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Estimating the Effectiveness of First Dose of COVID-19 Vaccine Against Mortality in England: A Quasi-Experimental Study

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Estimating real-world vaccine effectiveness is vital to assessing the coronavirus disease 2019 (COVID-19) vaccination program and informing the ongoing policy response. However, estimating vaccine effectiveness using observational data is inherently challenging because of the nonrandomized design and potential for unmeasured confounding. We used a regression discontinuity design to estimate vaccine effectiveness against COVID-19 mortality in England using the fact that people aged 80 years or older were prioritized for the vaccine rollout. The prioritization led to a large discrepancy in vaccination rates among people aged 80–84 years compared with those aged 75–79 at the beginning of the vaccination campaign. We found a corresponding difference in COVID-19 mortality but not in non-COVID-19 mortality, suggesting that our approach appropriately addressed the issue of unmeasured confounding factors. Our results suggest that the first vaccine dose reduced the risk of COVID-19 death by 52.6% (95% confidence limits: 15.7, 73.4) in those aged 80 years, supporting existing evidence that a first dose of a COVID-19 vaccine had a strong protective effect against COVID-19 mortality in older adults. The regression discontinuity model's estimate of vaccine effectiveness is only slightly lower than those of previously published studies using different methods, suggesting that these estimates are unlikely to be substantially affected by unmeasured confounding factors.

COVID-19; quasi-experiment; regression discontinuity; vaccination; vaccine effectiveness

Abbreviations: CL, confidence limits; COVID-19, coronavirus disease 2019; LATE, local average treatment effect; RDD, regression discontinuity design.

On December 8, 2020, the United Kingdom launched an ambitious vaccination program to combat the coronavirus disease 2019 (COVID-19) pandemic. As of June 8, 2021, 77.3% of the adult population (aged 18 or older) has received the first dose of a vaccine against COVID-19 (1).

Clinical trials have shown high vaccine efficacy for all currently UK-authorized and deployed vaccines. For the BNT162b2 mRNA vaccine (Pfizer-BioNTech, New York, New York), 95% efficacy was reported against laboratory-confirmed COVID-19 (2). The ChAdOx1 vaccine (Oxford-AstraZeneca, Cambridge, United Kingdom) was found to have 70% efficacy against symptomatic COVID-19 among seronegative participants (3). The mRNA-1,273 vaccine (Moderna, Cambridge, Massachusetts), which was reported to have 95% efficacy against confirmed COVID-19, only started to be administered in the United Kingdom in April 2021 (4).

Monitoring real-world vaccine effectiveness is vital to assess the impact of the vaccination program on the pandemic and inform the policy response. However, estimating real-world vaccine effectiveness without randomized control trials is challenging. Unvaccinated individuals are likely to differ from vaccinated individuals in ways that are not easy to measure, particularly when uptake is very high. Several studies have estimated vaccine effectiveness against the risk of infection, hospitalization, and death by comparing outcomes of vaccinated and unvaccinated individuals, adjusting for a range of individual characteristics (5–8). However, unmeasured confounders and temporal changes in the background infection rates may bias the estimates of

vaccine effectiveness, toward overstating the effect. Indeed, many of these studies report large effectiveness in the first few days after vaccination, for instance, because those who recently tested positive or self-isolating were asked to delay their vaccination.

If vaccine eligibility is based on a continuous variable such as age, regression discontinuity design (RDD) can be used to obtain unbiased estimates of vaccine effectiveness, even in the presence of unmeasured confounding factors (9, 10). RDD approaches have been previously used to demonstrate that the childhood Bacillus Calmette-Guérin (BCG) is not effective against COVID-19, indicating that the correlation between BCG vaccination coverage and reduced impact of COVID-19 in different countries was due to unmeasured confounders (11). RDD has also been used to investigate the effectiveness of the human papillomavirus (HPV) vaccine against cervical dysplasia based on birth date (12). In these examples, a policy change generated a cutoff in vaccine eligibility for a particular birth date; therefore, outcomes such as mortality could be compared around this cutoff to determine their relationship to vaccination. RDD has been proposed as a method to estimate COVID-19 vaccine effectiveness due to the age-based rollout that many countries have adopted but has not, to our knowledge, hitherto been used (13).

In this study, we used a RDD to estimate vaccine effectiveness against COVID-19 mortality in England, exploiting the fact that the vaccination campaign in the United Kingdom was rolled out following age-based priority groups (14). People aged 80 years or older and health and social care professionals were targeted first by the vaccination campaign. Using data from the period where there was a substantial difference in the vaccination coverage of those aged just over 80 years compared with those just under 80 years, we used a fuzzy RDD to estimate the effect of protection by a first dose vaccination on the risk of COVID-19 death. We also estimated the effect of vaccination on the risk of non-COVID-19 death as a falsification test. We then calculated vaccine effectiveness based on the results from the fuzzy RDD.

