Covid-19 vaccinations and all-cause mortality -a long-term differential analysis among municipalities

Preprint · July 2022

DOI: 10.13140/RG.2.2.33994.85447

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Covid-19 vaccinations and all-cause mortality - a long-term differential analysis among municipalities

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Abstract

We analyse the relation between covid-19 vaccinations and all-cause-mortality in *N*=340 Dutch municipalities (17.3M people, ~99% of population), during the entire pandemic period. We do not use covid-19-attributed mortality, mortality predictions and excess mortality, thereby bypassing the ambiguities of case-identification and mortality-modeling.

Municipal demographics such as age, culture and population density are strong confounders of mortality and vaccine-uptake. We account for these by normalizing results to prepandemic year 2019, where covid was absent but demographics were highly representative for later years. Normalized to 2019, we found no correlation between municipal mortality in 2020 with vaccination uptake in 2021, which shows the effectiveness of our confounder accounting.

We could not observe a mortality-reducing effect of vaccination in Dutch municipalities after vaccination and booster campaigns. We did find a 4-sigma-significant mortality-enhancing effect during the two periods of high unexplained excess mortality. Our results add to other recent findings of zero mRna-vaccine effectiveness on all-cause mortality, calling for more research on this topic.

Introduction

After the first covid vaccination campaign in The Netherlands, high excess mortality rates were observed in the second half of 2021. It was known that covid variants could escape vaccine protection [1], but the excess mortality could not be related to covid. Based on the sparse publicly available Dutch data on excess mortality and vaccination rates, an early analysis was made indicating a possible increased mortality in the few weeks following vaccination [2]. This inspired Dutch parliament in December 2021 to require a more thorough analysis to be performed by the academic world [3]. As the Dutch government did not provide medical data for this purpose, no such analysis could be performed. In June 2022, the Dutch central bureau of statistics (CBS) published a report [4] finding no relation between excess mortality and covid or vaccines, while still offering no alternative explanation for the excess mortality. The academic world's response was critical [5].

In continued lack of better datasets, we performed a vaccine/mortality analysis using a dataset that to our knowledge has not been used yet: the weekly all-cause mortality for each Dutch municipality reported by CBS [6]. There are approximately 350 municipalities in The Netherlands, cohorts that are very similar and clearly not suited to isolate phenomena related to age, gender or health-status. Their usefullness comes from being similar while having slight variations in vaccination coverage that are random/unrelated to health, e.g. due to vaccination logistics.

Figure 1 shows an earlier result that motivated this short report, a strong positive correlation between vaccination coverage and mortality rate in the 2nd half of 2021. Demographics differ across municipalities in various ways strongly affecting vaccin-uptake, see Figure 2. For covid, age is the strongest indicator for mortality [7], which subsequently causes vaccination-preparedness in the elderly. We will take these confounders into account by extending the

analysis to prepandemic year 2019, in which covid and vaccines were absent but demographics were obviously very similar.

