

1 Causal evidence that herpes zoster vaccination prevents a 2 proportion of dementia cases 3

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19 **Abstract**

20 The root causes of dementia are still largely unclear, and the medical community lacks highly
21 effective preventive and therapeutic pharmaceutical agents for dementia despite large
22 investments into their development. There is growing interest in the question if infectious agents
23 play a role in the development of dementia, with herpesviruses attracting particular attention. To
24 provide causal as opposed to merely correlational evidence on this question, we take advantage
25 of the fact that in Wales eligibility for the herpes zoster vaccine (Zostavax) for shingles
26 prevention was determined based on an individual's exact date of birth. Those born before
27 September 2 1933 were ineligible and remained ineligible for life, while those born on or after
28 September 2 1933 were eligible to receive the vaccine. By using country-wide data on all
29 vaccinations received, primary and secondary care encounters, death certificates, and patients'
30 date of birth in weeks, we first show that the percentage of adults who received the vaccine
31 increased from 0.01% among patients who were merely one week too old to be eligible, to
32 47.2% among those who were just one week younger. Apart from this large difference in the
33 probability of ever receiving the herpes zoster vaccine, there is no plausible reason why those
34 born just one week prior to September 2 1933 should differ systematically from those born one
35 week later. We demonstrate this empirically by showing that there were no systematic
36 differences (e.g., in pre-existing conditions or uptake of other preventive interventions) between
37 adults across the date-of-birth eligibility cutoff, and that there were no other interventions that
38 used the exact same date-of-birth eligibility cutoff as was used for the herpes zoster vaccine
39 program. This unique natural randomization, thus, allows for robust causal, rather than
40 correlational, effect estimation. We first replicate the vaccine's known effect from clinical trials of
41 reducing the occurrence of shingles. We then show that receiving the herpes zoster vaccine
42 reduced the probability of a new dementia diagnosis over a follow-up period of seven years by
43 3.5 percentage points (95% CI: 0.6 – 7.1, $p=0.019$), corresponding to a 19.9% relative reduction

44 in the occurrence of dementia. Besides preventing shingles and dementia, the herpes zoster
45 vaccine had no effects on any other common causes of morbidity and mortality. In exploratory
46 analyses, we find that the protective effects from the vaccine for dementia are far stronger
47 among women than men. Randomized trials are needed to determine the optimal population
48 groups and time interval for administration of the herpes zoster vaccine to prevent or delay
49 dementia, as well as to quantify the magnitude of the causal effect when more precise
50 measures of cognition are used. Our findings strongly suggest an important role of the varicella
51 zoster virus in the etiology of dementia.

52 **Main**

53 Despite decades of large-scale investments into research on dementia¹, including hundreds of
54 failed phase 2 and phase 3 clinical trials of pharmaceutical agents for the prevention or
55 treatment of dementia^{2,3}, the root causes of dementia still remain largely unclear⁴. Recently,
56 there has been growing scientific recognition that viruses may play a role in the pathogenesis of
57 dementia⁵⁻⁷. Different lines of evidence⁸, including the observation that herpesviruses can seed
58 β -amyloid – a hallmark of Alzheimer’s dementia – in mice⁹, suggest a possible role for
59 herpesviruses in particular in the pathogenesis of dementia. Currently, the US National Institute
60 on Aging is funding a phase 2 proof-of-concept trial to test the effect of an antiviral drug on
61 cognitive and functional ability among patients with mild Alzheimer’s dementia¹⁰. A second,
62 different, approach to antiviral drugs for targeting herpesviruses is vaccination.

63
64 To date, studies in cohort and electronic health record data on the relationship between
65 vaccination receipt (with most studies focusing on influenza vaccination¹¹) and dementia have
66 simply compared the occurrence of dementia among those who received a given vaccination
67 versus those who did not. These studies have to assume that all characteristics that differentiate
68 those who are vaccinated from those who are not (and that are also related to dementia) have
69 been perfectly measured and modelled in the analysis, such that no unmeasured factors
70 confound the relationship between vaccination receipt and dementia¹². This assumption is
71 usually implausible because it has to be assumed that the study perfectly measured factors that
72 are difficult to measure, such as personal motivation or health literacy. It is also an assumption
73 that cannot be empirically verified. Strong indications that these studies suffer from significant
74 confounding is that i) vaccination receipt in these studies is not only associated with dementia
75 but also a host of other health outcomes that are unlikely to be due to the vaccine¹³; ii) the
76 direction and magnitude of the association of dementia with vaccination receipt is highly

77 dependent on the precise analytical specifications¹⁴; iii) the reported magnitude of association is
78 frequently implausibly large¹⁵⁻²⁰; and iv) for each existing vaccination given in adulthood, studies
79 (often with conflicting evidence of harm or benefit¹⁴) exist that report an association between
80 receiving the vaccination and dementia¹¹.

81

82 We employ a fundamentally different approach, called regression discontinuity²¹⁻²⁴, that takes
83 advantage of the fact that eligibility for the herpes zoster vaccine in Wales was determined
84 based on the exact date of birth of individuals. That is, starting on September 1 2013, those
85 born on or after September 2 1933 were eligible for the vaccine while those born earlier never
86 became eligible²⁵ (see Methods for details). By using a rich country-wide dataset that combines
87 information on vaccinations received, all primary and secondary care encounters, as well as
88 death certificates, and that contains patients' date of birth in weeks, we are able to compare
89 adults who were ineligible for the vaccine because they were born one week before the eligibility
90 cutoff date with those who were born one week later. There is no plausible reason why those
91 born one week before September 2 1933 would systematically differ from those who are born
92 just one week later, as long as September 2 1933 is not used as the date-of-birth eligibility cutoff
93 for other interventions (e.g., another vaccination program or an educational policy) that affect
94 the occurrence of dementia. We provide empirical evidence that no such other interventions
95 exist. In exploiting this unique quasi-experimental setting, we are able to establish the *causal*
96 effect (rather than merely an association) of herpes zoster vaccination on the occurrence of
97 dementia.

98

99 We find that adults born one week after the September 2 1933 date-of-birth eligibility cutoff had
100 a 47.2 percentage point higher probability (from 0.01% to 47.2%) of ever receiving the herpes
101 zoster vaccine than those born just one week earlier. We then use this "natural randomization"
102 in a regression discontinuity analysis to first replicate the known finding from clinical trials that

103 receiving the herpes zoster vaccine reduces new diagnoses of shingles. Second, we extend this
104 approach to an outcome – dementia – that was never assessed in clinical trials of the herpes
105 zoster vaccine, and find that receiving the vaccine causes an approximately one-fifth reduction
106 in the probability of a new dementia diagnosis over a seven-year follow-up period. Third, to
107 further substantiate that our findings are not driven by confounding, we show that receiving the
108 herpes zoster vaccine only reduced the occurrence of dementia but not of any other common
109 causes of mortality or morbidity. Similarly, we show that receipt of the herpes zoster vaccine did
110 not lead to increased uptake of other vaccinations or preventive health measures. Fourth, we
111 provide empirical evidence that no other intervention (e.g., health insurance eligibility) in Wales
112 used the identical date of birth (September 2 1933) as eligibility cutoff as was used to define
113 eligibility for the herpes zoster vaccine. Finally, we show in exploratory analyses that the
114 vaccine’s protective effects are far stronger among women than men for all-cause dementia and
115 Alzheimer’s disease, while there was no significant effect heterogeneity by gender for vascular
116 dementia. Our study focuses on the live attenuated herpes zoster vaccine (Zostavax; henceforth
117 simply referred to as “zoster vaccine”) because the newer recombinant subunit zoster vaccine
118 (Shingrix) became available in the UK only after our follow-up period ended²⁶.

119

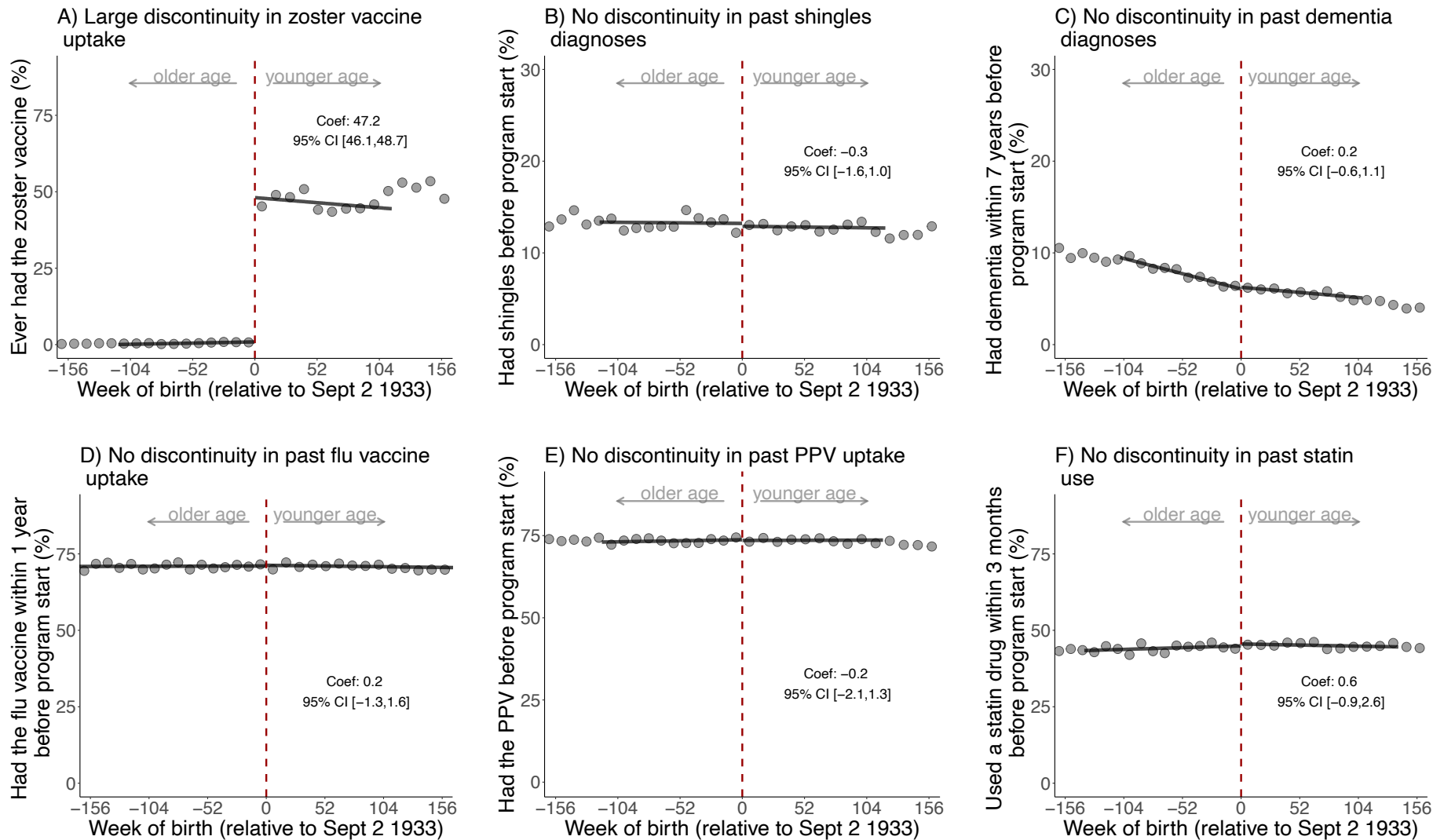
120 **A large difference in zoster vaccination receipt because of a mere one-week difference in** 121 **age**