METHODS

Study data

We linked vaccination data from the National Immunisation Management System (NIMS) to the Office for National Statistics (ONS) Public Health Data Asset (PHDA) based on the National Health Service (NHS) number. The ONS PHDA is a linked data set combining the 2011 Census, mortality records, the General Practice Extraction Service (GPES) data for pandemic planning and research, and the Hospital Episode Statistics (HES). To obtain NHS numbers for the 2011 Census, we linked the 2011 Census to the 2011–2013 NHS Patient Registers using deterministic and probabilistic matching, with an overall linkage rate of 94.6%. All subsequent linkages were performed based on NHS numbers.

The study population consisted of people aged 75–84 years, alive on December 8, 2020, who were resident in England, registered with a general practitioner, and enumerated at the 2011 Census. Of 3,322,785 adults aged 75–84 years who received a first dose of a COVID-19 vaccine in NIMS by May 3, 2021, 3,118,492 (93.9%) were linked to the ONS PHDA.

Outcomes

Vaccine effectiveness was estimated against mortality involving COVID-19. A death was defined as involving COVID-19 if COVID-19 was recorded as an underlying or contributory cause of death on the death certificate, as identified by either of *International Classification of Diseases, Tenth Revision* (ICD-10), codes U07.1 (confirmed) or U07.2 (suspected). Death where COVID-19 was not mentioned on the death certificate was also investigated as a falsification test, to provide a check for bias in the results.

Intervention

Treatment was defined as having received a first dose of a vaccine against COVID-19 (Pfizer-BioNTech or Oxford-AstraZeneca) for long enough to be likely to have reached seropositivity and be protected. The expected proportion of people reaching seropositivity at different lengths of time after vaccination was estimated from a study investigating antibody response following vaccination using data from the COVID-19 Infection Survey (15). In the survey, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody levels were measured using an enzyme-linked immunosorbent assay (ELISA) detecting antitrimeric spike immunoglobulin G (IgG) using a fluorescence detection mechanism, up to February 26, 2021, then by a CE-marked (meets general safety and performance requirements in the European Economic Area) version of the assay, the OmniPATH 384 Combi SARS-CoV-2 IgG ELISA (Thermo Fisher Scientific, Waltham, Massachusetts), using the same antigen with a colorimetric detection system. A threshold of $\geq$42 ng/ml was used to identify IgG-positive samples. We used these estimates of percentages reaching seropositivity by age and by time from vaccination to define the treatment indicator.

For each number of days after vaccination, we constructed cumulative incidence curves for the proportion of people who reached this number of days after vaccination on each day. We then weighted these proportions by the proportion of people expected to reach seropositivity for that number of days after vaccination using the COVID-19 Infection Survey data (7). Pfizer-BioNTech and Oxford-AstraZeneca vaccinations were weighted separately to account for the differing response curves of these vaccines. The percentages of 80 year olds reaching the threshold antibody level 28 days after the first vaccination dose were 85.2% (95% confidence limits (CL): 80.5, 88.9) and 73.7% (95% CL: 65.9, 80.3) for those vaccinated with the Pfizer-BioNTech and Oxford-AstraZeneca vaccines, respectively. The estimates of the proportion of people reaching seropositivity for the different numbers of days after vaccination were combined to provide an overall estimate of the proportion of people who had

reached seropositivity on each day. A weighted value for the proportion treated for each age (in months) group was calculated over the analysis period, accounting for the time elapsed since vaccination and the changes over the analysis period. More details are presented in the Web Appendix 1 (available at https://doi.org/10.1093/aje/kwac157).

We used this threshold antibody level to define treatment, rather than vaccination, because protection is likely to be limited until this level is reached. Also of relevance is that for the RDD, we were interested in the overall level of protection that the vaccine provides in the population.

Eligibility

The vaccination program in the United Kingdom was rolled out following age-based priority groups, with people aged 80 years or older being targeted first (14). Therefore, eligibility for the vaccine was defined as being aged 80 or older at the beginning of the vaccination campaign (December 8, 2020).

Statistical analyses

We aimed to estimate the effect on the risk of COVID-19 death of being protected by the first dose of a vaccine (defined as being vaccinated for long enough to be likely to have reached seropositivity) compared with being unprotected (being unvaccinated or not having reached seropositivity after the first dose) for people aged 80. To do so, we used a fuzzy RDD, exploiting the fact that people aged 80 or older were prioritized for vaccination at the start of the vaccination campaign, but the compliance was imperfect (16). Because those aged 75–79 rapidly became eligible for vaccination, we restricted the analysis window to the period where there was a large difference in vaccination rates between those above and below 80 years old.

