1 # The effect of herpes zoster vaccination at different stages of the
2 # disease course of dementia: Two quasi-randomized studies

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Abstract

The varicella zoster virus, a neurotropic herpesvirus, has been hypothesized to play a role in the pathophysiology of dementia, such as through neuroinflammatory processes or intracerebral vasculopathy. Using unique natural experiments, our group has previously found that live-attenuated herpes zoster (HZ) vaccination reduced the incidence of new diagnoses of dementia in both Wales and Australia. To inform further research and ultimately clinical care, it is crucial to understand at which stage of the disease course of dementia the HZ vaccine has its effect. Representing the two opposing ends of the dementia disease course as it can be ascertained from electronic health record data, the aims of this study were twofold: to determine the effect of HZ vaccination on i) new diagnoses of mild cognitive impairment (MCI) among individuals without any record of cognitive impairment, and ii) deaths due to dementia among individuals living with dementia. Our approach took advantage of the fact that at the time of the start date (September 1 2013) of the HZ vaccination program in Wales, individuals who had their eightieth birthday just after this date were eligible for HZ vaccination for one year whereas those who had their eightieth birthday just before were ineligible and remained ineligible for life. This eligibility rule created comparison groups just on either side of the September 2 1933 date-of-birth eligibility threshold who differed in their age by merely a week but had a large difference in their probability of receiving HZ vaccination. The key strength of our study is that these comparison groups should be similar in their health characteristics and behaviors except for a minute difference in age. We used regression discontinuity analysis to estimate the difference in our outcomes between individuals born just on either side of the date-of-birth eligibility threshold for HZ vaccination. Our dataset consisted of detailed country-wide electronic health record data from primary care in Wales, linked to hospital records and death certificates. We restricted our dataset to individuals born between September 1 1925 and September 1 1942. Among our study cohort of 282,557 without any record of cognitive impairment at baseline, HZ vaccination eligibility and receipt reduced the incidence of a new MCI diagnosis by 1.5 (95% CI: 0.5 – 2.9, p=0.006) and 3.1 (95% CI: 1.0 – 6.2, p=0.007) percentage points over nine years, respectively. Similarly, among our study cohort of 14,350 individuals who were living with dementia at baseline, being eligible for and receiving HZ vaccination reduced deaths due to dementia by 8.5 (95% CI: 0.6 – 18.5, p=0.036) and 29.5 (95% CI: 0.6 – 62.9, p=0.046) percentage points over nine years, respectively. Except for dementia, HZ vaccination did not have an effect on any of the ten most common causes of morbidity and mortality among adults aged 70 years and older in Wales in either of our two study cohorts. The protective effects of HZ vaccination for both MCI and deaths due to dementia were larger among women than men. Our findings suggest that the live-attenuated HZ vaccine has benefits for the dementia disease process at both ends of the disease course of dementia.

Introduction

Given the key role of neuroinflammation in the development and progression of dementia[1], it is conceivable that neurotropic viruses could be a factor that causes or accelerates the dementia disease process. Neurotropic herpesviruses have thus far received the greatest research attention in this regard[2–4] because they remain latent for life in the nervous system after primary infection, are more likely to reactivate with increasing age, and can cause encephalitis[5]. Recently, several findings have further spurred interest in neurotropic herpesviruses, including the observation that they can seed β-amyloid in mice[6] and that the Epstein Barr Virus appears to be a causative factor in the development of Multiple Sclerosis[7].

The neurotropic herpesvirus (the varicella zoster virus) that causes chickenpox and shingles has recently been linked to amyloid deposition and aggregation of tau proteins[8], as well as cerebrovascular disease that resembles the patterns commonly seen in Alzheimer's disease, such as small to large vessel disease, ischemia, infarction, and hemorrhage[9–14]. Reducing clinical and subclinical reactivations of the virus through herpes zoster (HZ) vaccination might, thus, have a beneficial impact on the development or progression of dementia. Moreover, as has been detailed recently elsewhere[15], it is possible that HZ vaccination, and potentially vaccinations in older age more generally, act on the dementia disease process through a pathogen-independent immune mechanism. Such an effect would add to the growing body of evidence suggesting that vaccines frequently have broader health benefits beyond their intended target[16–18]. Of importance with respect to this present study, these beneficial off-target effects have often been found to be far stronger among female than male individuals[17], and for live-attenuated rather than other types of vaccines[16–19].

In a recent preprint[20], we were able to take advantage of a unique quasi-randomization in Wales to provide evidence on the effect of HZ vaccination on new dementia diagnoses that is more likely to be causal than the previously existing associational evidence[21–30]. This opportunity arose because the UK National Health Service rolled out the live-attenuated HZ vaccine (Zostavax, Merck) using strict date of birth-based eligibility rules[31]. These rules resulted in an increase in the probability of ever receiving the HZ vaccine of almost 50 percentage points between individuals who differed in their age by merely a week across the date of birth-based eligibility threshold for the vaccination program. We, thus, had the opportunity to compare dementia incidence between eligible and ineligible groups of individuals who were not expected to differ in their characteristics other than a difference in age of merely a few weeks and a large difference in ever receiving the HZ vaccine. We found that HZ vaccination averted an estimated one in five new dementia diagnoses over a seven-year follow-up period. Crucially, unlike the previously existing associational evidence[21–29], this study is not subject to the fundamental concern in associational studies that those who opt to be vaccinated differ from those who do not in a variety of characteristics that are difficult to measure[32]. Most recently, taking advantage of a similar date of birth-based rollout of HZ vaccination in Australia, we have shown that this protective effect for new diagnoses of dementia from HZ vaccination also exists in the Australian population[33].

To guide further research in this area and, ultimately, inform appropriate clinical care, it is critical to understand at which stage of the disease course of dementia the HZ vaccine has its benefit. Our previous analyses in Wales and Australia have left this question unanswered. The aims of this study, therefore, were twofold: to determine the effect of HZ vaccination on i) new diagnoses of mild cognitive impairment (MCI) among individuals without any record of cognitive impairment, and ii) deaths due to dementia among individuals living with dementia. In the absence of more widespread testing for amyloid β and tau pathology during the study period (2013 to 2022), these two aims represent the two opposite ends of the disease course of

112   dementia (considering the limitations in ascertaining different disease stages in electronic health
113   record data). Thus, observing a beneficial effect from HZ vaccination in both aims would
114   suggest that the vaccine appears to act across the entire disease course of dementia.
115
116

Methods

117

The herpes zoster vaccine rollout in Wales:

118

119   Starting on September 1 2013, the National Health Service ([NHS], the United Kingdom's
120   single-payer single-provider healthcare system(*34*)) in Wales made the live-attenuated HZ
121   vaccine (Zostavax, Merck) available to a catch-up cohort of individuals using a staggered rollout
122   system based on specific date-of-birth eligibility thresholds(*31*). Individuals who did not yet have
123   their 80th birthday on the start date of the program (i.e., born on or after September 2 1933)
124   were eligible for one year. By contrast, those who had their 80th birthday prior to the program
125   start date (i.e., born before September 2 1933) never became eligible. A more detailed
126   description of the rollout is provided in **Supplement Text S1**.
127

128   **Data source:**
129   This study used the Secure Anonymised Information Linkage (SAIL) Databank(*35*, *36*). This
130   databank provides detailed electronic health record data from primary care in the NHS through
131   the Welsh Longitudinal General Practice dataset(*37*), which contains data on diagnoses, clinical
132   signs and observations, symptoms, laboratory tests and results (via the Welsh Results Report
133   Service(*38*)), procedures performed (including vaccinations), prescribed medications, and
134   administrative items(*39*). Using individuals' unique NHS number, SAIL links this primary care
135   dataset to a series of databases. For our study, these databases consisted of the Welsh
136   Demographic Service Dataset(*40*), the Patient Episode Database for Wales (containing
137   hospital-based inpatient care data)(*41*), the Outpatient Database for Wales (containing
138   specialist-based ambulatory care data)(*42*), the Welsh Cancer Intelligence and Surveillance Unit
139   (containing data on care for cancer)(*43*), and the Annual District Death Extract (containing
140   cause-of-death data)(*44*). Our data included individuals' date of birth in weeks (with weeks
141   starting on a Monday). A detailed description of each dataset is provided in **Supplement Text
142   S2**.
143

144   **Study cohorts and follow-up period:**
145   We restricted our dataset to all individuals born between September 1 1925 and September 1
146   1942 who were ever registered with a primary care provider in Wales, which is the case for over
147   98% of Wales's adult population(*45*), and who were alive and residing in Wales as of the start
148   date of the HZ vaccination program (September 1 2013). Given that each patient in our dataset
149   had a unique NHS number, we were able to follow patients over time even if they changed
150   primary care provider. We defined one study cohort for each of our two aims. For determining
151   the effect of HZ vaccination on the incidence of MCI, we excluded patients whose electronic
152   health record data suggested any cognitive impairment at any time prior to the start date of the
153   HZ vaccination program. To do so, we used the code list for cognitive impairment published by
154   Moran et al. (also shown in **Supplement Materials**)(*46*), which consists of detailed Read codes
155   for any symptoms, signs, and diagnoses relating to cognitive impairment, such as disturbances
156   of memory, orientation, concentration, or reasoning, as well as formal diagnoses of MCI and
157   dementia. For determining the effect of HZ vaccination on the occurrence of deaths due to
158   dementia, we restricted our analysis cohort to those patients with a diagnosis of dementia made
159   at any time prior to the start date of the HZ vaccination program. This cohort is henceforth
160   referred to as patients living with dementia at baseline. The Read and ICD codes used to define
161   dementia (as well as all other diagnoses used in this study) are provided in **Supplement
162   Materials**.

