13.1	-1.0 (-3.5 to 1.5)	.44
COVID-19	10.1	9.1	1.1 (-1.3 to 3.4)	.38
Back pain	4.5	4.7	-0.2 (-1.9 to 1.5)	.81
Depression	2.9	4.1	-1.1 (-2.6 to 0.3)	.12
Gout	3.1	2.4	0.7 (-0.3 to 1.7)	.19
Hematologic conditions	3.7	4.5	-0.8 (-2.4 to 0.7)	.29
Chronic kidney disease	6.1	7.0	-1.0 (-3.0 to 1.0)	.34
Stroke or TIA	3.8	3.8	0.0 (-1.4 to 1.4)	.98
Influenza vaccination	54.3	55.4	-1.2 (-5.4 to 3.0)	.59
PPV	26.3	25.6	0.6 (-3.3 to 4.6)	.75
Statin use	29.4	26.1	3.3 (-0.5 to 7.0)	.09
Antihypertensive use	30.0	28.7	1.3 (-1.8 to 4.5)	.40
DPT vaccination	9.0	8.1	0.9 (-1.3 to 3.1)	.42
Cancer screening	1.7	1.9	-0.2 (-1.6 to 1.2)	.79



Horizontal bars depict 95% CIs. The codes used to define each condition are shown in the eTable in Supplement 1. Cancer screening refers to the uptake of colorectal or breast cancer screening, which, in accordance with Australian cancer screening guidelines, was defined as uptake of fecal occult blood testing (for colorectal cancer screening) and mammography (for breast cancer screening).[37,38] DPT indicates diphtheria, tetanus, and pertussis; PPV, pneumococcal polysaccharide vaccine; and TIA, transient ischemic attack.

probability of receiving HZ vaccination, whereas there was, as expected, no difference between these individuals in past chronic disease diagnoses, preventive health services uptake, or dementia risk factors. During the subsequent 7.4 years, being born immediately after November 2, 1936 (thus being eligible for HZ vaccination), vs being born immediately before November 2, 1936 (thus being ineligible), led to a significant reduction in the probability of receiving a diagnosis of dementia. We observed this effect only for dementia but not any other common diagnoses in our data. Our results were robust across a wide range of analytic specifications, as well as when using time-to-event models and restricting the study population to frequent primary care visitors.

In conjunction with findings from a similar quasi-experiment in Wales,[9] the results of our study suggest that HZ vaccination is a low-cost, high-reward intervention to reduce the burden of dementia. We believe that our findings call for investments into further research in this area, including clinical trials; further replications in other settings, populations, and health systems; and mechanistic research. Regarding mechanistic studies, several potential mechanisms have already been recognized. For example, reactivations of the varicella zoster virus have been linked to long-lasting cognitive impairment through vasculopathy,[39,40] amyloid deposition and aggregation of tau proteins,[41] neuroinflammation,[42-45] and cerebrovascular disease resembling that observed in Alzheimer disease, including small to large vessel disease, ischemia, infarction, and hemorrhage.[42-47] Additionally, there is a substantial body of evidence suggesting that the herpes simplex virus may contribute to the development of dementia,[2,48] along with suggestive evidence that reactivations of the varicella zoster virus may lead to reactivations of the herpes simplex virus in the brain.[49] Last, it is possible that live attenuated HZ vaccination affects the dementia disease process through a pathogen-independent immunomodulatory pathway, a hypothesis that has been elaborated recently elsewhere.[50]

Strengths and Limitations

The key strength of this study is its quasi-experimental design. Australia implemented its HZ vaccination program using a specific (maximum) date-of-birth eligibility threshold,[24] which created population groups that differed in their

age only minutely but had large differences in the probability of receiving the HZ vaccine. The rollout of the HZ vaccine therefore created 2 comparison groups born immediately on either side of the eligibility threshold who were likely to be similar to each other on observed and unobserved characteristics except for this difference in their probability of receiving HZ vaccination. Given our approach, a potentially confounding variable can only bias our findings if it changes abruptly at the date-of-birth eligibility threshold that was used for the HZ vaccination program.[32,33] Our tests found no evidence for the presence of such bias. Our conclusions are also unlikely to be affected by ascertainment bias. If attending a primary care clinic for HZ vaccination provided an opportunity for the health system to identify previously undetected cases of dementia, our analysis would underestimate, rather than overestimate, the vaccine's effectiveness in reducing the incidence of new diagnoses of dementia. Additionally, if health care visits for HZ episodes were an important way for the health system to identify previously undiagnosed chronic conditions, we would have expected to observe effects of HZ vaccination eligibility on a wider range of common diagnoses beyond just dementia. We would have also expected a substantially smaller or absent effect of HZ vaccination on the incidence of dementia diagnoses among patients who frequently visit their primary care clinician because 1 additional health care visit is presumably less likely to have an important influence on diagnosing previously undetected dementia in this population. We, however, found no such pattern.