122 We used the Secure Anonymised Information Linkage (SAIL) Databank^{27,28}, which contains
123 detailed country-wide electronic health record data on primary care visits, as well as records of
124 secondary care, in Wales linked to the country’s death register data. The study population for
125 our primary analyses consisted of all adults born between September 1 1925 and August 31
126 1942 who were registered with a primary care provider (which is the case for over 98% of adults
127 residing in Wales²⁹) at the time of the start of the zoster vaccine program in Wales (on
128 September 1 2013). For all analyses (except those with shingles and postherpetic neuralgia as

129 outcomes), we excluded the 13,783 individuals who had already received a diagnosis of
130 dementia prior to September 1 2013. Basic sociodemographic and clinical characteristics of the
131 resulting sample of 282,541 adults in our primary analysis cohort are shown in **Supplement**
132 **Table S1**. The Methods section provides more details on how we defined the study population
133 for our analyses.

134
135 In Wales, individuals born between September 2 1933 and September 1 1934 (16,595 adults in
136 our data) became eligible for the zoster vaccine on September 1 2013. Eligibility was then
137 progressively extended to younger, but not older, age cohorts on an annual basis based on their
138 exact date of birth (details are provided in the Methods section). In the section “Analyses
139 demonstrating that the zoster vaccine’s effects on dementia are causal”, we provide detailed
140 evidence against the remote possibility that the date of birth of September 2 1933 was used as
141 the eligibility threshold for any other interventions that affect dementia risk than the zoster
142 vaccine program. We find that being born just one week after September 2 1933, and thus
143 being eligible for the zoster vaccine, caused an abrupt increase in the probability of ever
144 receiving the zoster vaccine from 0.01% to 47.2% ($p < 0.001$; **Fig. 1**). This provides a unique
145 opportunity to determine the causal effects of the zoster vaccine because it is by virtue of the
146 design of the vaccination program rollout implausible that individuals just around the date-of-
147 birth eligibility threshold systematically differ from each other by anything but a one-week
148 difference in age and a large difference in the probability of receiving the zoster vaccine. We
149 substantiate this empirically by showing that neither the prevalence of common health outcomes
150 (including having been diagnosed with dementia prior to the vaccination program rollout) nor the
151 prevalence of preventive behaviors (other than zoster vaccine uptake) display a discontinuity at
152 the date-of-birth eligibility threshold for the zoster vaccine (**Fig. 1** and **Supplement Fig. S1** and
153 **S2**). Thus, just like in a randomized clinical trial, the two study groups (one with a low and one
154 with a high probability of receiving the zoster vaccine) are exchangeable with each other on all

155 observed and *unobserved* potential confounding variables^{18–20}. Of note, our approach does *not*
156 compare individuals who were eligible for the vaccine and received the vaccine with those who
157 were eligible and did not receive the vaccine. Thus, the fact that not all those who were eligible
158 received a zoster vaccination does not bias our analysis.



9
 0 **Fig. 1:** The date-of-birth eligibility cutoff led to a large discontinuity in zoster vaccine receipt but there is baseline exchangeability across the cutoff
 1 for uptake of other preventive interventions as well as past shingles and dementia diagnoses.^{1,2}

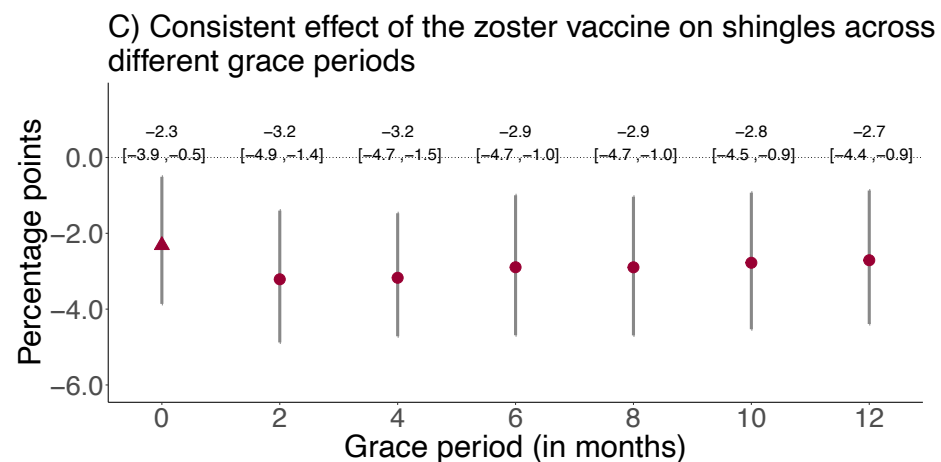
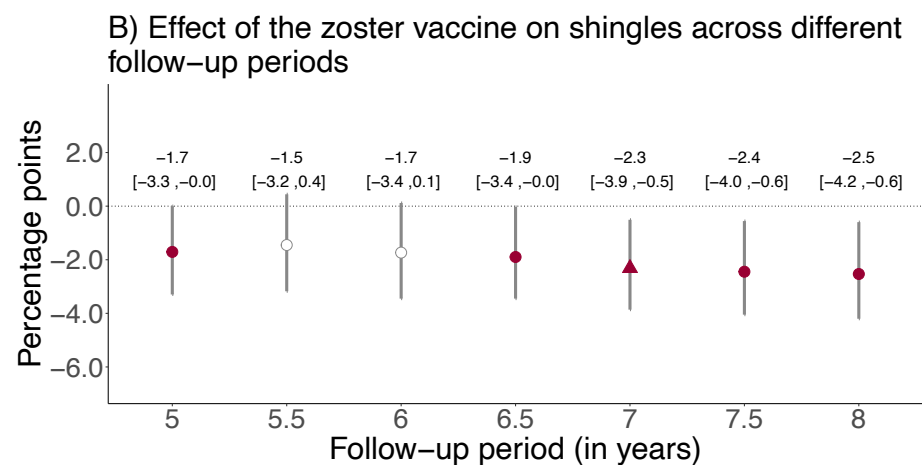
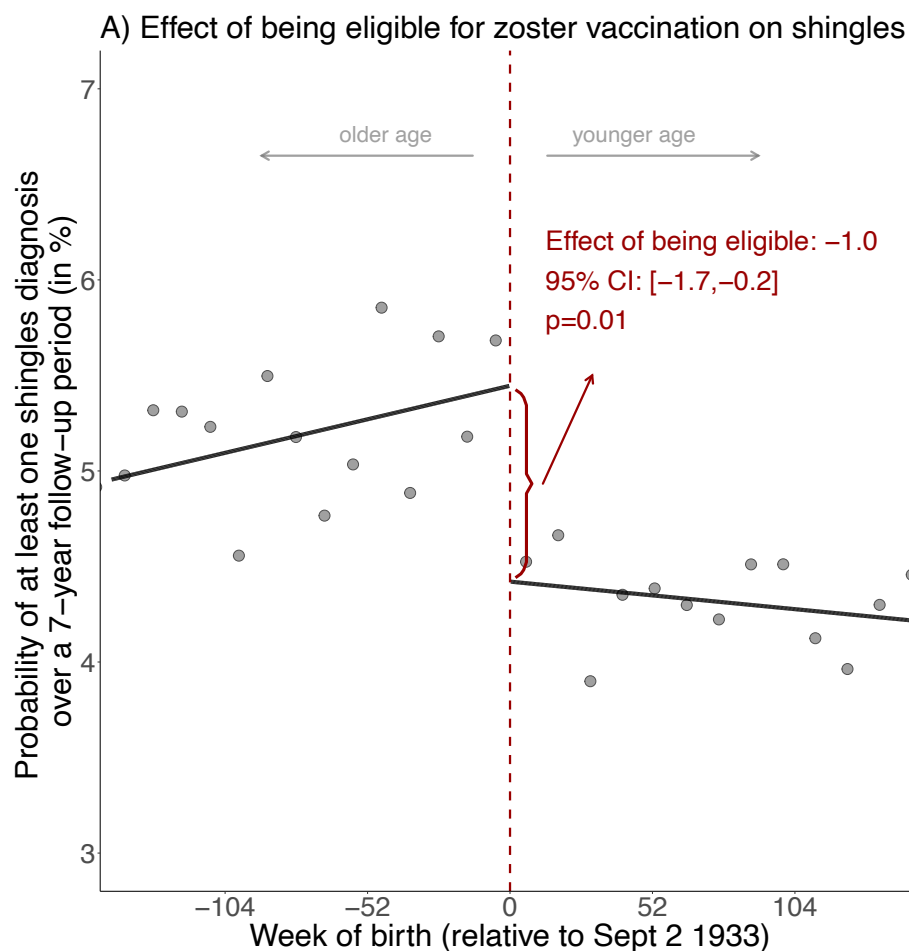
2 ¹ All analyses were run on the same sample as those for the effect of the zoster vaccine on dementia occurrence. The exception is Panel C for which we did not exclude individuals
 3 with a diagnosis of dementia prior to the start of the zoster vaccine program.