163
164 The follow-up period for all primary analyses was nine years, starting on September 1 2013 (the
165 start date of the HZ vaccination program) and ending on August 31 2022. In secondary
166 analyses, we show all results when using follow-up periods from one to nine years in one-year
167 increments.
168
169 **Exposure and outcome definition:**
170 The exposure was eligibility for HZ vaccination based on one's date of birth. As shown in
171 **Supplement Figs. S1** and **S2**, most eligible patients (especially in the first two eligibility cohorts
172 of the phased rollout, which are the focus of our analysis) in each of our two study populations
173 took up HZ vaccination during their first year of eligibility.
174
175 For determining the effect of HZ vaccination on MCI, our primary outcome was MCI as defined
176 by a record of a Read code (see **Supplement Materials**) for MCI in our electronic health record
177 data. As robustness check, we required that the first diagnosis of MCI not be followed by a new
178 dementia diagnosis within three and within six months to examine the sensitivity of our findings
179 to the possibility of a patient with mild-to-moderate dementia being falsely classified as having
180 MCI. For determining the effect of HZ vaccination on deaths due to dementia, our primary
181 outcome was defined as dementia being named as the underlying (i.e., primary) cause of death
182 in the patient's death certificate (see **Supplement Materials** for ICD-10 codes used). We
183 defined dementia as dementia of any type because of our reduced statistical power when
184 studying less common outcomes, as well as the neuropathological overlap between dementia
185 types and difficulty in distinguishing dementia types clinically(*47–49*). Dates of deaths were for
186 the date of death registration as opposed to occurrence, whereby the median delay between
187 death occurrence and registration in Wales in the years from 2001 to 2021 was five days(*50*).
188
189 We used all-cause mortality among patients living with dementia at baseline as a secondary
190 outcome. The rationale for analyzing this secondary outcome was that if HZ vaccination
191 reduced deaths due to dementia, it will be important to ascertain whether this effect led to an
192 increase in remaining life expectancy (in which case we would also observe a reduction in all-
193 cause mortality) or merely to the replacement of dementia as the underlying cause of death on
194 the death certificate with the mentioning of another cause (in which case we would observe no
195 effect on all-cause mortality). The Read and ICD codes used to define all our outcomes,
196 including those used as baseline balance checks and in negative control outcome analyses, as
197 well as HZ vaccination are provided in **Supplement Materials**.
198
199 **Statistical analysis**
200 The two authors who analyzed the data (M.E. and M.X.) conducted all parts of the analysis
201 independently, compared their results, and, in the case of any discrepancies, agreed on the
202 preferred coding approach through discussion.
203
204 *Regression discontinuity analysis:*
205 Patients born immediately before versus immediately after September 2 1933 would be
206 expected to be exchangeable (i.e., similar in observable and unobservable characteristics) with
207 each other except for their probability of receiving HZ vaccination (as a result of their eligibility
208 status for HZ vaccination). Our analysis approach was guided by this expectation.
209
210 Regression discontinuity (RD) is a well-established method for causal effect estimation for such
211 threshold-based exposure assignments(*51*). This technique estimates the outcome probability
212 for individuals just on either side of the September 2 1993 date-of-birth eligibility threshold. As
213 per recommended practice for RD(*52–54*), we used a mean squared error (MSE)-optimal

214   bandwidth with robust bias-corrected standard errors(*55*), and assigned a higher weight to
215   observations closer to either side of the September 2 1933 date-of-birth eligibility threshold
216   using triangular kernel weights. The MSE-optimal bandwidth was calculated separately for each
217   combination of study cohort and outcome definition. We used local linear regression because it
218   is the recommended and most reliable approach for RD analyses even when the relationship
219   between date of birth and the outcome in the entire dataset is exponential(*56*). However, in
220   robustness checks, we also analyzed our data using local quadratic instead of linear regression.
221   Higher polynomial regressions are not recommended for RD(*56*). In addition, we verified that
222   our results were not dependent on the choice of i) bandwidth (by using bandwidth choices of
223   0.50, 0.75, 1.25, 1.50, 1.75, and 2.00 times the MSE-optimal bandwidth), and ii) grace period
224   (i.e., the time since the index date after which follow-up time is considered to begin to allow for
225   the time needed for a full immune response to develop after vaccine administration). In an
226   additional robustness check, we adjusted the follow-up period to account for the staggered
227   rollout of the HZ vaccination program. Thus, instead of starting the follow-up period for all
228   individuals on September 1 2013, we started the follow-up period for each individual on the date
229   on which they first became eligible for HZ vaccination (as detailed in **Supplement Text S1**). We
230   added cohort fixed effects in these analyses to control for the one- to two-year (depending on
231   the program year) differences between eligibility cohorts in the start of their follow-up period.
232
233   For all outcomes, we estimated both the effect of being eligible for HZ vaccination based on
234   one's date of birth (the intent-to-treat [ITT] effect), as well as the effect of actually receiving HZ
235   vaccination (the complier average causal effect [CACE]). To estimate the CACE, we followed
236   standard practice for RD by implementing a so-called fuzzy RD(*54*). While still comparing
237   individuals just on either side of the date-of-birth eligibility threshold, fuzzy RD corrects the effect
238   estimates for the fact that a proportion of eligible individuals did not receive the vaccine and a
239   small proportion of ineligible individuals did receive the vaccine. Fuzzy RD is implemented by
240   using an instrumental variable approach(*54*). In our analysis, the instrumental variable was a
241   binary indicator for whether or not an individual was eligible for HZ vaccination (i.e., born on or
242   after versus born before September 2 1933). This analysis, therefore, adjusted the effect size
243   for being eligible for HZ vaccination for the magnitude of the abrupt change in the probability of
244   receiving HZ vaccination at the September 2 1933 threshold. Importantly, fuzzy RD does not
245   compare eligible vaccine recipients with eligible vaccine non-recipients because these groups
246   likely have different health characteristics and behaviors (and, thus, confounding is likely).
247
248   Given its implementation using local linear regression, RD yields absolute as opposed to
249   relative effect estimates. All regression equations used in our analyses are shown in
250   **Supplement Text S3**.
251
252   *Testing for confounding from a competing intervention:*
253   The key advantage of our quasi-randomization approach is that a confounding variable can only
254   bias our analysis if the variable changes abruptly at precisely the September 2 1933 date-of-
255   birth threshold(*52, 53*). Thus, confounding bias is unlikely unless another intervention existed
256   that used the identical date-of-birth eligibility threshold (i.e., September 2 1933) as the HZ
257   vaccination program. We investigated whether such a competing intervention was likely to exist
258   in four ways.
259
260   First, if another intervention that used the identical date-of-birth eligibility threshold had been
261   implemented prior to the HZ vaccination program, then we may expect to observe differences in
262   patients' health characteristics or past uptake of preventive health services at the time of the
263   start date of the HZ vaccination program. We, therefore, tested for differences (using the same
264   RD approach as we used for our primary outcomes) across the September 2 1933 date-of-birth

265   threshold in the prevalence of i) diagnoses made at any time prior to September 1 2013 for each
266   of the ten most common causes of disability-adjusted life years (DALYs) and mortality among
267   the age group 70+ years in Wales(57), and ii) indicators of past preventive health services
268   uptake. The indicators of past preventive health services uptake available in our data were
269   influenza vaccine receipt in the 12 months preceding program start, receipt of the
270   pneumococcal vaccine as an adult, current statin use (defined as a new or repeat prescription of
271   a statin in the 12 months preceding program start), current use of an antihypertensive
272   medication (defined as a new or repeat prescription of an antihypertensive drug in the 12
273   months preceding program start), and breast cancer screening participation (defined as the
274   proportion of women with a record of referral to, attendance at, or a report from "breast cancer
275   screening" or mammography at any time prior to the start date of the HZ vaccination program).
276   The codes used to define each of these variables is provided in **Supplement Materials**.
277
278   Second, if a dementia-specific intervention that used the identical date-of-birth eligibility
279   threshold had been implemented before the HZ vaccination program, then we may expect to
280   observe differences in the incidence of our outcomes across the September 2 1933 threshold
281   prior to the start date of the HZ vaccination program. We, thus, conducted the identical analysis
282   as for our primary outcomes except for starting the follow-up period nine years prior to the start
283   date (September 1 2013) of the HZ vaccination program.
284
285   Third, if an annual intervention used September 2 as a date-of-birth eligibility criterion, then we
286   may expect to observe significant differences in our outcomes at the September 2 date-of-birth
287   threshold for birth years other than 1933. We, thus, implemented the same analyses as we did
288   for the September 2 1933 threshold for the September 2 threshold of each of the three years of
289   birth preceding and succeeding 1933 (i.e., date-of-birth thresholds of September 2 1930,
290   September 2 1931, September 2 1932, September 2 1934, September 2 1935, and September
291   2 1936). To ensure that our analyses at these additional date-of-birth thresholds compared
292   individuals of the same age range as in our primary analyses, we shifted the start and end date
293   of the follow-up period to the same extent as the date-of-birth threshold. To maintain the same
294   follow-up period in all comparisons, we, therefore, had to use a follow-up period of six as
295   opposed to nine years. As an example, when comparing individuals across the September 2
296   1930 threshold, we started the follow-up period on September 1 2010 and ended the follow-up
297   period on August 31 2016.
298
299   Fourth, unless another intervention that used the identical date-of-birth eligibility threshold was
300   specifically designed to affect MCI and dementia only, we may expect to see an effect of such
301   an intervention on health outcomes other than MCI, dementia, and deaths due to dementia. We,
302   thus, conducted the same analysis as for our primary outcomes but for diagnoses of, and
303   deaths due to, each of the ten leading causes of DALYs and mortality in Wales for the age
304   group 70+ years(57), as well as indicators of preventive health services uptake available in our
305   data. The indicators of preventive health services uptake were breast cancer screening among
306   women (defined as a record of referral to, attendance at, or a report from "breast cancer
307   screening" or mammography at any time after the start date of the HZ vaccination program),
308   and, for the 12 months after the start of the HZ vaccination program, uptake of influenza
309   vaccination as well as any prescription of a statin or antihypertensive medication.
310
311   *Testing for ascertainment bias:*
312   If healthcare seeking for episodes of shingles constituted an important opportunity for the health
313   system to identify previously undiagnosed MCI, then our analysis for the effect of HZ
314   vaccination on MCI could suffer from ascertainment bias. We conducted three analyses to
315   investigate whether this potential ascertainment bias was likely to represent an important source

316 of bias in this study. First, if shingles episodes were an important opportunity for the health
317 system to detect previously undiagnosed chronic conditions, then we may expect to observe an
318 effect of HZ vaccination not only on MCI but also on other common chronic conditions. As
319 described in the preceding section, we, therefore, implemented the same RD analysis as for
320 MCI but for each of the ten leading causes of DALYs and mortality in Wales in 2019 for the age
321 group 70+ years as outcomes(*57*). Second, if healthcare utilization for shingles had an
322 important bearing on the health system's ability to diagnose MCI, then we may expect that
323 controlling for indicators of healthcare utilization during the follow-up period would attenuate our
324 effect estimates. We, therefore, adjusted our regressions for the number of primary care visits,
325 outpatient visits, hospital admissions, and influenza vaccinations received during our nine-year
326 follow-up period. Third, patients who frequently visit their primary care provider may be more
327 likely to be (whether formally or informally) screened for MCI. An analysis in this cohort of
328 patients should, therefore, be less susceptible to ascertainment bias. We, thus, also
329 implemented our analysis when restricting our study population to the sample of those 135,712
330 (48.0% of the analysis cohort for our primary analyses for MCI) patients who had made at least
331 one visit to their primary care provider during each of the five years preceding the start of the HZ
332 vaccination program.

