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Age-adjusted non-COVID-19 mortality rates according to the COVID-19 vaccination status

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Abstract

Excess mortality has been observed in several countries since 2021 and has not yet been explained. The aim of this study was to determine whether the age-adjusted mortality rates of non-COVID-19 deaths differed between those who had received one, two, three or four doses compared with the unvaccinated. Data were obtained from the Office for National Statistics of England and categorized by age groups and vaccinations status (unvaccinated or 1 - 4 doses, given at least 21 days previously). Rates among the unvaccinated were used as a benchmark, assuming that COVID-19 vaccination should have no positive or negative effect on the age-adjusted non-COVID-19 mortality rate. The age-adjusted non-COVID-19 mortality rate was higher in all age groups who have received dose 1, but mainly in the elderly. The age-adjusted non-COVID-19 mortality rate also peaked in all those who have received dose 2, mainly in the elderly. Interestingly, age-adjusted non-COVID-19 mortality has a tendency to peak across age groups following the age-dependent timing of vaccination campaigns, both in the first and second vaccination rounds. A fourth finding was the substantially higher age-adjusted non-COVID-19 mortality rates in the 18 – 39 age group among those who had received dose 4. Relevant comorbidities among the vaccinated population may explain the differences (healthy non-vaccinee bias), but these data were not available. Although a causal relationship between excess mortality and vaccination against COVID-19 cannot be established, a higher age-adjusted non-COVID-19 mortality rate among the COVID-19 vaccinated in several age groups was found, that, together with vaccination timing associated mortality peaks require further research.

Keywords: COVID-19 vaccination; excess mortality; non-COVID-19 deaths; age-adjusted mortality rate; England

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Introduction

Since 2021, excess mortality has increased and remains high in several countries.[1,2] In Germany, excess deaths reached 34,000 in 2021 and 66,000 in 2022.[3] This increase was unexpected.[4] It was speculated that an inadequate vaccination level might be the cause.[4] A further analysis showed that excess mortality in Germany was positively correlated with COVID-19 infection in 2020. However, a significant positive correlation was observed between the increase in excess mortality and the COVID-19 vaccination rates of the 16 German federal states in 2021 and 2022.[5] In Cyprus, one study reported a lack of association between vaccination rates and excess mortality,[6] whereas another

study described that excess mortality increased and was particularly high in 2021 and 2022.[7] Economidou et al. raised serious concerns about the potential impact of the COVID-19 vaccination campaign and other causes of mortality.[7] In contrast, in Israel, a cohort of the COVID-19 vaccinated population showed a similar all-cause mortality rate in 2021 compared with the average mortality rate between 2017 and 2019, suggesting no effect of the COVID-19 vaccines on non-COVID-19 mortality, although no distinction was made between the doses of vaccine given.[8]

Excess mortality is often described as a finding that occurs despite high vaccination coverage,[9] suggesting that the vaccination itself is only expected to reduce overall mortality. Faust et al. reported that between January 2020 and July 2022 excess mortality and the number of new COVID-19 cases were decoupled,[10] suggesting that causes other than COVID-19 may explain the excess mortality.

In 2021, the possible association between vaccination and excess deaths has been raised,[11] but the hypothesis that COVID-19 vaccines might kill some of the recipients was strongly rejected,[12] although later in 2021 it was reported that vaccine-associated deaths occur with all major COVID-19 vaccines.[13] In June 2023, the German Federal Minister of Health, Karl Lauterbach, was asked in the parliament whether the excess mortality could be explained by the COVID-19 vaccines. He clearly stated that there was no evidence that the excess mortality could be caused by the vaccinations administered, that there was no evidence for this and it was not medically plausible.[14]

The Office for National Statistics of England publishes the number of deaths and the age-adjusted mortality rates by vaccination status and distinguishes between COVID-19-related deaths and non-COVID-19 deaths. The aim of this study was to find out whether the age-adjusted mortality rates of non-COVID-19 deaths differed between those who had received one, two, three or four doses and those who had not been unvaccinated.

Methods

The study did not have a pre-registered protocol. The data were obtained from the Office for National Statistics of England, where they are freely available.[15] The analyses were exploratory. To assess possible differences in non-COVID-19 and COVID-19 mortality rates, the age-adjusted mortality rates were extracted by age group (18 – 39 years, 40 – 49 years, 50 – 59 years, 60 – 69 years, 70 – 79 years, 80 – 89 years and 90 years or older) and by vaccination status (unvaccinated, vaccinated with one, two, three or four doses at least 21 days previously. The case numbers in the category “vaccinated within the last 21 days” were also available, but lower and therefore prone to outliers, so that the data analysis was restricted to those with a dose of vaccine given at least 21 days ago.

The age-adjusted non-COVID-19 mortality rate among the unvaccinated was set as the benchmark, assuming that COVID-19 vaccination should have no positive or negative effect on the age-adjusted non-COVID-19 mortality rate, resulting in similar rates in each age group regardless of the COVID-19 vaccination status.

Results

Benchmark rates of the COVID-19 unvaccinated

The age-standardized non-COVID-19 mortality rate per 100,000 was within a stable range in all age groups except the cohort aged 90 years and older, that showed peaks in mortality in mid-winter 2021 and 2022 (Figure 1). It was between 22.9 and 70.5 in the age group 18 – 39 years, between 100.9 and 278.5 in the age group 40 - 49 years, between 369.2 and 740.6 in the age group 50 - 59 years, between 894.6 and 2,425.2. in the age group 60 - 69 years, between 2,646.4 and 5,862.0 in the age group 70 - 79 years, between 5,767.2 and 13,745.6 in the age group 80 - 89 years and between 16,441.3 and 30,234.8 among those in the age group 90 years or older. A higher non-COVID-19 mortality rate per 100,000 was found for those aged 60 years or over during the winter period, indicating a seasonality in the non-COVID-19 mortality rate.

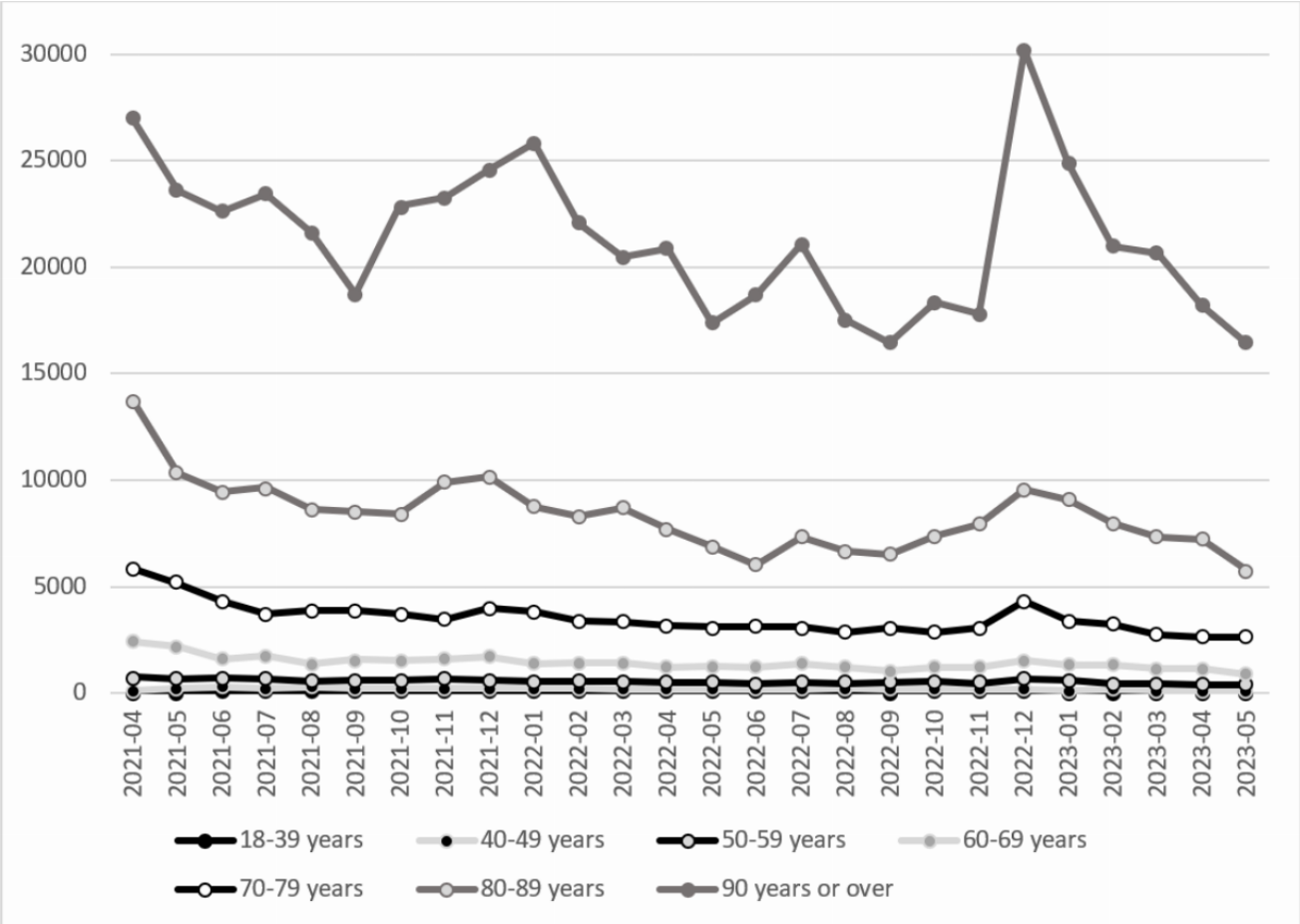

Figure 1. Age-standardized non-COVID-19 mortality rate per 100,000 in England among those not vaccinated against COVID-19 in seven age groups, used as the benchmark below; data from the Office of National Statistics [15]

All age groups

The age-standardized non-COVID-19 mortality rate per 100,000 of the COVID-19 unvaccinated ranged from 901.6 in May 2023 to 1956.3 in April 2021 (Figure 2). It was higher, ranging from +580.9 to +4809.4, compared with the unvaccinated in 25 of the 26 months among those who have received one dose of the vaccine. It was lower between April and October 2021 ranging from -123.4 to -1249.7, and higher between November 2021 and January 2023, ranging from +340.7 to +1522.2 among those who had received two doses of the vaccine. It was also lower between November 2021 and April 2022, ranging from -33.5 to -721.6, and higher between May 2022 and May 2023, ranging from +213.1 to +842.1 for those who had received three doses of the vaccine. And it was substantially higher in March 2022 (+1254.5) and between June and September 2022 (range between +714.1 and +1291.8) for those who had received four doses of the vaccine.