We estimated the discontinuities in treatment and outcome over 15-day periods to ensure sufficient data to estimate the effect of being protected on COVID-19 mortality, with start dates ranging from January 7, 2021, to February 26, 2021. We started the analytical window 30 days after the start of the vaccination campaign, allowing time for vaccinated people to become protected. By the end of February 2021, the difference in vaccination rates between people aged 75–79 and 80–84 years was very small. For our main analysis, we selected the period where the probability of being vaccinated and having reached antibody threshold for those aged above 80 years was approximately 5 times of that for those aged less than 80 years (January 16–30, 2021). We also reported results for alternative analysis periods.

First, we estimated the effect of eligibility (being aged 80 or older at the beginning of the rollout of the vaccination program) on the probability of being protected. We calculated the proportion of people who were protected, by age in months. We then estimated the discontinuity in vaccination at the cutoff by fitting a linear regression model, with a binary variable for being aged 80 or older as the exposure of interest, and adjusted for age in months and a term for interaction between the exposure and age in months, to allow for the effect of age to vary on both sides of the cutoff, as is standard practice in RDD studies (16).

Second, we calculated the effect of eligibility (being aged 80 or older at the beginning of the rollout of the vaccination program) on the 15-day COVID-19 mortality rates by age-in-month groups, by deriving multistate cumulative incidence curves for deaths involving COVID-19 and for deaths not involving COVID-19 for all people in our sample alive on the first day of the analysis period (January 16). We then estimated the discontinuity in the 15-day COVID-19 mortality rate at the cutoff by fitting a linear model, with a binary variable for being aged 80 or older as the exposure of interest, and adjusted for age in months and a term for interaction between the exposure and age in months.

Finally, using the proportion of people who were protected, by age in months, we estimated the effect of vaccination on COVID-19 mortality by fitting a fuzzy RDD, using eligibility (being 80 or older) as an instrumental variable for the treatment. We thereby obtained an estimate of the local average treatment effect (LATE); in this case, the LATE is the effect of the vaccine on people aged 80 who received the vaccine when eligible (i.e., among the compliers). To calculate the vaccine effectiveness, we fitted the same model but used the log odds of COVID-19 mortality as the dependent variable instead of the COVID-19 mortality rate. This allowed us to estimate the odds ratio of being vaccinated and to derive the vaccine effectiveness as one minus the odds ratio. All analyses were weighted by the number of people in that age group in the analysis data set.

Sensitivity analyses

The validity of the RDD rests on the assumption that in the absence of the intervention there would have been no discontinuity in the outcome. While this assumption cannot be tested directly, we checked for continuity across the eligibility cutoff in predetermined characteristics, such as sex, quintiles of Index of Multiple Deprivation (IMD), and prevalence of a comorbidity (Web Figure 1).

In our main analysis, we estimate the LATE of vaccination on mortality using data for people aged 75–84 years, hence using a bandwidth of 5 years (on each side of the eligibility cutoff). As a sensitivity analysis, we estimated the LATE using different bandwidths, from 10 to 60 months. (Web Table 1). A smaller bandwidth may reduce bias but may result in less precise estimates. We also removed people very close to the cutoff, as their eligibility status could be misclassified (Web Figure 2).

The fuzzy RDD relied on the assumption that the discontinuity in age affected COVID-19 mortality only through its effect on vaccination. To check that the discontinuity in COVID-19 mortality rates is caused by eligibility for the vaccine, we estimated discontinuity in outcomes at arbitrarily chosen cutoffs, where we would expect no discontinuity (Web Table 2). We also present results for different analysis periods (below and in Web Table 3).

The code used for the analysis can be found in our Github repository (17).

Table 1. Characteristics of Study Population, Alive on December 8, 2020, Followed to May 3, 2021, England