4 ² Grey dots show the mean value for each 10-week increment in week of birth.

5 Abbreviations: PPV=pneumococcal polysaccharide vaccine

166 **Replicating the known causal effect that zoster vaccination prevents shingles**

167 Before we use our approach to determine the effect of the zoster vaccine on an outcome never
168 studied in clinical trials of the vaccine, we first demonstrate that this approach successfully
169 reproduces the known causal effect from trials that the vaccine reduces the occurrence of
170 shingles³⁰. Specifically, using a regression discontinuity design (a well-established approach for
171 causal inference^{18–20}), we compared the occurrence of shingles between adults close to either
172 side of the date-of-birth eligibility threshold for the zoster vaccine. In line with the approach used
173 by clinical trials of the zoster vaccine³⁰, our outcome was whether or not an individual had at
174 least one shingles diagnosis during the follow-up period. During our follow-up period of seven
175 years, 14,465 (among 296,324) adults had at least one diagnosis of shingles. Over the same
176 follow-up time, we find that being eligible for the vaccine reduced the probability of having at
177 least one shingles diagnosis by 1.0 (95% CI: 0.2 – 1.7; $p=0.010$) percentage points (**Fig. 2**,
178 Panel A). Scaled by the magnitude of the jump in the probability of ever receiving the zoster
179 vaccine at the date-of-birth eligibility threshold (i.e., taking into account that not all those who
180 were eligible took up the vaccine), we find that receiving the zoster vaccine reduced the
181 probability of having at least one shingles diagnosis by 2.3 (95% CI: 0.5 – 3.9; $p=0.011$)
182 percentage points over the seven-year follow-up period (**Fig. 2**, Panel B). We show that our
183 estimated effect is neither sensitive to the chosen functional form of the regression used to
184 model the relationship of shingles occurrence with week of birth (**Supplement Fig. S3**), the
185 width of the week-of-birth window (“bandwidth”) drawn around the date-of-birth eligibility cutoff
186 (**Supplement Fig. S4**, Panel A), nor to different grace periods (**Fig. 2**, Panel C). With “grace
187 periods” we refer to time periods since the index date after which follow-up time is considered to
188 begin (see Methods for details) to allow for the time needed for a full immune response to
189 develop after vaccine administration. There was also strong indication that the zoster vaccine
190 reduced the probability of having at least one diagnosis of postherpetic neuralgia, although this
191 effect did not reach statistical significance in all specifications (**Supplement Fig. S5**).



2

3 **Fig. 2:** Effect estimates of being eligible (A) and having received the zoster vaccine (B and C) on the probability of having at least one shingles
4 diagnosis during the follow-up period.^{1,2,3,4,5}

5 ¹ Triangles (rather than points) depict our primary specification.

6 ² Red (as opposed to white) fillings denote statistical significance ($p < 0.05$).

7 ³ With “grace periods” we refer to time periods since the index date after which follow-up time is considered to begin to allow for the time needed for a full immune response to
8 develop after vaccine administration.

9 ⁴ Grey vertical bars depict 95% confidence intervals.

0 ⁵ Grey dots show the mean value for each 10-week increment in week of birth.

201 **Zoster vaccination reduces new diagnoses of dementia**

202 Given the neuropathological overlap between dementia types and the difficulty in distinguishing
203 dementia types clinically^{31–33}, we defined dementia as dementia of any type or cause in our
204 primary analyses. In exploratory analyses, we analyzed the effect of the zoster vaccine
205 separately for vascular dementia, Alzheimer’s disease, and dementia of unspecified type. We
206 considered an individual to have developed dementia if there was a new diagnosis of dementia
207 in our electronic health record data (which includes all diagnoses made in primary or secondary
208 care) or dementia was listed as a primary or contributory cause of death on the death certificate.
209 The Read and ICD-10-codes used to define dementia are listed in **Supplement Materials**.
210 When using a seven-year follow-up period (ending the follow-up period just prior to the COVID-
211 19 pandemic), 35,307 adults in our sample developed dementia, which compares to 40,063
212 adults when using our maximum follow-up period of eight years.

213
214 Using our regression discontinuity approach, we find that being eligible for the zoster vaccine
215 caused a 1.3 (95% CI: 0.2 – 2.7; p=0.022) percentage point absolute, and 8.5% relative,
216 reduction in the probability of a new dementia diagnosis over our seven-year follow-up period
217 (**Fig. 3**, Panel A). Scaled to account for the fact that not all those who were eligible received the
218 vaccine, we find that actually receiving the zoster vaccine reduced the probability of a new
219 dementia diagnosis by 3.5 (95% CI: 0.6 – 7.1; p=0.019) percentage points, corresponding to a
220 relative reduction of 19.9%. Examining the magnitude of the *absolute* effect over different follow-
221 up periods ranging from four to eight years, we find no indication that the effectiveness of the
222 vaccine for reducing the probability of a new dementia diagnosis wanes over time (**Fig. 3**, Panel
223 B). However, given that the proportion of patients who received a new diagnosis of dementia
224 increased over time as the follow-up period lengthened, the *relative* effect of the vaccine on the
225 probability of receiving a new dementia diagnosis did decrease over time, from 22.5% after five

226 years to 19.9% after seven years and 17.0% after eight years of follow-up. The effect estimates
227 were generally not sensitive to different grace periods (**Fig. 3**, Panel C), the functional form of
228 our regressions (**Supplement Fig. S6**), nor the width of the week-of-birth window (“bandwidth”)
229 drawn around the date-of-birth eligibility cutoff (**Supplement Fig. S4**, Panel B).

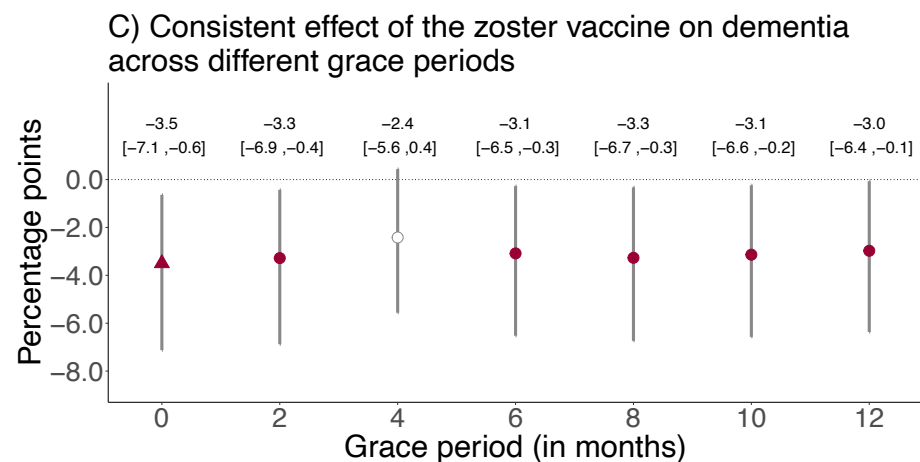
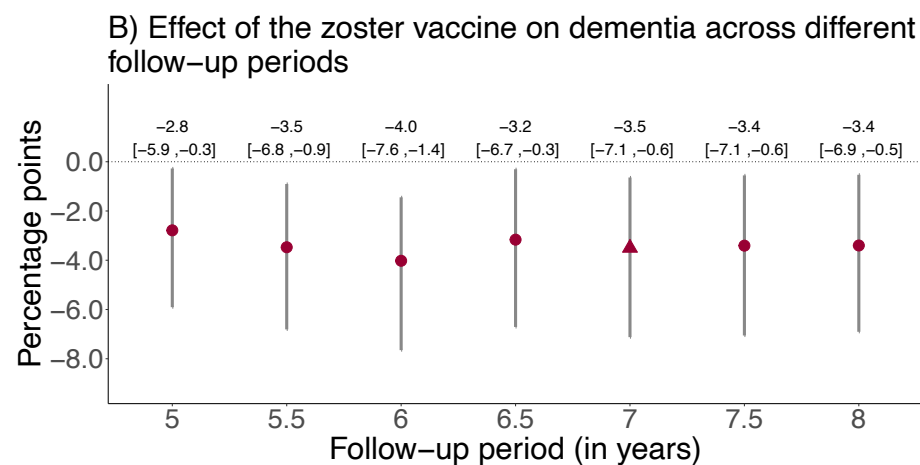
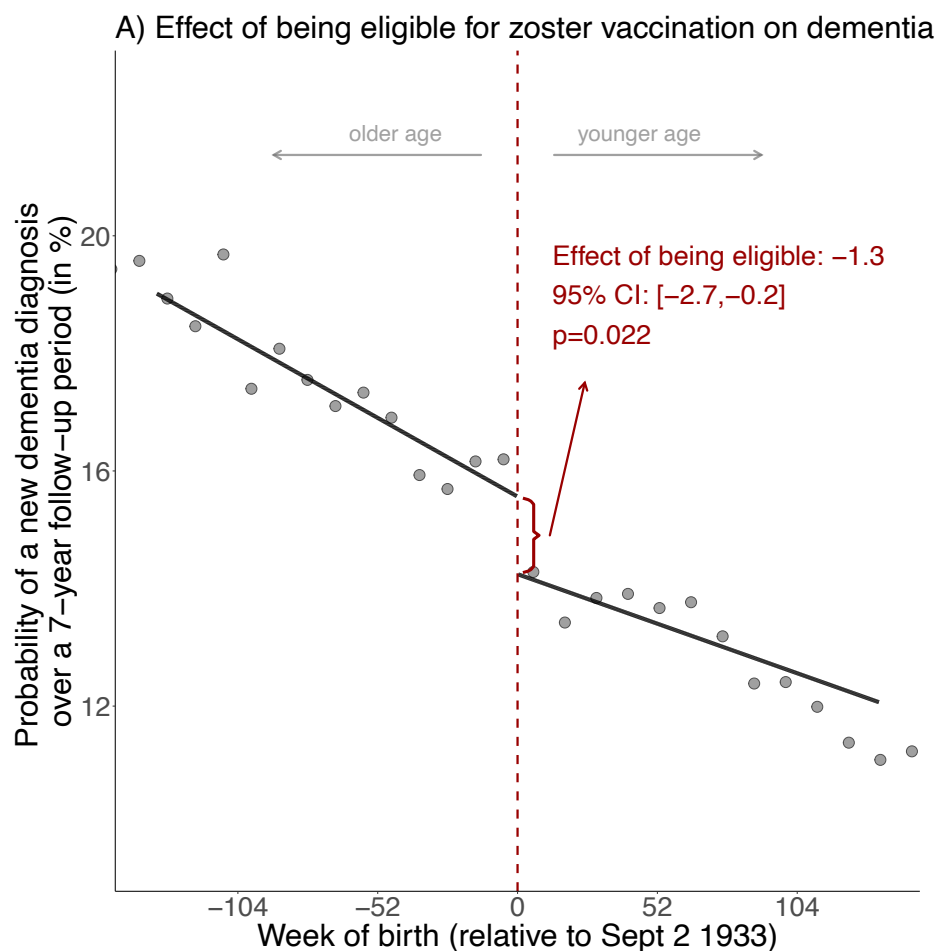