The age-standardized COVID-19 mortality rate per 100,000 of the COVID-19 unvaccinated ranged from 46.1 in May 2023 to 649.0 in January 2022. It was mostly lower (range between 1.6 and 575.4) among all those ever vaccinated (Figure S1).

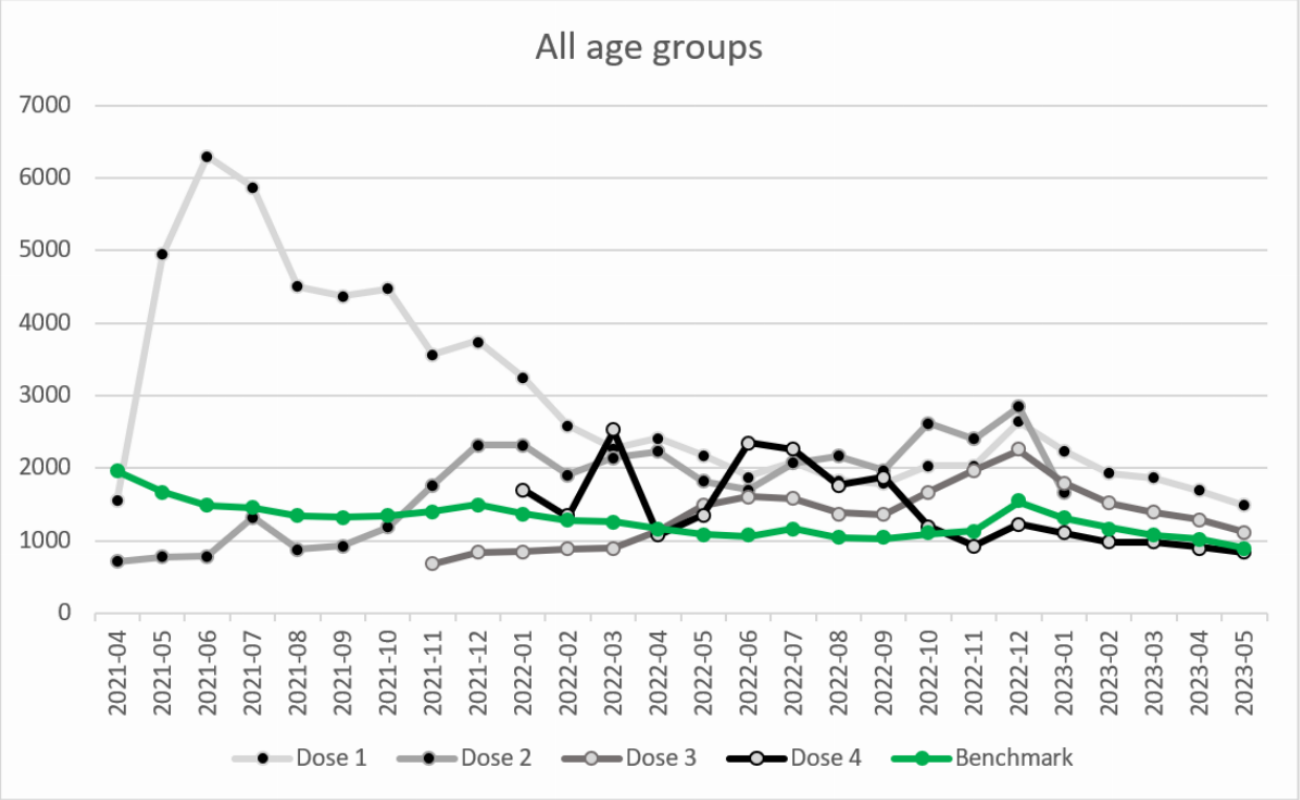

Figure 2. Age-standardized non-COVID-19 mortality rate per 100,000 in England among those aged 18 or older by COVID-19 vaccination status; unvaccinated rates are used as benchmark; cases were included if a vaccine dose was administered at least 21 days previously; data from the Office of National Statistics [15]

Age group 18 – 39 years

In the age group 18 – 39 years, the age-standardized non-COVID-19 mortality rate per 100,000 of the COVID-19 unvaccinated ranged from 22.9 in May 2023 to 70.5 in December 2021 (Figure 3). It was higher, ranging from +11.0 to +80.0, compared with the unvaccinated in 22 of the 26 months among those who have received one dose of the vaccine. It was higher between April and August 2021, ranging from +3.5 to +39.7, and lower between September 2021 and May 2023, ranging from -0.8 to -35.1, among those who had received two doses of the vaccine. It was also lower in all 19 months for those who had received three doses of the vaccine, ranging from -1.0 to -28.5. And it was substantially higher in all 13 months for those who had received four doses of the vaccine (range between +57.2 and +537.6).

The age-standardized COVID-19 mortality rate per 100,000 of the COVID-19 unvaccinated ranged from 0.6 in May 2021 to 27.6 in December 2021. It was consistently lower (range between 0.5 and 8.8) among all those ever vaccinated (Figure S2).

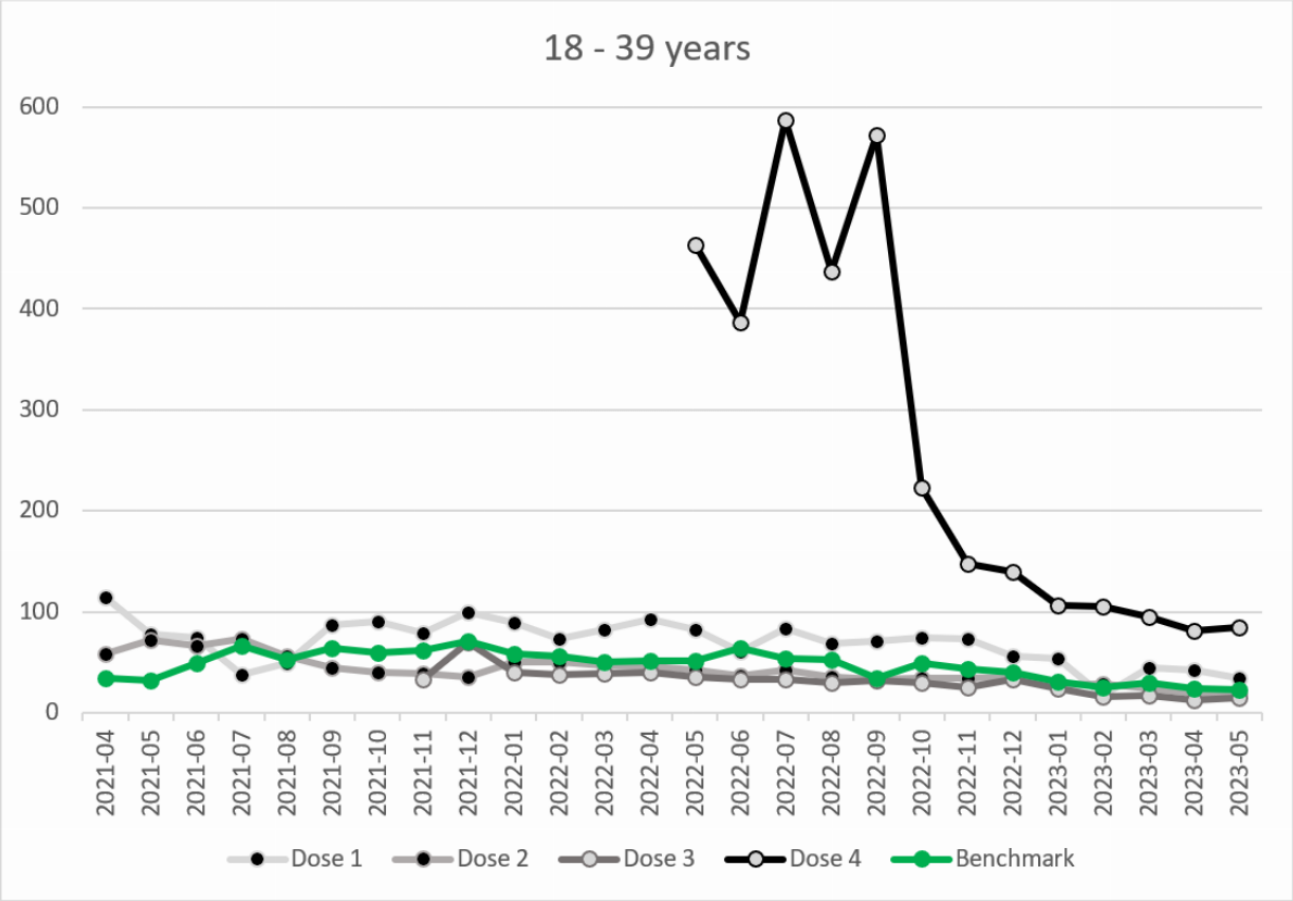

Figure 3. Age-standardized non-COVID-19 mortality rate per 100,000 in England among those aged 18 – 39 years by COVID-19 vaccination status; unvaccinated rates are used as benchmark; cases were included if a vaccine dose was administered at least 21 days previously; data from the Office of National Statistics [15]

Age group 40 – 49 years

In the age group 40 – 49 years, the age-standardized non-COVID-19 mortality rate per 100,000 of the COVID-19 unvaccinated ranged from 100.9 in May 2023 to 278.5 in June 2021 (Figure 4). It was higher (range between +76.5 and +369.9) compared to the unvaccinated, in 23 of the 26 months among those who have received one dose of the vaccine. It was higher (range between +2.2 and +19.4) in four months and lower (range between -2.4 and -162.6) in 22 months among those who had received two doses of the vaccine. It was also lower (range between -30.3 and -127.8) at all 19 months for those who had received three doses of the vaccine. And it was substantially higher (range between +68.9 and +732.4) in all 13 months for those who had received four doses of the vaccine.

The age-standardized COVID-19 mortality rate per 100,000 of the COVID-19 unvaccinated showed seasonality, ranging from 5.1 in April 2021 to 134.1 in December 2021. With the dominance of the omicron variant in January 2022, age-standardized COVID-19 mortality rate was low ranging from 5.0 to 57.0. It was mostly lower among all those ever vaccinated until December 2021 (range between 2.8 and 37.9) but was in a similar range to the unvaccinated starting with the dominance of the omicron in January 2022 (Figure S3).