Characteristic	Overall (3,422,644)		Age Range, years			
			75–79 (1,993,782)		80–84 (1,428,862)	
	No.	%	No.	%	No.	%
Death						
COVID 19-related	17,127	0.5	7,338	0.4	9,789	0.7
Other deaths	46,894	1.4	20,555	1.0	26,339	1.8
Vaccination status[a]						
Oxford-AstraZeneca	1,267,635	37.0	931,619	46.7	336,016	23.5
Pfizer-BioNTech	1,853,060	54.1	896,608	45.0	956,452	67.0
Moderna	333	0.0	250	0.0	83	0.0
Unknown manufacturer	569	0.0	397	0.0	172	0.0
Not vaccinated	301,047	8.8	164,908	8.3	136,139	9.5
Sex						
Male	1,563,857	45.7	929,897	46.6	633,960	44.4
Female	1,858,787	54.3	1,063,885	53.4	794,902	55.6
Age, years[b]	78.95 (2.9)		76.84 (1.4)		81.88 (1.4)	
Comorbidities, ≥1	1,538,299	44.9	847,384	42.5	690,915	48.4
Ethnicity						
Bangladeshi and Pakistani	30,443	0.9	15,266	0.8	15,177	1.1
Black	51,317	1.5	25,826	1.3	25,491	1.8
Chinese	9,203	0.3	5,080	0.3	4,123	0.3
Indian	54,998	1.6	30,600	1.5	24,398	1.7
Mixed	13,847	0.4	8,227	0.4	5,620	0.4
Other	30,791	0.9	18,618	0.9	12,173	0.9
White	3,232,045	94.4	1,890,165	94.8	1,341,880	93.9

Abbreviation: COVID-19, coronavirus disease 2019.
[a] Oxford-AstraZeneca (Cambridge, United Kingdom); Pfizer-BioNTech (New York, New York), and Moderna (Cambridge, Massachusetts).
[b] Values are expressed as mean (standard deviation).

RESULTS

Characteristics of the study population are shown in Table 1. Out of the 3,422,644 people aged 75–84 years included in our study, 91.2% had received a first dose of a COVID-19 vaccine by May 3, 2021; 54.3% were women. The average age at December 8, 2020, was 79.0, and 44.9% had at least 1 long-term health problem known to increase the risk of severe COVID-19 outcomes (as defined by the QCovid risk model (18)).

Cumulative incidence curves for the proportion of people aged 75–79 years and 80–84 years who had received a first dose of a COVID-19 vaccine are shown in Figure 1. Due to the earlier administration of vaccines for people aged 80 or older, there was a clear difference in the proportion of each age group that was vaccinated at the beginning of the vaccination campaign. On January 8, 2021, 1 month after the start of the vaccination rollout, 34% of people aged 80–84 had received a first dose of a vaccine, compared with 5% of those aged 75–79. Vaccination was then extended to younger age groups. On February 8, 2021, 92% of people aged 80–84 and 90% of those aged 75–79 had received their first dose; 13% of people aged 80–84 and 0.5% of those aged 75–79 had received their second dose (Web Figure 3). In addition, the rapid increase in the proportions vaccinated in both groups can be seen, which was taken into account when calculating the proportion protected for the analysis period.

Main results

The weighted proportion protected (vaccinated and likely to have reached threshold antibody level) by age in months (expressed in the figure in years) for the analysis period is shown in Figure 2A. The proportion of people who had been vaccinated and reached threshold antibody level was much lower among people aged 75–79 years than among those aged 80 or older, who had been prioritized for the vaccination. There is evidence of a clear discontinuity at age

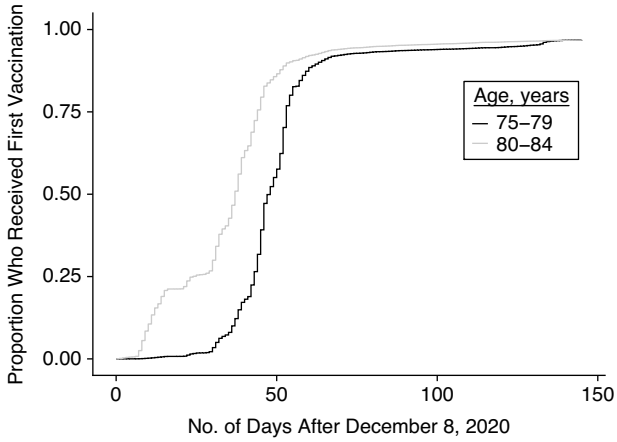

Figure 1. Cumulative incidence of first-dose COVID-19 vaccination by age group (75–79 years, 80–84 years) from December 8, 2020 (date of first UK vaccination), to May 3, 2021, England.

80, with people near the eligibility cutoff being 5.5 times more likely to be protected just above than just below.

The probabilities of COVID-19 mortality and mortality from other causes are shown in Figure 2B and 2C, respectively. A decrease in the probability of COVID-19 mortality can be seen at age 80. Being eligible for vaccination (e.g., being 80 or older) was estimated to reduce the risk of COVID-19 mortality by 23.5 (95% CL: 7.2, 39.7) deaths per 100,000 days at risk. As expected, there was no discontinuity in probability of mortality from other causes. This provides reassurance that the relationship between treatment and reduced COVID-19 mortality was not due to residual confounding.

