BRIEF REPORT

REVISED Mortality involving and not involving COVID-19 among vaccinated vs. unvaccinated in England between Apr 21 and May 23

[version 2; peer review: 1 approved, 1 not approved]
Previously titled: The temporal protection and declining health of the COVID-19 vaccinated in England: A 26-month comparison of the mortality involving and not involving COVID-19 among vaccinated vs. unvaccinated

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Abstract

Background

Comparing non-randomized groups, such as COVID-19 vaccinated and unvaccinated, even in the presence of seemingly relevant control variables, is challenging, but in this study, using English data, I show an achievable approach.

Methods

First, I estimated age-standardized all-cause mortality among vaccinated and unvaccinated ten years and older, covering 26 months from Apr 21 to May 23. Then, I estimated mortality not involving COVID-19, and finally, I differentiated the calculations.

Results

First, I found that all-cause mortality among unvaccinated was higher than among vaccinated. But, as the pattern was similar concerning mortality not involving COVID-19, the discrepancy is attributed mainly to unvaccinated having inferior health at the outset. There was nonetheless significant protection for vaccinated between July 21 and Jan 22. Absent of control variables as a means to compare non-randomized groups, I reached that finding by differentiating all-cause

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version 2 (revision) 03 Apr 2025	✓ view	
version 1 27 Jan 2025	✗ view	✗ view

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mortality from mortality not involving COVID-19. However, while mortality not involving COVID-19 decreased among unvaccinated compared to the first observation month, it was high among vaccinated, i.e., a relative increase in mortality among vaccinated.

Conclusions

An interpretation is that vaccination, despite temporary protection, increased mortality. Strengthening the interpretation was relatively high mortality among vaccinated not involving COVID-19 counterintuitively following periods of excess mortality. Further strengthening the interpretation was relatively high mortality not involving COVID-19 among vaccinated, corresponding with excess mortality during much of the same period. An implication of the study, which particularly has relevance for future pandemics, is that vaccinated may have a limited time window of protection and can even be exposed to detrimental health consequences. The pattern should be followed up over an extended period in future research. Also, future research should examine different age groups, vaccination types, and the number of doses given.

Keywords
COVID-19 vaccination; all-cause mortality; mortality involving COVID-19; mortality not involving COVID-19; excess mortality.

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REVISED **Amendments from Version 1**

The title of the revised manuscript has changed. The previous title was as follows: "Mortality involving and not involving COVID-19 among vaccinated vs. unvaccinated in England between Apr 21 and May 23". The new one is as follows: "Mortality involving and not involving COVID-19 among vaccinated vs. unvaccinated in England between Apr 21 and May 23". I have extended the abstract by adding implications and addressing avenues for future research. Also, I have improved the literature review and the explanation of the paper's core concepts. In addition, I have improved the presentation of the methods section and the results section. Finally, I have improved the discussion by better highlighting the study's contribution, implications, limitations, and future research. Figures 1C1nd 1C2 from the previous version have been moved to the Notes section under the new names Figure 5A and 5B. Figure 2C has also been moved to the Notes section under the new name Figure 6. Figure 2D is now Figure 3, and Figure 3 is Figure 4. All changes have been made following the referees' suggestions.

Any further responses from the reviewers can be found at the end of the article

Introduction

According to the UK Office for National Statistics,[1] rates for COVID-19 unvaccinated adults in England "were higher for Black Caribbean, Black African and White Other ethnic groups. Rates were also higher for those living in deprived areas, who have never worked or are long-term unemployed, who are limited a lot by a disability, … or who are male." The statement aligns with vaccine hesitancy research[2,3] and further indicates that unvaccinated have inferior health at the outset compared to vaccinated, inducing biased comparisons as the groups are not randomly assigned. Therefore, matching, balancing,[4] or controlling for potential confounders, e.g., ethnicity, employment-, disability-, socioeconomic status, and gender, may debias the results.[5] However, variables accounting for potentially confounding effects are often unavailable or unknown, and including those available but unknowingly improper can increase bias.[6] In line with the reasoning, York (Ref. 6, p. 675) showed that "unless *all* potential confounding factors are included in an analysis (which is unlikely to be achievable with most real-world data-sets), adding control variables to a model in many circumstances can make estimated effects … less accurate."Norwegian research exemplifies that showing 30% lower all-cause mortality among COVID-vaccinated compared unvaccinated, 18-44 years, and 58% when including control variables.[7] The findings are unattributable to a vaccine effect as close to zero young people died of COVID-19 in Norway,[8] and illuminate two issues: (i) COVID-19 vaccinated and unvaccinated have different health status at the outset and (ii) including control variables can make estimates less, not more, accurate, both consistent with my outline above.

Hence, I argue there is a research gap concerning valid estimations between non-randomized groups, such as COVID-19 vaccinated and unvaccinated, which is challenging even when including seemingly relevant control variables that can actually deteriorate the results.[7] To address the research gap, using English data covering 26 months from Apr 21 to May 23,[9] I elaborate an achievable approach by comparing all-cause mortality among COVID-19 vaccinated and unvaccinated with mortality not involving COVID-19. In the Methods section, I explain it in full detail.

The study's research question is accordingly as follows: Applying the approach addressed above (which I further elaborate on in the Methods section), how do the mortality patterns differ in England from Apr 21 to May23 between COVID-19 vaccinated and unvaccinated? The study's major contribution is to illustrate how comparing mortality involving and not involving COVID-19 can assess valid estimates between non-randomized groups of vaccinated and unvaccinated.

COVID-19 vaccination has been recommended to most population groups, including people with comorbidities.[10]

Studies have further indicated that COVID-19 vaccination can prevent mortality,[11–17] but along with research showing that antibody levels were a superior predictor,[18] the effect declines,[19] and research has even shown "a positive correlation between people fully vaccinated and COVID-19 mortality".[20] Applying my approach to the English data, I particularly contribute to the research on the link between COVID-19 vaccination and mortality, as most previous studies have been carried out in non-randomized contexts and, accordingly, even in the presence of control variables, exposed to challenges concerning validity addressed above.

Methods

Sample and data

I used publicly available data on the population in England ten years and older provided by the UK Office for National Statistics[9] for this study. Particularly, I applied their data on monthly age-standardized all-cause mortality and mortality

not involving COVID-19 by vaccination status,[21,22] and present further details below. The period for which data were available and included in this study was between Apr 21 and May 23, 26 months.

Measures of variables

The study includes the two effect variables, monthly mortality rates and monthly odds ratios (ORs) of mortality. As noted, I distinguished between all-cause mortality and mortality not involving COVID-19. All-cause mortality implies anybody who died independent of cause. Mortality not involving COVID-19 implies those who died but did *not* have COVID-19 mentioned on the death certificate in terms of ICD10 codes U07.1 (COVID-19, virus identified) or U07.2 (COVID-19, virus not identified).

COVID-19 vaccinated for this study were defined as those having received one or more doses, labeled as "ever vaccinated" in the raw data, and unvaccinated were defined as those not having received any dose. Each month, I classified those who either died of any cause (all-cause mortality) or survived as either COVID-19-vaccinated or unvaccinated. Hence, each month, a person in the data was classified as (i) dead and vaccinated, (ii) alive and vaccinated, (iii) dead and unvaccinated, or (iv) alive and unvaccinated. I made similar classifications concerning mortality not involving COVID-19.

To exemplify how I classified the data, in Apr 21, the age-standardized all-cause mortality rate among "ever vaccinated", i.e., defined as vaccinated in this study, was 812.7 per 100,000 person-years, which were 2,124,523 that month.[9] The expression (812.7/100,000)*2,124,523 gives 17,266 estimated deaths in an estimated population of 25,494,276, which was reached by multiplying 2,124,523 by 12. I.e., the age-standardized all-cause mortality rate per 100,000 vaccinated in Apr 21 was 17,266 divided by 25,494,276 multiplied by 100,000, taking the value of 67.7. Similar estimations of all-cause mortality and mortality not involving COVID-19, were carried out each month for vaccinated and unvaccinated. (In the Notes section, I also present estimations *involving* COVID-19. I.e., estimations excluding mortality not involving COVID-19.) I carry out the exercise, assessing how many died or survived of a population in a given month, vaccinated or unvaccinated, to estimate as statistically correct standard errors as possible using logistic regression.

Models and data analysis procedure

The data were applied in logistic regressions using Stata 17.[23] I used the margin effect command to estimate mortality rates,[24] followed by OR estimations.

Initially, I (i) estimated monthly age-standardized all-cause mortality rate per 100,000 among COVID-19 vaccinated and unvaccinated. Then, I (ii) estimated mortality rate not involving COVID-19, and finally, using `xlincom`,[25] an extension of Stata's[23] `lincom` algorithm, I differentiated the results of (i) and (ii), and presented the results as ORs. Concerning OR estimations, I particularly explain and show in the Results section how the `xlincom` algorithm was used to differentiate log odds (the logarithm of the ORs) estimates. Also, I explain the substantial interpretation of differentiated estimates.

As all-cause mortality estimates include cases involving COVID-19, I show that differentiating those from estimates not involving COVID-19 cases can identify potentially genuine effects of vaccination between populations with potentially different health statuses at the outset. The following paragraph illuminates my argument.