334 *Triangulation via a different quasi-experimental approach:*
335 We used a second quasi-experimental approach, namely a difference-in-differences (DID)
336 analysis, to further investigate the robustness of our RD findings. After restricting our sample to
337 patients born between March 1 1926 and February 28 1934, we implemented our DID approach
338 by dividing our sample into yearly birth cohorts centered around September 1. We then divided
339 each yearly birth cohort into a pre-September birth "season" and a post-September birth
340 season. The pre-September birth season was, thus, defined as the six-months period of March
341 1 to August 31 and the post-September birth season as the six-months period from September
342 1 to February 28 of the succeeding year. Our DID model tested whether the difference in
343 outcomes across birth seasons was different for the 1933/1934 birth cohort compared to other
344 yearly birth cohorts. The rationale for our DID was that HZ vaccination eligibility only differed
345 between the two birth seasons in the 1933/1934-cohort but not in other yearly birth cohorts. The
346 DID approach naturally adjusts for any potential systematic differences between pre-September
347 and post-September birth seasons. The regression equations for this DID approach are detailed
348 in **Supplement Text S3**.

350 Importantly, our DID did not rely on the continuity assumption (i.e., the assumption that potential
351 confounding variables do not abruptly change at exactly the September 2 1933 date-of-birth
352 eligibility threshold) made by RD. Instead, our DID relied on the assumption that had the HZ
353 vaccination program not existed, then the difference in our outcomes between the pre- and
354 post-September birth seasons would have been the same in the 1933/1934-cohort as in other
355 yearly cohorts. A strength of our approach is that we were able to investigate whether this
356 assumption was likely to be met by testing whether there were significant between-birth-season
357 differences in our outcomes in cohorts other than the 1933/1934-cohort. We did identify such
358 significant differences for MCI among patients without a record of cognitive impairment at
359 baseline, but not for deaths due to dementia among patients living with dementia at baseline.
360 Details are provided in **Supplement Fig. S3**. We, therefore, used the DID approach only when
361 analyzing the effect of HZ vaccination on deaths due to dementia.

363 *Effect heterogeneity by gender:*
364 In our previous analysis for the effect of HZ vaccination on new diagnoses of dementia(*20*), we
365 found a stronger effect among women than men. We, therefore, tested for an effect
366 heterogeneity by gender in both of our aims. To do so, in addition to analyzing the effect among

367   women and men separately, we implemented an interaction model that estimated the difference
368   in effects by gender (the regression equations for this analysis are provided in **Supplement**
369   **Text S3**).
370
371   **Ethics:**
372   Approval was granted by the Information Governance Review Panel (IGRP, application number:
373   1306), which oversees and approves applications to use the SAIL databank. All analyses were
374   approved and considered minimal risk by the Stanford University Institutional Review Board on
375   June 9 2023 (protocol number: 70277).
376
377

378   ## Results
379   **Sample characteristics:**
380   Our dataset consisted of 304,940 individuals born between September 1 1925 and September 1
381   1942 who were alive and residing in Wales as of September 1 2013. Of these individuals,
382   282,557 did not have a record of any cognitive impairment prior to September 1 2013 and were,
383   thus, included in our study cohort for analyzing the effect of HZ vaccination on MCI. Our study
384   cohort for analyzing the effect of HZ vaccination on deaths due to dementia consisted of the
385   14,350 individuals in our dataset who had received a diagnosis of dementia prior to September
386   1 2013. The sample characteristics of each of these two cohorts are shown in **Table 1**.
387

Among patients without cognitive impairment at baseline

Variable		Full sample (born Sept 1 1925 to Sept 1 1942)						Sample in the MSE-optimal bandwidth					
		All		Women		Men		All		Women		Men	
		n	%	n	%	n	%	n	%	n	%	n	%
		282,557	100.0	154,237	54.6	128,319	45.4	58,569	100.0	32,311	55.2	26,258	44.8
Quintile of Welsh Index of Multiple Deprivation	1 (most deprived)	47,321	16.7	26,071	16.9	21,249	16.6	9,654	16.5	5,391	16.7	4,263	16.2
	2	53,628	19.0	29,516	19.1	24,112	18.8	11,060	18.9	6,248	19.3	4,812	18.3
	3	61,528	21.8	33,596	21.8	27,932	21.8	12,854	21.9	7,081	21.9	5,773	22.0
	4	58,352	20.7	31,461	20.4	26,891	21.0	12,117	20.7	6,569	20.3	5,548	21.1
	5 (least deprived)	61,728	21.8	33,593	21.8	28,135	21.9	12,884	22.0	7,022	21.7	5,862	22.3
Clinical diagnoses													
	Past shingles	34,280	12.1	20,461	13.3	13,819	10.8	7,611	13.0	4,592	14.2	3,019	11.5
	Ischemic heart disease	45,456	16.1	17,928	11.6	27,528	21.5	10,488	17.9	4,168	12.9	6,320	24.1
	COPD	33,191	11.7	15,586	10.1	17,605	13.7	7,164	12.2	3,314	10.3	3,850	14.7
	Past stroke	20,938	7.4	10,028	6.5	10,910	8.5	4,879	8.3	2,362	7.3	2,517	9.6
	Past lower respiratory tract infection	145,299	51.4	80,214	52.0	65,085	50.7	30,880	52.7	16,980	52.6	13,900	52.9
	History of lung cancer	1,179	0.4	554	0.4	625	0.5	268	0.5	130	0.4	138	0.5
	Past fall(s)	52,620	18.6	35,997	23.3	16,623	13.0	11,897	20.3	8,161	25.3	3,736	14.2
	History of colorectal cancer	5,662	2.0	2,445	1.6	3,217	2.5	1,295	2.2	557	1.7	738	2.8
	History of lower back pain	126,210	44.7	72,250	46.8	53,960	42.1	26,471	45.2	15,379	47.6	11,092	42.2
	History of breast cancer	6,506	2.3	6,449	4.2	57	0.4	1,327	3.2	1,319	4.1	8	< 0.1
	History of pancreatic cancer	162	0.6	81	< 0.1	81	< 0.1	28	< 0.1	14	< 0.1	14	< 0.1
	Diabetes mellitus	55,354	19.6	26,289	17.0	29,065	22.7	12,185	20.8	5,903	18.3	6,282	23.9
Uptake of preventive health measures													
	Breast cancer screening	35,759	12.7	34,680	22.5	-	-	6,195	10.6	5,952	18.4	-	-
	PPV-23	172,149	70.3	106,803	69.2	91,874	71.6	42,872	73.2	23,109	71.5	19,763	75.3
	Influenza vaccine	193,856	68.6	103,678	67.2	90,178	70.3	41,412	70.7	22,248	68.9	19,164	73.0
	Recent statin use	130,175	46.1	65,910	42.7	64,265	50.1	27,747	47.4	14,449	44.7	13,298	50.6
	Recent antihypertensive use	198,677	61.0	93,025	60.3	79,124	61.7	37,712	64.4	20,651	63.9	17,061	65.0

Among patients living with dementia at baseline

Variable		Full sample (born Sept 1 1925 to Sept 1 1942)						Sample in the MSE-optimal bandwidth					
		All		Women		Men		All		Women		Men	
		n	%	n	%	n	%	n	%	n	%	n	%
		14,350	100.0	8,957	62.4	5,393	37.6	3,418	100.0	2,064	60.4	1,354	39.6
Quintile of Welsh Index of Multiple Deprivation	1 (most deprived)	2,734	19.1	1,699	19.0	1,035	19.2	648	19.0	408	19.8	240	17.7
	2	3,012	21.0	1,897	21.2	1,115	20.7	729	21.3	458	22.2	271	20.0
	3	3,021	21.1	1,932	21.6	1,089	20.2	730	21.4	440	21.3	290	21.4
	4	2,788	19.4	1,718	19.2	1,070	19.8	655	19.2	379	18.4	276	20.4
	5 (least deprived)	2,795	19.5	1,711	19.1	1,084	20.1	656	19.2	379	18.4	277	20.5
Clinical diagnoses													
	Past shingles	1,761	12.3	1,176	13.1	585	10.8	400	11.7	254	12.3	146	10.8
	Ischemic heart disease	2,975	20.7	1,513	16.9	1,462	27.1	725	21.2	360	17.4	365	27.0
	COPD	2,073	14.4	1,133	12.6	940	17.4	475	13.9	253	12.3	222	16.4
	Past stroke	2,654	18.5	1,461	16.3	1,193	22.1	640	18.7	325	15.7	315	23.3
	Past lower respiratory tract infection	8,661	60.4	5,365	59.9	3,296	61.1	2,013	58.9	1,196	57.9	817	60.3
	History of lung cancer	58	0.4	28	0.3	30	0.6	20	0.6	10	0.5	10	0.7
	Past fall(s)	6,652	46.4	4,608	51.4	2,044	37.9	1,476	43.2	983	47.6	493	36.4
	History of colorectal cancer	285	2.0	138	1.5	147	2.7	60	1.8	25	1.2	35	2.6
	History of lower back pain	6,530	45.5	4,161	46.5	2,369	43.9	1,573	46.0	996	48.3	577	42.6
	History of breast cancer	300	2.1	298	3.3	< 10	< 0.1	68	2.0	68	3.3	< 10	< 0.1
	History of pancreatic cancer	< 10	< 0.1	< 10	< 0.1	< 10	< 0.1	< 10	0.1	< 10	0.1	< 10	< 0.1
	Diabetes mellitus	3,332	23.2	1,926	21.5	1,406	26.1	853	25.0	486	23.5	367	27.1
Uptake of preventive health measures													
	Breast cancer screening	1,384	9.6	1,327	14.8	-	-	343	10.0	323	15.6	-	-
	PPV-23	10,478	73.0	6,330	70.7	4,148	76.9	2,512	73.5	1,473	71.4	1,039	76.7
	Influenza vaccine	9,586	66.8	5,840	65.2	3,746	69.5	2,263	66.2	1,331	64.5	932	68.8
	Recent statin use	6,596	46.0	3,863	43.1	2,733	50.7	1,650	48.3	938	45.4	712	52.6
	Recent antihypertensive use	7,535	52.5	4,608	51.4	2,927	54.3	1,801	52.7	1,058	51.3	743	54.9