Fig. 3: Effect estimates of being eligible (A) and having received the zoster vaccine (B and C) on new diagnoses of dementia.^{1,2,3,4,5}

¹ Triangles (rather than points) depict our primary specification.

² Red (as opposed to white) fillings denote statistical significance ($p < 0.05$).

³ With “grace periods” we refer to time periods since the index date after which follow-up time is considered to begin to allow for the time needed for a full immune response to develop after vaccine administration.

⁴ Grey vertical bars depict 95% confidence intervals.

⁵ Grey dots show the mean value for each 10-week increment in week of birth.

238 **Analyses demonstrating that the zoster vaccine's effects on dementia are causal**

239 We conducted a series of analyses to confirm that our regression discontinuity approach indeed
240 yields unbiased causal effects. A confounding factor in our study must be an intervention that
241 used the identical date-of-birth cutoff (September 2 1933) as eligibility criterion as the zoster
242 vaccine program. Such an intervention is unlikely to only affect the risk of developing dementia
243 without also influencing other health outcomes. Thus, one confirmatory type of analysis is to
244 demonstrate that the observed effects of the vaccine are specific to dementia. We, therefore,
245 implemented the same regression discontinuity approach as we have done for shingles and
246 dementia for the ten leading causes of disability-adjusted life years (a composite measure of
247 morbidity and premature mortality³⁴) and mortality for the age group 70+ years in Wales in
248 2019³⁵. We show that being eligible for the zoster vaccine did not have an effect on any of these
249 common health outcomes (**Supplement Fig. S7**). The Read and ICD-10-codes for each of
250 these diagnoses are provided in **Supplement Materials**.

251
252 To more definitively rule out that another intervention (e.g., a different vaccination program) that
253 affects the risk of developing dementia used exactly the same date-of-birth eligibility cutoff as
254 was used for zoster vaccine eligibility, we undertook three additional types of analysis. First, we
255 demonstrate that the September 2 1933 date-of-birth threshold does not affect the probability of
256 taking up other preventive health interventions, including receiving the influenza vaccine, using
257 a statin or antihypertensive drug, or being screened for breast cancer during our follow-up
258 period (**Supplement Fig. S8**). Similarly, as shown in **Fig. 1** and **Supplement Fig. S2**, there was
259 no difference in the probability of uptake of these preventive health interventions between
260 participants around the September 2 1933 date-of-birth eligibility threshold prior to the start of
261 the zoster vaccine program. Second, we verified that the day-month (i.e., September 2) cutoff
262 used for zoster vaccine eligibility was not also used for other interventions that affect dementia
263 risk. We did so by implementing the identical analysis as for September 1 2013 (the actual date

264 on which the zoster vaccine program started) for September 1 of each of the three years prior
265 to, and after, 2013. Thus, for instance, when shifting the start date of the program to September
266 1 2012, we compared those around the September 2 1932 eligibility threshold with the follow-up
267 period starting on September 1 2012. To be able to do so while using the same length of follow-
268 up for all comparisons, we had to reduce the follow-up period to five years for this robustness
269 check. As an additional check that allowed us to maintain the length of the seven-year follow-up
270 period used in our primary analyses, we shifted the program start date to September 1 of each
271 of the six years preceding (but not after) 2013. As expected, for both of these checks we only
272 find a significant effect on dementia occurrence for September 1 of 2013 (**Supplement Fig. S9**
273 **and S10**). Third, we carried out the identical age-cohort comparison (that is, comparing cohorts
274 just around the September 2 1933 date-of-birth cutoff) as we do in our primary regression
275 discontinuity analysis, except that we started the follow-up period seven years earlier (on
276 September 1 2006) and ended the follow-up period on August 31 2013 (i.e., before the first
277 group became eligible for the zoster vaccine). In this way, we implemented the same age-cohort
278 comparison and have the same duration of follow-up (without overlapping with the period during
279 which one age cohort was eligible for the zoster vaccine while the other was not) as in our
280 primary analysis. This specification tests our identifying assumption that there were no pre-
281 existing differences in dementia. We find that there is no difference in the seven-year incidence
282 of dementia between age cohorts around the September 2 1933 date-of-birth threshold for the
283 seven-year period prior to the zoster vaccine rollout (**Supplement Fig. S11**). Taken together,
284 these analyses are strong evidence against the possibility that, in theory, the exact day-month-
285 year combination (September 2 1933) that was used as the date-of-birth eligibility threshold for
286 the zoster vaccine rollout could have also been used by another relevant intervention or policy
287 in the past.

288

289

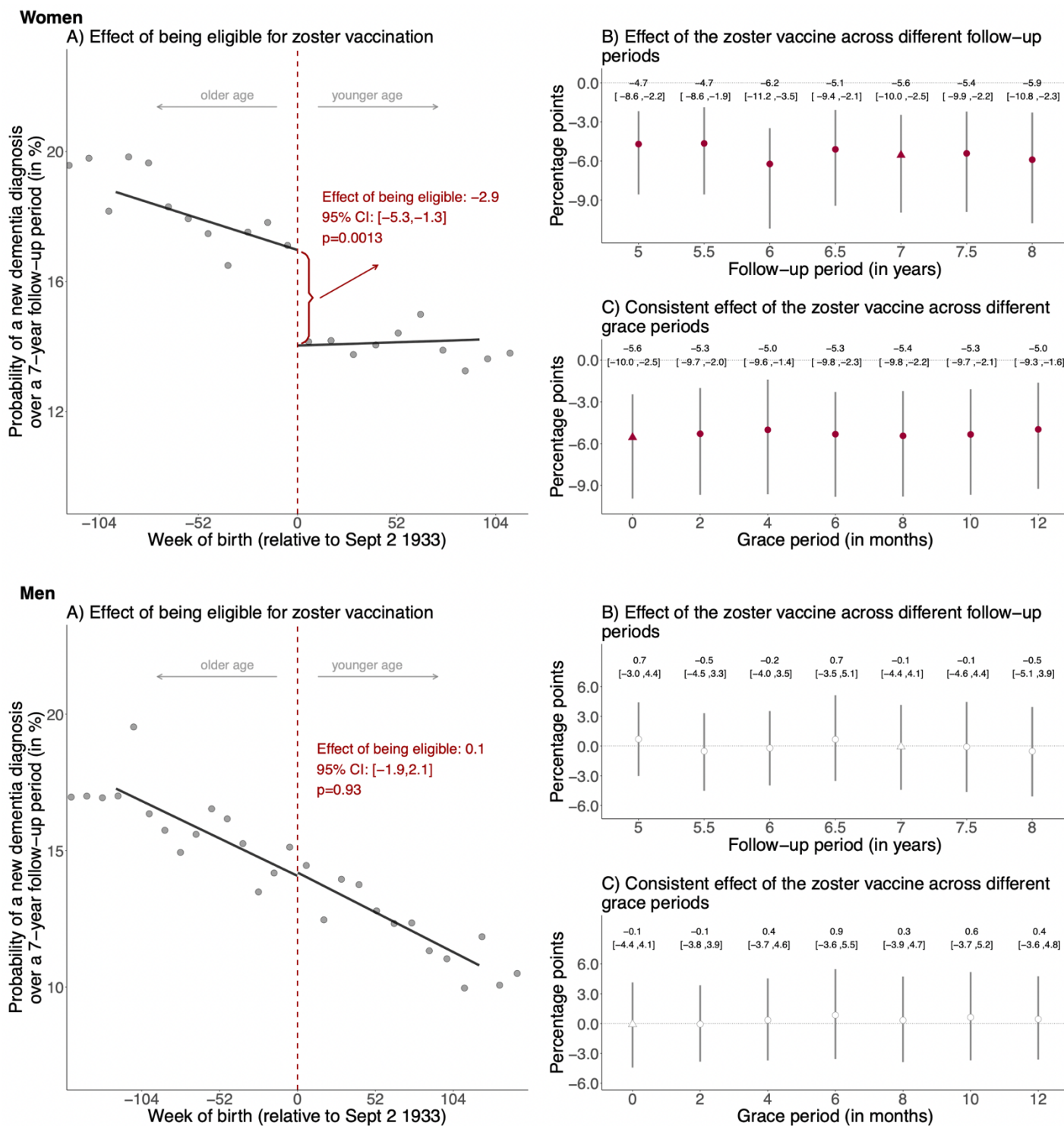
290 **Effect heterogeneity by dementia type and gender**