Assuming a 60% higher all-cause mortality rate among unvaccinated compared to vaccinated, in the absence of other information, can have two explanations: (i) the unvaccinated have inferior health at the outset compared to the vaccinated or (ii) vaccination protects against mortality. In addition, there can be a combination of (i) and (ii). If the mortality not involving COVID-19 is also 60% higher among unvaccinated, explanation (i) has more validity. The reason is that COVID-19 vaccination unlikely protects against mortality not involving COVID-19.[26] Conversely if the mortality rate not involving COVID-19 is equal between unvaccinated and vaccinated, explanation (ii) has higher validity. The reason is that there is no other likely explanation than a vaccine effect as to why the all-cause mortality among unvaccinated compared to unvaccinated is higher than the mortality not involving COVID-19. Finally, if the mortality not involving COVID-19 is 20% higher among unvaccinated compared to the vaccinated, a combination of explanations (i) and (ii) has more validity. I.e., 20% higher mortality not involving COVID-19 among unvaccinated can be explained as inferior health status at the outset, while vaccination protection can explain 33% higher mortality among unvaccinated (((1.6/1.2)-1)*100). The explanations hinge on the assumption of non-systematic skewness in classifying false positives concerning mortality involving COVID-19 and false negatives concerning mortality not involving COVID-19, which I address in the Discussion. Further, the explanations hinge on the assumption that the mortality involving COVID-19 is not zero, which I address in Note 3.

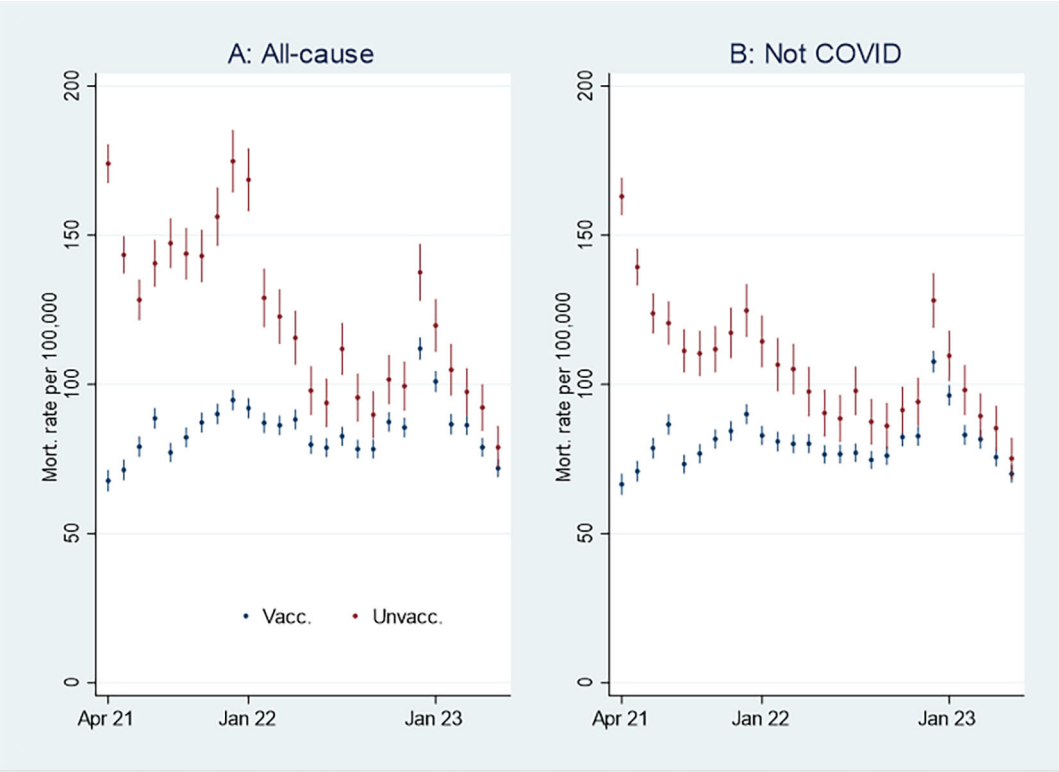

Figure 1. Monthly mortality rates per 100,000 with 95% CIs.

Results

I first present the empirical results of age-standardized mortality rates among vaccinated and unvaccinated ten years and older, shown in Figure 1. Aided by odds ratios (ORs) calculations shown in Figure 2, I then address the results' substantial interpretation.

Initial mortality rate analyses

Figure 1A shows that the monthly all-cause mortality rate, particularly at the beginning of the period, was higher among unvaccinated than vaccinated. The rate decreased among the unvaccinated, but among the vaccinated, it was relatively stable or had a slight increase. Consequently, the mortality among unvaccinated and vaccinated almost was tangent at the end of the period.

Figure 1B shows that the mortality rate not involving COVID-19 was similar to the all-cause mortality rate (Figure 1A), except for being lower among unvaccinated between the last half of 21 and the beginning of 22.

An interpretation of Figure 1A can be that the vaccinated had a temporal but declining mortality protection. However, as the pattern was similar concerning mortality not involving COVID-19 (Figure 1B), the difference can alternatively be attributed to unvaccinated having inferior health at the outset (cf. my explanation at the end of the Methods section, and which I further elaborate on below).

Odds ratio analyses

To learn more about the above issues, Figure 2A shows ORs of all-cause mortality and mortality not involving COVID-19 among unvaccinated compared to vaccinated as a reference group [1]. At the beginning of the period, the ORs of mortality among unvaccinated were about 2 and 2,5 compared to vaccinated, and significant (95% CIs). A similar pattern concerning all-cause mortality and mortality not involving COVID-19 indicates that vaccination did not have a preventive effect (as it logically cannot have a preventive effect against mortality not involving COVID-19, cf. my explanation at the end of the Methods section). However, between the last half of 21 and the beginning of 22, the ORs

[1]Vertical axes in Figure 2 are log-transformed using the natural logarithm.

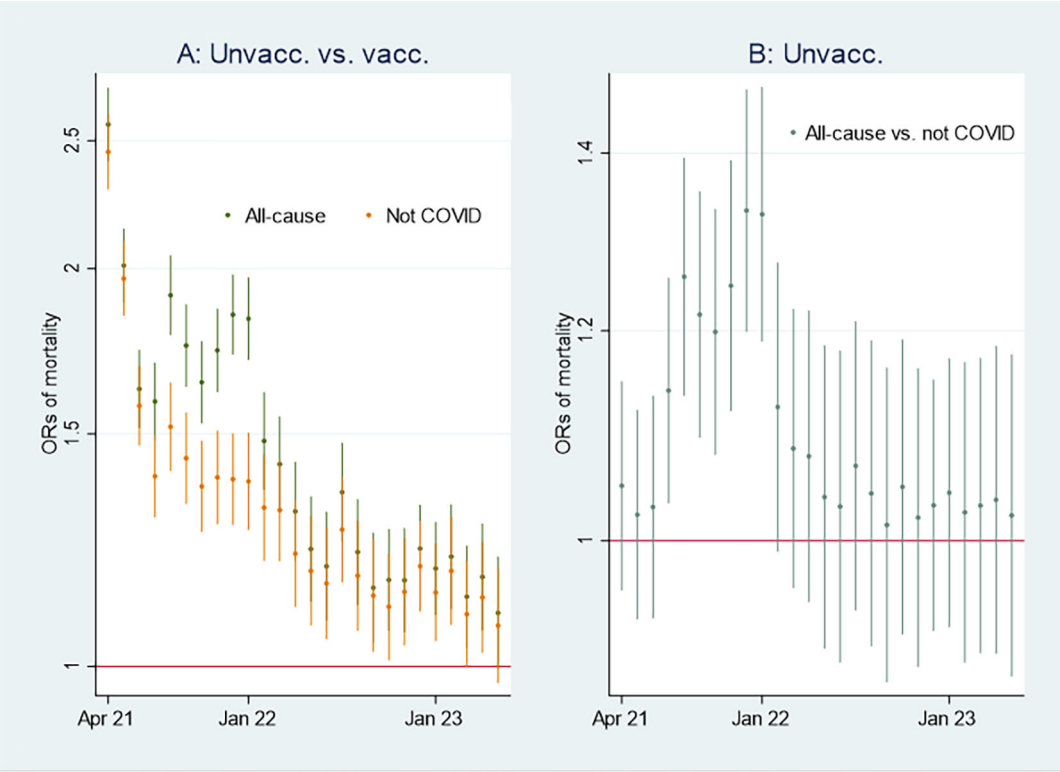

Figure 2. Monthly ORs of mortality with 95% CIs.

were higher for all-cause mortality than for mortality not involving COVID-19, which indicates a temporal preventive vaccine effect.

Figure 2B adds further information showing that ORs of all-cause mortality compared to mortality not involving COVID-19 between July 21 and Jan 22 were significant (95% CIs), with most values above 1.2. The results were reached by using Stata's[23] `xlincom` algorithm[25] first to differentiate the log odds (the logarithm of the ORs) of estimates reported in Figure 2A, and next generate the new ORs from the differentiated log odds [2]. Accordingly, a conclusion so far is that vaccinated were significantly (CIs 95%) protected between July 21 and Jan 22 [3].