The results from the fuzzy RDD, using eligibility as an instrument for being protected, indicated that receiving a first dose of a vaccine and reaching seropositivity reduced COVID-19 mortality by 112 (95% CL: 33, 191) deaths per 100,000 people in the 15 days from January 16, 2021.

This yields a vaccine effectiveness of 52.6% (95% CL: 15.7, 73.4) for people aged 80 who have been vaccinated for long enough to be likely to have reached seropositivity and therefore be protected.

The estimated discontinuity at age 80 years in the weighted proportion of people who were protected for different analysis periods is reported in Figure 3A. The discontinuity at age 80 widened at the beginning of the vaccination campaign, as the ≥80 group was prioritized. It then fell as the vaccination campaign was extended to people below 80. The estimates of the effect of eligibility on the 15-day COVID-19 mortality rate (Figure 3B) also varied depending on the chosen analysis period due to the changing relative proportions of people protected in the eligible and ineligible groups and the underlying COVID-19 infection rate. The estimated discontinuities in non-COVID-19 mortality were all not different from zero (Figure 3C). The estimates of the effect of receiving a first dose of a vaccine and reaching seropositivity on COVID-19 mortality, for people aged 80, were relatively stable (Figure 3D) and varied with the underlying COVID-19 infection rate. The estimates of vaccine effectiveness are mostly consistent with the wide confidence intervals on the final estimate for the January 16, 2021, analysis (Figure 3E). The estimates of COVID-19 mortality rate in the unprotected population increased for later time periods. As more people became vaccinated, the unprotected population shrank and became different from the general population. The estimates therefore became less representative of the COVID-19 mortality rate in the general population for unvaccinated people for these analysis periods.

Sensitivity analyses

Sensitivity analyses demonstrated the applicability and robustness of RDD as a technique for estimating the vaccine effectiveness. The bandwidth used in our main analysis (60 months on either side of the cutoff) resulted in the same value for the LATE as a bandwidth of 50 months, but smaller bandwidths led to less precisely estimated LATE (Web Table 1). Excluding data points close to the cutoff did not significantly affect the results (Web Figure 2).

Predetermined characteristics, such as sex, Index of Multiple Deprivation quintile, and prevalence of comorbidities, were continuous across the eligibility cutoff at 80 years (Web Figure 1). The discontinuity in the outcome variable was directly related to the discontinuity in the treatment variable and not influenced by confounding factors. We also found that the discontinuity in the outcome variable (COVID-19 mortality) occurred only at the eligibility cutoff of 80 years, and not at any other age in our age range, testing in 10-month steps from the eligibility cutoff, further confirming the relationship between the outcome and treatment discontinuities (Web Table 2). There was no discontinuity in the probability of non-COVID-19 mortality at the eligibility cutoff nor at any other age cutoff.

A longer period introduced more variation due to the changing vaccination status of the population and the changing infection levels. Shorter periods reduced the precision of the estimates because they did not contain enough mortality data to calculate reliable mortality rates by age in months (Web Table 3). A 15-day period reduced the relative uncertainty in the LATE compared with shorter periods. However, periods more than 15 days did not further reduce uncertainty, therefore indicating that there was sufficient mortality data to calculate the probabilities of COVID-19 mortality by age in months required to estimate the LATE.

DISCUSSION

In this study, we used a RDD approach to determine the effectiveness of the vaccination program in England in preventing COVID-19 mortality for the population with age close to 80 years. By using a RDD approach, we obtained an estimate of vaccine effectiveness unlikely to be substantially biased by confounding factors, whether measured or not. Our results demonstrate a causal impact of vaccinations on reducing COVID-19 mortality, with effectiveness slightly lower but comparable to previously published studies (5, 6, 19–21). The lack of an impact on non-COVID-19 mortality