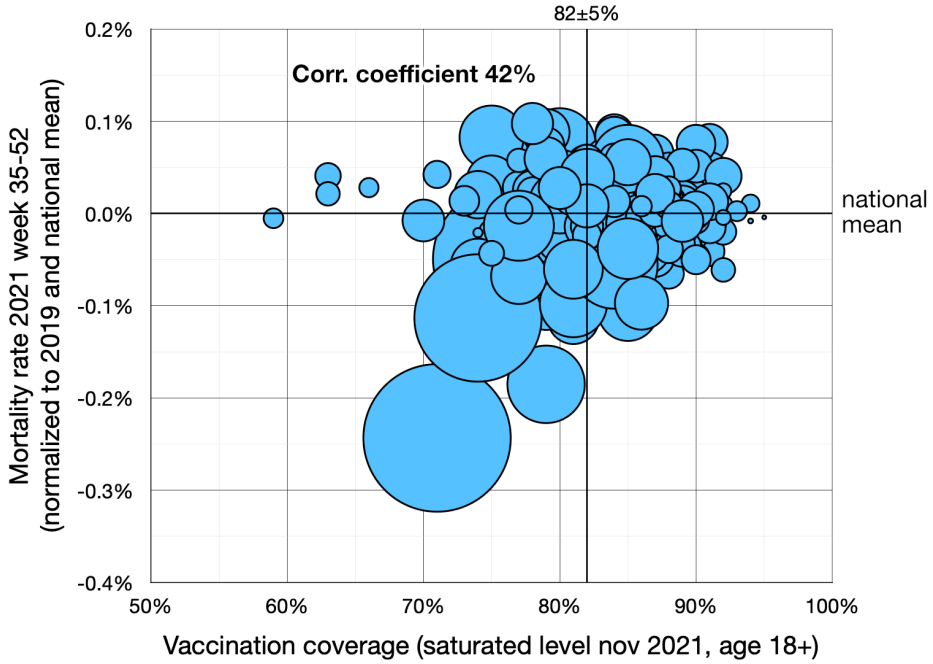

Figure 1: Preliminary result that motivated this report. Municipal vaccination-coverage and mortality-rate correlate strongly at the end of 2021.

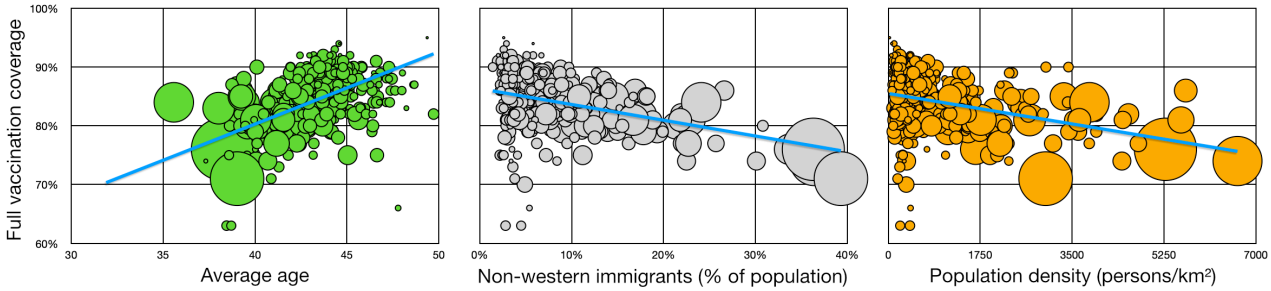

Figure 2: Municipal demographics provide strong counfounders such as average age, culture (immigration) and population density, all of which affect vaccination uptake and/or mortality. All correlation coëfficients between quantities shown are in the order of ±50%.

We focus on longer-term effects of vaccination on mortality during the entire pandemic, as by now it is clear that protective effects of vaccines against covid wane quickly and can even become negative after about half a year, see e.g. [8,9]. We base our results only on all-cause mortality, without reference to covid mortality, expected mortality and excess mortality. That way, we bypass the inevitable ambiguities in covid diagnostics (death with or because of covid) and mortality-modeling during a developing pandemic. Further, vaccines are known to have effects beyond their target disease, recently shown specifically for covid vaccins [10], advocating for all-cause mortality analyses.

Method

We use the following quantities, with $1 \leq g \leq 340$ the municipality (group), and *t* a time period:

$M_g(t)$ All-cause mortality rate (% of municipal population) [6]

V_g End-level of vaccination coverage (% of municipal population) [11]

w_g Relative municipal population size (% of analysed national population) [12]

$K(t)$ Proportionality scalar, our main outcome: municipal differental of *M* per differental of *V*

During 2019-2022, several municipalities have split and merged. In our analysis, we use only *N* = 340 municipalities that existed during the entire analysis period. This brings the total number of people in the analysis at 17.3M, about 99% of The Netherlands. The analysis will weigh every municipality by relative population size w_g (the w_g's sum up to exactly 1).

We use vaccination coverage at saturated-level reached in November 2021, for full-vaccination of people aged 18+, rounded off to integer-valued percentages of the municipal population [11]. It has municipal-weighted (national) mean V_μ and standard deviation V_σ of 82±5%. Non-rounded data and/or coverage at earlier dates are not publicly available. The later booster uptake (as of end of May 2022 [13]) correlates 96% with full-vaccination, see Figure 3, and is not additionally informative in our analysis.