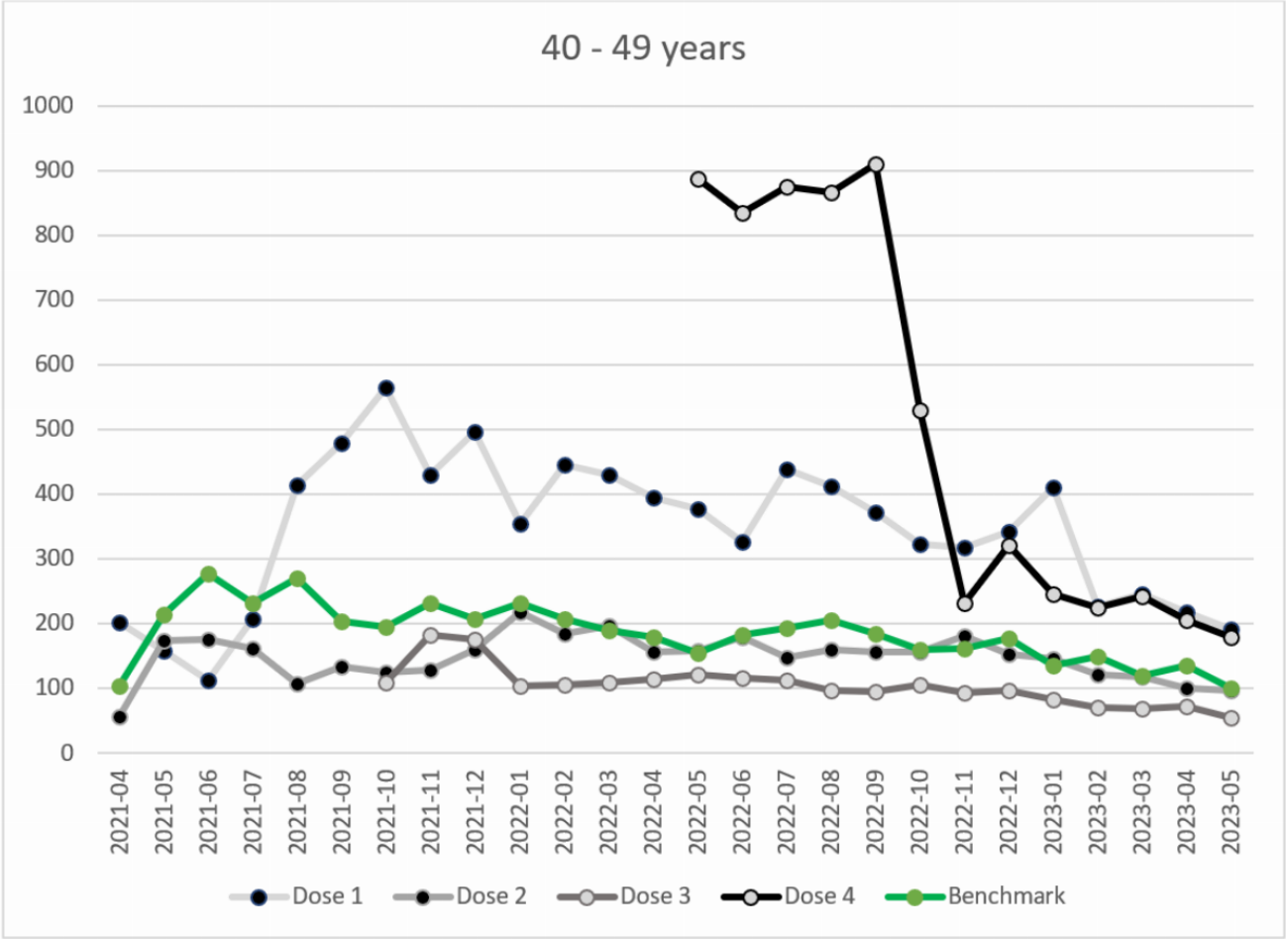

Figure 4. Age-standardized non-COVID-19 mortality rate per 100,000 in England among those aged 40 – 49 years by COVID-19 vaccination status; unvaccinated rates are used as benchmark; cases were included if a vaccine dose was administered at least 21 days previously; data from the Office of National Statistics [15]

Age group 50 – 59 years

In the 50 – 59 age group, the age-standardized non-COVID-19 mortality rate per 100,000 of the COVID-19 unvaccinated ranged from 369.2 in May 2023 to 740.6 in April 2021 (Figure 5). It was higher (range between +4.8 and +1,080.7) compared with the unvaccinated in 23 of the 26 months among those who have received one dose of the vaccine. It was lower (range between -272.8 and -549.7) between April and November 2021, higher (range between +41.7 and +404.0) in the following eight months, and close to the benchmark in the last ten months among those who had received two doses of the vaccine. It was also lower in all 19 months for those who had received three vaccine doses (range between -72.7 and -450.6). And it was substantially higher (range between +324.2 and +1,280.5) between April and October 2022 and lower (range between -126.4 and -366.9) between November 2022 and May 2023 among those who had received four doses of the vaccine.

The age-standardized COVID-19 mortality rate per 100,000 of the COVID-19 unvaccinated was higher until March 2022, ranging from 28.7 in May 2021 to 327.9 in August 2021. After the dominance of the omicron variant, age-standardized COVID-19 mortality rate was lower, ranging mostly between 11.2 and 27.0. It was mostly lower among all those ever vaccinated until March 2022 (range between 2.5 and 214.0), but after the dominance of the omicron variant, it was in a similar range to the unvaccinated (Figure S4).

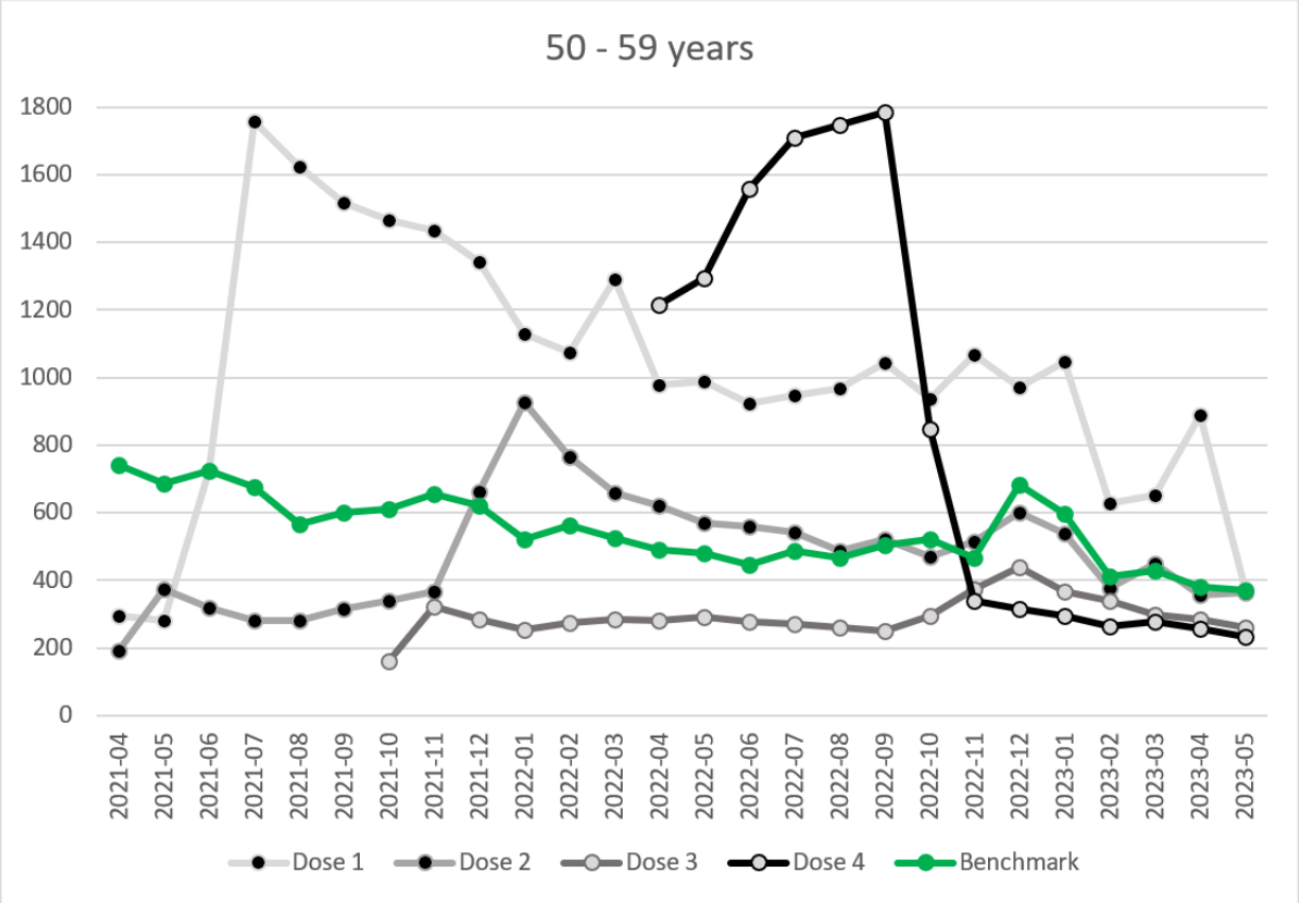

Figure 5. Age-standardized non-COVID-19 mortality rate per 100,000 in England among those aged 50 – 59 years by COVID-19 vaccination status; unvaccinated rates are used as benchmark; cases were included if a vaccine dose was administered at least 21 days previously; data from the Office of National Statistics [15]

Age group 60 – 69 years

In the age group 60 – 69 years, the age-standardized non-COVID-19 mortality rate per 100,000 of the COVID-19 unvaccinated ranged from 894.6 in May 2023 to 2,425.2 in April 2021 (Figure 6). It was higher (range between +653.1 and +5,481.4) with a peak in the summer 2021 compared to the unvaccinated in 24 of the 26 months among those who have received one dose of the vaccine. It was lower (range between -391.6 and -1,608.0) between April and November 2021 and higher (range between +139.7 and +2,069.0) in the following 18 months among those who had received two doses of the vaccine. It was lower (range between -170.5 and -1,120.6) between October 2021 and October 2022 and close to the benchmark in the following seven months for those who had received three doses of the vaccine. And it was higher (range between +196.6 and +2,416.2) between April and October 2022 and lower (range between -259.5 and -716.0) between November 2022 and May 2023 for those who had received four doses of the vaccine.

The age-standardized COVID-19 mortality rate per 100,000 of the COVID-19 unvaccinated was higher until January 2022, ranging from 100.2 in May 2021 to 787.7 in December 2021. After the dominance of the omicron variant, age-standardized COVID-19 mortality rate was lower, ranging mostly between 42.7 and 145.7. It was mostly lower among all those ever vaccinated until January 2022, but after the dominance of the omicron variant, it was in a similar range to the unvaccinated, except for lower rates between February and September 2022 (dose 3) and for higher rates between April 2022 and May 2023 (dose 1) (Figure S5).