Odds ratios and mortality rate analyses indicate declining health among vaccinated

Figure 3 shows that while mortality not involving COVID-19 decreased among unvaccinated compared to the first observation month, it was high among vaccinated [4]. The results reflect mortality rates in Figure 1B, which were almost

[2]Overlapping 95% CIs July 21 in Figure 2A appears inconsistent with significant OR (95% CI) for the same month in Figure 2B, but the issue is discussed by Knol, Pestman and Grobbee.[35]

[3]One may attribute the seemingly non-significant vaccine protection from Feb 22 (Figure 2B) to relatively low mortality involving COVID-19 during that period (Figure 5 below shows the data where A and B are identical, except for different scaling). The reason for the argument is that the effects in Figure 2B would be absent if the mortality involving COVID-19 approached zero (which explains the non-significant effect between Apr and Jun 21). However, among the vaccinated, the mortality rate in several months from Feb 22 was higher than in months between Jul 21 and Jan 22, countering that argument. Moreover, Figure 6 below shows that the ORs of mortality among unvaccinated (compared to vaccinated as a reference group) involving COVID-19 were down from about 10 at the beginning to about 2 at the end. It implies that not only was the mortality among unvaccinated not involving COVID-19 relatively low at the end (Figure 2A), but also the mortality involving COVID-19 (Figure 6). Taken together, the decrease in mortality involving COVID-19 largely occurred among the unvaccinated. The ORs in Figure 6 were significant (95% CIs) during the whole period, which can be due to (i) vaccine protection and (ii) unvaccinated having inferior health at the outset.[1] However, as the ORs were only about a fifth since Feb 22 compared to the first months, explanation (ii) is more likely during that period.

[4]The overall pattern among unvaccinated was similar both concerning all-cause mortality and mortality not involving COVID-19. Therefore, one cannot claim that the overall decrease in mortality not involving COVID-19 was due to mortality involving it.

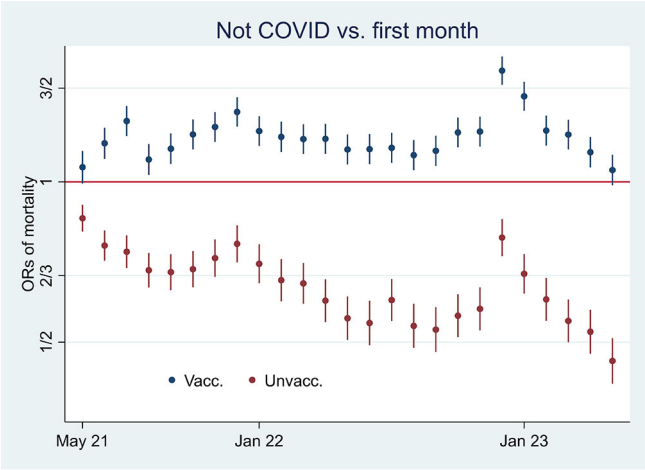

Figure 3. Monthly ORs of mortality with 95% CIs.

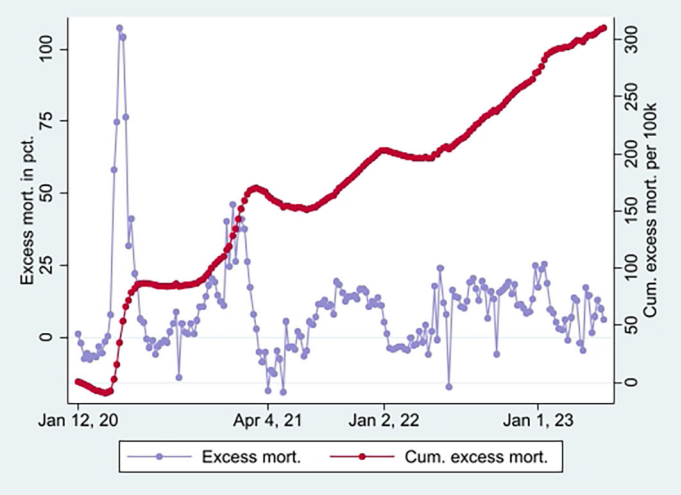

Figure 4. Weekly UK excess mortality in percent and cumulative excess mortality.

tangent at the end of the period. Also, they reflect the declining ORs of unvaccinated reported in Figure 2A, taking a non-significant value of a little over 1 at the end (95% CI). Hence, the data show a relatively high and relative increase in mortality not involving COVID-19 among vaccinated. An interpretation is that vaccination, despite temporary protection, increased mortality. Strengthening the interpretation was relatively high mortality among vaccinated not involving COVID-19 counterintuitively following periods of excess mortality (Figure 4) [5]. Further strengthening the interpretation was the relatively high mortality not involving COVID-19 among the vaccinated, corresponding with excess mortality during much of the same period (ibid.) [6].

[5]Assuming that the excess mortality among the unvaccinated segment before Apr 21 was *a* percent, taking a positive value, one may assume that it was *a*b* percent among the vaccinated segment, where $0<b<1$. One may assume $b<1$ because the vaccinated segment had relatively good health at the outset,[1] and one may assume $0<b$ because there were, nonetheless, people vulnerable to COVID-19 among them. I.e., *a*b* was lower than *a* but still higher than zero. According to the reasoning, one should expect a decline in mortality among vaccinated during the study period due to previous excess mortality, but not necessarily as marked as observed among unvaccinated. Alternatively, one may argue the opposite as among the vaccinated segment, "some very comorbid patients [in care homes] got vaccine side effects that probably accelerated an already progressing death process" (Ref. 36, p. 3 - my translation from Norwegian).

[6]Figure 4 shows weekly UK excess mortality in percent and cumulative excess mortality.[37] English monthly data[38] show similar patterns concerning excess mortality in percent. For an extensive review of all-cause mortality in England and Wales, please see Jones and Ponomarenko (2023).[39]

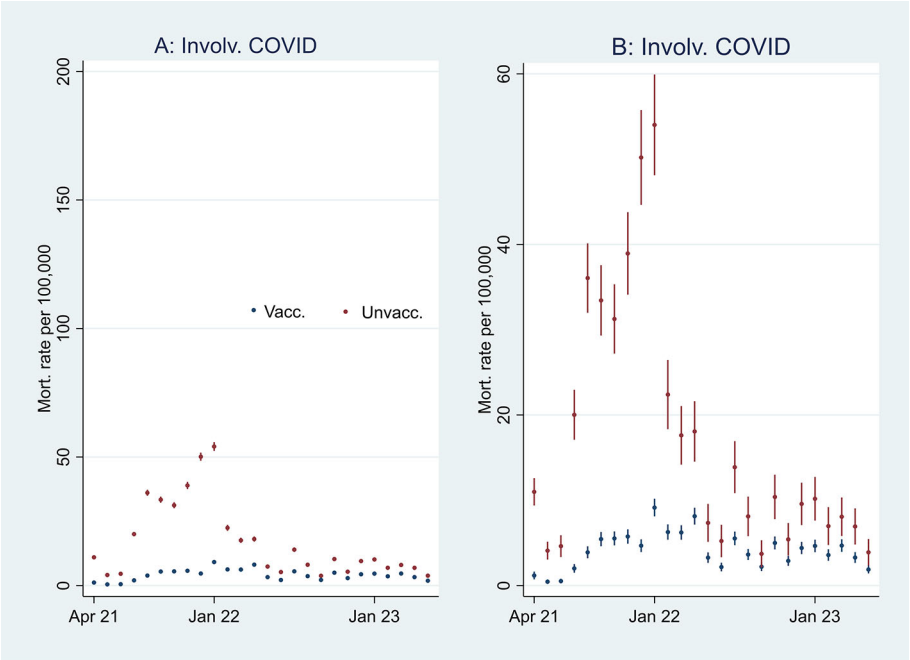

Figure 5. **Monthly mortality rates involving COVID-19 with 95% CIs.**

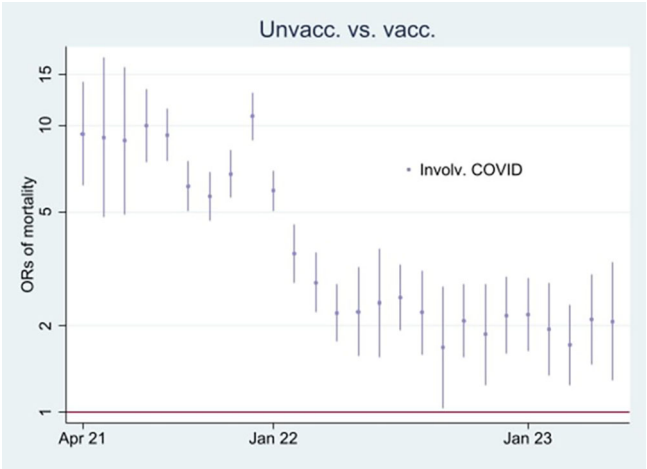

Figure 6. **Monthly ORs of mortality involving COVID-19 with 95% CIs.**

Discussion

This study found that COVID-19 vaccination protected against mortality, but the effect was temporal and declined after a few months. Also, the study found that COVID-19 vaccination may have increased mortality in a longer perspective.