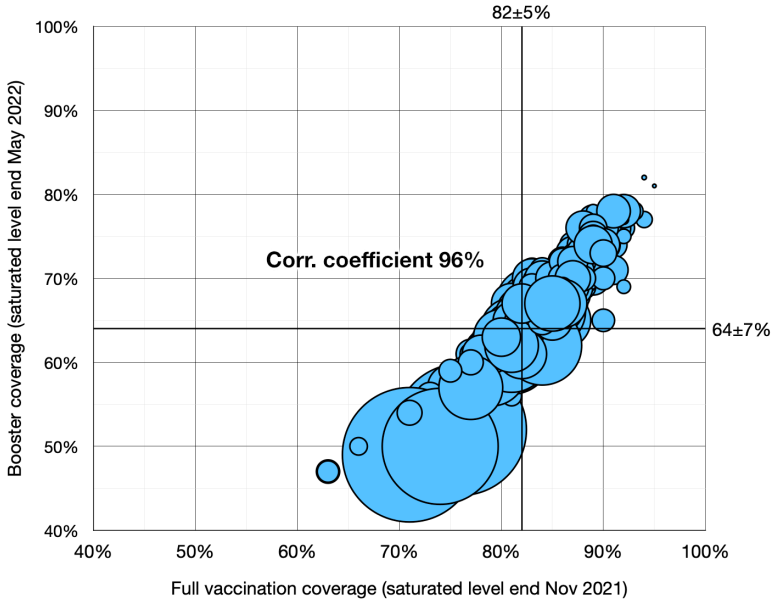

Figure 3: Booster coverage correlates very strongly with full-vaccination coverage, and is not further informative in our analysis.

The essence of our approach is to regard all-cause-mortality $M_g(t)$ as an *N*-dimensional vector with a component for each municipality. One is free to transform any vector by rewriting it as a weighted sum of *N* orthogonal basis-vectors:

$$M_g(t) = K_1(t) \cdot 1_g \quad + \quad K_2(t) \cdot \Delta V_g \quad + \quad K_3(t) \cdot \ldots + K_N(t) \cdot \text{Nth base vector} \qquad (1)$$

Each of the base-vectors can be seen as a "pattern" of mortality across all municipalities, with each K the amount of that pattern occurring in or contributing to the total mortality pattern M. The first base-vector is 1_g which has every component equal to 1, or equivalently, a uniform equal

spread of mortality-rate across all municipalities. We choose the 2nd base-vector as ΔV_g, the municipality's deviation in vaccination coverage compared to the national weighted mean V_μ:

$$\Delta V_g = V_g - V_\mu \qquad V_\mu = \sum_\gamma w_\gamma V_\gamma \tag{2}$$

Vectors 1_g and ΔV_g are orthogonal (their weighted inner product $\sum 1_\gamma w_\gamma \Delta V_\gamma$ is zero).

The rationale of this approach is that the mortality rate M is expected to be a quite uniform pattern over all municipalities (first base vector 1_g), and that the remaining mortality variations will be distributed among all other *N*-1 base vectors. If there is a signal present in mortality correlating with vaccine coverage, it will manifest specifically in $K_2(t)$ while other influences on mortality are thinned out over all remaining *N*-2 (= 338) base vectors, improving the odds of detecting relevant events.

We do not have to define any of the other base-vectors 3 to *N*, as they are not needed to compute the first two K's. Solving (1) gives trivially $K_1(t) = M_\mu(t)$ with M_μ and ΔM_g defined similarly as in (2). The $K_2(t)$ is our main and only focus, from now on we will omit the 2. We obtain its value by:

$$K(t) = \frac{\sum_\gamma \Delta M_\gamma(t) w_\gamma \Delta V_\gamma}{\sum_\gamma \Delta V_\gamma w_\gamma \Delta V_\gamma} \tag{3}$$

The source data for $M_g(t)$ [6] is given in weekly t periods. As K is linear in ΔM, we can easily recombine weekly computed K values to longer or smoothed periods. As weekly data is highly volatile, we will smooth K values to a month-period by a centered, weighted moving average of 5 weeks (weights are 0.1, 0.25, 0.3, 0.25, 0.1). This lowers volatility but leaves the unit of K unchanged at mortality-rate/vaccination-coverage per *week*.

We will compute K from Jan 2019 to April 2022. Values before vaccination refer to correlation of mortality with vaccination-*preparedness*, while values in weeks after vaccination refer to correlation of mortality with vaccination-*coverage*. In the absence of confounders, an effective vaccine will result in $K < 0$ in the period after vaccination. Before vaccination, however, the expectation of an effective vaccine will result in $K > 0$, as vulnerable people are more vaccination-prepared.