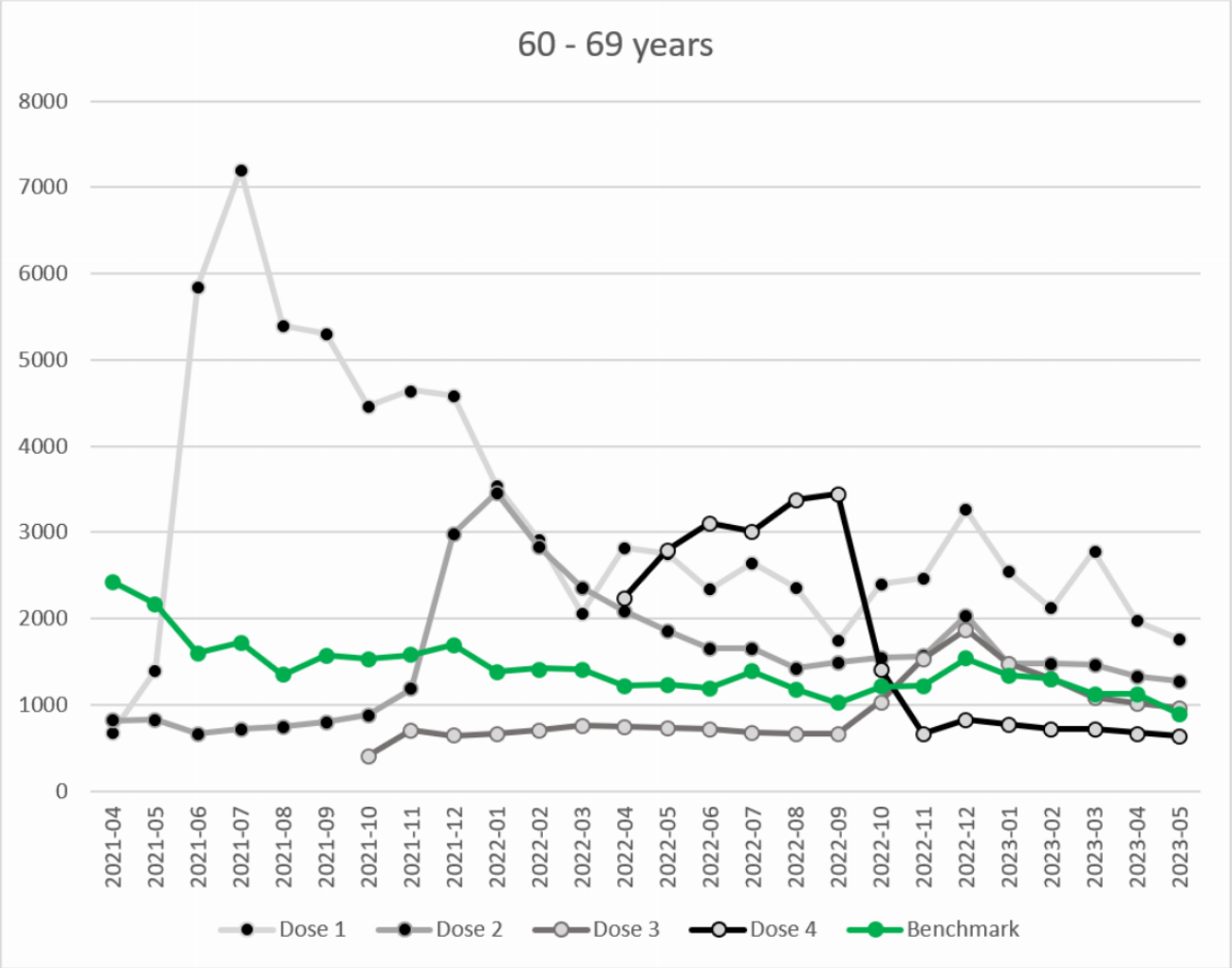

Figure 6. Age-standardized non-COVID-19 mortality rate per 100,000 in England among those aged 60 – 69 years by COVID-19 vaccination status; unvaccinated rates are used as benchmark; cases were included if a vaccine dose was administered at least 21 days previously; data from the Office of National Statistics [15]

Age group 70 – 79 years

In the age group 70 – 79 years, the age-standardized non-COVID-19 mortality rate per 100,000 of the COVID-19 unvaccinated ranged from 2,646.4 in May 2023 to 5,862.0 in April 2021 (Figure 7). It was higher (range between +1,396.4 and +20,329.3) compared to the unvaccinated in 25 of the 26 months, with a peak in the summer 2021 among those who have received one dose of the vaccine. It was lower (range between -965.0 and -3,864.3) between April and October 2021 and higher (range between +788.5 and +10,250.9) in the following 19 months among those who had received two doses of the vaccine. It was lower between October 2021 and October 2022 (range between -965.0 and -3,864.4) with a peak in December 2021 and close to the benchmark in the last seven months for those who had received three doses of the vaccine. It was substantially higher (+4,134.2) in March 2022, close to the benchmark between April and October 2022 and lower (range between -746.4 and -1,818.4) between November 2022 and May 2023 for those who had received four doses of the vaccine.

The age-standardized COVID-19 mortality rate per 100,000 of the COVID-19 unvaccinated was higher until April 2022, ranging from 114.1 in May 2021 to 1,972.8 in January 2022. After the dominance of the omicron variant, age-standardized COVID-19 mortality rate was lower, ranging mostly between 108.9 and 444.7. For all those ever vaccinated it was mostly in a similar range to the unvaccinated, except for lower rates between April and December 2021 (dose 2) and for lower rates between October 2021 and May 2022 (dose 3) (Figure S6).

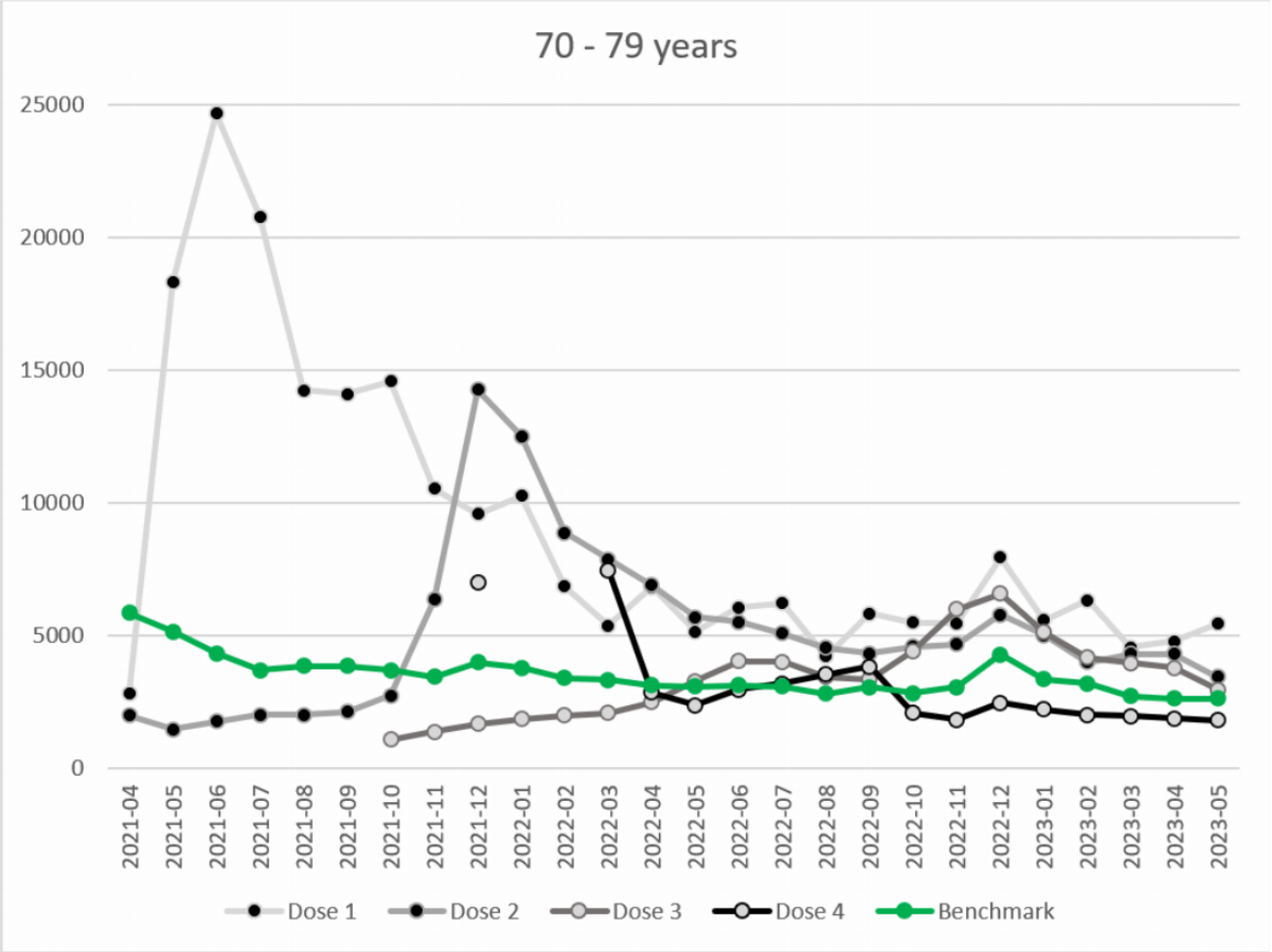

Figure 7. Age-standardized non-COVID-19 mortality rate per 100,000 in England among those aged 70 – 79 years by COVID-19 vaccination status; unvaccinated rates are used as benchmark; cases were included if a vaccine dose was administered at least 21 days previously; data from the Office of National Statistics [15]

Age group 80 – 89 years

In the age group 80 – 89 years, the age-standardized non-COVID-19 mortality rate per 100,000 of the COVID-19 unvaccinated ranged from 5,767.2 in May 2023 to 13,745.6 in April 2021 (Figure 8). It was higher (range: +1,562.6 – +35,931.3) with a peak in the early summer 2021 compared to the unvaccinated in all of the 26 months among those who have received one dose of vaccine. It was lower (range: -1,969.7 – -9,636.7) between April and October 2021 and higher (range: +2,358.8 – +22,336.8) between November 2021 and May 2023 for those who had received two doses of the vaccine. It was lower (range: -1,791.0 – -5,581.5) between October 2021 and March 2022 and higher (range: +1,920.1 – +8,722.8) between April 2022 and May 2023 for those who had received three vaccine doses. It was higher between January and March 2022 (range: +2,961.2 – +8,130.7), lower in April (-5,239.2) and then approached the benchmark level for those who had received four doses of the vaccine.

The age-standardized COVID-19 mortality rate per 100,000 of the COVID-19 unvaccinated was higher between August 2021 and April 2022, ranging from 1781.6 in March 2022 to 4,131.3 in January 2022. After the dominance of the omicron variant, age-standardized COVID-19 mortality rate was lower, ranging mostly between 268.2 and 1,300.3. For all those ever vaccinated it was mostly in a similar range to the unvaccinated, except for lower rates between April and October 2021 (dose 2), lower rates between October 2021 and April 2022 (dose 3), and higher rates in January 2022 (doses 1 and 2) (Figure S7). Overall, COVID-19 vaccination was much less associated with the age-standardized COVID-19 mortality rate per 100,000 than with the non-COVID-19 mortality rate per 100,000.