As the study found that COVID-19 vaccination prevented mortality, it contributes to and aligns with other research showing similar effects.[11–17] As it found that the vaccine protection was temporal, it further contributes to and aligns with other research showing that it declines.[19] Finally, as the study found that COVID-19 may have increased mortality in a longer perspective, it contributes to and aligns with other research also showing that COVID-19 vaccination can have adverse effects[27–29] and increase mortality.[30]

In addition to contributing to the other research streams concerning the COVID-19 vaccine effect on mortality, the study's perhaps major contribution was to elaborate a useful tool to compare non-randomized groups in the absence of control variables, which even in their presence can even make statistical conclusions less, not more, accurate.[6] Thus, as most previous studies on the link between COVID-19 vaccination and mortality have been carried out in non-randomized

contexts and, accordingly, even in the presence of control variables exposed to challenges concerning validity, this study has illustrated and applied a useful tool to address those limitations. Moreover, I argue that the tool has general applicability as it can also be used in other research contexts.

Implications

Predicting outcomes of future potential pandemics is challenging,[31] highlighting the importance of high-quality healthcare sectors as they have been shown to prevent adverse outcomes.[32] Lessons from the COVID-19 pandemic have nonetheless taught that the "proportion of adults hospitalized with COVID-19 who experienced critical outcomes decreased with time",[33] but the statement does not undermine its challenge on the society at large and the health care sector in particular. This study has shown that vaccination, although having a temporal preventive effect, can even have adverse long-term consequences. Policymakers and the healthcare sector should be aware of these findings, considering that the effect of the COVID-19 vaccine is not necessarily genuinely positive.

Limitations and future research

During the study period, a share of people in the unvaccinated group were transferred to the vaccinated. Assuming they had inferior health status at the outset, it may explain the relative increase (decrease) in mortality among the vaccinated (unvaccinated). However, those who *remained* unvaccinated, on the contrary, had inferior health status at the outset,[1] making the above reasoning implausible. Ceteris paribus, one may even oppositely conclude that it would decrease (increase) relative mortality among vaccinated (unvaccinated) [7]. Since most elderly candidates had been offered vaccine before Apr 21,[1,34] I nonetheless assume the estimates were not substantially skewed over the study period, as relatively few people die in younger age cohorts.

The study's validity hinges on non-systematic skewness in classifying false positives concerning mortality involving COVID-19 and false negatives concerning mortality not involving COVID-19. However, I cannot see any substantial reason for substantial skewness in false positives and negatives between vaccinated and unvaccinated, but it may induce some cautiousness when interpreting the data.

The validity of the finding that vaccinated had significant protection between July 21 and Jan 22 hinges on non-systematic skewness in classifying false positives concerning mortality involving COVID-19 and false negatives concerning mortality not involving COVID-19. A relevant issue in this regard is that the English data excluded ICD10 death certificate codes U09.9 (Post-COVID condition, where the acute COVID had ended before the condition immediately causing death occurred) and U10.9 (Multisystem inflammatory syndrome associated with COVID-19) as criteria when classifying mortality involving COVID-19, but as this was the case only when the U07.1 (COVID-19, virus identified) or U07.2 (COVID-19, virus not identified) were *not* mentioned, I cannot see substantial skewness in false positives and negatives between vaccinated and unvaccinated. The potential limitation may nonetheless induce cautiousness when interpreting the data, which I encourage future research to address.

The validity of the finding that vaccinated had non-significant protection from Feb 22 also has limitations, as relatively low mortality involving COVID-19 can be an alternative explanation. However, in Note [3], I elaborate extensively on the issue, concluding that the alternative explanation is not very likely, but I nonetheless encourage cautiousness when interpreting the data.

This study included those ten years and older. I, therefore, encourage future research to analyze different age cohorts separately to assess how findings may converge or eventually diverge. As this study merely distinguished between those vaccinated and those who were not, I also encourage future research to distinguish between those who received one or more doses and different vaccine types, although it may be methodologically challenging.

Ethics and consent

Ethical approval and consent were not required.

Data availability

UK Office for National Statistics.[9] Deaths by vaccination status, England 2023: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsbyvaccinationstatusengland I used the dataset labeled "Deaths occurring between 1 April 2021 and 31 May 2023 edition of this dataset", Table 1: Unvaccinated and Ever vaccinated. The Methods section explains in detail how I modeled the data.

[7]People in England under 70 years old but clinically extremely vulnerable were prioritized vaccination with those aged between 70-74.[34] Hence, they were prioritized early.

References

1. **UK Office for National Statistics. Coronavirus (COVID-19) latest insights: Vaccines 2023.**
Reference Source

2. Lamot M, Kirbiš A: **Understanding Vaccine Hesitancy: A Comparison of Sociodemographic and Socioeconomic Predictors with Health Literacy Dimensions.** *Vaccines (Basel).* 2024; **12**(10).
PubMed Abstract | Publisher Full Text | Free Full Text

3. Meyer C, Goffe L, Antonopoulou V, *et al.*: **Using the precaution adoption process model to understand decision-making about the COVID-19 booster vaccine in England.** *Vaccine.* 2023; **41**(15): 2466–2475.
PubMed Abstract | Publisher Full Text | Free Full Text

4. King G, Nielsen R: **Why Propensity Scores Should Not Be Used for Matching.** *Polit. Anal.* 2019; **27**(4): 435–454.
Publisher Full Text

5. Wysocki AC, Lawson KM, Rhemtulla M: **Statistical Control Requires Causal Justification.** *Adv. Methods Pract. Psychol. Sci.* 2022; **5**(2): 25152459221095823.
Publisher Full Text

6. York R: **Control variables and causal inference: a question of balance.** *Int. J. Soc. Res. Methodol.* 2018; **21**(6): 675–684.
Publisher Full Text

7. Dahl J, Tapia G, Boas H, *et al.*: **COVID-19 mRNA-vaccination and all-cause mortality in the adult population in Norway during 2021-2023: a population-based cohort study.** *medRxiv.* 2024; 2024.2012.2015.24319058.

8. Statistikk FHI: Dødsfall etter kjønn, alder og dødsårsak, antall. Retrieved 24. januar.
Reference Source

9. UK Office for National Statistics: **Deaths by vaccination status, England 2023.**
Reference Source

10. Wekking D, Senevirathne TH, Pearce JL, *et al.*: **The impact of COVID-19 on cancer patients.** *Cytokine Growth Factor Rev.* 2024; **75**: 110–118.
Publisher Full Text

11. Halford F, Yates K, Clare T, *et al.*: **Temporal changes to adult case fatality risk of COVID-19 after vaccination in England between May 2020 and February 2022: a national surveillance study.** *J. R. Soc. Med.* 2023; **117**(6): 202–211.
PubMed Abstract | Publisher Full Text | Free Full Text

12. Harrison C, Frain S, Jalalinajafabadi F, *et al.*: **The impact of COVID-19 vaccination on patients with congenital heart disease in England: a case-control study.** *Heart.* 2024; **110**(23): 1372–1380.
PubMed Abstract | Publisher Full Text | Free Full Text

13. Kirwan PD, Charlett A, Birrell P, *et al.*: **Trends in COVID-19 hospital outcomes in England before and after vaccine introduction, a cohort study.** *Nat. Commun.* 2022; **13**(1): 4834.
PubMed Abstract | Publisher Full Text | Free Full Text

14. Lopez-Doriga Ruiz P, Gunnes N, Michael Gran J, *et al.*: **Short-term safety of COVID-19 mRNA vaccines with respect to all-cause mortality in the older population in Norway.** *Vaccine.* 2023; **41**(2): 323–332.
PubMed Abstract | Publisher Full Text | Free Full Text

15. Haas EJ, Angulo FJ, McLaughlin JM, *et al.*: **Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data.** *Lancet.* 2021; **397**(10287): 1819–1829.
PubMed Abstract | Publisher Full Text | Free Full Text

16. Bernal JL, Andrews N, Gower C, *et al.*: **Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study.** *BMJ-Br. Med. J.* 2021; **373**.

17. Watson OJ, Barnsley G, Toor J, *et al.*: **Global impact of the first year of COVID-19 vaccination: a mathematical modelling study.** *Lancet Infect. Dis.* 2022; **22**: 1293–1302.
PubMed Abstract | Publisher Full Text | Free Full Text

18. Mink S, Saely CH, Leiherer A, *et al.*: **Antibody levels versus vaccination status in the outcome of older adults with COVID-19.** *JCI Insight.* 2024; **9**(20).
PubMed Abstract | Publisher Full Text | Free Full Text

19. Nordstrom P, Ballin M, Nordstrom A: **Risk of infection, hospitalisation, and death up to 9 months after a second dose of COVID-19 vaccine: a retrospective, total population cohort study in Sweden.** *Lancet.* 2022; **399**(10327): 814–823.
PubMed Abstract | Publisher Full Text | Free Full Text

20. Coccia M: **COVID-19 Vaccination is not a Sufficient Public Policy to face Crisis Management of next Pandemic Threats.** *Public Organ. Rev.* 2023; **23**(4): 1353–1367.
Publisher Full Text

21. UK Office for National Statistics: **Weekly COVID-19 age-standardised mortality rates by vaccination status, England: methodology 2021.**
Reference Source

22. UK Office for National Statistics: **Impact of registration delays on mortality statistics in England and Wales: 2022 2024.**
Reference Source

23. *StataCorp. Version 17.* College Station, TX: StataCorp LP; 2021.