Age and other demographics are strong confounders for mortality, covid, and vaccin-uptake, which all bias K. To detect significant values/events in $K(t)$, we compute mean K_μ and standard deviation K_σ over all weeks in prepandemic year 2019, and use that as z-score $Z(t)$:

$$Z(t) = \frac{K(t) - K_\mu(2019wk1..52)}{K_\sigma(2019wk1..52)} \tag{4}$$

Clearly, in 2019 covid was absent but municipal demographics were very representative for the next few years.

One must bear in mind that K refers to a ratio of differential mortality-rate and differential vaccination-coverage, and one cannot extend it to an absolute relation $M = KV$. The differential effect is probably caused by a limited part of the population for which the vaccine has a substantial effect (elderly, people with comorbidities, youngsters/adults with unlucky susceptibility to adverse effects). When this part is accounted for, a non-linear saturation effect on mortality may occur, for which our linear model (1) does not account.

Our method is mathematically equivalent with computing weighted trendlines between ΔM and ΔV, with *K* the resulting regression coefficient. It could very well happen that at some periods covariances between ΔM and ΔV are relatively small (<20%) and that so-called modeling-strength R^2 is in the order of a few percent. In such cases, it would be false to conclude that the trendlines *K* are thus unreliable. In fact a low R^2 would just reflect the relative size of a mortality-vaccination effect amidst a much larger overall mortality rate. We will not compute R^2 or similar, instead we will use the z-score with K_μ and K_σ to determine event significance.

Results

Figure 4 shows w_g , V_g and an example M_g for the period of week 50 of 2021 to get an impression of the municipal variation.

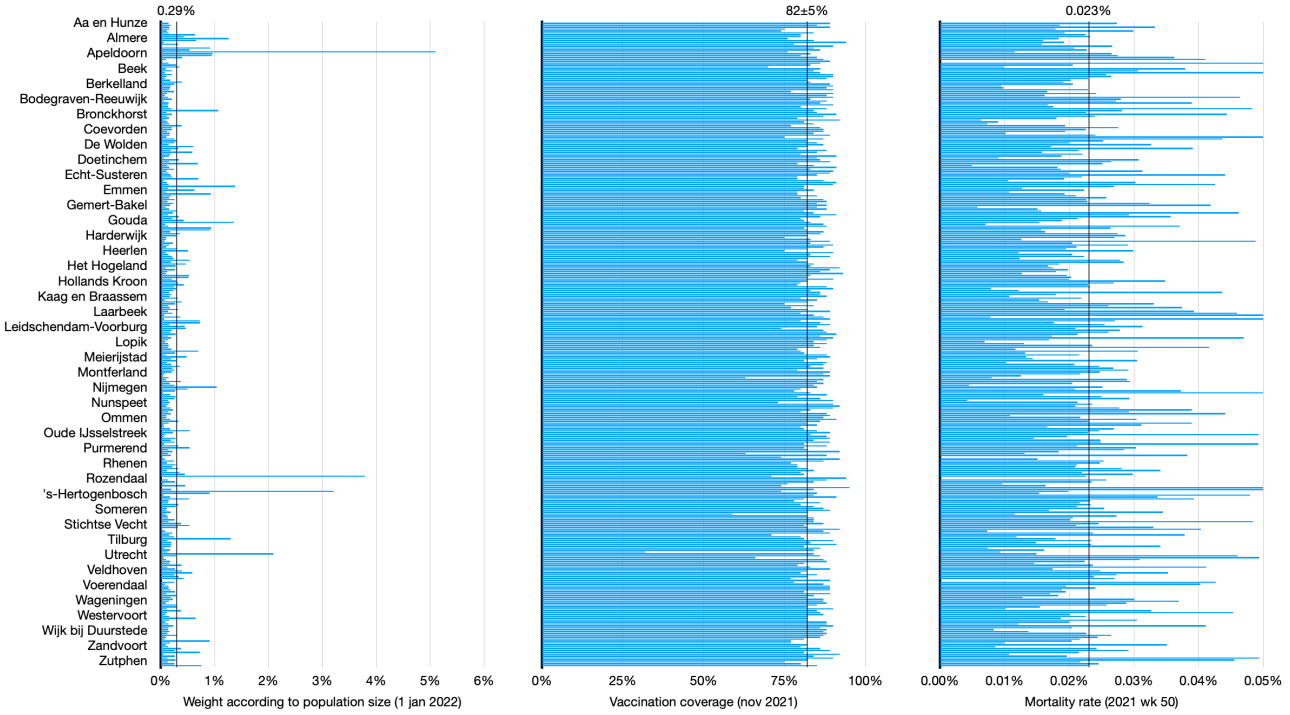

Figure 4: Municipal differences in population size, vaccination coverage and mortality rate (example for week 50 of 2021). A subset of all 340 municipalities' names appear on the left.