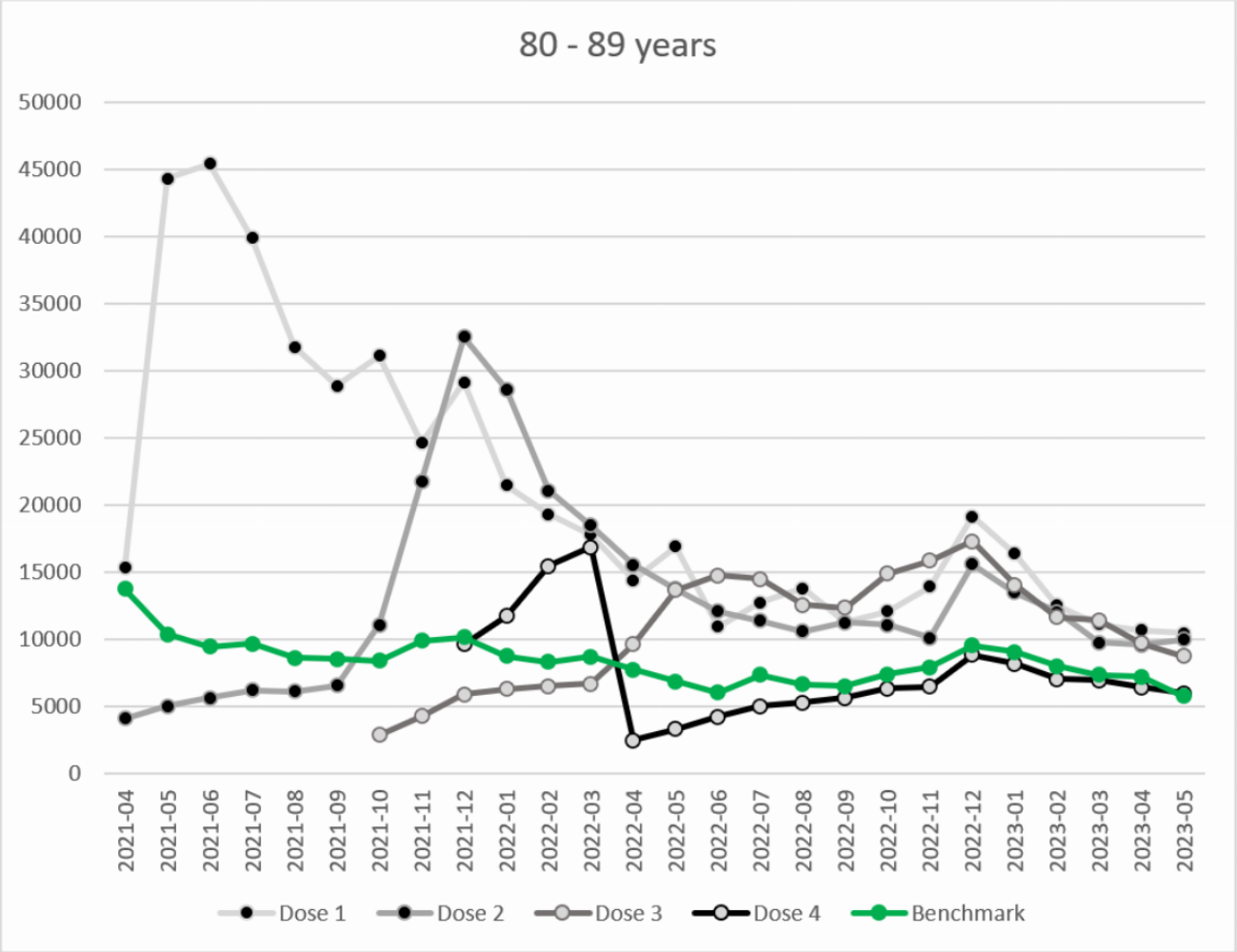

Figure 8. Age-standardized non-COVID-19 mortality rate per 100,000 in England among those aged 80 – 89 years by COVID-19 vaccination status; unvaccinated rates are used as benchmark; cases were included if a vaccine dose was administered at least 21 days previously; data from the Office of National Statistics [15]

Age group 90 years or over

In the age group of 90 years and older, the age-standardized non-COVID-19 mortality rate per 100,000 of the COVID-19 unvaccinated ranged from 16,441.3 in May 2023 to 30,234.8 in December 2022 (Figure 9). It was higher (range: +1,009.8 – +56,184.6) compared to the unvaccinated in 25 of the 26 months among those who have received one dose of the vaccine. It was lower (range: -3,347.7 – -13,535.1) between April and August 2021 and higher (range: +458.8 – +39,592.1) between September 2021 and May 2023 for those who had received two vaccine doses. It was lower (range: -285.5 – -11,949.3) between April and September 2021 and higher (range: +4,494.4 – +15,971.1) between October 2021 and May 2023 for those who had received three vaccine doses. It was substantially higher in January 2022 (+18,350.2) and March 2022 (+25,825.2), lower in April 2022 (-10,360.4) and then approached the benchmark level for those who had received four vaccine doses.

The age-standardized COVID-19 mortality rate per 100,000 of the COVID-19 unvaccinated was higher between August 2021 and April 2022, ranging from 2,977.4 in September 2021 to 10,560.8 in January 2022. After the dominance of the omicron variant, age-standardized COVID-19 mortality rate was lower, ranging mostly between 788.3 and 3,313.3. For all those ever vaccinated it was mostly in a similar range to the unvaccinated, except for lower rates between April and December 2021 (dose 2), lower rates between October 2021 and April 2022 (dose 3), and a higher rate in January 2022 (dose 2) (Figure S8). Overall, COVID-19 vaccination was much less associated with the age-standardized COVID-19 mortality rate per 100,000 than with the non-COVID-19 mortality rate per 100,000.

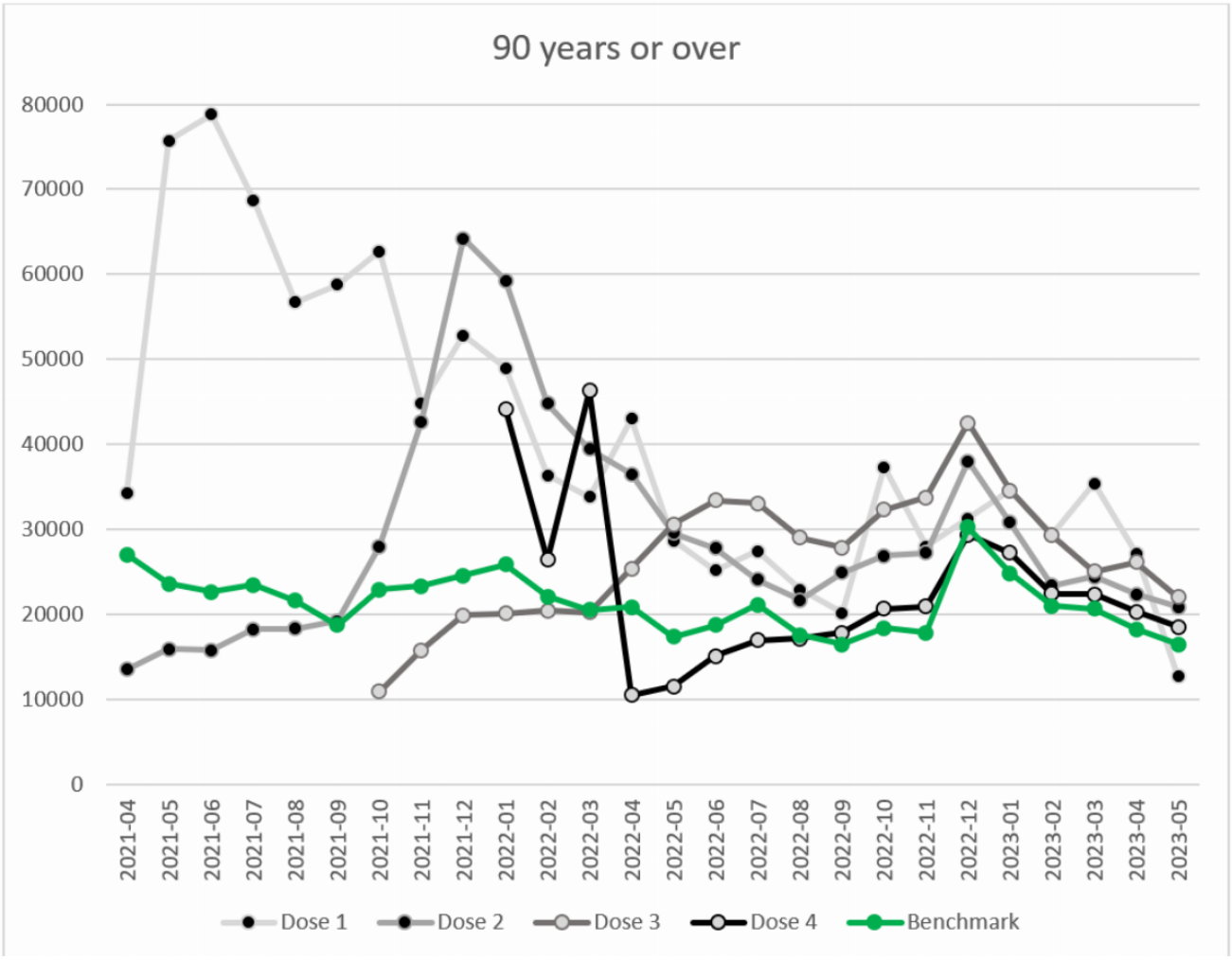

Figure 9. Age-standardized non-COVID-19 mortality rate per 100,000 in England among those aged 90 years or over by COVID-19 vaccination status; unvaccinated rates are used as benchmark; cases were included if a vaccine dose was administered at least 21 days previously; data from the Office of National Statistics [15]

Discussion

To our knowledge, this is the first report of non-COVID-19 age-adjusted mortality rates according to COVID-19 vaccination status. The rates were expected to be in a similar range in each age group, assuming that there is no association between the vaccination status and the non-COVID-19 mortality rates. However, this is not consistently the case. Several striking patterns emerged.

First, the age-adjusted non-COVID-19 mortality rates among those who have received 1 dose of the vaccine were mostly higher in all age groups. The most striking difference was found in those aged 70 – 79 years (maximum: 5.7-fold higher), followed by those aged 80 – 89 years (maximum: 4.8-fold higher) and those aged 60 – 69 years (maximum: 4.2-fold higher). The highest peaks were typically found in the first three months between April and July 2021. A further observation is that the peaks of elevated age-adjusted non-COVID-19 mortality rates appear to follow the vaccination rollout described by the National Audit Office in February 2022,[16] with peaks in May 2021 among those aged 80 years or older, a peak in June May 2021 among those aged 70 - 79 year, and a delayed peak in July 2021 among those aged 50 – 69 years, providing further support for the COVID-19 vaccination as a possible cause of the elevated age-adjusted non-COVID-19 mortality rates (Figure S9).