291 Next, as an exploratory analysis, we examined whether the effect of the zoster vaccine differs
292 by type of dementia. For this analysis, we focused on the three types of dementia recorded in
293 our data: vascular dementia, Alzheimer's disease, and dementia of unspecified type. Of the
294 35,307 individuals who were diagnosed with dementia during our seven-year follow-up period,
295 11,247 were diagnosed with vascular dementia, 14,481 with Alzheimer's disease, and 12,000
296 with dementia of unspecified type. 2,421 individuals were diagnosed with both Alzheimer's
297 disease and vascular dementia. Because shingles occurs more commonly among women than
298 men^{36,37}, and the growing evidence that the pathogenesis of dementia, particularly for
299 Alzheimer's disease, may differ in important aspects by sex³⁸⁻⁴⁰, we also investigated whether i)
300 our estimates for the effect of the zoster vaccine on dementia differ significantly between
301 women and men, and ii) any such effect heterogeneity by gender was stronger for Alzheimer's
302 disease than for vascular dementia and dementia of unspecified type.

303
304 Given that some types of dementia in our data are more common than others, we would expect
305 that the absolute effect magnitudes (and their corresponding level of statistical significance)
306 differ by type of dementia. As such, the *relative* effect sizes by dementia type are more
307 informative. We find that the relative effect sizes (Alzheimer's disease: 17.9%, dementia of
308 unspecified type: 19.1%, and vascular dementia: 18.8%) are similar across the three types of
309 dementia (**Supplement Table S2**). These findings, however, are merely suggestive because
310 there is likely substantial misclassification and overlap between dementia types in our data.

311
312 The vaccine's effect on new diagnoses of dementia was markedly greater among women than
313 men (**Fig. 4** and **Supplement Table S3**, Column 1). In fact, among men, the point estimates
314 were close to zero across all specifications. Nonetheless, the 95% confidence interval for the
315 effect among men included the possibility of a relative protective effect on dementia over a

316 seven-year follow-up period of up to 23.9%. We can, therefore, not exclude the possibility that
317 the vaccine also had a protective effect on dementia among men. When examining the effect
318 heterogeneity by gender separately for each type of dementia, we found that the protective
319 effect of the vaccine for dementia was significantly stronger for women than men for Alzheimer's
320 disease ($p=0.018$), but not for vascular dementia ($p=0.376$) and dementia of unspecified type
321 ($p=0.358$) (**Supplement Table S3**, Columns 2-4). The magnitude of the jump in vaccine uptake
322 at the September 2 1933 date-of-birth eligibility threshold was similar between men and women
323 (**Supplement Fig. S12**). Likewise, there was no significant difference between men and women
324 in the effect of the zoster vaccine on diagnoses of shingles and postherpetic neuralgia
325 (**Supplement Table S3**, Columns 5-6).



6

7 **Fig 4:** Effect estimates of being eligible (A) and having received the zoster vaccine (B and C) on new
 8 diagnoses of dementia of any type, separately for women and men.^{1,2,3,4,5}

9 ¹ Triangles (rather than points) depict our primary specification.

0 ² Red (as opposed to white) fillings denote statistical significance (p<0.05).

1 ³ With “grace periods” we refer to time periods since the index date after which follow-up time is considered to begin to allow for the
 2 time needed for a full immune response to develop after vaccine administration.

3 ⁴ Grey vertical bars depict 95% confidence intervals.

4 ⁵ Grey dots show the mean value for each 10-week increment in week of birth.

335 **Additional robustness checks**

336 Further to the robustness checks already detailed in preceding sections, we conducted four
337 additional analyses to ensure that our findings are robust to different analytical specifications.
338 First, we show that we also find significant causal effects of the zoster vaccine on reducing
339 dementia diagnoses if a diagnosis is defined only as dementia being listed as a primary or
340 contributory cause of death in the death certificate (**Supplement Table S4**, Column 2), as well
341 as when defining dementia solely as a new prescription of a medication (donepezil
342 hydrochloride, galantamine, rivastigmine, or memantine hydrochloride) that is frequently
343 prescribed to slow the progression of Alzheimer’s disease (**Supplement Table S4**, Column 3)⁴¹.
344 Second, we implemented our analyses when restricting the analysis cohort to the 237,196
345 (84.0% of the analysis cohort for our primary analyses) patients who visited their primary care
346 provider at least once a year during each of the five years preceding the start of the zoster
347 vaccine rollout. This robustness check aims to determine the causal effect of the zoster vaccine
348 among patients who interact frequently with the health system and may, thus, be more likely to
349 be screened for dementia. The effect sizes among this cohort do not differ significantly from
350 those of our primary analytical cohort (**Supplement Table S4**, Column 4). Third, while not
351 required for unbiasedness of regression discontinuity estimates, in a separate analysis, we
352 adjusted our regressions for indicators of health service utilization during the follow-up period.
353 These variables were the probability of receiving at least one influenza vaccination and the
354 number of i) primary care visits, ii) outpatient visits, and iii) hospital admissions. The effect sizes
355 remain similar (**Supplement Table S4**, Column 5). Fourth, we compared the effect sizes when
356 the index date (i.e., the date at which the quasi-randomization to intervention or control group
357 occurred) was defined as September 1 2013 for all cohorts, versus when it was defined as the
358 date at which each cohort first became eligible for the zoster vaccine (see Methods for details).
359 The effect sizes do not vary significantly between these two analytical choices (**Supplement**
360 **Fig. S13** and **Supplement Table S4**, Column 6).

361 **Discussion**

362 This study found that the zoster vaccine reduced the probability of a new dementia diagnosis by
363 approximately one fifth over a seven-year follow-up period. By taking advantage of the fact that
364 the unique way in which the zoster vaccine was rolled out in Wales constitutes a natural
365 experiment, and meticulously ruling out each possible remaining source of bias, our study
366 provides causal rather than associational evidence. Given that our effect sizes remain stable
367 across a multitude of specifications and analysis choices, it is also improbable that our finding is
368 a result of chance. The evidence provided by this study is, thus, fundamentally different to
369 studies that have simply correlated (with adjustment for, or matching on, certain covariates)
370 vaccine receipt with dementia.

371
372 Our rigorous causal approach allows for the conclusion that herpes zoster vaccination is very
373 likely an effective means of preventing or delaying the onset of dementia. Our substantial effect
374 sizes, combined with the relatively low cost of the zoster vaccine^{42–44}, imply that the zoster
375 vaccine is both far more effective as well as cost-effective in preventing or delaying dementia
376 than existing pharmaceutical interventions^{45–47}. In addition, and arguably even more importantly,
377 the finding that the zoster vaccine reduces the occurrence of dementia could help elucidate the
378 pathogenesis of dementia, which in turn could lead to additional, and potentially even more
379 effective, interventions.

380
381 Our findings create an imperative for research in the following areas. First, in addition to
382 confirming our conclusions, randomized trials are needed for determining the optimal timing and
383 frequency of zoster vaccination for dementia prevention. Our results demonstrate that zoster
384 vaccination is effective in preventing or delaying dementia if administered in individuals' late
385 seventies. We were, however, unable to ascertain whether providing the vaccine at younger

386 ages would result in additional averted dementia cases and whether there is an age above
387 which zoster vaccination has little to no effect on dementia occurrence. In addition, given
388 evidence that the effectiveness of the zoster vaccine for preventing shingles episodes declines
389 over time, which is the case for both the live attenuated and, albeit less so, the recombinant
390 subunit zoster vaccine^{48–50}, it may well be the case that the optimal strategy for preventing
391 dementia is regular ‘booster shots’ of the vaccine. Our study provides suggestive evidence that
392 such booster shots may be required as we observed waning effectiveness (on the relative
393 scale) over time for zoster vaccination reducing the probability of a new dementia diagnosis.
394 Second, our findings strongly suggest that investments into researching the role of the varicella
395 zoster virus and the immune response to the zoster vaccine in the pathogenesis of dementia
396 could provide critical insights into how a significant proportion of dementia cases can be
397 prevented or effectively treated. Our study also suggests that the varicella zoster virus plays a
398 greater role in the pathogenesis of dementia among women than men, particularly for
399 Alzheimer’s disease. Third, research should be conducted to determine if the zoster vaccine
400 reduces, or potentially even reverses, cognitive decline among those with mild cognitive
401 impairment or mild-to-moderate dementia. A clinical trial is underway to test the effect of daily
402 valacyclovir among patients with mild dementia who test positive for herpes simplex virus-1 or
403 herpes simplex virus-2 serum antibodies on change in cognitive and functional ability over a 78-
404 week follow-up period¹⁰. Similar efforts are required for the zoster vaccine.