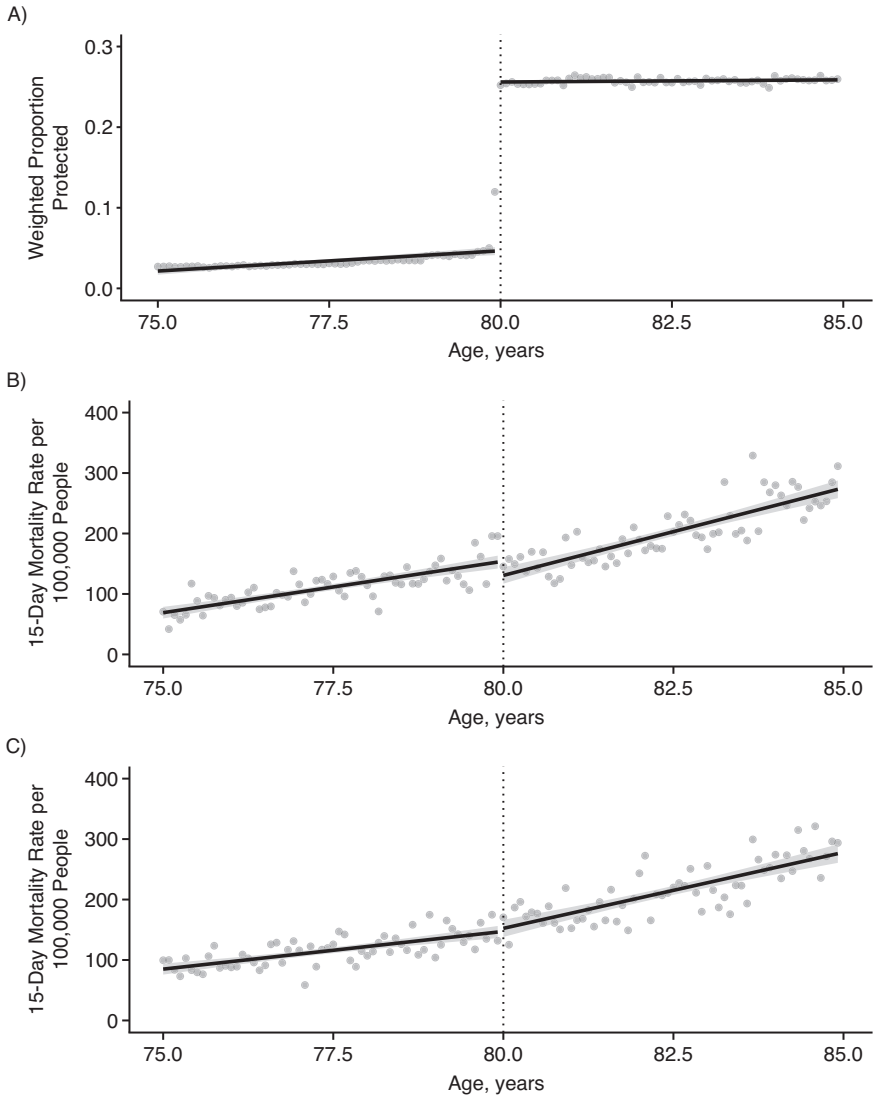

Figure 2. Regression discontinuity design plots for treatment and outcome variables by age in months (shown here in terms of years) for the 15-day period starting January 16, 2021, England. A) Weighted proportion of people who were vaccinated and reached threshold antibody level over the 15-day period, by age in months. The discontinuity in the weighted proportion with antibodies at age 80 years is 0.209 (95% confidence limits: 0.204, 0.215; *P* value < 0.0001). B) Probability of COVID-19 mortality during the 15-day period. The discontinuity in probability of COVID-19 mortality at age 80 years was -23.5 (95% confidence limits: -39.7, 7.2; *P* value = 0.008) per 100,000 days at risk. C) Probability of non-COVID-19 mortality during the 15-day period. There is not a statistically significant discontinuity in the probability of non-COVID-19 mortality at age 80 years (*P* value = 0.6). All data are fitted using a linear regression model, which adjusted for age in months and age in months $\times$ a binary variable for being aged 80 or older.

as a falsification test confirms that the estimate is unlikely to be biased when using this technique.

The main strength of our study is using a RDD approach to evaluate vaccine effectiveness. The RDD minimizes the risk of bias due to unobserved factors driving both the assignment of treatment and the outcome. In this way, the fuzzy RDD is similar to a randomized control trial with imperfect compliance. The technique is particularly useful where it may be challenging to account for all confounding factors, such as in clinical records where the information on people's sociodemographic characteristics are sparse. Studies investigating the effectiveness of the Bacillus Calmette-Guérin vaccine against COVID-19 comparing COVID-19 outcomes in countries with different vaccine coverage rates, found a spurious association between vaccination coverage and COVID-19 mortality; a RDD approach based on birth cohort, which determined vaccine eligibility, found no evidence of a protective effect, suggesting that unmeasured confounding factors drive the apparent effect on COVID-19 outcomes (11). This is also a potential problem for COVID-19 vaccine effectiveness studies due to the differing characteristics, some unmeasured, between the vaccinated and