Another pattern is that the age-adjusted non-COVID-19 mortality rates after dose 2 show peaks in those aged 70 – 79 years (maximum: 3.6-fold higher; December 2021), those aged 80 – 89 years (maximum: 3.3-fold higher; January 2022), those aged 90 years or older (maximum: 2.6-fold higher; December 2021), and those aged 60 – 69 years (maximum: 2.5-fold higher; January 2022). These results are supported by findings from Norway, where the vaccination

campaign began in nursing home residents with the first vaccine-related death reported already on 4 January 2021. The number increased to 142 deaths by May 2021. Autopsies were performed in May 2021 on 100 deceased nursing home residents who died after receiving the COVID-19 vaccine, mostly 8 days after the injection. The average age was 87.7 years. In ten cases, the vaccination was probably the cause of death, and in 26 cases it was possibly the cause. The researchers concluded that in some cases, the vaccination may have accelerated the process of death that had already begun. They therefore recommended that the benefits and risks should be weighed carefully in each individual case, even in elderly and frail people.[17] In Germany, deaths after vaccination of residents were reported from several nursing homes in the winter of 2021, but were not officially considered as potential serious adverse reactions. The population groups with the highest non-COVID-19 mortality rates without vaccination, with highly elevated non-COVID-19 mortality rates after dose 1, now also have a higher non-COVID-19 mortality rate after dose 2. Therefore, the higher non-COVID-19 mortality may possibly explain a relevant proportion of the excess deaths during this period.

The results are not easy to explain. The first two patterns may be explained by the assumption that those who preferred to not be vaccinated may have been very healthy, so that they thought they did not need the vaccine, resulting in a healthy non-vaccinee bias, especially in the elderly. In the absence of co-variate data on comorbidities and other variables that compare non-vaccinated with different dose vaccinated people, it is not possible to determine if the differences can be explained by the vaccination status or the comorbidities in the vaccinated populations. The results may also be explained by an vaccine-induced increased susceptibility to other diseases than COVID-19, which has raised the demand already to study the non-specific effects of mRNA vaccines on the overall mortality in depth.[18] However, it has been reported from Japan that after mass vaccination with the third dose of mRNA vaccines in 2022, significant excess mortality was observed for all cancers and some specific cancers, including prostate cancer, pancreatic cancer and breast cancer.[19] This is unlikely to explain a higher rate shortly after a vaccination, but may partly explain the increased rates associated with dose 3 in people aged 80 years and over from May 2022.

In rats, the mRNA vaccines mRNA1273 (Moderna) and BNT162b2 (BioNTech/Pfizer) were found to induce specific dysfunctions of the heart. mRNA1273 caused induced both arrhythmic and completely irregular contractions, while BNT162b2 increased cardiomyocyte contraction at the cellular level. Both changes can significantly increase the risk of acute cardiac events and may therefore explain the excess mortality after vaccination[20] and the increase in “sudden unexpected deaths”. This may also partly explain the generally higher non-COVID-19 mortality rate in all age groups. Vaccine-associated myocarditis has also been described to be potentially fatal,[21] with most hospitalized cases of myocarditis occurring among male adolescents.[22]

A third striking pattern are the higher age-adjusted non-COVID-19 mortality rates among those aged 18 – 39 years (maximum: 16.7 times higher), which decreased with increasing age, as shown for those aged 40 – 49 years (maximum: 5.7 times higher), those aged 50 – 59 years (maximum: 3.7 times higher) and those aged 60 – 69 years (maximum: 3.4 times higher). An assumed “non-healthy vaccinee bias” is not evident to appear only after dose 3. We currently have no medical explanation for this surprising finding. Moderna’s bivalent booster vaccine was approved in the UK in August 2022, so that it may only explain the increased rates after August 2022, but not those between April and July 2022.

Age-standardized COVID-19 mortality rates were mostly only lower among the ever vaccinated before the dominance of the omicron variant. A lower vaccine efficacy against the omicron variant has been reported, which includes a lower effectiveness against death.[23] The comparison between the age-standardized non-COVID-19 mortality rates per 100,000 and the age-standardized COVID-19 mortality rates per 100,000 shows that both the level of non-COVID-19 mortality and the vaccine-associated increase in non-COVID-19 mortality were higher compared to the COVID-19 mortality and the vaccine-associated decrease in COVID-19 mortality, suggesting an overall negative benefit-risk-evaluation for the COVID-19 vaccines regarding mortality.

However, our analyses have relevant limitations. First, we were unable to adjust for comorbidities, sex, socioeconomic and other risk factors that affect mortality risk in the general population. In addition, it is possible that vaccinated and unvaccinated individuals may have different age distributions (even more so in the upper age stratum), and thus this crude age adjustment does not fully adjust for age.

Second, there may also be an important selection bias, especially among the elderly. Some of those who died may have been so ill that they were unable or unwilling to receive a second dose if they were thought to be terminally ill, or if they were unable to tolerate the first dose because of their general weakness. People with two doses may have had, on average, more comorbidities than the unvaccinated. The older people who chose not to be vaccinated may have been mostly healthy. Although this is only speculation, it may provide an alternative explanation for the increased age-adjusted non-COVID-19 mortality among those who received the COVID-19 vaccine.

Third, selection biases such as the healthy vaccinee type or, conversely, healthy non-vaccinee type, may also have affected the results. This type of bias is different among countries, settings, time periods, and health systems. For example, countries like Israel, Austria and USA have documented mostly healthy vaccinee bias rather than healthy non-vaccinee bias.[24,25,26] Possibly the results presented here may be explained by a healthy non-vaccinee bias.

Fourth, it is possible that COVID-19 and non-COVID-19 deaths were misclassified to an unknown extent. However, the possible effect of misclassification on the overall results cannot be predicted.

In 2022, an estimate of 18.2 million COVID-19 deaths worldwide was made for the years 2020 and 2021, despite a number of confirmed COVID-19-associated deaths of 5.9 million. It is important to note that the number of "confirmed" COVID-19-associated deaths is likely to be overestimated because of the April 2020 guidelines from the WHO.[27] It states: “With reference to section 4.2.3 of volume 2 of ICD-10, the purpose of mortality classification (coding) is to produce the most useful cause of death statistics possible. Thus, whether a sequence is listed as ‘rejected’ or ‘accepted’ may reflect interests of importance for public health rather than what is acceptable from a purely medical point of view. Therefore, always apply these instructions, whether they can be considered medically correct or not.” This invites the non-medically correct attribution of a death to COVID-19 if it is judged to be "in the interest of public health". The April 2020 guidelines also state that “a manual plausibility check is recommended for certificates where COVID-19 is reported, in particular for certificates where COVID-19 was reported but not selected as the underlying cause of death for statistical tabulation.” In The Netherlands it has been argued that strict compliance to these WHO guidelines may have contributed to a overreporting of COVID-19 deaths.[28]

But regardless of the unanswered questions about confirmed COVID-19 deaths, the even higher estimate of 18.2 million COVID-19 deaths worldwide was based on total excess mortality, although there is no evidence to support the simplified approach of considering total excess mortality as COVID-19 mortality.[29] Based on the results of this study, it seems reasonable to assume that an unknown proportion of the additional 12.3 million deaths may be explained by the COVID-19 vaccination starting in 2021, based on the substantially higher age-adjusted non-COVID-19 mortality rates after dose 1 between April and December 2021 among those aged 50 years and older. This assumption is further supported by the finding that the participants of the phase 3 randomized controlled trial of BNT162b2, when followed up for 6 months instead of 20 weeks as previously published after completing the vaccination,[30] found 21 deaths among the vaccinated and 17 deaths among the unvaccinated.[31] The authors found evidence of an over 3.7-fold increase in number of deaths due to cardiac events in the BNT162b2 vaccinated individuals compared to those who received only the placebo. In addition, a fatal case post vaccination has been reported who still had vaccine in the right ventricle including multiple healing myocardial injuries dating two to three weeks prior to death and overlapping with the time of application of the second vaccine injection 19 days prior to death.[32]

We acknowledge that the excess deaths are subject to many uncertainties and that causal explanations require great caution.[33] However, despite the many uncertainties, it should be considered that the COVID-19 vaccines may have contributed to the excess mortality, to whatever extent.

Conclusions

Although a causal relationship between excess mortality and vaccination against COVID-19 has not been firmly established, a higher age-adjusted non-COVID-19 mortality rates among the COVID-19 vaccinated in several age groups was found that requires further research

References

1.

Mostert S, Hoogland M, Huibers M, Kaspers G. 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 Heal [Internet]. 2024 May 3 [cited 2024 Jun 4];2(1):e000282. Available from: https://bmjpublichealth.bmj.com/content/2/1/e000282

2.

Ioannidis JPA, Zonta F, Levitt M. Variability in excess deaths across countries with different vulnerability during 2020-2023. Proc Natl Acad Sci U S A [Internet]. 2023 [cited 2024 Jun 4];120(49):e2309557120. Available from: https://pubmed.ncbi.nlm.nih.gov/38019858/

3.

Kuhbandner C, Reitzner M. Estimation of Excess Mortality in Germany During 2020-2022. Cureus. 2023;15(5):e39371.

4.

Morfeld P, Timmermann B, Lewis P, Erren T. Increased Mortality in Germany and in the Individual German States During the SARS-CoV-2/COVID-19 Pandemic in 2020 and 2021. Dtsch Arztebl Int [Internet]. 2022 Aug 22 [cited 2024 Apr 17];119(33–34):560–1. Available from: https://pubmed.ncbi.nlm.nih.gov/36422870/

5.

Kuhbandner C, Reitzner M. Differential Increases in Excess Mortality in the German Federal States During the COVID-19 Pandemic. Researchgate [Internet]. 2024 [cited 2024 Apr 17];preprint. Available from: https://www.researchgate.net/publication/378124684_Differential_Increases_in_Excess_Mortality_in_the_German_Federal_States_During_the_COVID-19_Pandemic

6.

Lytras T, Athanasiadou M, Demetriou A, Stylianou D, Heraclides A, Kalakouta O. Lack of association between vaccination rates and excess mortality in Cyprus during the COVID-19 pandemic. Vaccine [Internet]. 2023 May 2 [cited 2024 Jun 3];41(18):2941–6. Available from: https://pubmed.ncbi.nlm.nih.gov/37012116/

7.