The weights w_g have (unweighted) average 1/*N* (~0.29%). As there are clearly a few very large municipalities (Amsterdam, Rotterdam, The Hague, etc) one may wonder if these will dominate the results, effectively lowering *N*. The effective number of same-sized-groups in our analysis, however, is still in the order of hundreds:

$$N_{effective} = e^{-\sum_g w_g \ln w_g} \approx 209 \qquad (5)$$

For the example week 50 of 2021 we find:

$$M_\mu(2021wk50) \approx 0.023\,\%$$
$$K(2021wk50) \approx 0.024\,\% \tag{6}$$

This municipal-average mortality rate M_μ corresponds to the ~4k deaths registered by the Dutch CBS [14] (0.023% times the full Dutch population of 17.5M people).

The K value in this period after vaccination is positive, while a negative value is expected for an effective vaccine, in the absence of confounders. It is even about the same size as M_μ reflecting at least a huge impact of confounders such as age. Further, the value of K refers to differential mortality per differential vaccination coverage, with the latter having ΔV_σ of just 5%. The net result is that vaccination-correlated mortality-rate is 5% of average mortality rate M_μ, or approx. 200 people in this one week. These are *not* 200 additional deaths related to vaccination, it means that 200 out of 4k deaths were distributed over municipalities in the same pattern as vaccination coverage.

Figure 5 shows our main result, weekly $Z(t)$ values (moving monthly averages) during the whole analysis period from Jan 2019 to Apr 2022, with our z-score using K_μ and K_σ computed over prepandemic year 2019:

$$K_\mu(2019wk1-52) \approx 1.68x10^{-4} \approx 0.0017\,\%$$
$$K_\sigma(2019wk1-52) \approx 3.25x10^{-5} \approx 0.0003\,\% \tag{7}$$

For context, national prognosed, actual all-cause, and covid mortality-rates are shown, plus primary-vaccination and booster campaigns.