The estimated effect size in our analysis was large in relative terms. However, it is important to recognize 2 limitations of our data when interpreting this effect size. First, the 95% CIs around our estimates were comparatively wide, meaning that our data were compatible with considerably smaller effect sizes than our point estimates. The width of our CIs may also be the reason we did not observe the same sex effect heterogeneity observed in the study in Wales.[9] Second, there likely was substantial underdiagnosis of dementia in our data. For instance, an estimated 8.4% of all Australians older than 65 years are living with dementia,[51] whereas only approximately 1.4% of patients in the PenCS data in the same age group in 2023 have received a diagnosis of dementia. The underdiagnosis of conditions is a well-recognized limitation of working with primary care records from Australia and not unique to dementia or the PenCS data.[52-54]

Underreporting in our data was also the reason we refrained from scaling our effect estimates to the proportion of eligible patients who received the vaccine. Scaling would have allowed us to estimate the effect of actually receiving (as opposed to merely being eligible for) HZ vaccination. We reasoned that HZ vaccination is likely substantially underreported in our data because uptake of preventive health services in general appeared to be severely underreported. For instance, pneumococcal vaccination coverage (within the last 5 years) and influenza vaccination coverage (in the last year) among adults aged 65 years and older in Australia are thought to be approximately 55% and 75%, respectively.[55] In our data, however, the corresponding percentages in this age group were only 21% and 33%, respectively. If the degree of underreporting of HZ vaccination was similar to or larger than that for influenza and pneumococcal vaccination, then any attempt to estimate the effect of receiving (as opposed to merely being eligible for) HZ vaccination using RD would greatly overestimate the effect of HZ vaccination receipt on dementia incidence. We therefore chose to analyze only the effect of being eligible for HZ vaccination.

Our study has several additional limitations. First, our analysis provided only "local" estimates of the effect of HZ vaccination on the incidence of dementia (ie, estimates for patients who were approximately 79 and 80 years old at the start of the HZ vaccination program). Second, given that we had data from a nonrandom sample of primary care practices in Australia, our dataset was unlikely to be representative of all primary care patients in the country. Third, because the recombinant subunit HZ vaccine (Shingrix [GSK]) was covered by the National Immunisation Programme starting only on November 1, 2023,[56] our effect estimates apply to the live attenuated HZ vaccine (Zostavax) only. Fourth, our sample restrictions might introduce a spurious association between eligibility for the HZ vaccine and dementia, especially if we are conditioning on collider variables, or variables that are influenced both by our treatment and outcome (eFigure 14 in Supplement 1). However, such variables would have to change abruptly at the November 2, 1936, date-of-birth threshold to introduce bias into our analysis. Fifth, the mean squared error optimal bandwidth—482 weeks—that we adopted for our RD analysis on dementia is relatively large. However, within this bandwidth, our analysis assigned higher weights to individuals born nearest the November 2, 1936, eligibility threshold. In addition, our results were not substantially different when we adopted narrower bandwidths. Our estimates remained negative and statistically significant for bandwidths as small as 2 years around the threshold, and they remained statistically significant using 90% CIs with a 1.5-year bandwidth. Even with a 1-year bandwidth, although we lost significance because of a substantially smaller sample size, our point estimates were nearly unchanged. Most important, regardless of the size of the bandwidth, our RD design merely assumed that among patients in our bandwidth there do not exist confounding variables that change abruptly at the November 2, 1936, date-of-birth threshold.[32,33]

Conclusions

In conclusion, corroborating findings from a similar quasi-experiment in Wales,[9] we found that being eligible for HZ vaccination based on date of birth significantly reduced the incidence of new dementia diagnoses during a 7.4-year follow-up period. Due to their ability to compare individuals who had large differences in their probability of receiving HZ vaccination merely because of being born somewhat earlier or later, this study and the analysis in Wales provide evidence that is more robust to confounding concerns (eg, healthy vaccinee bias) than is the existing associational evidence.

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