Economidou EC, Markou N, Prokopi K, Avraam D, Soteriades ES. Excess Mortality in Cyprus during the COVID-19 Epidemic. J Community Med Public Heal. 2024;8(1):407.

8.

Haklai Z, Goldberger NF, Gordon ES. Mortality during the first four waves of COVID-19 pandemic in Israel: March 2020-October 2021. Isr J Health Policy Res [Internet]. 2022 Dec 1 [cited 2024 Jun 5];11(1):24. Available from: https://pubmed.ncbi.nlm.nih.gov/35642003/

9.

Alicandro G, Remuzzi G, Centanni S, Gerli A, La Vecchia C. Excess total mortality during the Covid-19 pandemic in Italy: updated estimates indicate persistent excess in recent months. Med Lav [Internet]. 2022 Apr 26 [cited 2024 Jun 5];113(2):e2022021. Available from: https://pubmed.ncbi.nlm.nih.gov/35481574/

10.

Faust JS, Renton B, Chen AJ, Du C, Liang C, Li SX, et al. Uncoupling of all-cause excess mortality from COVID-19 cases in a highly vaccinated state. Lancet Infect Dis [Internet]. 2022 Oct 1 [cited 2024 Jun 5];22(10):1419–20. Available from: https://pubmed.ncbi.nlm.nih.gov/36007530/

11.

Liu JY, Chen TJ, Hou MC. Does COVID-19 vaccination cause excess deaths? J Chin Med Assoc [Internet]. 2021 Sep 1 [cited 2024 Jun 3];84(9):811–2. Available from: https://pubmed.ncbi.nlm.nih.gov/34524211/

12.

Wadman M. Scientists quit journal board, protesting 'grossly irresponsible' study claiming COVID-19 vaccines kill. Science (80-). 2021 Jul 1;online.

13.

Sessa F, Salerno M, Esposito M, Di Nunno N, Zamboni P, Pomara C. Autopsy Findings and Causality Relationship between Death and COVID-19 Vaccination: A Systematic Review. J Clin Med [Internet]. 2021 Dec 1 [cited 2022 Aug 9];10(24):5876. Available from: /pmc/articles/PMC8709364/

14.

Häring N. Karl Lauterbach und die Übersterblichkeit [Internet]. 2023 [cited 2023 Jun 30]. Available from: https://norberthaering.de/news/lauterbach-uebersterblichkeit/

15.

Office for National Statistics. Deaths by vaccination status, England [Internet]. 2023 [cited 2024 May 29]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsbyvaccinationstatusengland

16.

Davies G. The rollout of the COVID-19 vaccination programme in England [Internet]. 2022 [cited 2025 Feb 6]. Available from: https://www.nao.org.uk/wp-content/uploads/2022/02/The-rollout-of-the-COVID-19-vaccination-programme-in-England.pdf

17.

Wyller TB, Kittang BR, Ranhoff AH, Harg P, Myrstad M. Nursing home deaths after COVID-19 vaccination. Tidsskr Nor Laegeforen. 2021/05/22. 2021;141.

18.

Rubio-Casillas A, Rodriguez-Quintero CM, Redwan EM, Gupta MN, Uversky VN, Raszek M. Do vaccines increase or decrease susceptibility to diseases other than those they protect against? Vaccine [Internet]. 2024 Jan 25 [cited 2024 May 29];42(3):426–40. Available from: https://pubmed.ncbi.nlm.nih.gov/38158298/

19.

Gibo M, Kojima S, Fujisawa A, Kikuchi T, Fukushima M, GIBO M, et al. Increased Age-Adjusted Cancer Mortality After the Third mRNA-Lipid Nanoparticle Vaccine Dose During the COVID-19 Pandemic in Japan. Cureus [Internet]. 2024 Apr 8 [cited 2024 Apr 17];16(4):e57860. Available from: https://www.cureus.com/articles/196275-increased-age-adjusted-cancer-mortality-after-the-third-mrna-lipid-nanoparticle-vaccine-dose-during-the-covid-19-pandemic-in-japan

20.

Schreckenberg R, Woitasky N, Itani N, Czech L, Ferdinandy P, Schulz R. Cardiac side effects of RNA-based SARS-CoV-2 vaccines: Hidden cardiotoxic effects of mRNA-1273 and BNT162b2 on ventricular myocyte function and structure. Br J Pharmacol [Internet]. 2024 Feb 1 [cited 2024 May 24];181(3):345–61. Available from: https://pubmed.ncbi.nlm.nih.gov/37828636/

21.

Hulscher N, Hodkinson R, Makis W, McCullough PA. Autopsy findings in cases of fatal COVID-19 vaccine-induced myocarditis. ESC Hear Fail [Internet]. 2024 [cited 2024 Jun 3]; Available from: https://pubmed.ncbi.nlm.nih.gov/38221509/

22.

Montag K, Kampf G. Hospitalised Myocarditis and Pericarditis Cases in Germany Indicate a Higher Post-Vaccination Risk for Young People Mainly after COVID-19 Vaccination. J Clin Med [Internet]. 2022 Oct 1 [cited 2024 Jun 3];11(20):6073. Available from: https://pubmed.ncbi.nlm.nih.gov/36294393/

23.

Paul P, El-Naas A, Hamad O, Salameh MA, Mhaimeed N, Laswi I, et al. Effectiveness of the pre-Omicron COVID-19 vaccines against Omicron in reducing infection, hospitalization, severity, and mortality compared to Delta and other variants: A systematic review. Hum Vaccin Immunother [Internet]. 2023 [cited 2024 Jun 4];19(1):2167410. Available from: https://pubmed.ncbi.nlm.nih.gov/36915960/

24.

Chalupka A, Riedmann U, Richter L, Chakeri A, El-Khatib Z, Sprenger M, et al. Effectiveness of the First and Second Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine Dose: A Nationwide Cohort Study From Austria on Hybrid Versus Natural Immunity. Open Forum Infect Dis [Internet]. 2024;11(10):ofae547. Available from: https://doi.org/10.1093/ofid/ofae547

25.

Høeg TB, Duriseti R, Prasad V. Potential “Healthy Vaccinee Bias” in a Study of BNT162b2 Vaccine against Covid-19. N Engl J Med. 2023;389(3):284–5.

26.

Xu S, Huang R, Sy LS, Glenn SC, Ryan DS, Morrissette K. COVID-19 Vaccination and Non – COVID-19 Mortality Risk — Seven Integrated Health Care Organizations ,. MMWR - Morb Mortal Wkly Rep. 2021;70(43):1520–4.

27.

WHO. INTERNATIONAL GUIDELINES FOR CERTIFICATION AND CLASSIFICATION (CODING) OF COVID-19 AS CAUSE OF DEATH Based on ICD International Statistical Classification of Diseases [Internet]. 2020 [cited 2023 Aug 3]. Available from: https://www.who.int/docs/default-source/classification/icd/covid-19/guidelines-cause-of-death-covid-19-20200420-en.pdf

28.

Smulders M. Oversterfte: met of door covid-19? Med Contact (Bussum). 2024;79(5):18–21.

29.

Wang H, Paulson KR, Pease SA, Watson S, Comfort H, Zheng P, et al. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. Lancet (London, England) [Internet]. 2022 Apr 16 [cited 2024 May 29];399(10334):1513–36. Available from: https://pubmed.ncbi.nlm.nih.gov/35279232/

30.

Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020/12/11. 2020;383(27):2603–15.

31.

Michels C, Perrier D, Kunadhasan J, Clark E, Gehrett J, Gehrett B, et al. Forensic analysis of the 38 subject deaths in the 6-Month Interim Report of the Pfizer/BioNTech BNT162b2 mRNA Vaccine Clinical Trial. Int J Vaccine Theory, Pract Res. 2023;3(1):973–1008.

32.

Krauson AJ, Casimero FVC, Siddiquee Z, Stone JR. Duration of SARS-CoV-2 mRNA vaccine persistence and factors associated with cardiac involvement in recently vaccinated patients. NPJ vaccines [Internet]. 2023 Dec 1 [cited 2024 Jun 19];8(1):141. Available from: https://pubmed.ncbi.nlm.nih.gov/37758751/

33.

Ioannidis JPA, Zonta F, Levitt M. Flaws and uncertainties in pandemic global excess death calculations. Eur J Clin Invest. 2023;53(8):e14008.

Peer Review of: Age-adjusted non-COVID-19 mortality rates according to the COVID-19 vaccination status

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Review: Age-adjusted non-COVID-19 mortality rates according to the COVID-19 vaccination status

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[A] Kampf and Fornerod examine age-adjusted non-COVID-19 mortality rates according to the COVID-19 vaccination status using data from England covering the period from April 2021 to May 2023. I have not been able to verify the raw numbers and I advise the authors to examine them again as there are often updates and revisions in these datasets. Also I understand that the study did not have a pre-registered protocol and the analyses are exploratory – if so, this should be stated. Some other aspects of the analytical design are not reported and adherence to STROBE guidelines may improve the manuscript. It should also be explained why only England data were used and not other parts of the UK and/or other countries, where hopefully some similar data can be retrieved. Also why were the first 4 months of the vaccination campaign excluded from analyses.

[B] Assuming the raw numbers are correct, the authors observe that the age-adjusted non-COVID-19 mortality rate was higher in COVID-19 vaccinated groups. For doses 1 and 2, the relative increase was highest in the elderly, while for the dose 4 the relative increase was highest in the young (18-39 years old) stratum. The authors then proceed to speculate about various explanations for these observations and many of them center on the possibility of death risk increase related to the COVID-19 vaccines. I find these interpretations very erratic, given that everything that they observe can be readily explained with much anticipated, commonplace selection biases, mostly of the “healthy non-vaccinee bias” type (but also some “healthy vaccine bias”) in these specific data. I do worry that some people may read the discussion and treatment of the results by Kampf and Fornerod and be misled into thinking that COVID-19 vaccines are responsible for a sizeable part of the excess mortality seen in many countries.

[C] Specifically, all the mortality estimates presented in the paper use only age-adjustment, since only age grouping was available (unclear why gender was also not used, since it must have been readily retrievable). This leaves out all the comorbidities and socioeconomic and other risk factors that largely shape mortality risk in a general population. Even the age-adjustment may be not perfect, since it includes very crude age groups where the upper versus the lower end of each age bracket may differ several fold in mortality risk. Thus even within the same age bin, vaccinated and unvaccinated individuals may have different age distributions (even more so in the upper age stratum) and thus this crude age adjustment does not fully adjust even for age. This is obvious even in the benchmark group, the unvaccinated cohort, where the authors claim that the age-adjusted rates are stable over time, but in fact there are easily 2- and 3-fold differences across different time periods, meaning that the composition and risk factor profile of the unvaccinated group itself changes substantially over time. Besides bias due to simple selection/choice to vaccinate, potential survivorship biases and harvesting effects may all intermingle to create very complex patterns that cannot be dissected simply by the group-level information available to Kampf and Fornerod.