24. Williams R: **Using the margins command to estimate and interpret adjusted predictions and marginal effects.** *Stata J.* 2012; **12**(2): 308–331.
Publisher Full Text

25. Wakker W: **XLINCOM: Stata module to estimate multiple linear combinations of parameters.** 2023.

26. Alessandria M, Malatesta G, Di Palmo G, *et al.*: **All-cause mortality according to COVID-19 vaccination status: An analysis of the UK office for National statistics public data.** *F1000Res.* 2024; **13**: 886.
Publisher Full Text

27. Fraiman J, Erviti J, Jones M, *et al.*: **Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults.** *Vaccine.* 2022; **40**(40): 5798–5805.
PubMed Abstract | Publisher Full Text | Free Full Text

28. Mostert S, Hoogland M, Huibers M, *et al.*: **Excess mortality across countries in the Western World since the COVID-19 pandemic: 'Our World in Data' estimates of January 2020 to December 2022.** *BMJ Public Health.* 2024; **2**(1): e000282.
Publisher Full Text

29. Faksova K, Walsh D, Jiang Y, *et al.*: **COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals.** *Vaccine.* 2024; **42**(9): 2200–2211.
PubMed Abstract | Publisher Full Text

30. Aarstad J: **Deaths among young people in England increased significantly in 10 of 11 weeks after COVID-19 vaccination and doubled in three.** *EXCLI J.* 2024; **23**: 908–911.
PubMed Abstract | Publisher Full Text

31. Coccia M: **Sources, diffusion and prediction in COVID-19 pandemic: lessons learned to face next health emergency.** *AIMS Public Health.* 2023; **10**(1): 145–168.
PubMed Abstract | Publisher Full Text | Free Full Text

32. Coccia M, Benati I: **Effective health systems facing pandemic crisis: lessons from COVID-19 in Europe for next emergencies.** *Int. J. Health Gov.* 2024; **29**(2): 89–111.
Publisher Full Text

33. Griggs EP, Mitchell PK, Lazariu V, *et al.*: **Clinical Epidemiology and Risk Factors for Critical Outcomes Among Vaccinated and Unvaccinated Adults Hospitalized With COVID-19—VISION Network, 10 States, June 2021–March 2023.** *Clin. Infect. Dis.* 2023; **78**(2): 338–348.
PubMed Abstract | Publisher Full Text | Free Full Text

34. UK Office for National Statistics: **UK COVID-19 vaccines delivery plan 2021.**
Reference Source

35. Knol MJ, Pestman WR, Grobbee DE: **The (mis) use of overlap of confidence intervals to assess effect modification.** *Eur. J. Epidemiol.* 2011; **26**(4): 253–254.
PubMed Abstract | Publisher Full Text | Free Full Text

36. Wyller TB, Kittang BR, Ranhoff AH, *et al.*: **Dødsfall i sykehjem etter covid-19-vaksine.** *Tidsskr. Nor. Legeforen.* 2021; **141**(10): 1–8.
Publisher Full Text

37. Our World in Data: **Coronavirus (COVID-19) Vaccinations 2024.**
Reference Source

38. UK Office for National Statistics: **Excess mortality within England: 2023 data - statistical commentary 2024.**

39. Jones RP, Ponomarenko A: **COVID-19-Related Age Profiles for SARS-CoV-2 Variants in England and Wales and States of the USA (2020 to 2022): Impact on All-Cause Mortality.** *Infect. Dis. Rep.* 2023; **15**(5): 600–634.
PubMed Abstract | Publisher Full Text | Reference Source

Open Peer Review

Current Peer Review Status: ✔ ✘

Version 2

Reviewer Report 11 April 2025

https://doi.org/10.5256/f1000research.179445.r375385

✔ **Mario Coccia**
CNR -- National Research Council of Italy, Collegio Carlo Alberto, Torino, Italy

I have read thoroughly the revised version of paper.
The authors have done considerable additional work, and addressed all concerns and criticisms in the revised manuscript, which I believe has improved substantially in the theoretical framework, study design and discussion of results.
Now, the paper is OK and has a good level to show interesting results to scholars and/or policymakers interested in these topics.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: COVID-19 vaccination; health policies

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 05 March 2025

https://doi.org/10.5256/f1000research.176950.r368449

✘ **Gregory Barnsley**
London School of Hygiene and Tropical Medicine, London, UK

This report investigates the impact of COVID-19 vaccination on mortality in England between mid-2021 and mid-2023. The author observes that the age-stratified non-COVID mortality rates in the vaccinated population increase or remain stable over this period, whilst those in the unvaccinated population decrease. The author states that this observation is consistent with a vaccination-related decline in health. The author also observes periods where the COVID-19-related mortality rates in the unvaccinated are higher than those in the vaccinated, potentially showing a protective effect of vaccination against COVID-19-related disease. However, the author posits an alternative theory based on the unvaccinated population being generally more "unhealthy" (i.e. healthy vaccinee effect) as evidenced by higher rates of all-cause and non-covid related mortality in the unvaccinated population at the study start. The author claims that their approach can adjust for unobserved variables that explain the differences in health between the two comparison groups.
The author has mixed his methods/reasoning into the report's introduction and results sections. It would be better to explore the approach in the methods section and highlight any potential limitations. The results should describe any major observations and the theorising should be limited to the discussion. Alternatively, the author could be more explicit about the theories he wants to test in the methods section; either way, the presentation should be improved. In Figure 3, the author should highlight how this relates to the other figures by overlaying the data or plotting on the same time scale.
A third of the methods section describes how the author converted the ONS's age-stratified mortality rates (per 10000 person-years) to "mortality probability." The author should know that this process does not calculate a probability and rescales the given mortality rates. It is the equivalent of dividing the age-stratified mortality rates by 12*10000, calculating the age-stratified mortality rate per person-month. The report should compare the ONS rates as these are already at a more sensible scale.
The report should also consider explicitly how the ONS definition of COVID-19-related death would impact these results. Excluding ICD10 codes U09.9 and U10.9 as COVID-related could bias these findings. The author should clearly explain the reasoning around how the assumption that *COVID-19 vaccination does not prevent non-COVID-19 deaths* supports the theory that *the difference in COVID-19 death rates (between unvaccinated and vaccinated) is explainable by inferior health at the onset*.
The report does not sufficiently consider alternative explanations for the observed data. While the healthy-vaccinee effect might be strong in clinical trials (since these tend to recruit healthy volunteers), this effect might not be so strong in mass vaccination campaigns, particularly ones like COVID-19 that specifically target vulnerable populations. If we assume that this effect does explain the initial difference in non-COVID-19 mortality rates and that many of the unvaccinated (but not all, i.e. the vaccine-hesitant) are acutely ill, then we would expect to see a trend towards parity in the non-covid mortality rates of the two. As the acutely ill expire (or recover and get vaccinated), the mortality rates in the non-vaccinated would reduce in future months. This trend would be strong if the vulnerable and very elderly were targeted first for vaccination as they are at higher risk of becoming ill later (thus contributing to the mortality rate in the vaccinated population). This is to say nothing about the countless other confounding variables that could explain temporal differences in mortality across these groups, such as different temporal vaccine uptake in different ethnic or SES groups and different rates of adherence to restrictions.
These alternative theories do not disprove the theory put forward in this report. However, they highlight that the methodology here cannot convincingly adjust for the potential health differences between the two comparison groups. While improper adjustment for confounding can increase bias, that is no excuse to ignore potential confounding. This report must focus on the actual observation it is theorising around (i.e. a decrease in the non-covid health gap between the

vaccinated and the unvaccinated) and more convincingly explore/counter alternative explanations and consider sensitivities to their results.
In conclusion, this report needs considerable reworking regarding its statistical and epidemiological content.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
No

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology and mathematic modelling. I am not a demographer so I cannot comment on any particularities of looking at mortality rates.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 14 Mar 2025

Jarle Aarstad

Dear Referee 2,

I highly appreciate your time and efforts in giving constructive feedback on my previous version of the paper. In the following, you will read how I have addressed your comments. For your information, I have also made minor corrections and editions in the text to improve accuracy and readability. Hopefully, the revised version will be uploaded shortly.

I look forward to hearing from you.

Sincerely,

The author.

This report investigates the impact of COVID-19 vaccination on mortality in England between mid-2021 and mid-2023. The author observes that the age-stratified non-COVID mortality rates in the vaccinated population increase or remain stable over this period, whilst those in the unvaccinated population decrease. The author states that this observation is consistent with a vaccination-related decline in health. The author also observes periods where the COVID-19-related mortality rates in the unvaccinated are higher than those in the vaccinated, potentially showing a protective effect of vaccination against COVID-19-related disease. However, the author posits an alternative theory based on the unvaccinated population being generally more "unhealthy" (i.e. healthy vaccinee effect) as evidenced by higher rates of all-cause and non-covid related mortality in the unvaccinated population at the study start. The author claims that their approach can adjust for unobserved variables that explain the differences in health between the two comparison groups.