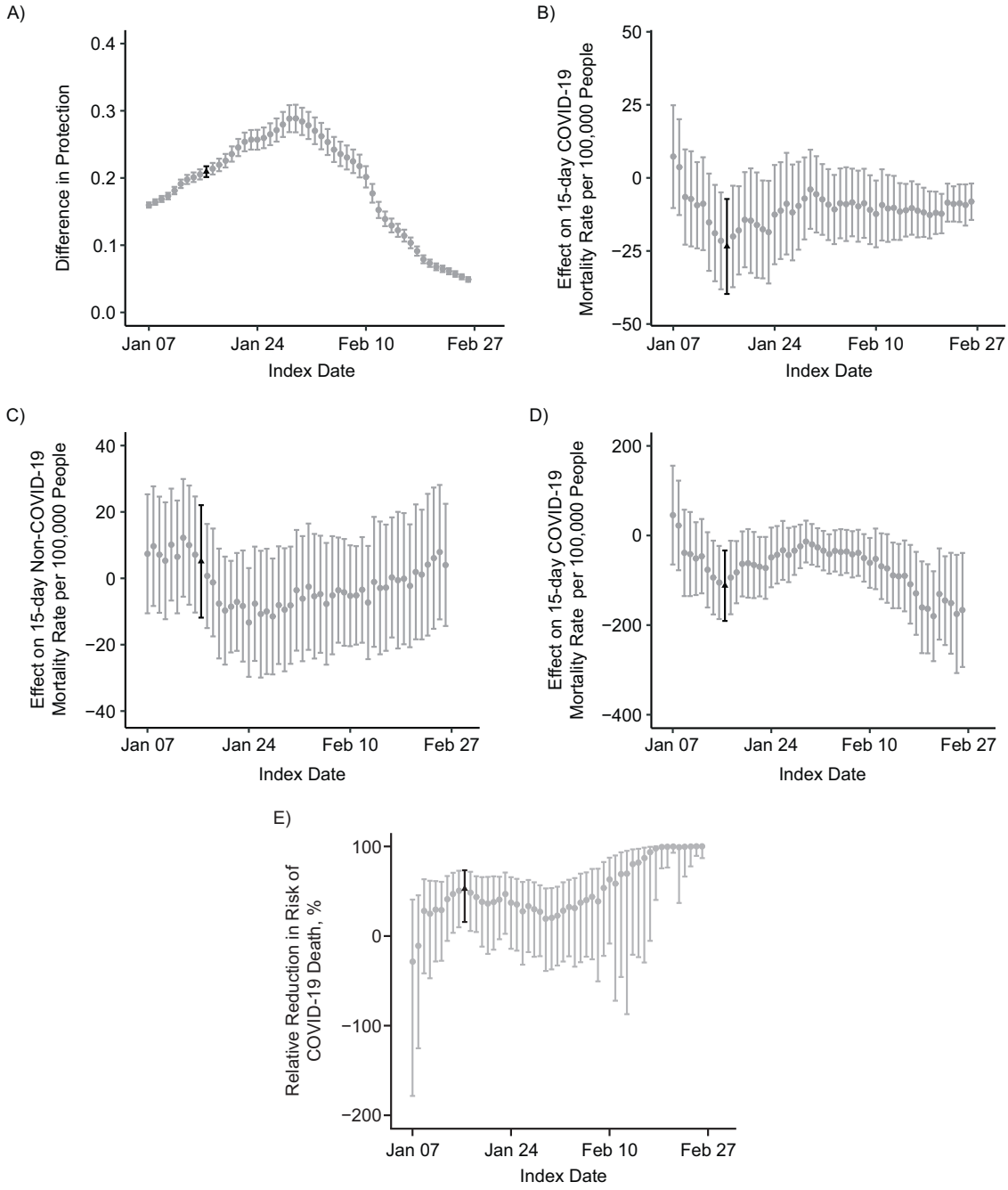

Figure 3. Estimated discontinuities, local average treatment effects, and vaccine effectiveness for alternative analysis periods, England, 2021. A) Discontinuity in the weighted proportion of people who have been vaccinated and reached threshold antibody level over the 15-day period; B) discontinuity in the 15-day COVID-19 mortality rate; C) discontinuity in the 15-day non-COVID-19 mortality rate; D) effect of vaccination on COVID-19 mortality in people aged 80 (= (B)/(A)); E) vaccine effectiveness (= 1 − odds ratio for being protected).

unvaccinated populations. The RDD result therefore acts as a verification of observational studies based on other designs and provides an estimate of the effectiveness unlikely to be severely biased by unmeasured confounding. Another strength of our study is the use of population-wide data for England, covering approx. 93.9% of the population aged 75–84 years who received a first dose of a COVID-19 vaccine recorded in National Immunization Management System by May 3, 2021.