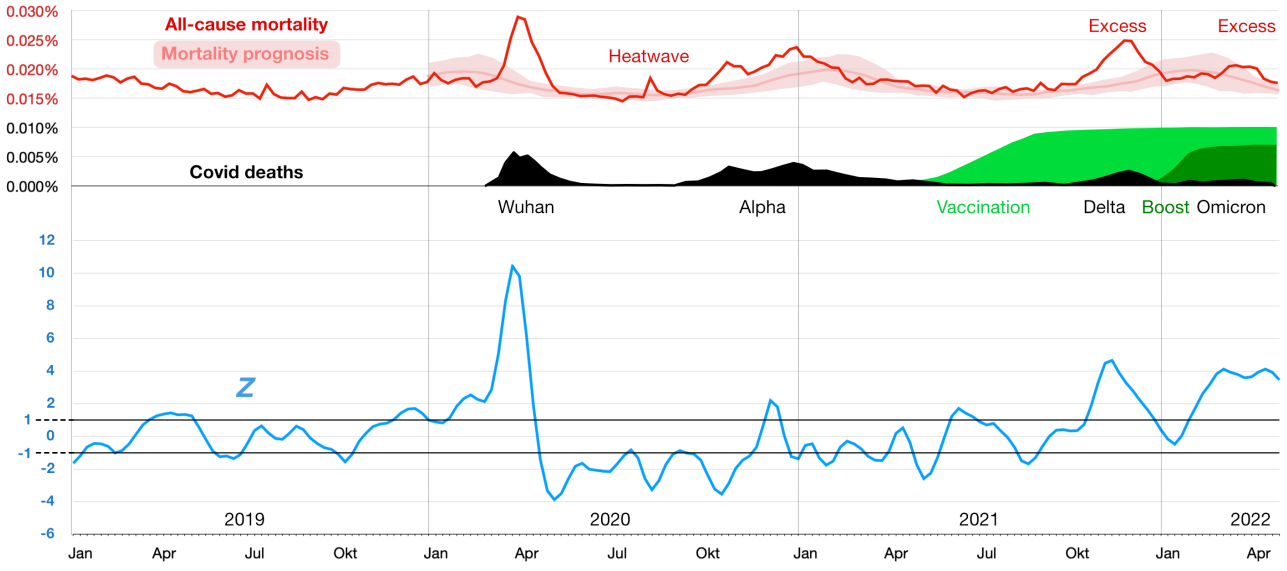

Figure 5: Main result, K from Jan 2019 to Apr 2022 by z-score Z defined over prepandemic year 2019. Added for context are all-cause mortality, mortality prognosis (from 2020 onwards), reported covid deaths and vaccination-coverage over time.

From this graphic, we observe:

- Mortality in the 1st Wuhan wave correlates extremely strong (>10 sigma) with vaccination-preparedness, in contrast with the 2nd Alpha wave (Z ~ 0 on average, short peak at 2 sigma) and the seasonal mortality-peak at the beginning of 2019 (-1.5 sigma).

- After the Wuhan peak, Z is significantly below zero (approx -3 sigma) for many months and similar for Alpha wave (at -1 sigma). The average of *Z* over 2020 is very close to zero (~ -0.04)[1], meaning mortality over the entire covid-year before vaccination does *not* correlate with vaccination-preparedness.

- After the vaccination campaign, Z rises to +4σ at the 3rd Delta wave, then briefly dips between Delta and Omicron waves during the booster campaign, to rise directly again to +4σ during the much milder Omicron wave. The rises coincide with both unexplained excess mortality periods.

Conclusions

In the absence of publicly available high-quality covid/mortality/vaccination datasets in the Netherlands, we examined the available data of municipal vaccination-coverage and weekly all-cause mortality in a differential approach. Although municipal variations are relatively small, the amount of municipalities is sufficiently high to find significant correlations. We accounted for strong demographic confounders (e.g. age, culture, population density) by normalizing all results to prepandemic year 2019.

Municipalities that suffered the highest mortality during the 1st covid wave beginning of 2020 were most willing to be vaccinated later in 2021 (10 sigma). The 2nd wave in 2020 as well as the seasonal mortality peak at beginning of 2019 did not contribute to vaccine-preparedness. Directly after the 1st and 2nd waves a prolonged municipal mortality-rate reversal was observed, with a net result that vaccination coverage is *not* correlated with total mortality from pre-vaccination year 2020. This absence of correlation reflects the effectiveness of our approach to account for mortality-vaccination confounders, enabling the following observation to be significant.

After both vaccination and booster campaigns, we did not observe the negative correlation between mortality and vaccination expected for an effective vaccine. Instead, during Delta and milder Omicron waves, correlation was significantly positive (4 sigma), coinciding exactly with the two periods of excess mortality in The Netherlands peaking in Nov 2021 and Mar/Apr 2022.

Discussion

We could not observe a mortality-reducing effect of vaccines in Dutch municipalities, while we did find a 4-sigma-significant mortality-enhancing effect during the two periods of high unexplained excess mortality. These results add to recent findings of zero mRna-vaccine effectiveness on all-cause mortality [10].

Clearly, our study has many shortcomings: we made use of very limited publicly available data. Our several requests for improved data (non-rounded vaccination coverages at more time instances) were unfortunately not granted by the Dutch government. The variability of our dataset

[1] Proper calculation of the 2020 overall Z-value involves multiplying the found average of -0.04 by the number of *independent Z* values in 2020, which is 52 divided by (5) applied to our weekly-to-monthly-moving-average weights 0.1, 0.25, 0.35, 0.25, 0.1, which is 52 / 4.55 = 11.43. The resulting Z over 2020 is approx -0.47, well below the significance limit of ±1.

was also limited, e.g. municipal vaccination-coverages have a spread of only ±5%. Our simple linear model between mortality and vaccines does not capture nonlinear effects or non-uniform populations. Especially with respect to the latter, our approach is cohortless, while covid and thus vaccine effectiveness against mortality are highly age-dependent [7].

Our main result remains alarming and calls for more research on the effect of current covid vaccines on all-cause mortality.

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