Response: Below, I will address the particular issues you have raised in detail.

The author has mixed his methods/reasoning into the report's introduction and results sections. It would be better to explore the approach in the methods section and highlight any potential limitations.

Response: I agree with you, and in the revised version, I have removed the methodological approach from the Introduction, but mention the following: “To address the research gap [explained above in the Introduction], using English data covering 26 months from Apr 21 to May 23, 5 I elaborate an achievable approach by comparing all-cause mortality among COVID-19 vaccinated and unvaccinated with mortality not involving COVID-19. In the Methods section, I explain it in full detail.”
Also, I highlight more extensively the potential limitations of the approach in the latter part of the Discussion, writing as follows: “The validity of the finding that vaccinated had significant protection between July 21 and Jan 22 hinges on non-systematic skewness in classifying false positives concerning mortality involving COVID-19 and false negatives concerning mortality not involving COVID-19. A relevant issue in this regard is that the English data excluded ICD10 death certificate codes U09.9 (Post-COVID condition, where the acute COVID had ended before the condition immediately causing death occurred) and U10.9 (Multisystem inflammatory syndrome associated with COVID-19) as criteria when classifying mortality involving COVID-19, but as this was the case only when the U07.1 (COVID-19, virus identified) or U07.2 (COVID-19, virus not identified) were *not* mentioned, I cannot see substantial skewness in false positives and negatives between vaccinated and unvaccinated. The potential limitation may nonetheless induce cautiousness when interpreting the data, which I encourage future research to address. The validity of the finding that vaccinated had non-significant protection from Feb 22 also has limitations, as relatively low mortality involving COVID-19 can be an alternative explanation. However, in Note [3], I elaborate extensively on the issue, concluding that the alternative explanation is not very likely, but I nonetheless encourage cautiousness when interpreting the data.”
Please note that the revised text is an extension and further elaboration of the previous text

addressing limitations.
Please also see #4, which addresses revisions I have carried out in the Introduction by following advice from the other referee.

The results should describe any major observations and the theorising should be limited to the discussion. Alternatively, the author could be more explicit about the theories he wants to test in the methods section; either way, the presentation should be improved.

Response: In the revision, I have added a paragraph at the end of the Methods section where I argue in detail how distinctions between all-cause mortality and mortality not involving COVID-19 among vaccinated and unvaccinated, absent of control variables in populations with potentially different health statuses at the outset, can assess eventually genuine health effects. Please see #18. I agree with the referee that extensive discussions of empirical findings should not be conducted in the Results section, but presenting them without any interpretation will make it more difficult for the reader to interpret the text, I argue. Therefore, I point to findings, and briefly explain their potential meaning. In the revision, I have excluded some figures and included them in the Notes section (please see #6). As such, I have aimed to reduce the complexity of presenting the data and hope that the results are more interpretable. Also, a couple of places in the Results section, I refer to my explanation at the end of the Methods section.

In Figure 3, the author should highlight how this relates to the other figures by overlaying the data or plotting on the same time scale.

Response: I agree with your point, but unfortunately, it is challenging to carry out as the time scales are different; the English data I apply in my study use monthly observations, while the Our World in Data uses weekly ones. I find it challenging to convert the different time scales into one, as there is no distinct overlap in weekly and monthly observations. Moreover, in the revision, I have edited the text in the Results section and Abstract writing, “Further strengthening the interpretation was the relatively high mortality not involving COVID-19 among the vaccinated, corresponding with excess mortality during much of the same period”, as it more precisely reflects the genuine interpretation of the data.

A third of the methods section describes how the author converted the ONS's age-stratified mortality rates (per 10000 person-years) to "mortality probability." The author should know that this process does not calculate a probability and rescales the given mortality rates. It is the equivalent of dividing the age-stratified mortality rates by 12*10000, calculating the age-stratified mortality rate per person-month. The report should compare the ONS rates as these are already at a more sensible scale.

Response: In the revision, I use the term monthly mortality rate per 100,000. (Of course, I could have used a yearly rate, but in my opinion, a monthly rate is more logical in the current context since I analyze monthly data.) I carry out the exercise, as I do, to assess how many died or survived of a population in a given month, vaccinated or unvaccinated, to estimate as statistically correct standard errors as possible using logistic regression.

The report should also consider explicitly how the ONS definition of COVID-19-related death would impact these results. Excluding ICD10 codes U09.9 and U10.9 as COVID-related could bias these findings.

Response: Thanks for this comment. In the revised version, I address the issue in the revision writing as follows: "The validity of the finding that vaccinated had significant protection between July 21 and Jan 22 hinges on non-systematic skewness in classifying false positives concerning mortality involving COVID-19 and false negatives concerning mortality not involving COVID-19. A relevant issue in this regard is that the English data excluded ICD10 death certificate codes U09.9 (Post-COVID condition, where the acute COVID had ended before the condition immediately causing death occurred) and U10.9 (Multisystem inflammatory syndrome associated with COVID-19) as criteria when classifying mortality involving COVID-19, but as this was the case only when the U07.1 (COVID-19, virus identified) or U07.2 (COVID-19, virus not identified) were *not* mentioned, I cannot see substantial skewness in false positives and negatives between vaccinated and unvaccinated. The potential limitation may nonetheless induce cautiousness when interpreting the data, which I encourage future research to address."

The author should clearly explain the reasoning around how the assumption that *COVID-19 vaccination does not prevent non-COVID-19 deaths* supports the theory that *the difference in COVID-19 death rates (between unvaccinated and vaccinated) is explainable by inferior health at the onset*.

Response: At the end of the Methods section, I write as follows in the revision: "Assuming a 60% higher all-cause mortality rate among unvaccinated compared to vaccinated, in the absence of other information, can have two explanations: (i) the unvaccinated have inferior health at the outset compared to the vaccinated or (ii) vaccination protects against mortality. In addition, there can be a combination of (i) and (ii). If the mortality not involving COVID-19 is also 60% higher among unvaccinated, explanation (i) has more validity. The reason is that COVID-19 vaccination unlikely protects against mortality not involving COVID-19. [16] Conversely, if the mortality rate not involving COVID-19 is equal between unvaccinated and vaccinated, explanation (ii) has higher validity. The reason is that there is no other likely explanation than a vaccine effect as to why the all-cause mortality among unvaccinated compared to unvaccinated is higher than the mortality not involving COVID-19. Finally, if the mortality not involving COVID-19 is 20% higher among unvaccinated compared to the vaccinated, a combination of explanations (i) and (ii) has more validity. I.e., 20% higher mortality not involving COVID-19 among unvaccinated can be explained as inferior health status at the outset, while vaccination protection can explain 33% higher mortality among unvaccinated (((1.6/1.2)-1)*100). The explanations hinge on the assumption of non-systematic skewness in classifying false positives concerning mortality involving COVID-19 and false negatives concerning mortality not involving COVID-19, which I address in the Discussion. Further, the explanations hinge on the assumption that the mortality involving COVID-19 is not zero, which I address in Note 3."

The report does not sufficiently consider alternative explanations for the observed data. While the healthy-vaccinee effect might be strong in clinical trials (since these tend to recruit healthy volunteers), this effect might not be so strong in mass

vaccination campaigns, particularly ones like COVID-19 that specifically target vulnerable populations. If we assume that this effect does explain the initial difference in non-COVID-19 mortality rates and that many of the unvaccinated (but not all, i.e. the vaccine-hesitant) are acutely ill, then we would expect to see a trend towards parity in the non-covid mortality rates of the two. As the acutely ill expire (or recover and get vaccinated), the mortality rates in the non-vaccinated would reduce in future months. This trend would be strong if the vulnerable and very elderly were targeted first for vaccination as they are at higher risk of becoming ill later (thus contributing to the mortality rate in the vaccinated population). This is to say nothing about the countless other confounding variables that could explain temporal differences in mortality across these groups, such as different temporal vaccine uptake in different ethnic or SES groups and different rates of adherence to restrictions. These alternative theories do not disprove the theory put forward in this report. However, they highlight that the methodology here cannot convincingly adjust for the potential health differences between the two comparison groups. While improper adjustment for confounding can increase bias, that is no excuse to ignore potential confounding. This report must focus on the actual observation it is theorising around (i.e. a decrease in the non-covid health gap between the vaccinated and the unvaccinated) and more convincingly explore/counter alternative explanations and consider sensitivities to their results.