405
406 Although validation studies on the ability of electronic health record data to reliably ascertain
407 dementia occurrence have generally been encouraging^{51–53}, our outcome ascertainment
408 undoubtedly still suffers from some degree of under-detection both in whether and how timely
409 dementia is diagnosed. Crucially, however, for this under-detection in dementia (as well as any
410 false diagnoses of dementia) to bias our relative effect sizes, it would have to be the case that
411 the degree of under-detection of dementia differed substantially between those born just before

412 versus just after the September 2 1933 date-of-birth eligibility threshold for zoster vaccination.
413 There are only two mechanisms through which the zoster vaccination eligibility threshold could
414 have affected the degree to which dementia is underdiagnosed. The first mechanism is that
415 receiving the zoster vaccine presented an opportunity for the health system to diagnose
416 previously undetected dementia. This scenario, however, would bias our effect estimates
417 towards the zoster vaccine *increasing* (rather than having the protective effect observed in this
418 study) dementia occurrence, thus leading us to underestimate the protective effect of the zoster
419 vaccine for dementia. The second mechanism is that zoster vaccination reduced healthcare
420 utilization for shingles episodes, which translated to fewer opportunities for the health system to
421 diagnose dementia. This mechanism cannot plausibly be of sufficient magnitude to significantly
422 bias our findings because both the size of our effect estimates and the occurrence of new
423 diagnoses during the follow-up period were substantially smaller for our shingles than our
424 dementia outcome. Thus, even under the most extreme assumption that every adult in our study
425 population without a dementia diagnosis had undetected dementia throughout the entire follow-
426 up period and that healthcare utilization for shingles episodes presented a certain way for the
427 health system to diagnose undetected dementia, this bias would merely account for a small
428 fraction of the effect of the zoster vaccine on reducing dementia. Providing further reassurance,
429 adjusting our regressions for the frequency of health service utilization (the number of primary
430 care visits, outpatient visits, hospital admissions, and influenza vaccinations received) during
431 the follow-up period did not substantially change our effect estimates.

432

433 Our study has several additional limitations. First, we were limited to a maximum follow-up
434 period of adults of eight years. Our study can therefore not inform on the effectiveness of the
435 zoster vaccine for reducing dementia occurrence beyond this time period. Second, we are
436 unable to provide estimates for the effectiveness of the zoster vaccine for reducing dementia
437 occurrence in age groups other than those who were weighted most heavily in our regression

438 discontinuity analyses (primarily those aged 79 to 80 years). Third, the COVID-19 pandemic
439 likely affected the timeliness with which dementia was diagnosed. However, the follow-up period
440 used in our primary analyses ended prior to the start of the COVID-19 pandemic. In addition,
441 because the pandemic affected those born just before versus just after September 2 1933
442 equally, pandemic-related under-detection of dementia does not bias our relative effect
443 estimates; it may merely have reduced the magnitude of our effect estimates on an absolute
444 scale (and only for the analyses that used a follow-up period of eight years). Fourth, our
445 comparison of effect sizes between dementia types is limited by the difficulty of classifying
446 dementia into types clinically, as evidenced by the fact that around a third of new dementia
447 diagnoses over our seven-year follow-up period were labelled as dementia of unspecified type.
448 Fifth, because the newer recombinant subunit zoster vaccine (“Shingrix”) only became available
449 in the UK in September 2021²⁶, which is after our follow-up period ended, our effect estimates
450 apply to Zostavax only.

451

452 **Data availability:** The data that support the findings of this study are available from the SAIL
453 Databank²⁷. Researchers must request access to the data directly from SAIL. The authors have
454 no permission to share the data.

455

456 **Code availability:** All Read and ICD-10 codes to define variables are available in the
457 Supplement. All statistical analysis code (in R) will be made available in a publicly accessible
458 GitHub repository upon acceptance of the manuscript for publication.

459

460

461 **Methods**

462 **Description of the zoster vaccine rollout in Wales**

463 The live attenuated zoster vaccine (Zostavax) was made available to eligible individuals in
464 Wales through a staggered rollout system starting on September 1 2013. Under this system,
465 individuals aged 71 years or older were categorized into three groups on September 1 of each
466 year: i) an ineligible cohort of those aged 71 to 78 years (or 77 years, depending on the year of
467 the program), who would expect to become eligible in the future; ii) a catch-up cohort, consisting
468 of individuals aged 79 years (or 78 years, again depending on the year of the program); and iii)
469 those who were ineligible as they were aged 80 years or older and who would never again
470 become eligible.

471
472 Our analysis focused on adults born between September 1 1925 (88 years old at program start)
473 and September 1 1942 (71 years old at program start). Those born between September 1 1925
474 and September 1 1933 never became eligible, whereas those born between September 2 1933
475 and September 1 1942 became progressively eligible in a catch-up cohort. Specifically, the
476 vaccine was offered to those born between September 2 1933 and September 1 1934 in the
477 first year of the program (September 1 2013 to August 31 2014); those born between
478 September 2 1934 and September 1 1936 in the second year (September 1 2014 to August 31
479 2015); those born between September 2 1936 and September 1 1937 in the third year
480 (September 1 2015 to August 31 2016); and those born between September 2 1937 and
481 September 1 1938 in the fourth year (September 1 2016 to August 31 2017). As of April 1 2017,
482 individuals become eligible for the vaccine on their 78th birthday and remain eligible until their
483 80th birthday. Our analysis principally compared individuals born on or shortly after September 2
484 1933, to individuals who never became eligible as they were born shortly before September 2
485 1933.

486 **Data source**

487 Healthcare in Wales is provided through the Welsh National Health Service (NHS), which is part
488 of the United Kingdom's single-payer single-provider healthcare system⁵⁴. NHS Wales and the
489 Welsh government have partnered up with Swansea University to create the Secure
490 Anonymised Information Linkage (SAIL) Databank^{27,28}. The SAIL databank includes full
491 electronic health record data for primary care visits in Wales linked to information on hospital-
492 based care as well as the country's death register data.

493
494 SAIL generates a list of all individuals who have ever been registered with a primary care
495 provider in Wales (which is the case for over 98% of adults residing in Wales²⁹) from the Welsh
496 Demographic Service Dataset⁵⁵. This dataset also contains individuals' unique anonymized
497 NHS number, date of birth, anonymized address, primary care provider registration history, as
498 well as the Welsh Index of Multiple Deprivation (the official measure of relative deprivation for
499 small areas in Wales⁵⁶). SAIL then links this universe of individuals to each of the following
500 datasets. Electronic health record data from primary care providers is made available in SAIL
501 through the Welsh Longitudinal General Practice dataset⁵⁷, which contains data from
502 approximately 80% of primary care practices in Wales and 83% of the Welsh population. These
503 electronic health record data use Read codes, which provide detailed information on patients
504 and their care encounters, including diagnoses, clinical signs and observations, symptoms,
505 laboratory tests and results, procedures performed, and administrative items⁵⁸. As specialist
506 care in the NHS is only provided based on a referral from the patient's primary care provider
507 (i.e., primary care providers are the "gate-keepers" to the wider health system)⁵⁴, referrals to,
508 and diagnoses made in, specialist care are also recorded in the primary care electronic health
509 record data. Additionally, diagnoses made and procedures performed in the hospital setting (as
510 part of inpatient admissions or day-case procedures) are provided in SAIL through linkage to the
511 Patient Episode Database for Wales⁵⁹, which begins in 1991 and contains data for all hospital-

512 based care in Wales as well as hospital-based care provided in England to Welsh residents.
513 Procedures are encoded using OPCS-4 codes⁶⁰ and diagnoses using ICD-10 codes⁶¹.
514 Attendance information at any NHS Wales hospital outpatient department is provided through
515 linkage to the Outpatient Database for Wales⁶², which starts in 2004. ICD-10 encoded
516 diagnoses of cancers are identified through linkage to the Welsh Cancer Intelligence and
517 Surveillance Unit⁶³, which is the national cancer registry for Wales that records all cancer
518 diagnoses provided to Welsh residents wherever they were diagnosed or treated. This dataset
519 begins in 1994. Finally, cause-of-death data is provided for all Welsh residents (regardless of
520 where they died in the United Kingdom) through linkage to the Annual District Death Extract⁶⁴,
521 which begins in 1996 and includes primary and contributory causes of death from death
522 certificates. Cause-of-death data uses ICD-9 coding until 2001 and ICD-10 coding thereafter.

523

524 **Study cohort, follow-up period, and loss to follow-up**

525 Our study population consisted of 296,603 individuals born between September 1 1925 and
526 September 1 1942 who were registered with a primary care provider (which is the case for more
527 than 98% of adults residing in Wales²⁹) in Wales on the start date of the zoster vaccine program
528 rollout (September 1 2013). Since we only had access to the date of the Monday of the week in
529 which an individual was born, we were unable to determine whether the individuals born in the
530 cutoff week starting on August 28 1933 were eligible for the zoster vaccine in the first year of its
531 rollout. Therefore, we excluded 279 individuals born in this particular week. Among the
532 remaining individuals, 13,783 had a diagnosis of dementia prior to September 1 2013 and were,
533 thus, excluded from the analyses with dementia occurrence as outcome. The size of our final
534 analysis cohort for all primary analyses for dementia occurrence was, therefore, 282,541. This
535 analysis cohort was also used for all analyses with uptake of other preventive health
536 interventions as well as the leading causes of disability-adjusted life years (DALYs) and
537 mortality in Wales as outcome (henceforth referred to as negative outcome control analyses and

538 detailed under the “Statistical analysis” section below). Our analyses with episodes of shingles
539 and postherpetic neuralgia as outcomes used the same study cohort except that we did not
540 exclude individuals with a dementia diagnosis prior to September 1 2013. With 296,324
541 individuals, the size of this study cohort was, thus, larger.