Table 1. Sample characteristics at baseline of the two study cohorts in our analysis[1,2,3,4,5]

[1] The baseline date was September 1 2013 (the start date of the HZ vaccination program).
[2] The length of the MSE-optimal bandwidth was 95.1 weeks for patients without cognitive impairment at baseline and 97.5 weeks for patients living with dementia at baseline.
[3] Deciles of the Welsh Index of Multiple Deprivation (WIMD) were calculated based on the 2011 WIMD survey(58).
[4] Breast cancer screening was defined as the proportion of women with a record of referral to, attendance at, or a report from "breast cancer screening" or mammography at any time prior to September 1 2013. "PPV-23" was defined as receipt of the pneumococcal vaccine as an adult at any time prior to September 1 2013. "Influenza vaccine" was defined as influenza vaccine receipt in the 12 months preceding September 1 2013. Recent statin and antihypertensive use was defined as a new or repeat prescription of a statin or antihypertensive drug, respectively, in the 12 months preceding September 1 2013.
[5] Diabetes mellitus referred to both diabetes mellitus type 1 or type 2.
Abbreviations: Sept = September; MSE = mean squared error-optimal; COPD = Chronic Obstructive Pulmonary Disease; PPV-23 = Pneumococcal Polysaccharide Vaccine

A one-week difference in age led to a large difference in HZ vaccination uptake:
In both of our study cohorts, a one-week difference in age across the September 2 1933 date-of-birth eligibility threshold resulted in a large difference in the probability of ever receiving HZ vaccination (**Fig. 1**). Specifically, among individuals without any record of cognitive impairment prior to the start of the HZ vaccination program, being born one week after September 2 1933, and thus being eligible for HZ vaccination, led to an abrupt increase in the probability of ever receiving HZ vaccination from 0.0% to 45.9% (p<0.001). The corresponding abrupt increase

412 among patients living with dementia on the start date of the HZ vaccination program was from
413 0.0% to 28.7% (p<0.001). Thus, in both of our study cohorts, the eligibility rules of the HZ
414 vaccination program created comparison groups born just on either side of the September 2
415 1933 date-of-birth threshold who were likely similar to each other except for a minor difference
416 in age and a large difference in the probability of receiving HZ vaccination.

418 Prior to the start date of the HZ vaccination program, there were no significant differences at the
419 September 2 1933 date-of-birth threshold in the uptake of preventive health services, the
420 prevalence of any of the ten most common causes of DALYs and mortality among adults aged
421 70+ years in Wales (except ischemic heart disease among those living with dementia at
422 program start), the occurrence of HZ, diagnoses of MCI, and deaths due to dementia
423 (**Supplement Figs. S4** and **S5**).
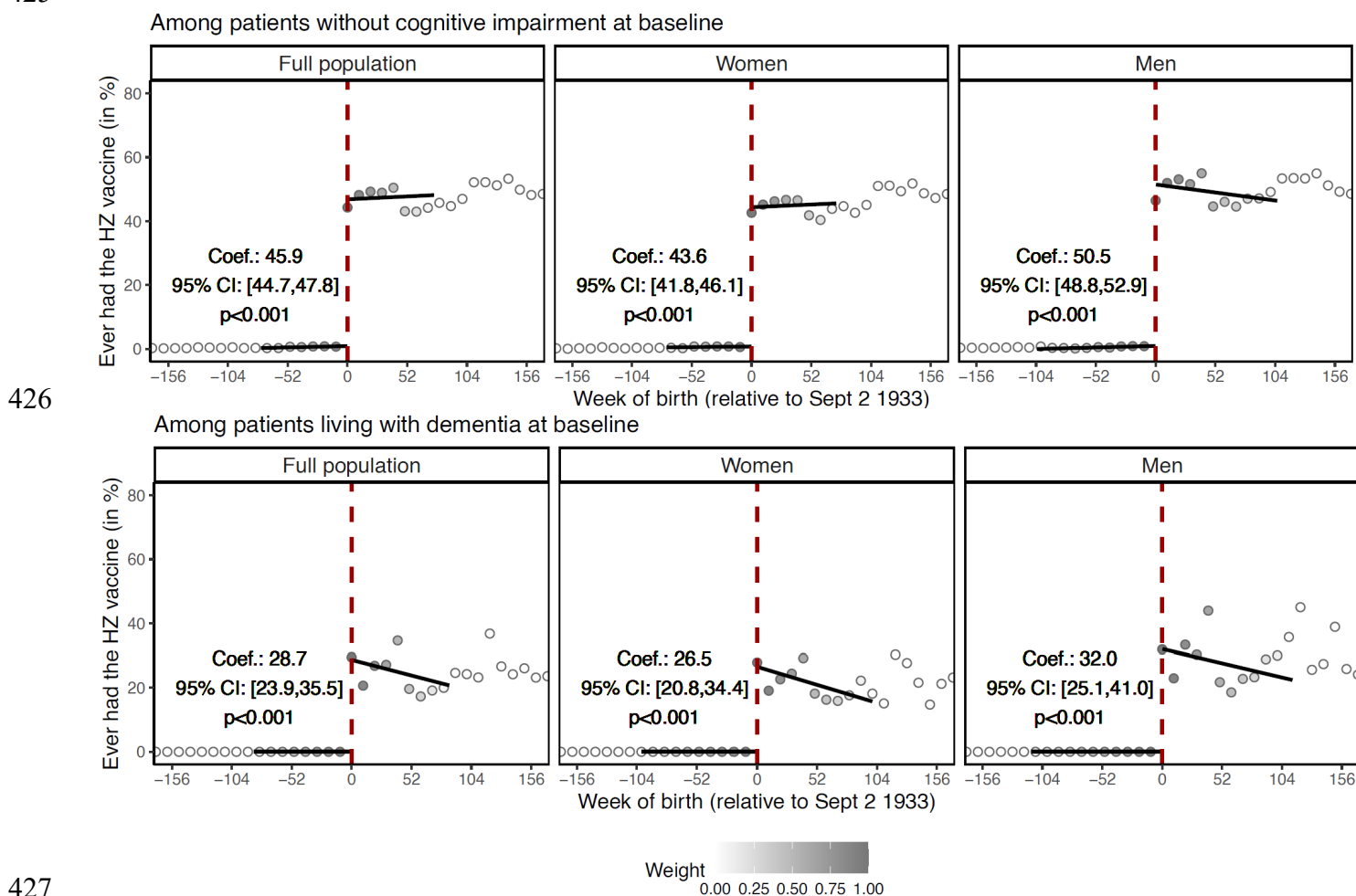
Fig. 1. The abrupt change in the probability of receiving HZ vaccination at the September 2 1933 date-of-birth eligibility threshold.[1,2,3,4]
[1] "Baseline" refers to the start date of the HZ vaccination program (i.e., September 1 2013).
[2] Linear regression lines were drawn in the MSE-optimal bandsdwidth only.
[3] Grey dots show the mean value for each 10-week increment in week of birth.
[4] The grey shading of the dots is in proportion to the weight that observations from this 10-week increment received in the analysis.
Abbreviations: HZ = herpes zoster; Coef. = coefficient; CI = confidence interval; Sept = September