The main limitation of our study is that the RDD yielded an estimate of the vaccine effectiveness that is valid only for people aged around 80. Hence, it cannot be generalized to other age groups. The estimate is also valid only for the compliers, that is, the people who decided to be vaccinated

when invited to do so. Another limitation of the method is that people aged 75–79 years rapidly became vaccinated, leaving a short window where the RDD could be applied. To mitigate the contamination of the control group, we estimated the discontinuity in mortality rates over a short time window (15 days), using dates where the difference in vaccination rates between people aged below and above 80 was the largest. We also estimated the discontinuity in weighted proportion of people who were vaccinated and were likely to have developed antibodies, rather than just focusing on the proportion of people who had received the vaccine. Nonetheless, our results may underestimate vaccine effectiveness.

Another limitation is that the outcome variable, COVID-19-related death, may be measured with an error, as not all COVID-19-related deaths may have been captured on death certificates and, conversely, not all deaths for which COVID-19 was mentioned on the death certificate may have involved the disease. As there is no reason to believe that the outcome misclassification is related to the eligibility for vaccination, this is unlikely to bias the estimate of vaccine effectiveness, but it may result in a loss of precision. Because the exposure was defined not only by having received a first dose of a vaccine against COVID-19 but also the time since vaccination, based on the proportion of people reaching seropositivity at different lengths of time after vaccination, it was likely to be misclassified for some individuals. The exposure misclassification is unlikely to be different between people aged just over and under 80, so is unlikely to cause any systematic bias, but may nonetheless lead to an attenuation bias, resulting in the estimate of vaccine effectiveness being biased toward the null. In addition, our analysis only provides an estimate of vaccine effectiveness for the first dose of COVID-19 vaccines. Another limitation is that our approach does not account for the different antibody responses in people who have previously been infected with COVID-19.

The RDD estimate of vaccine effectiveness against COVID-19 mortality of 52.6% is comparable to, but slightly lower than, previously reported by other studies based on different designs. In the United Kingdom, the effectiveness of a single dose of the Pfizer-BioNTech vaccine against COVID-19 mortality has been reported as 85% for those aged ≥80 years(19) and 80%–85% for those aged 70 years or older, rising to 97% effective for 2 doses (5, 6). The effectiveness of the Oxford-AstraZeneca vaccine has been reported as 80% in those aged 70 years or older (5). International studies have reported effectiveness of 96.7% for the Pfizer-BioNTech vaccine after 7 days (20), and for mRNA vaccines 98.7% at least 7 days after the second dose, and 64.2% at least 14 days after one dose (22).

The RDD may underestimate vaccine effectiveness compared with methods investigating vaccine effectiveness on mortality with a delay after vaccination, due to deaths occurring soon after a person has been vaccinated that are caused by an infection prior to vaccination. The weighting reduces the effect of such deaths but does not completely eliminate it, and we cannot determine when an infection has been acquired. In contrast, the published studies may overestimate the vaccine effectiveness by not accounting for all confounding factors. In addition, the estimand in our study is different from that of other reported studies. We estimated the effectiveness of a first dose in people aged 80 who decided to be vaccinated very soon after they became eligible, while other studies estimate the vaccine effectiveness in a much more diverse population. This may also explain why our estimate is lower than those reported in other studies.

Typically, RDD-based studies of vaccine effectiveness have been applied where a policy change generated a cutoff in vaccine eligibility for a particular birth date; therefore, outcomes such as mortality could be compared around this cutoff to determine their relationship to vaccination (9, 11). The outcomes are measured on a much longer time scale than the time taken for the vaccine to produce protection in an individual, and individuals do not change their vaccination status during the study. However, in this study, the rapid increase in vaccinations necessitated a short analysis period (here 15 days), and the changing status of individuals as they became vaccinated or developed higher levels of protection had to be taken into account. We used the proportion who were vaccinated for long enough to be likely to have reached threshold antibody level after 1 dose as an estimate of the proportion that are protected. However, there may be some level of protection for those who had not yet reached threshold level, as well as higher levels of protection for those who had developed greater than the threshold antibody level, possibly due to receiving a second dose. The number of second-dose vaccinations in our data was small (less than 6% of people in our analysis data set had received a second vaccination by the end of the analysis period); therefore, we only accounted for first vaccinations in the model.

Because COVID-19 vaccines are already approved and licensed for use, real-world vaccine effectiveness has to be estimated from observational data, which is challenging because of the potential for residual confounding. The RDD estimates of vaccine effectiveness against COVID-19 mortality are unlikely to be biased by unmeasured confounding and are comparable to estimates obtained using different approaches. This suggests that residual confounding is unlikely to substantially bias estimates of vaccine effectiveness, at least for this age group.

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The ONS COVID-19 Public Health Linked Data Asset is available on the ONS Secure Research Service for Accredited researchers. Researchers can apply for accreditation through the Research Accreditation Service. The derived data used to estimate the regression discontinuity model will be made publicly available.

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