542
543 We followed these individuals from September 1 2013 to August 31 2021, which allowed for a
544 maximum follow-up period of eight years. In our primary specification, we selected a follow-up
545 period of seven years (i.e., until August 31 2020) because this allowed us to include grace
546 periods of up to 12 months whilst still keeping the follow-up period constant for individuals on
547 either side of the date-of-birth eligibility cutoff. We, however, also show all results for follow-up
548 periods of 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, and 8.0 years. Owing to the unique anonymized NHS
549 number assigned to each patient, we were able to follow individuals across time even if they
550 changed primary care provider. Patients were, thus, only lost to follow-up in our cohort if they
551 emigrated out of Wales or changed to one of the approximately 20% of primary care practices in
552 Wales that did not contribute data to SAIL. Over our seven-year follow-up period, this was the
553 case for 23,049 (8.2%) of adults in our primary analysis cohort, with no significant difference in
554 this proportion between those born just before versus just after the September 2 1933 eligibility
555 threshold.

556

557 **Definition of outcomes**

558 Dementia was defined as dementia being named as a primary or contributory cause of death in
559 the death certificate, or a diagnosis of dementia made either in primary care (as recorded in the
560 primary care electronic health record data), specialist care, or hospital-based care. The date of
561 the first recording of dementia across any of these data sources was used to define the date on
562 which the patient was diagnosed with dementia. Because of the neuropathological overlap
563 between dementia types and difficulty in distinguishing dementia types clinically^{31–33}, we chose

564 to define dementia as dementia of any type or cause in our primary analyses. In exploratory
565 analyses, we examined the effect of the zoster vaccine separately for vascular dementia,
566 Alzheimer's disease, and dementia of unspecified type. Because of evidence that the
567 pathogenesis of Alzheimer's disease may vary by sex³⁸⁻⁴⁰, we additionally implemented these
568 analyses separately for women and men.

569
570 Shingles and postherpetic neuralgia were similarly defined as a diagnosis of shingles or
571 postherpetic neuralgia made in primary or hospital-based care. Again, the date of the first
572 recording of a diagnosis of shingles or postherpetic neuralgia across any of these data sources
573 was used to define the date on which the outcome occurred. The Read and ICD-10 codes used
574 to define dementia, each type of dementia, shingles, postherpetic neuralgia, and each negative
575 control outcome are detailed in the Supplement (**Supplement Materials**).

576

577 **Statistical analysis**

578 The two authors who analyzed the data (M.E. and M.X.) have coded all parts of the analysis
579 independently. Occasional minor differences, resulting from different data coding choices, were
580 resolved through discussion.

581

582 *Our regression discontinuity approach:*

583 Our statistical approach exploits the fact that, unless another intervention uses the exact same
584 date-of-birth eligibility threshold (September 2 1933) as the zoster vaccine rollout, those who
585 were born just after the date-of-birth eligibility threshold must be exchangeable (i.e., comparable
586 in observable and unobservable characteristics) with those born just before except for being
587 ineligible for the zoster vaccine. We used a regression discontinuity design to analyze our data,
588 which is a well-established method for causal inference in the social sciences⁶⁵. Regression
589 discontinuity analysis estimates expected outcome probabilities just left and just right of the

590 cutoff, to obtain an estimate of the treatment effect. Based on current best practice for
591 regression discontinuity analyses⁶⁶, we used local linear triangular kernel regressions (assigning
592 a higher weight to observations lying closer to the date-of-birth eligibility threshold) in our
593 primary analyses and quadratic polynomials in robustness checks. An important choice in
594 regression discontinuity analyses is the width of the data window (the “bandwidth”) that is drawn
595 around the threshold. Following standard practice, we used a mean squared error (MSE)-
596 optimal bandwidth⁶⁷, which minimizes the mean squared errors of the regression fit, in our
597 primary analyses. In robustness checks, we examined the degree to which our point estimates
598 vary across different bandwidth choices ranging from 0.25 times to two times the MSE-optimal
599 bandwidth. We used robust bias-corrected standard errors for inference⁶⁸.

600

601 *Estimating the effect of being eligible for the zoster vaccine:*

602 In the first step, we determined the effect of being eligible for the zoster vaccine (regardless of
603 whether the individual actually received the vaccine) on our outcomes. To do so, we estimated
604 the following regression equation:

605

$$(1) Y_i = \alpha + \beta_1 D_i + \beta_2 \cdot (WOB_i - c_0) + \beta_3 D_i \cdot (WOB_i - c_0) + \epsilon_i,$$

607

608 where Y_i is a binary variable equal to one if an individual experienced the outcome (e.g.,
609 shingles or dementia). The binary variable D_i indicates eligibility for the zoster vaccine and is
610 equal to one if an individual was born on or after the cutoff date of September 2 1933. The term
611 $(WOB_i - c_0)$ indicates an individual’s week of birth centered around the cutoff date. The
612 interaction term $D_i \cdot (WOB_i - c_0)$ allows for the slope of the regression line to differ on either
613 side of the threshold. The parameter β_1 identifies the absolute effect of being eligible for the
614 vaccine on the outcome. Wherever we report relative effects, we calculated these by dividing

615 the absolute effect estimate β_1 by the mean outcome just left of the date-of-birth eligibility
616 threshold, i.e., the estimate of α .

617

618 *Estimating the effect of actually receiving the zoster vaccine:*

619 In the second step, we estimated the effect of actually receiving the zoster vaccine on our
620 outcomes. This effect is commonly referred to as the complier average causal effect (CACE) in
621 the econometrics literature²¹. As is standard practice²¹, we used a so-called fuzzy regression
622 discontinuity design to estimate the CACE. Fuzzy regression discontinuity analysis takes into
623 account the fact that the vaccine is not deterministically assigned at the week-of-birth cutoff.
624 Instead, a proportion of ineligible individuals still received the vaccine and a proportion of
625 eligible individuals did not receive the vaccine. To account for this fuzziness in the assignment,
626 the fuzzy regression discontinuity design employs an instrumental variable approach, with the
627 instrumental variable being the binary variable that indicates whether or not an individual was
628 eligible to receive the vaccine, i.e., is born on or after September 2 1933. As we verify in our plot
629 of vaccine receipt by week of birth (**Fig. 1**, Panel A), individuals who were born just after the
630 date-of-birth eligibility threshold had a far higher probability of receiving the zoster vaccine than
631 those born just before the threshold. Other than the abrupt change in the probability of receiving
632 the zoster vaccine, there is no other difference in characteristics that affect the probability of our
633 outcomes occurring between those born just after versus just before the date-of-birth eligibility
634 threshold. Thus, the indicator variable for the date-of-birth eligibility threshold is a valid
635 instrumental variable to identify the causal effect of receipt of the zoster vaccine on our
636 outcomes. To compare the probability of experiencing the outcome between those who actually
637 received the zoster vaccine versus those who did not, the instrumental variable estimation
638 scales the effect size for being eligible for the zoster vaccine by the size of the abrupt change in
639 the probability of receiving the vaccine at the date-of-birth eligibility threshold. The size of the
640 jump is estimated via the following first-stage regression equation:

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$$(2) V_i = \alpha + \beta_1 D_i + \beta_2 \cdot (WOB_i - c_o) + \beta_3 D_i \cdot (WOB_i - c_o) + \epsilon_i,$$

where V_i is a binary variable indicating if the individual received the zoster vaccine and β_1 identifies the discontinuous increase in vaccine receipt at the date-of-birth eligibility threshold. All other parameters are the same as in regression equation (1).

To compute relative effect sizes for the effect of actually receiving the zoster vaccine, we divided the CACE estimate obtained from the instrumental variable estimation described above by the mean outcome among unvaccinated compliers (those who do not receive the vaccine because they are not eligible) just at the threshold. Since, among the ineligible group, compliers are not distinguishable from never-takers (those who do not take the vaccine irrespective of their eligibility), their mean outcome must be estimated. To do this, we followed standard practice²³. By construction, the mean outcome among vaccinated patients at the date-of-birth threshold is approximately equal to the population-weighted average of the mean outcomes among vaccinated compliers (those who only receive the vaccine because they are eligible) and eligible always-takers (those who would always receive the vaccine irrespective of their eligibility). This relationship can be solved for the mean outcome among vaccinated compliers because all missing unknown quantities in this relationship can be computed from our data: the mean outcome of eligible always-takers can be computed as the mean outcome among vaccinated individuals just left of the threshold; the population share of always-takers can be computed as the share of vaccinated individuals left of the threshold; and the population share of vaccinated compliers corresponds to the treatment effect of the first stage regression (equation 2 above). Finally, we subtracted the estimate for the CACE from the mean outcome among vaccinated compliers to obtain the mean outcome among unvaccinated compliers.