Response: You mention that "[w]hile the healthy-vaccinee effect might be strong in clinical trials (since these tend to recruit healthy volunteers), this effect might not be so strong in mass vaccination campaigns, particularly ones like COVID-19 that specifically target vulnerable populations." Considering that statement, I cannot see that it aligns with the UK Office for National Statistics stating that "rates for COVID-19 unvaccinated adults in England "were higher for Black Caribbean, Black African and White Other ethnic groups. Rates were also higher for those living in deprived areas, who have never worked or are long-term unemployed, who are limited a lot by a disability, … or who are male." Nor does it align with vaccine hesitancy (to which I refer in the revision), and Norwegian data showing much higher mortality among young unvaccinated in a population where practically zero young people died of COVID-19. Also, in the revised version, I explain in detail why vaccination cannot explain the difference in mortality not involving COVID-19. From my reading off the comment, it seems that the referee points to the dynamic of the group of people being transferred from the group of unvaccinated to the group of vaccinated during the time studied. That is definitely a relevant issue, which I have addressed in the Discussion, writing as follows (the text in the paper includes relevant references): "During the study period, a share of people in the unvaccinated group were transferred to the vaccinated. Assuming they had inferior health status at the outset, it may explain the relative increase (decrease) in mortality among the vaccinated (unvaccinated). However, those who remained unvaccinated, on the contrary, had inferior health status at the outset, making the above reasoning implausible. Ceteris paribus, one may even oppositely conclude that it would decrease (increase) relative mortality among vaccinated (unvaccinated). (In Note 7, I add: "People in England under 70 years old but clinically extremely vulnerable were prioritized vaccination with those aged between 70-74. Hence, they were prioritized early.") Since most elderly candidates had been offered vaccine before Apr 21, I nonetheless assume the estimates were not substantially skewed over the study period, as relatively few people die

in younger age cohorts."

In conclusion, this report needs considerable reworking regarding its statistical and epidemiological content.

Response: Above, you will read how I have addressed the issues raised.

Competing Interests: No competing interests were disclosed.

Reviewer Report 13 February 2025

https://doi.org/10.5256/f1000research.176950.r363090

Mario Coccia
CNR -- National Research Council of Italy, Collegio Carlo Alberto, Torino, Italy

The temporal protection and declining health of the COVID-19 vaccinated in England: A 26-month comparison of the mortality involving and not involving COVID-19 among vaccinated vs. unvaccinated

The topics of this paper is interesting but the structure and content must be revised, and results have to be explained by authors.

Title has to be shorter, indicating the period under study.

Abstract has to clarify the goal and health policy implications to face the next pandemics similar to COVID-19.

Introduction has to better clarify the research questions of this study, indicating the gap presents in literature that this study endeavors to cover, and provide more theoretical background about these topics. After that authors can focus on the topics of this study to provide a correct analysis for fruitful discussion (See suggested readings that must be all read and used in the text).

The methods of this study is not clear. The section of Materials and methods must be re-structured with the following three sections:
- Sample and data
- Measures of variables
- Models and Data analysis procedure.

Results.
Figure 1 and 2 are not clear for readers. First clarify the measure on y-axis. Second I suggest merging some of them. The legend is not clear and has to be put for all graphs. Lines are better than dots, using continuous vs. dotted lines for vaccinated vs. unvaccinated. In Figure 1, C1 and C2 have the same title...
Insert a vertical line in figures to divide the COVID and post-covid period to be clear.
Frankly these figures are messy. Do other better and clearer otherwise the information about results are useless.
The paper has a lot of figures/graphs (in Figure 1 and 2) that are difficult to digest, some of them can be put in appendix and inserting in the text the most important ones to improve the readability...

Discussion.
First, authors have to synthesize the main results in a simple table to be clear for readers and then show what this study adds compared to other studies.
Although the Results section provides a detailed description of the data collected and analyzed, there needs to be a more critical synthesis and comparison of the findings with the literature. Better comment on whether the results were expected for each set of findings; go into greater depth to explain unexpected findings. If appropriate, note any unusual or unanticipated patterns or trends that emerged from your results (directly in figures) and explain their meaning concerning the research problem under study here.
Unvaccinated have higher all causes of mortality during the COVID-19 because there was some restrictions to make diagnostics or to have access to hospitals?
Moreover, the higher mortality of vaccinated can be due to the effects of vaccines on immune system that has created some disorder to face diseases.

Moreover, either compare your results with the findings from other studies or use the studies to support results. Insert a claim for how the results can be applied more generally, beyond England.
Authors have to describe lessons learned, proposing recommendations that can help improve a next pandemic crises, or highlighting best practices.

The conclusion is better as an autonomous section. Conclusion has not to be a summary, but authors have to focus on manifold limitation. In addition, now the Conclusion does not adequately discuss the theoretical and managerial implications of the study. Discuss better how a gap in literature has been addressed. Make sure you clarify: 1) Theoretical Implications, 2) Policy Implications based on health systems improvement and good governance to face next emergencies, and 3) Future Research.

Overall, then, the paper is interesting, but Theoretical framework is weak, and some results create confusion... structure of the paper has to be improved; study design, discussion and presentation of results have to be clarified using suggested comments.

Suggested readings of relevant papers that have to be read and used to improve the paper.

Harrison, C.,et al., 2024 [1]

Meyer, C.et al., 2023.[2]

Coccia M. 2023. [3]

Halford, F., et al., 2024. [4]

Coccia, M. and Benati, I. (2024), [5]

Griggs, E.P., et., 2024. [6]

Mink, S., et al., 2024. [7]

Coccia M. 2022. [8]

Jones, R.P., Ponomarenko, A. 2023. [9]

Kirwan, P.D., et al., 2022. [10]

Wekking, D., et al., 2024. [11]

References

1. Harrison C, Frain S, Jalalinajafabadi F, Williams SG, et al.: The impact of COVID-19 vaccination on patients with congenital heart disease in England: a case-control study.*Heart*. 2024; **110** (23): 1372-1380 PubMed Abstract | Publisher Full Text
2. Meyer C, Goffe L, Antonopoulou V, Graham F, et al.: Using the precaution adoption process model to understand decision-making about the COVID-19 booster vaccine in England.*Vaccine*. 2023; **41** (15): 2466-2475 PubMed Abstract | Publisher Full Text
3. Coccia M: Sources, diffusion and prediction in COVID-19 pandemic: lessons learned to face next health emergency.*AIMS Public Health*. 2023; **10** (1): 145-168 PubMed Abstract | Publisher Full Text
4. Halford F, Yates K, Clare T, Lopez-Bernal J, et al.: Temporal changes to adult case fatality risk of COVID-19 after vaccination in England between May 2020 and February 2022: a national surveillance study.*J R Soc Med*. 2024; **117** (6): 202-211 PubMed Abstract | Publisher Full Text
5. Coccia M, Benati I: Effective health systems facing pandemic crisis: lessons from COVID-19 in Europe for next emergencies. *International Journal of Health Governance*. 2024; **29** (2): 89-111 Publisher Full Text
6. Griggs EP, Mitchell PK, Lazariu V, Gaglani M, et al.: Clinical Epidemiology and Risk Factors for Critical Outcomes Among Vaccinated and Unvaccinated Adults Hospitalized With COVID-19-VISION Network, 10 States, June 2021-March 2023.*Clin Infect Dis*. 2024; **78** (2): 338-348 PubMed Abstract | Publisher Full Text
7. Mink S, Saely CH, Leiherer A, Reimann P, et al.: Antibody levels versus vaccination status in the outcome of older adults with COVID-19.*JCI Insight*. 2024; **9** (20). PubMed Abstract | Publisher Full Text
8. Coccia M: COVID-19 Vaccination is not a Sufficient Public Policy to face Crisis Management of next Pandemic Threats. *Public Organization Review*. 2023; **23** (4): 1353-1367 Publisher Full Text
9. Jones RP, Ponomarenko A: COVID-19-Related Age Profiles for SARS-CoV-2 Variants in England and Wales and States of the USA (2020 to 2022): Impact on All-Cause Mortality.*Infect Dis Rep*. 2023; **15** (5): 600-634 PubMed Abstract | Publisher Full Text
10. Kirwan PD, Charlett A, Birrell P, Elgohari S, et al.: Trends in COVID-19 hospital outcomes in England before and after vaccine introduction, a cohort study.*Nat Commun*. 2022; **13** (1): 4834

PubMed Abstract | Publisher Full Text
11. Wekking D, Senevirathne TH, Pearce JL, Aiello M, et al.: The impact of COVID-19 on cancer patients.*Cytokine Growth Factor Rev*. 2024; **75**: 110-118 PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: COVID-19 vaccination; health policies

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 14 Mar 2025

Jarle Aarstad

Dear Referee 1,

I highly appreciate your time and efforts in giving constructive feedback on my previous version of the paper. In the following, you will read how I have addressed your comments. For your information, I have also made minor corrections and editions in the text to improve accuracy and readability. Hopefully, the revised version will be uploaded shortly.

I look forward to hearing from you.

Sincerely,

The author.

1. The temporal protection and declining health of the COVID-19 vaccinated in England: A 26-month comparison of the mortality involving and not involving COVID-19 among vaccinated vs. unvaccinated

The topics of this paper is interesting but the structure and content must be revised, and results have to be explained by authors.

Response: Thanks for this overall positive feedback. Below, you will read how I have addressed each of your comments.