437 **The effect of HZ vaccination on new diagnoses of mild cognitive impairment:**
438 Among our study cohort of individuals without any record of cognitive impairment prior to the
439 start date of the HZ vaccination program, 20,712 (7.3%) were newly diagnosed with MCI during
440 our nine-year follow-up period. Being born immediately after versus immediately before
441 September 2 1933, and thus being eligible for HZ vaccination, decreased the incidence of new
442 diagnoses of MCI over nine years by 1.5 (95% CI: 0.5 – 2.9, p=0.006) percentage points (**Fig.**
443 **2**). Scaled to the proportion of individuals who took up HZ vaccination if they were eligible using
444 the fuzzy RD approach, the effect of actually receiving HZ vaccination was a 3.1 (95% CI: 1.0
445 – 6.2, p=0.007) percentage point reduction in new diagnoses of MCI over nine years. The effect
446 across different follow-up periods is shown in **Supplement Fig. S6**. Both the effect of being
447 eligible for HZ vaccination and the effect of actually receiving HZ vaccination were robust across
448 different choices of bandwidth, grace period, and functional form (using local quadratic instead
449 of local linear regression), when requiring that a new MCI diagnosis not be followed by a new
450 dementia diagnosis within three and six months, when adjusting for the staggered rollout of the
451 program, when adjusting for indicators of health service utilization, and when restricting the
452 analysis cohort to frequent primary care visitors (**Supplement Fig. S7**).
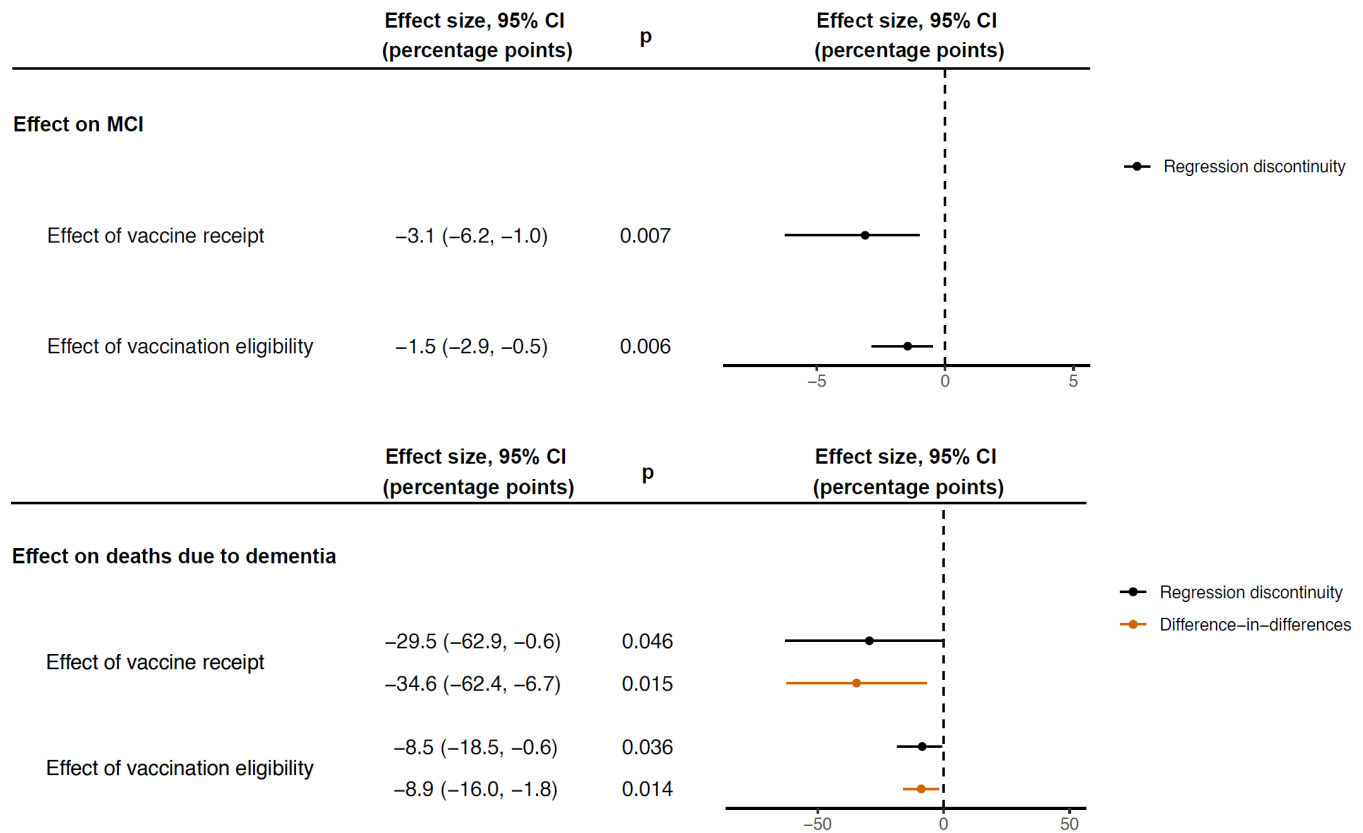453
454 **The effect of HZ vaccination on deaths due to dementia:**
455 Among our study cohort of individuals with a diagnosis of dementia received prior to the start
456 date of the HZ vaccination program, 7,049 (49.1%) died due to dementia over the nine-year
457 follow-up period. Being eligible for HZ vaccination (i.e., being born shortly after versus shortly
458 before September 2 1933) decreased the incidence of deaths due to dementia over nine years
459 by 8.5 (95% CI: 0.6 – 18.5, p=0.036) percentage points (**Fig. 2**). The effect of actually receiving
460 HZ vaccination was a 29.5 (95% CI: 0.6 – 62.9, p=0.046) percentage point reduction in deaths
461 due to dementia over nine years. Our DID analysis yielded similar results as our RD analysis
462 (**Fig. 2**). The effect across different follow-up periods is shown in **Supplement Fig. S8**. As for
463 MCI as outcome, the point estimates for the effect of being eligible for HZ vaccination and the
464 effect of actually receiving HZ vaccination were robust across different choices of bandwidth,
465 grace period, and functional form (using local quadratic instead of local linear regression), and
466 when adjusting for the staggered rollout of the program (**Supplement Fig. S9**). In addition, the
467 effect remained significant when adding a dichotomous covariate that indicated whether an
468 individual had been diagnosed with ischemic heart disease prior to the start date of the HZ
469 vaccination program (**Supplement Fig. S9**).

Effect size, 95% CI (percentage points)	p	Effect size, 95% CI (percentage points)
Effect on MCI		
		Regression discontinuity
Effect of vaccine receipt — −3.1 (−6.2, −1.0)	0.007	
Effect of vaccination eligibility — −1.5 (−2.9, −0.5)	0.006	

Effect size, 95% CI (percentage points)	p	Effect size, 95% CI (percentage points)
Effect on deaths due to dementia		
		Regression discontinuity — Difference−in−differences
Effect of vaccine receipt −29.5 (−62.9, −0.6)	0.046	
−34.6 (−62.4, −6.7)	0.015	
Effect of vaccination eligibility −8.5 (−18.5, −0.6)	0.036	
−8.9 (−16.0, −1.8)	0.014	

Fig. 2. The effect of HZ vaccination on new diagnoses of MCI and deaths due to dementia.[1,2,3]

[1] Dots show the point estimate and horizontal bars the 95% confidence interval.
[2] New diagnoses of MCI were analyzed among a study cohort of patients who did not have any record of cognitive impairment prior to the start date of the HZ vaccination program.
[3] Deaths due to dementia were analyzed among a study cohort of patients who had received a diagnosis of dementia prior to the start date of the HZ vaccination program.
Abbreviations: MCI = mild cognitive impairment; CI = confidence interval

Testing for confounding:
Given the focus of our RD approach on changes in the outcome variable at the date-of-birth eligibility threshold, a confounding variable would only bias our analysis if it changed abruptly at precisely the September 2 1933 date-of-birth threshold. Such bias could arise if another intervention used the identical date-of-birth eligibility threshold (i.e., September 2 1933) as the HZ vaccination program. As detailed in the Methods section, we tested for this possibility in four ways.

First, the September 2 date-of-birth eligibility threshold only had a significant effect on our primary outcomes in the birth year (1933) that was used by the HZ vaccination program, but not in any of the three birth years prior to and after 1933 (**Supplement Fig. S10**). This finding reduces the probability that an annual intervention existed that also used September 2 as a date-of-birth eligibility criterion.
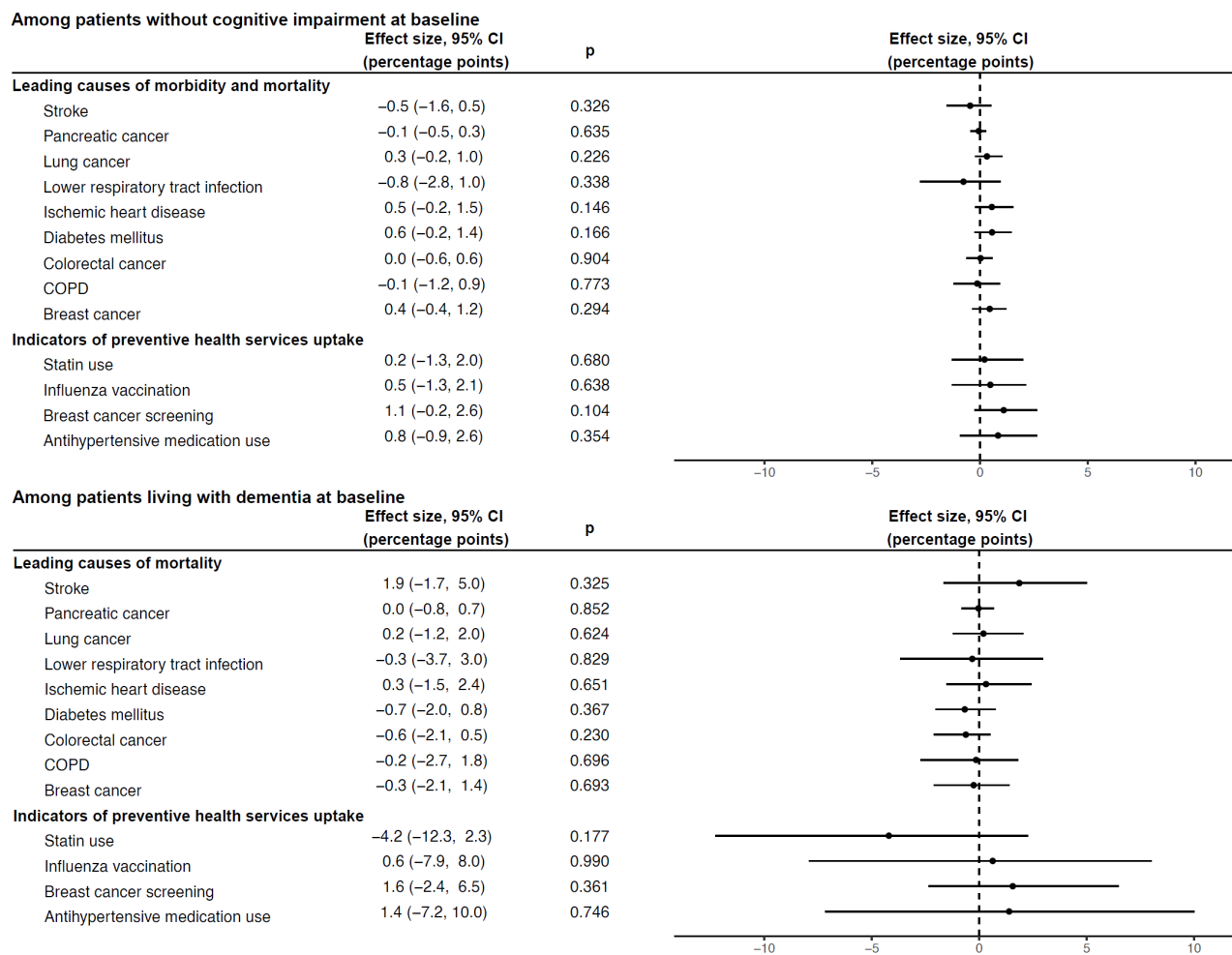
Second, at the time of the start date of the HZ vaccination program, we did not observe systematic differences across the September 2 1933 date-of-birth threshold in past preventive