668 *Empirical tests that the key assumption of regression discontinuity is met:*

669 The key assumption made by regression discontinuity designs is the continuity assumption²¹. In
670 our setting, the continuity assumption is that if September 2 1933 had not been used as the
671 date-of-birth eligibility threshold for the zoster vaccine program, then the probability of a new
672 dementia diagnosis during our follow-up period would be identical for individuals born just
673 before versus just after September 2 1933. Two scenarios could violate this assumption. First,
674 the continuity assumption would be violated if week of birth in our data was recorded with
675 systematic bias such that individuals with a differential risk of dementia are systematically more
676 likely to be categorized to one side of the date-of-birth vaccine eligibility threshold. Given that
677 vaccine prescribers and administrators in our data are not able to change the recorded date of
678 birth for a patient, it is not possible that this concern is a source bias in our analysis. If this
679 concern was a source of bias, then we would expect to see bunching in the number of patients
680 with a week of birth just on one side of the September 2 1933 threshold. As shown in
681 **Supplement Fig. S14**, this is not the case. We also formally tested for bunching using the
682 McCrary density test⁶⁹, which confirms ($p=0.28$) that there is no evidence of such bunching in
683 the week-of-birth variable in our data. Second, the continuity would be violated if the exact same
684 date-of-birth eligibility threshold (September 2 1933) as for the zoster vaccine was also used for
685 other interventions (e.g., other vaccinations or an educational policy) that affect the probability of
686 being diagnosed with dementia during our follow-up period. We conducted a series of
687 robustness checks (described in detail in the next section) to verify that no such competing
688 interventions exist.

689

690 *Robustness checks to confirm that our findings are causal:*

691 Our analysis can only be confounded if the confounding variable changes abruptly at the
692 September 2 1933 date-of-birth eligibility threshold such that individuals very close to either side
693 of this threshold would no longer be exchangeable with each other. The only plausible scenario

694 of such a confounding variable would be the existence of an intervention that used the exact
695 same date-of-birth eligibility threshold as the zoster vaccine rollout and that also affected the
696 probability of a dementia diagnosis during our follow-up period. We conducted three analyses to
697 demonstrate that the existence of such an intervention is extremely unlikely, by establishing that
698 measures of outcomes and behaviors that would be affected by such an intervention are
699 smooth across the date-of-birth eligibility cutoff.

700

701 First, across a range of birthdates around the September 2 1933 eligibility threshold, we plotted
702 the probability of having received the following diagnoses or interventions prior to the start of the
703 zoster vaccine program (on September 1 2013): diagnosis of shingles, influenza vaccine receipt
704 in the preceding 12 months, receipt of the pneumococcal vaccine as an adult, current statin use
705 (defined as a new or repeat prescription of a statin in the three months preceding program
706 start), current use of an antihypertensive medication (defined as a new or repeat prescription of
707 an antihypertensive drug in the three months preceding program start), participation in breast
708 cancer screening (defined as the proportion of women with a record of referral to, attendance at,
709 or a report from “breast cancer screening” or mammography), and each of the top ten leading
710 causes of disability-adjusted life years (DALYs) and mortality for Wales in 2019 as estimated by
711 the Global Burden of Disease Project³⁵. The Read codes for each of these variables are
712 provided in **Supplement Materials**. As shown in **Fig. 1** and **Supplement Fig. S1** and **S2**, none
713 of these variables displayed a significant jump at the September 2 1933 eligibility threshold. As
714 is the case for balance tables in clinical trials, these plots provide reassurance that individuals
715 close to either side of the September 2 1933 eligibility threshold are exchangeable with each
716 other.

717

718 Second, we conducted the same analysis as we did for individuals with birthdays on either side
719 of the September 2 1933 threshold also for people with birthdays around September 2 of each

720 of the three years of birth preceding and succeeding 1933. For example, when moving the start
721 date of the program to September 1 2011, we started the follow-up period on September 1 2011
722 and compared individuals around the September 2 1931 eligibility threshold. In order to ensure
723 the same length of follow-up in each of these comparisons, we had to reduce the follow-up
724 period to five years for this set of analyses. Thus, as an additional check, we only shifted the
725 start date of the program to September 1 of each of the six years preceding (but not
726 succeeding) 2013, which allowed us to maintain the same seven-year follow-up period as in our
727 primary analysis. If another intervention that affects dementia risk also used the September 2
728 threshold to define eligibility, then we would expect to observe effects on dementia incidence for
729 these comparisons of individuals just around the September 2 thresholds of other birth years.
730 As shown in **Supplement Fig. S9** and **S10**, the only year of birth for which the September 2
731 threshold has an effect on dementia incidence is 1933 (i.e., the year used as eligibility criterion
732 by the zoster vaccine program).

733
734 Third, we conducted the identical comparison of individuals around the September 2 1933 date-
735 of-birth threshold as in our primary analysis, except for starting the follow-up period seven years
736 prior to the start of the zoster vaccine program rollout. If there was an intervention that used the
737 September 2 1933 date-of-birth eligibility threshold but was implemented before the rollout of
738 the zoster vaccine program, then we would expect to see an effect of the September 2 1933
739 threshold on dementia incidence in this analysis. As shown in **Fig. 1**, Panel C, and **Supplement**
740 **Fig. S11**, there is no evidence of any such effect.

741
742 We conducted two additional analyses to further confirm that our observed effects on dementia
743 incidence are indeed causal. First, we verified that the effects that we observed in our analyses
744 for dementia incidence are specific to dementia. If an intervention that used the exact same
745 date-of-birth eligibility threshold as the zoster vaccine program indeed existed, it would be

746 unlikely to only affect dementia risk without also having an influence on other health outcomes.
747 We, thus, conducted the same analysis as with dementia incidence as outcome but for each of
748 the ten leading causes of DALYs and mortality in Wales in 2019 for the age group 70+ years³⁵.
749 The results of this analysis are shown in **Supplement Fig. S7** and demonstrate that the
750 September 2 1933 threshold has no effect on any of these common health outcomes other than
751 dementia. Second, we adjusted our regressions for the following variables as assessed during
752 our seven-year follow-up period: the number of primary care visits, outpatient visits, hospital
753 admissions, and influenza vaccinations received. If receipt of the zoster vaccine presented an
754 opportunity for the health system to additionally provide other preventive health interventions to
755 the patient, then we may expect this adjustment to alter our effect sizes. The effect sizes,
756 however, remained very similar (**Supplement Table S4**, Column 5). To provide further
757 reassurance in this regard, we also examined the effect of zoster vaccine receipt on the
758 probability of taking up preventive health measures (receipt of at least one influenza vaccine,
759 statin use, use of an antihypertensive drug, and participation in breast cancer screening) during
760 the follow-up period. None of these analyses showed significant effects (**Supplement Fig. S8**).

761

762 *Robustness checks to different analytical specifications:*

763 We conducted a series of additional robustness checks to ensure that our results are not
764 substantially affected by a specific analytical choice that we made in cases for which other
765 possible choices could have been justified. First, instead of starting the follow-up period for all
766 individuals on September 1 2013, we adjusted the follow-up period to account for the staggered
767 rollout of the program by beginning the follow-up period for each individual on the date on which
768 they first became eligible for the zoster vaccine (as detailed in the section “Description of the
769 zoster vaccine rollout in Wales”). We controlled for cohort fixed effects in these analyses to
770 account for the one- to two-year (depending on the year of the program) differences between
771 cohorts in the calendar year in which this moving follow-up window started. That is, we defined

772 one cohort fixed effect for ineligible individuals and the first catch-up cohort and then included
773 additional cohort fixed effects for each group of patients who became eligible at the same time.
774 The effects in this specification were very similar to those in our primary analysis (**Supplement**
775 **Fig. S13**). Second, we implemented the same analysis as our primary analysis but when
776 restricting the sample to those 237,196 (84.0% of the analysis cohort for our primary analyses)
777 patients who had made at least one visit to their primary care provider during each of the five
778 years preceding the start date of the zoster vaccine program. The rationale for this robustness
779 check is that it estimates the causal effect of the zoster vaccine among the group of patients
780 that is likely to be screened more regularly for dementia given that they interact frequently with
781 the health system. Our effect sizes are similar among this group as in our full sample
782 (**Supplement Table S4**, Column 4). Third, we varied our definition of a new diagnosis of
783 dementia by implementing our analysis separately for each of these two definitions of dementia:
784 i) dementia being named as a primary or contributory cause of death on the death certificate;
785 and ii) a new prescription of donepezil hydrochloride, galantamine, rivastigmine, or memantine
786 hydrochloride. We observed significant protective effects from the zoster vaccine on each of
787 these two different outcome definitions (**Supplement Table S4**, Columns 2 and 3). Fourth, we
788 show all results for our primary analysis with follow-up periods of 5.0., 5.5, 6.0, 6.5, 7.0, 7.5, and
789 8.0 years, grace periods (i.e., time periods since the index date after which follow-up time is
790 considered to begin) of 0, 2, 4, 6, 8, 10, and 12 months, and bandwidth choices of 0.25, 0.50,
791 0.75, 1.00, 1.25, 1.50, 1.75, and 2.00 times the MSE-optimal bandwidth. Our results were
792 consistent across these different specifications. Fifth, we verified that our results are similar
793 when using a local second-order polynomial specification instead of local linear regression
794 (**Supplement Fig. S6**).
795
796
797

798 **Ethics**

799 Approval was granted by the Information Governance Review Panel (IGRP, application number:
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802

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815 **Author contributions**

816 M.E. and M.X. contributed equally to this work. M.E. co-conceived the study, devised the
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819 draft. M.X. co-conceived the study, devised the methodology, analyzed and processed the data,
820 created data visualizations, interpreted the results, and reviewed and edited the original draft.
821 S.H. devised the methodology, interpreted the results, and reviewed and edited the original
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823 methodology, was responsible for administration and supervision, interpreted the results, and
824 wrote the original draft.

825

826 **Competing interests**

827 The authors declare no competing interests.

828

829 **Additional Information**

830 Supplementary Information is available for this paper. Correspondence and requests for
831 materials should be addressed to Pascal Geldsetzer, Email: pgeldsetzer@stanford.edu.

832

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