2. Title has to be shorter, indicating the period under study.

Response: In the revision, the title is shortened and indicates the period under study. It reads as follows: "Mortality involving and not involving COVID-19 among vaccinated vs. unvaccinated in England between Apr 21 and May 23"

3. Abstract has to clarify the goal and health policy implications to face the next pandemics similar to COVID-19.

Response: In the revision, I added the following sentences at the end of the Abstract: "An implication of the study, which particularly has relevance for future pandemics, is that COVID-19 vaccinated may have a limited time window of protection and can even be exposed to detrimental health consequences. The pattern should be followed up over an extended period in future research. Also, future research should examine different age groups, vaccination types, and the number of doses given."

4. Introduction has to better clarify the research questions of this study, indicating the gap presents in literature that this study endeavors to cover, and provide more theoretical background about these topics. After that authors can focus on the topics of this study to provide a correct analysis for fruitful discussion (See suggested readings that must be all read and used in the text).

Response: The Introduction has been substantially revised. The initial part of the first paragraph is largely unaltered, except that I address the concept of vaccine hesitancy and also include relevant references. The last sentences of the first paragraph, on the other hand, are novel, illustrating with Norwegian data that (1) COVID-19 vaccinated and unvaccinated have different health status at the outset and (2) including control variables can make estimates less, not more, accurate. I believe that the above issues better address the study's theoretical background concerning previous relevant research and substantial argument. The second paragraph addresses the study's research gap. Also, I explain there that I will empirically study English data covering 26 months from Apr 21 to May 23, but following your recommendation, I just briefly mention the methodological approach and emphasize that I will explain it in detail in the Methods section. In the third paragraph, I explicitly address the study's research question and major contribution. In the Introduction's final paragraph, I added more references concerning the literature on COVID-19 vaccination and outcomes. Finally, I conclude the Introduction by stating the following: "Applying my approach to the English data, I particularly contribute to the

research on the link between COVID-19 vaccination and mortality, as most previous studies have been carried out in non-randomized contexts and, accordingly, even in the presence of control variables, exposed to challenges concerning validity addressed above."

5. The methods of this study is not clear. The section of Materials and methods must be re-structured with the following three sections:
- Sample and data
- Measures of variables
- Models and Data analysis procedure.

Response: In the revision, I have followed your recommendation. The new subsections include extended and hopefully substantially improved information about the study's methodology concerning the requested issues. Please also see #16 and #18.

6. Results.
Figure 1 and 2 are not clear for readers. First clarify the measure on y-axis. Second I suggest merging some of them. The legend is not clear and has to be put for all graphs. Lines are better than dots, using continuous vs. dotted lines for vaccinated vs. unvaccinated. In Figure 1, C1 and C2 have the same title...
Insert a vertical line in figures to divide the COVID and post-covid period to be clear.
Frankly these figures are messy. Do other better and clearer otherwise the information about results are useless.
The paper has a lot of figures/graphs (in Figure 1 and 2) that are difficult to digest, some of them can be put in appendix and inserting in the text the most important ones to improve the readability...

Response: In the revision, I have followed your suggestions. All figures now include explanations of the vertical axes. Also, I have moved Figures 1 C1 and C2 to the Notes section (in the revision, they are part of Figure 5). (Figures 1 C1 and C2 had the same title because they were identical, except for different scaling.) Similarly, I have added Figure 2C to the Notes section. In the revision, it is Figure 6. Finally, Figure 2D is a separate figure in the revision, named Figure 3.
Concerning legends, I have done my utmost to use them as a tool to maximize graph readability.
You note that lines are better than dots. I would agree if the observations were linear, but since I study months as dummy observations, I find it more correct to include them as dots. Also, from my experience, it is normal to include observations as dots in other studies when dealing with time periods. Independent of opinion, I argue that the new figures are clearer to read as they are larger, particularly on the vertical axes.
You note that I should include a vertical line in the figures "to divide the COVID and post-covid period", but all months in the data include the COVID period.

7. Discussion.
First, authors have to synthesize the main results in a simple table to be clear for readers and then show what this study adds compared to other studies.
Although the Results section provides a detailed description of the data collected and analyzed, there needs to be a more critical synthesis and comparison of the findings with

the literature. Better comment on whether the results were expected for each set of findings; go into greater depth to explain unexpected findings. If appropriate, note any unusual or unanticipated patterns or trends that emerged from your results (directly in figures) and explain their meaning concerning the research problem under study here.
Unvaccinated have higher all causes of mortality during the COVID-19 because there was some restrictions to make diagnostics or to have access to hospitals?
Moreover, the higher mortality of vaccinated can be due to the effects of vaccines on immune system that has created some disorder to face diseases.

Response: The first part of the Discussion has been edited a lot. First, I address the study's core finding. Then, I address how they contribute to and align with the research literature. Concerning "a more critical synthesis and comparison of the findings with the literature" and the assessment of "deeper findings" I argue in the revision that "the study's perhaps major contribution was to elaborate a useful tool to compare non-randomized groups in the absence of control variables, which even in their presence can even make statistical conclusions less, not more, accurate. Thus, as most previous studies on the link between COVID-19 vaccination and mortality have been carried out in non-randomized contexts and, accordingly, even in the presence of control variables exposed to challenges concerning validity, this study has illustrated and applied a useful tool to address those limitations. Moreover, I argue that the tool has general applicability as it can also be used in other research contexts."
Concerning "unexpected" findings, I do not address the topic explicitly but emphasize that my approach has concluded that the vaccine likely has had a temporal but declining effect. Also, I show how the effect in the long term can be detrimental. These different findings align with the established research literature.
You write that "Unvaccinated have higher all causes of mortality during the COVID-19 because there was some restrictions to make diagnostics or to have access to hospitals?" That may be a possibility, but if yes, it aligns with the non-randomized difference between vaccinated and unvaccinated, which this study has emphasized in particular.
Finally, you write that "the higher mortality of vaccinated can be due to the effects of vaccines on immune system that has created some disorder to face diseases", and I agree with you. However, in line with your comment I refer to studies indicating that the vaccine can have adverse effects, but addressing your issue in detail, I argue is beyond the scope of the study.

8. Moreover, either compare your results with the findings from other studies or use the studies to support results. Insert a claim for how the results can be applied more generally, beyond England.
Authors have to describe lessons learned, proposing recommendations that can help improve a next pandemic crises, or highlighting best practices.

Response: I argue that the Discussion should address findings and contributions. Going very much more into detail by adding new research streams, I believe would increase the complexity and perhaps even blur my main objective for carrying out the analyses as I did. However, I have added a new section, "Implications", to address some of your issues and refer to your suggested studies.

9. The conclusion is better as an autonomous section. Conclusion has not to be a summary, but authors have to focus on manifold limitation. In addition, now the Conclusion does not adequately discuss the theoretical and managerial implications of the study. Discuss better how a gap in literature has been addressed. Make sure you clarify: 1) Theoretical Implications, 2) Policy Implications based on health systems improvement and good governance to face next emergencies, and 3) Future Research.

Response: I believe the revised Discussion better addresses the issues the referee has raised.

10. Overall, then, the paper is interesting, but Theoretical framework is weak, and some results create confusion... structure of the paper has to be improved; study design, discussion and presentation of results have to be clarified using suggested comments.

Response: I hope and believe that my revisions, which I have commented on elsewhere in this referee report, have improved the paper concerning theoretical framework, structure, study design, and the presentation of results.

11. Suggested readings of relevant papers that have to be read and used to improve the paper.
Harrison, C.,et al., 2024 [1]
Meyer, C.et al., 2023.[2]
Coccia M. 2023. [3]
Halford, F., et al., 2024. [4]
Coccia, M. and Benati, I. (2024), [5]
Griggs, E.P., et., 2024. [6]
Mink, S., et al., 2024. [7]
Coccia M. 2022. [8]
Jones, R.P., Ponomarenko, A. 2023. [9]
Kirwan, P.D., et al., 2022. [10]
Wekking, D., et al., 2024. [11]

Response: In the revision, I incorporate your suggested references (in addition to other references) as follows: “COVID-19 vaccination has been recommended to most population groups, including people with comorbidities (Wekking et al., 2024). Studies have further indicated that COVID-19 vaccination can prevent mortality (Halford et al., 2023; Harrison et al., 2024; Kirwan et al., 2022), but along with research showing that antibody levels were a superior predictor (Mink et al., 2024), the effect declines, and research has even shown ‘a positive correlation between people fully vaccinated and COVID-19 mortality’ (Coccia, 2023a, p. 1353).” I refer to Meyer, C.et al. (plus another reference) in the following sentence (at the beginning of the Introduction): “The statement aligns with vaccine hesitancy research (Lamot & Kirbiš, 2024; Meyer et al., 2023) and further indicates that unvaccinated have inferior health at the outset compared to vaccinated, inducing biased comparisons as the groups are not randomly assigned.” I refer to Jones, R.P., Ponomarenko, A. 2023 in Note 6, writing as follows: “For an extensive review of all-cause mortality in England and Wales, please see Jones and Ponomarenko (2023).”
Concerning the incorporated references to Coccia M. 2022, Coccia, M. and Benati, I. (2024),

and Griggs, E.P., et., 2024, please see #8.

Competing Interests: No competing interests were disclosed.