500   health services uptake nor the prevalence of the ten leading causes of DALYs and mortality
501   among adults aged 70+ years in Wales (**Supplement Fig. S4** and **S5**). Third, there were no
502   differences in the incidence of new MCI diagnoses (in our study cohort for analyzing the effect
503   on MCI) and deaths due to dementia (in our study cohort for analyzing the effect on deaths due
504   to dementia) across the September 2 1933 date-of-birth threshold in the nine years before the
505   start of the HZ vaccination program (**Supplement Fig. S11**). Together, these tests reduce the
506   likelihood that a competing intervention (i.e., another intervention that used the identical date-of-
507   birth eligibility threshold as the HZ vaccination program) existed that was implemented prior to
508   the HZ vaccination program.
509
510   Fourth, other than for dementia, we did not observe any significant effects of the September 2
511   1933 date-of-birth eligibility threshold on diagnoses of each the ten most common causes of
512   DALYs and mortality (in our study cohort for analyzing the effect on MCI) and deaths due to the
513   ten leading causes of mortality (in our study cohort for analyzing the effect on deaths due to
514   dementia) among adults aged 70+ years in Wales over our nine-year follow-up period (**Fig. 3**).
515   Neither did we observe any effects on indicators of preventive health services uptake during our
516   follow-up period (**Fig. 3**). These tests provide evidence against the existence of an intervention
517   that used the identical date-of-birth eligibility threshold as the HZ vaccination program and was
518   not specifically designed to only affect our primary outcomes.

Among patients without cognitive impairment at baseline

	Effect size, 95% CI (percentage points)	p	Effect size, 95% CI (percentage points)
Leading causes of morbidity and mortality			
Stroke	−0.5 (−1.6, 0.5)	0.326	
Pancreatic cancer	−0.1 (−0.5, 0.3)	0.635	
Lung cancer	0.3 (−0.2, 1.0)	0.226	
Lower respiratory tract infection	−0.8 (−2.8, 1.0)	0.338	
Ischemic heart disease	0.5 (−0.2, 1.5)	0.146	
Diabetes mellitus	0.6 (−0.2, 1.4)	0.166	
Colorectal cancer	0.0 (−0.6, 0.6)	0.904	
COPD	−0.1 (−1.2, 0.9)	0.773	
Breast cancer	0.4 (−0.4, 1.2)	0.294	
Indicators of preventive health services uptake			
Statin use	0.2 (−1.3, 2.0)	0.680	
Influenza vaccination	0.5 (−1.3, 2.1)	0.638	
Breast cancer screening	1.1 (−0.2, 2.6)	0.104	
Antihypertensive medication use	0.8 (−0.9, 2.6)	0.354	

519

Among patients living with dementia at baseline

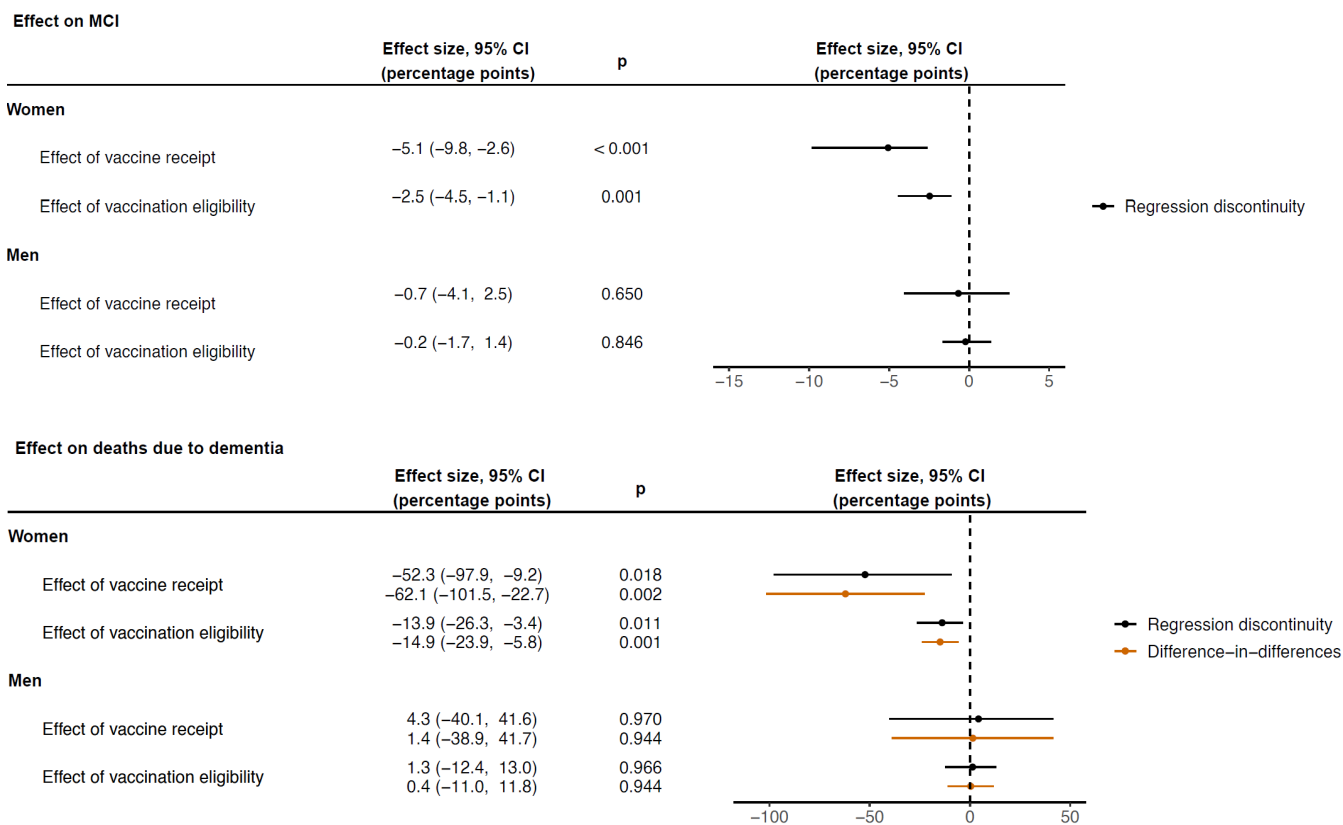|	Effect size, 95% CI (percentage points)	p	Effect size, 95% CI (percentage points)
Leading causes of mortality			
Stroke	1.9 (−1.7, 5.0)	0.325	
Pancreatic cancer	0.0 (−0.8, 0.7)	0.852	
Lung cancer	0.2 (−1.2, 2.0)	0.624	
Lower respiratory tract infection	−0.3 (−3.7, 3.0)	0.829	
Ischemic heart disease	0.3 (−1.5, 2.4)	0.651	
Diabetes mellitus	−0.7 (−2.0, 0.8)	0.367	
Colorectal cancer	−0.6 (−2.1, 0.5)	0.230	
COPD	−0.2 (−2.7, 1.8)	0.696	
Breast cancer	−0.3 (−2.1, 1.4)	0.693	
Indicators of preventive health services uptake			
Statin use	−4.2 (−12.3, 2.3)	0.177	
Influenza vaccination	0.6 (−7.9, 8.0)	0.990	
Breast cancer screening	1.6 (−2.4, 6.5)	0.361	
Antihypertensive medication use	1.4 (−7.2, 10.0)	0.746	

520
521

Fig. 3. No significant effect of being eligible for HZ vaccination on the leading causes of morbidity and mortality (other than dementia) nor on indicators of preventive health services uptake.[1,2,3,4,5,6,7,8]

[1] Baseline refers to the start date (September 1 2013) of the HZ vaccination program.

[2] Dots show the point estimate and horizontal bars the 95% confidence interval.

[3] Among patients without a record of cognitive impairment prior to the start date of the HZ vaccination program, the leading causes of morbidity and mortality were the ten (other than dementia) leading causes of DALYs and mortality among adults aged 70+ years in Wales as estimated by the Global Burden of Disease Project(57).

[4] Among patients with a diagnosis of dementia made prior to the start date of the HZ vaccination program, the leading causes of mortality were the ten (other than dementia) leading causes of mortality among adults aged 70+ years in Wales as estimated by the Global Burden of Disease Project(57).

[5] Influenza vaccination was defined as receipt of influenza vaccination at any time in the 12 months after the start date of the HZ vaccination program.

[6] Statin and antihypertensive medication use was defined as any prescription of these medications during the 12 months after the start date of the HZ vaccination program.

[7] Breast cancer screening was analyzed among women only. It was defined as a record of referral to, attendance at, or a report from "breast cancer screening" or mammography at any time after the start date of the HZ vaccination program.

[8] The Read and ICD codes used to define each variable shown in this figure are provided in **Supplement Materials**.

Abbreviations: COPD = Chronic Obstructive Pulmonary Disease; CI = Confidence Interval.

Effect heterogeneity by gender:

The effect of HZ vaccination both on reducing new diagnoses of MCI and deaths due to dementia was larger among women than men (**Fig. 4**). Among women, the effects of being eligible for, and actually receiving, HZ vaccination on new diagnoses of MCI were a reduction of 2.2 (95% CI: 0.9 – 4.2, p=0.002) and 4.7 (95% CI: 2.2 – 9.4, p=0.002) percentage points, respectively. The corresponding estimates for the effects on deaths due to dementia among women living with dementia at baseline were a decrease of 13.9 (95% CI: 3.4 – 26.3, p=0.011) and 52.3 (95% CI: 9.2 – 97.9, p=0.018) percentage points. For both MCI and deaths due to dementia, the estimates among men were statistically indistinguishable from zero. Formal interaction tests by gender showed that the interaction was significant for both new MCI diagnoses (p=0.029) and deaths due to dementia (p=0.039) (**Supplement Table S1**). The significant effects among women were robust across different choices of bandwidth, grace period, and functional form (using local quadratic instead of local linear regression), as well as when requiring that a new MCI diagnosis not be followed by a new dementia diagnosis within three and six months, adjusting for the staggered rollout of the program, adjusting for indicators of health service utilization, and restricting the analysis cohort to frequent primary care visitors (**Supplement Fig. S12** and **S13**).

Effect on MCI

	Effect size, 95% CI (percentage points)	p	Effect size, 95% CI (percentage points)	
Women				
Effect of vaccine receipt	−5.1 (−9.8, −2.6)	< 0.001		→ Regression discontinuity
Effect of vaccination eligibility	−2.5 (−4.5, −1.1)	0.001		
Men				
Effect of vaccine receipt	−0.7 (−4.1, 2.5)	0.650		
Effect of vaccination eligibility	−0.2 (−1.7, 1.4)	0.846		

(axis: −15 −10 −5 0 5)

Effect on deaths due to dementia

	Effect size, 95% CI (percentage points)	p	Effect size, 95% CI (percentage points)	
Women				
Effect of vaccine receipt	−52.3 (−97.9, −9.2)	0.018		→ Regression discontinuity
	−62.1 (−101.5, −22.7)	0.002		→ Difference−in−differences
Effect of vaccination eligibility	−13.9 (−26.3, −3.4)	0.011		
	−14.9 (−23.9, −5.8)	0.001		
Men				
Effect of vaccine receipt	4.3 (−40.1, 41.6)	0.970		
	1.4 (−38.9, 41.7)	0.944		
Effect of vaccination eligibility	1.3 (−12.4, 13.0)	0.966		
	0.4 (−11.0, 11.8)	0.944		

(axis: −100 −50 0 50)

Fig. 4. The effect of HZ vaccination on new diagnoses of MCI and deaths due to dementia, separately by gender.[1,2,3]
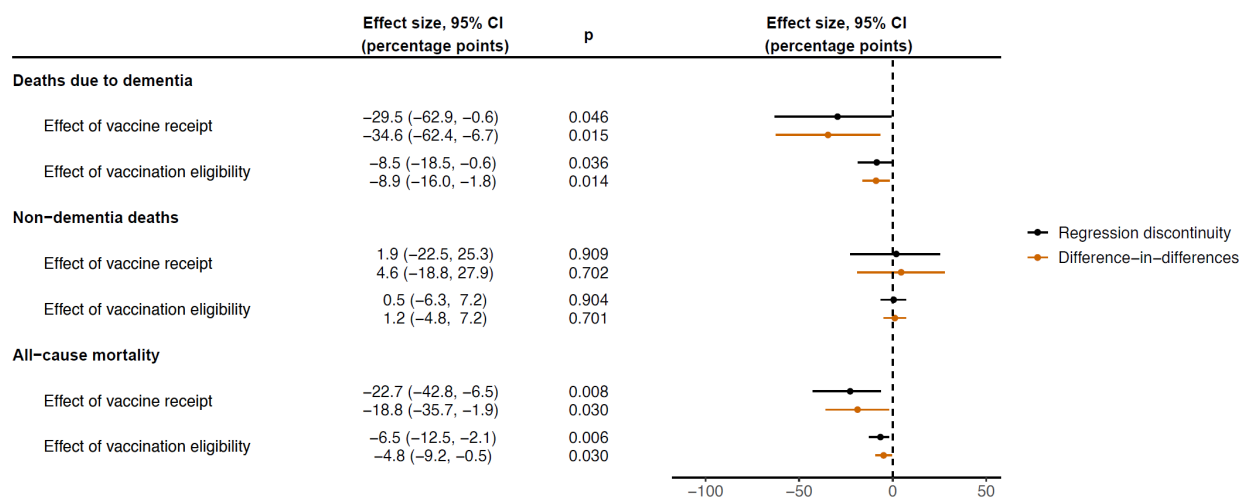
[1] Dots show the point estimate and horizontal bars the 95% confidence interval.

[2] New diagnoses of MCI were analyzed among a study cohort of patients who did not have any record of cognitive impairment prior to the start date of the HZ vaccination program.

[3] Deaths due to dementia were analyzed among a study cohort of patients who had received a diagnosis of dementia prior to the start date of the HZ vaccination program.

Abbreviations: MCI = mild cognitive impairment; CI = confidence interval

The effect of HZ vaccination on all-cause mortality:

Among patients living with dementia at baseline, being eligible for HZ vaccination (based on being born immediately after versus immediately before September 2 1933) decreased all-cause mortality over our nine-year follow-up period by 6.5 (95% CI: 2.1 – 12.5, p=0.006) percentage points (**Fig. 5**). Adjusted for the proportion who took up HZ vaccination if they were eligible using the fuzzy RD approach, the effect of actually receiving HZ vaccination was a 22.7 (95% CI: 6.5 – 42.8, p=0.008) percentage point reduction in all-cause mortality over nine years. There was no significant effect of HZ vaccination eligibility or receipt on non-dementia deaths. As for deaths due to dementia, the effects of HZ vaccination eligibility and receipt on all-cause mortality were larger among women and statistically indistinguishable from zero among men (**Supplement Fig. S14**). All results were similar for our DID as for our RD analysis. Both among the whole sample and among women only, the effect on all-cause mortality was robust across different choices of bandwidth and grace period, as well as when using local quadratic instead of local linear regression, adjusting for the staggered rollout of the program, and when adding a dichotomous covariate that indicated whether an individual had been diagnosed with ischemic heart disease prior to the start date of the HZ vaccination program (**Supplement Fig. S15** and **S16**).

Fig. 5. The effect of HZ vaccination on deaths due to dementia, non-dementia deaths, and all-cause mortality.[1,2,3]

[1] Dots show the point estimate and horizontal bars the 95% confidence interval.
[2] Deaths due to dementia were analyzed among a study cohort of patients who had received a diagnosis of dementia prior to the start date of the HZ vaccination program.
[3] Non-dementia deaths were defined as deaths for which dementia was recorded as neither the underlying nor a contributing cause of death in the death certificate.
Abbreviations: CI = confidence interval

Discussion

We found that HZ vaccination reduced both new diagnoses of MCI among those without any record of cognitive impairment and deaths due to dementia among patients living with dementia. The HZ vaccine, thus, appears to have a beneficial effect at both ends of the disease course of dementia. Whilst our point estimates indicate large effect sizes, the exact magnitude of the effect was difficult to ascertain in this analysis given the wide confidence intervals around our estimates. Lower statistical power compared to standard associational analyses was a result of our focus on individuals born in close proximity to the September 2 1933 date-of-birth threshold.

611
612   Our findings suggest that HZ vaccination could be an effective intervention both to prevent or
613   delay MCI and dementia, as well as to reduce disease progression among those already living
614   with dementia. Using the same quasi-randomization approach as in this study, our group has
615   previously shown that HZ vaccination reduced new diagnoses of dementia in both Wales as well
616   as Australia(*20, 33*). This effect could have been observed as a result of HZ vaccination
617   decreasing the transition from cognitively unimpaired to MCI, from MCI to dementia, or, because
618   of the delay in diagnosing dementia in the health system(*59–63*), from undiagnosed to
619   diagnosed dementia. This present study suggests that the HZ vaccine acts along the entire
620   disease course of dementia and, thus, that our previously reported effects were due to a
621   decrease in the transition along each of these dementia disease stages.
622
623   Given that it is a readily available, relatively inexpensive(*64–66*), one-off intervention, the finding
624   that HZ vaccination has a beneficial effect on the dementia disease process would be of great
625   significance to population health, clinical medicine, and dementia research. Thus, confirming our
626   previously reported findings from Wales and Australia is critical. In our view, it is key that such
627   confirmatory studies utilize quasi-randomization opportunities because more standard
628   associational analyses may lead to false confirmations as a result of confounding, such as the
629   healthy vaccinee bias (i.e., the common observation that healthier, more health-motivated,
630   individuals opt to be vaccinated(*32*)). Our quasi-randomized approach is far less vulnerable to
631   these biases because health status, health-related motivation, and other dementia-related
632   characteristics are unlikely to differ between individuals born just before versus just after a
633   specific date-of-birth eligibility threshold. Therefore, in addition to its principal finding that the HZ
634   vaccine appears to act along the entire disease course of dementia, an important contribution of
635   this present study is that it confirms our previously reported findings in two different study
636   populations (those without any record of cognitive impairment and those living with dementia)
637   and using two different dementia-related outcomes (MCI and deaths due to dementia). Deaths
638   with dementia as their primary cause among individuals living with dementia is a particularly
639   opportune outcome in this regard because it is directly related to dementia, but less reliant on a
640   timely diagnosis of dementia in the health system given that dementia is likely to be readily
641   apparent by the time that it is the primary cause of death. Similarly, our secondary outcome of
642   all-cause mortality among individuals living with dementia at baseline is entirely independent of
643   the health system's process for diagnosing dementia. These mortality outcomes are, thus,
644   largely measured differently than new diagnoses of dementia. In our view, being able to confirm
645   the benefits of HZ vaccination for dementia using a set of outcomes that are all related to
646   dementia, but measured differently, strengthens the evidence that HZ vaccination has an effect
647   on the dementia disease process itself rather than only its measurement (e.g., a diagnostic
648   pathway).
649
650   We found that, among individuals living with dementia at baseline, HZ vaccination did not only
651   lead to a decrease in deaths due to dementia but also a reduction in overall mortality.
652   Specifically, we observed a decrease, which was larger among women than men, in both
653   deaths due to dementia and all-cause mortality, but no effect on deaths for which dementia was
654   not mentioned as the underlying or a contributing cause on the death certificate. Our findings,
655   thus, imply that HZ vaccination among individuals living with dementia increased remaining life
656   expectancy. This reduction in deaths due to dementia is unlikely to be a result of averted
657   shingles episodes given that shingles has a low mortality rate(*67*). Instead, this study suggests
658   that the HZ vaccine may slow dementia disease progression. Nonetheless, identifying the exact
659   mechanism for this effect is in our view an important area of future research.
660

661   For each of our outcomes, we found that the protective effect of HZ vaccination was larger
662   among women than men. We observed the same gender effect heterogeneity in our previous
663   study in Wales for new diagnoses of dementia(20). However, although none of our results were
664   statistically significant among men, we cannot exclude the possibility of substantial beneficial
665   effects among men as well given the width of our confidence intervals. A strong gender effect
666   heterogeneity, with beneficial effects usually being more pronounced among females, has
667   frequently been observed for off-target effects of vaccines(17). Our observed effect
668   heterogeneity between women and men may, thus, reflect immunological sex differences.
669   These immunological sex differences may be pathogen-independent, but could also be specific
670   to the interaction of the immune system with the varicella zoster virus(68). The occurrence of
671   shingles has, for instance, been reported to be more common among women in several
672   studies(69, 70). Additionally, it is equally possible that our observed gender effect heterogeneity
673   reflects differences in the pathophysiology of some types of dementia between women and
674   men; an area that has received increasing research interest in recent years(71–73).

676   The key strength of this study is its quasi-randomized design. Prior to our analysis in Wales, all
677   epidemiological studies on the relationship between vaccines and dementia had simply
678   compared vaccine recipients with non-recipients whilst attempting to control for the myriad of
679   characteristics that differ between those who opt to be vaccinated versus those who do not(21–
680   29). Electronic health record data do not have detailed information on health behaviors, such as
681   physical activity and diet(74, 75), that are known to be linked to other health behaviors
682   (including vaccination) as well as dementia. These studies are, thus, vulnerable to
683   confounding(76). Our approach is fundamentally different in that we compare individuals who
684   were ineligible or eligible for HZ vaccination because they were born just before or just after the
685   date-of-birth eligibility threshold (September 2 1933) for HZ vaccination. On average, individuals
686   in Wales born in one week versus merely a week later would not be expected to differ in their
687   health characteristics and behaviors. In the case of the September 2 1933 threshold, however,
688   there was a large difference in the probability of ever receiving the HZ vaccine between these
689   groups who differed in age by merely a week. The eligibility rules of the HZ vaccination program
690   in Wales, thus, created two comparison groups just on either side of the September 2 1933
691   threshold who were likely similar to each other except for their probability of receiving the
692   intervention of interest (HZ vaccination). As a result, the findings from our analysis are more
693   likely to reflect a causal relationship than those from the associational epidemiological
694   evidence(21–30).

696   The critical advantage of our quasi-randomization approach is that a confounding variable can
697   only bias our analysis if it changes abruptly at precisely the September 2 1933 date-of-birth
698   threshold(52, 53). Such an abrupt change in a confounding variable at the September 2 1933
699   date-of-birth threshold might exist if there was another intervention that used the identical date-
700   of-birth threshold as its eligibility criterion as the HZ vaccination program. We conducted a
701   series of tests to investigate whether the existence of such an intervention is likely. Specifically,
702   individuals just on either side of the September 2 1933 date-of-birth threshold were well-
703   balanced at baseline in their past preventive health services uptake, prevalence of common
704   causes of morbidity and mortality, and past incidence of MCI and deaths due to dementia.
705   Similarly, there was no effect of the September 2 1933 date-of-birth threshold on common
706   health outcomes (other than dementia) during our nine-year follow-up period, nor on preventive
707   health services uptake indicators (other than HZ vaccination). Lastly, the September 2 date-of-
708   birth threshold only had an effect on MCI and deaths due to dementia in the birth year (1933)
709   that was used by the HZ vaccination program as its eligibility criterion. Thus, none of our tests
710   suggested the existence of another intervention that also used the date of birth of September 2
711   1933 as its eligibility criterion. It is in our view also unlikely that HZ vaccination led to increased

712   uptake of other preventive health services (e.g., the uptake of other vaccines at the same visit)
713   because we did not observe any effect of HZ vaccination eligibility on available indicators of
714   preventive health services among older adults in our data.
715
716   We believe that our repeated findings from quasi-randomization studies of a beneficial effect of
717   HZ vaccination for the dementia disease process call for further investments into this area of
718   research, not only to confirm the effects but also to elucidate the mechanisms. Several potential
719   mechanisms have already been identified. For instance, there is evidence that reactivations of
720   the varicella zoster virus can lead to long-lasting cognitive impairment through vasculopathy(*77,*
721   *78*), amyloid deposition and aggregation of tau proteins(*8*), neuroinflammation(*11–14*), as well
722   as a pattern of cerebrovascular disease that is similar to that seen in Alzheimer's disease, such
723   as small to large vessel disease, ischemia, infarction, and hemorrhage(*9–14*). In addition,
724   reactivations of the varicella zoster virus may lead to reactivations of the herpes simplex virus in
725   the brain(*79*). This finding in turn would link HZ to the more extensive literature on the herpes
726   simplex virus as a causative factor in the development of dementia(*3, 80*). Our repeated finding
727   of a strong effect heterogeneity by gender, however, may also instead point to a pathogen-
728   independent immunomodulatory mechanism(*17*). Some of these potential immune mechanisms
729   have recently been described elsewhere(*15*).
730
731   This study has several important limitations. First, given its implementation using local linear
732   regression, RD is only able to reliably estimate absolute as opposed to relative effects(*53, 54*).
733   Second, we were limited to information contained in electronic health record and death
734   certificate data to define our study cohorts and outcomes. It is likely that there is considerable
735   underascertainment in our data for cognitive impairment (to define the cognitively unimpaired
736   study cohort for our first aim), dementia (to define the study cohort of individuals living with
737   dementia for our second aim), MCI, and deaths due to dementia. Crucially, however, the degree
738   of underascertainment (as well as any delay in making these diagnoses or in changes in data
739   quality over time) is unlikely to differ between individuals born just before versus just after
740   September 2 1933. As such, other than potential underestimation of the true benefits of HZ
741   vaccination on an absolute scale, underascertainment of these variables was unlikely to bias
742   our analysis. Third, we were also limited to the information available in electronic health record
743   data to define the two stages of the disease course of dementia analyzed in this study. We, for
744   instance, had no information on amyloid β or tau pathology or results from detailed
745   neuropsychological assessments. Fourth, the COVID-19 pandemic started within our follow-up
746   period and may have delayed new diagnoses of MCI as well as changed mortality rates among
747   individuals living with dementia. However, as for our first limitation, the pandemic affected
748   individuals just on either side of the September 2 1933 date-of-birth threshold equally and is,
749   thus, unlikely to have introduced bias into our analysis. Fifth, some diagnoses of MCI in our data
750   may have mistakenly been made for individuals who already had mild-to-moderate dementia.
751   We believe that this is unlikely to be a major limitation of our analysis given that our effect
752   estimates remained significant when requiring that a new diagnosis of MCI not be followed by a
753   new diagnosis of dementia within three and within six months. Sixth, our findings pertain to
754   those age groups born near to the September 2 1933 date-of-birth threshold (primarily those
755   aged 79 to 80 years). We are unable to comment on the effects in other age groups. Seventh,
756   we observed an imbalance in past ischemic heart disease diagnoses across the September 2
757   1933 threshold among the study cohort for our second aim. We, however, show in the
758   Supplement that our results were robust to any adjustment for this imbalance. In our view, this
759   imbalance was likely a chance finding given that it was the only difference with a p-value less
760   than 0.05 in 36 (18 among each of our two study cohorts) baseline balance tests that we
761   conducted. Lastly, our results pertain to the live-attenuated HZ vaccine (Zostavax, Merck) only,
762   because the newer recombinant HZ vaccine (Shingrix, GSK) was introduced into the NHS after

763   our follow-up period ended(*81*). A recent study of data from the United States that focused on
764   comparing the association of HZ vaccination with dementia when only the older live-attenuated
765   vaccine was available with the association when the newer recombinant vaccine was available,
766   found that the newer vaccine was more strongly associated with a reduced risk of dementia(*30*).
767   The study, however, had to assume that (after matching on select variables available in the
768   electronic health record data) individuals who chose to be vaccinated for shingles when the
769   older, one-dose, vaccine was available were not different in any of their dementia-related
770   characteristics to those who chose to be vaccinated when the far more efficacious(*68*), two-
771   dose, vaccine was available. One limitation, for instance, is therefore the possibility that some
772   individuals may have delayed HZ vaccination to receive the more efficacious vaccine.
773
774   In conclusion, this study suggests that HZ vaccination slows or prevents disease progression
775   across the entire disease course of dementia. By taking advantage of the fact that the UK's
776   National Health Service assigned individuals who differed in their age by just a few weeks to
777   being eligible or ineligible for HZ vaccination based on their date of birth, we were able to
778   generate evidence that is more likely to be causal than those from more standard
779   epidemiological analyses. Our finding that HZ vaccination had a beneficial effect on two different
780   dementia-related outcomes in two different patient samples, and at two opposing ends of the
781   disease course of dementia, thus, provides promising evidence that HZ vaccination may prevent
782   or slow the dementia disease process in a substantial proportion of individuals.
783
784

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Authors' contributions
800   M.X. and M.E. contributed equally to this work. M.X. and M.E. co-devised the methodology,
801   analyzed and processed the data, created data visualizations, interpreted the results, and
802   reviewed and edited the original draft. C.B. co-devised the methodology, interpreted the results,
803   and reviewed and edited the original draft. H.A. interpreted the results, and reviewed and edited
804   the original draft. P.G. conceived the overall project, acquired funding, conceived the study,
805   devised the methodology, was responsible for administration and supervision, interpreted the
806   results, wrote the original draft, and reviewed and edited the original draft.
807

Competing interests
809   The authors declare no competing interests.
810

Data and materials availability
812   The data that support the findings of this study are available from the SAIL Databank(*33*).
813   Researchers must request access to the data directly from SAIL. The authors have no

814 permission to share the data. All Read and ICD codes to define variables are available in
815 Supplement Materials. All statistical analysis code (in R) will be made available in a publicly
816 accessible GitHub repository upon acceptance of the manuscript for publication.
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