[D] I wonder whether at least one could obtain information on nursing home status and stratify further accordingly. If so, some further adjustment/stratification for this may modestly improve the situation. Still, large proportions of the risk variance for death risk remain unaccounted and, rationally, one has to assume that any differences in non-COVID-19 deaths may be simply due to such unaccounted differences. Any other complex interpretation is quite implausible compared to this one based on plain Occam’s razor considerations.

[E] For example, it is probably not surprising that people who receive just a single dose are at the highest risk,

especially if they are elderly. One may speculate: perhaps many of them who died were so sick that they could not even get a second dose or did not want to get one if they were considered to have terminal disease or if they had a poor tolerance of the first dose given their overall debilitation – impossible to tell exactly what happened without having granular data on individuals and their risk profiles. People with two doses may also have more comorbidities on average than the unvaccinated, especially among the elderly. The elderly who decided to be unvaccinated were probably mostly very healthy. The selection biases can be complex, nevertheless. E.g. based on Figure 2, for 2 doses and 3 doses, it is probable that the first months witnessed mostly a healthy vaccinee bias (perhaps due to eager healthy people who wanted to get quickly vaccinated) but then this shifted to mostly non-healthy vaccine bias. As for the 4th dose, young people who decided to take a 4th dose may have included most of those who had serious comorbidities and strongly wished to get some extra protection. Again, one needs to have granular, individual level data to validate diverse speculations and make meaningful inferences.

[F] In all, I see nothing that is not possible to explain with selection biases in the England data. Of course, selection biases of the healthy vaccinee or, conversely, healthy non-vaccinee, types may not be the same in different countries, settings, time periods, and health systems. For example, other countries like Israel, Austria and USA have documented mostly healthy vaccinee bias rather than healthy non-vaccinee bias [1,2,3]. However, attributing these results and patterns not to these commonplace biases but to harmful or beneficial vaccine effects is a dangerous fallacious stretch. Better vaccine pharmacovigilance is definitely needed to understand any potential vaccine harms, but strong mortality extrapolations based on such data cause confusion and probably only show bias against vaccines. Furthermore, the authors do not even restrict themselves to COVID-19 vaccines in the discussion, but also cite selectively data on some other vaccines.

[G] Some other issues also create major problems in these analyses. First, there can be misclassification between COVID-19 and non-COVID-19 deaths. The impact on the types of analyses presented here is unpredictable.

[H] Second, a more appropriate approach would be to use time-to-event analyses with vaccination doses as variables introduced at time t=21 (or whatever is considered appropriate for a time window, even this can be contentious) instead of the crude age-adjustment comparison used here.

[I]Third, the whole discussion about excess deaths and the effort of the authors to raise the possibility that vaccines may have accounted for so many excess deaths is unrealistic. I sympathize with the authors that estimates of excess deaths are speculative and that attributing them mostly, if not entirely, to COVID-19, is probably very wrong. Moreover, it is likely that these estimates are inflated and the true excess deaths are substantially lower [4]. Non-COVID-19 deaths due to disruption of health care (sometimes due to measures taken), increase in drug use and overdose, alcohol, violence, mental health, poor cancer care and more may be key contributors to some of the excess deaths not accounted by COVID-19 deaths. In poor countries and in marginalized populations, starvation and devastation in vulnerable populations may also have contributed. But claiming that vaccines killed large numbers of people is implausible. This does not exclude that some adverse effects from vaccines may have resulted in some deaths. However, the scale of numbers of vaccine-related deaths, based on what we know (and what even the authors cite in the discussion, if the respective papers are read more carefully) is probably many log-scales lower than the excess deaths documented in 2021-2023.

[J] In all, I worry that a reader of this paper may start suspecting that COVID-19 vaccines killed millions of people. It is far more likely that they saved several millions of people. Probably not as many as are sometimes touted – but still a major beneficial contribution. More accurate estimates will require much better, detailed individual-level data and careful approaches to the problem. Even with the best possible data, some uncertainty will remain, given the observational nature of these datasets. Moreover, it is important to have granular, rich data on individual characteristics to understand also the duration of life gained or life lost rather than the simplistic lives saved or killed by adverse events. Eventually, the truth about COVID-19 vaccine effects may be somewhere between the extremes presented by zealot enthusiasts and zealot skeptics. Extreme interpretations will need to be tamed in order to try to understand the risk-benefits in different age groups, time periods, and settings.

References

1. Chalupka A, Riedmann U, Richter L, Chakeri A, El-Khatib Z, Sprenger M, Theiler-Schwetz V, Trummer C, Willeit P, Schennach H, Benka B, Werber D, Høeg TB, Ioannidis JPA, Pilz S. Effectiveness of the First and Second Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine Dose: A Nationwide Cohort Study from Austria on Hybrid Versus Natural Immunity. Open Forum Infectious Diseases, 11:ofae547, 2024. doi: 10.1093/ofid/ofae547.

2. Høeg TB, Duriseti R, Prasad V. Potential “healthy vaccinee bias” in a study of BNT162b2 vaccine against Covid-19. New England Journal of Medicine, 389:284–5, 2023.

3. Xu S, Huang R, Sy LS, et al. COVID-19 vaccination and non-COVID-19 mortality risk—seven integrated health care organizations, United States, December 14, 2020–July 31, 2021. Morbidity and Mortality Weekly Reports, 70:1520–4, 2021.

4. Ioannidis JPA, Zonta F, Levitt M. Flaws and uncertainties in pandemic global excess death calculations. European Journal of Clinical Investigation, 53:e14008, 2023. doi:10.1111/eci.14008.

Competing Interests

None.

Peer Review of: Age-adjusted non-COVID-19 mortality rates according to the COVID-19 vaccination status

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Review: Age-adjusted non-COVID-19 mortality rates according to the COVID-19 vaccination status

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It is not surprising that we see excess mortality following the pandemic lockdowns. Since lockdowns disrupted regular medical care, we should expect to see worse health outcomes down the road, including excess mortality. For example, cancer detection and treatment were interrupted during the lockdowns, and that is expected to have long-term negative impact on cancer survival. If not, we are wasting medical resources on useless cancer care.

Other things may also contribute to the post-pandemic excess mortality. Adverse reactions to the Covid vaccines have been suggested as one possible cause. Modelling studies have come to widely varying conclusions about the total number of lives saved or killed by the vaccines, ranging from 19.8 million saved [1] to 17 million killed [2]. There is enormous uncertainty in such estimates, due to their use of aggregated ecological data, questionable modelling assumptions and unreliable parameter estimates. Trying to make such worldwide estimates may be futile when we don’t even have proper randomized clinical trials (RCTs) to tell us whether the vaccines reduced mortality, as they were only designed to evaluate the efficacy at reducing symptomatic disease. The closest we have are pooled RCT data, with 95% confidence intervals showing that the adenovirus vector vaccine reduced overall mortality by somewhere between 30% and 81%, while the mRNA vaccines caused somewhere between a 37% decrease and a 71% increase in mortality [3]. This was for the mostly young population enrolled in the RCTs. There are no RCT estimates for older adults, who were at the highest risk of Covid mortality.

With the lack of RCT data, and the inherent weakness of aggregated data, we must use individual observational data. There is evidence that the vaccines reduce Covid mortality among older people [4]. To get a complete picture, it is also important to look at the potential effect on non-Covid mortality using individual data. Even if the vaccines saved millions of people from dying from Covid, it is important to know if they caused serious adverse reactions or non-Covid deaths. This is what Kampf and Fornerod have explored using public data from England (Kampf and Fornerod, 2025). Importantly, they have done this for different age groups and different number of vaccine doses.

The most interesting and striking observation is that during the spring and summer of 2021, the age-adjusted

non-Covid mortality rate was more than twice as high among those with only one vaccine dose compared to the non-vaccinated, while it was less for those who had two doses compared to the non-vaccinated. What could explain this curious finding?

One possible explanation is that the first dose of the vaccine causes a fatal adverse reaction in some individuals. If they survive the first dose though, it could mean that they are resistant to the fatal adverse reaction. It's like a situation with a bunch of swimmers and non-swimmers. Those that cannot swim will drown the first time you throw them in the water. If you throw the survivors in the water a second time, they will all survive since they have already proven that they can swim. Those that survive the first dose may also be generally healthier so that they have lower non-Covid mortality than the unvaccinated.

A second possible explanation is that it is not due to the vaccine but to underlying health differences in the different vaccine groups, since this is not a randomized study. If healthy people are more likely to be vaccinated, there is healthy vaccinee bias, which could explain that those with two doses have lower non-Covid mortality than the unvaccinated. On the other hand, if frail patients in for example nursing homes are more likely to be vaccinated, the bias could explain that those with one dose have higher non-Covid mortality than the unvaccinated. What's curious with these data is that to explain both results, there must be both a health vaccinee bias and a non-healthy vaccinee bias.

Primarily descriptive in nature, the results by Kampf and Fornerod need to be taken very seriously and further investigated. While there is no statistical significance testing or confidence intervals, the results are too consistent over time and age groups to be generated by chance.

To examine these data further, it is necessary to consider different vaccine brands. With different dose recommendations, as well as timing between doses, biases could operate in different directions for the different Covid vaccines. It is also necessary to look at the mortality data by cause of death. If the excess non-Covid mortality is due to one or more of the vaccines, it is likely to be manifest itself for only a few disease outcomes. On the other hand, if the results are due to healthy or unhealthy vaccination bias, one may expect the difference to be manifested across a wide variety of unrelated diseases.

My understanding is that such further analyses cannot be done using the data that is publicly available. In their important study, Kampf and Fornerod have done what is possible to do with the public data. Further analyses require permission from the data holders.

References

1. Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. Lancet Infect Diseases, 22:1293-1302, 2022. doi: 10.1016/S1473-3099(22)00320-6.

2. Rancourt D, Baudin M, Hickey J, Mercier J. COVID-19 vaccine-associated mortality in the Southern Hemisphere. Correlation Report, September 2023.

3. Benn CS, Schaltz-Buchholzer F, Nielsen S, Netea MG, Aaby P. Randomized clinical trials of COVID-19 vaccines: Do adenovirus-vector vaccines have beneficial non-specific effects? iScience, 26:106733, 2023. doi: 10.1016/j.isci.2023.106733.

4. Nordström P, Ballin M, Nordström 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, 399:814-823, 2022. doi: 10.1016/S0140-6736(22)00089-7.

5. Kampf G, Fornerod M, Age-adjusted non-COVID-19 mortality rates according to the COVID-19 vaccination status, Journal of the Academy of Public Health, 1, 2025.

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Author Rejoinder: Age-adjusted non-COVID-19 mortality rates according to the COVID-19 vaccination status

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Many thanks for the helpful comments that have helped to improve the quality of the manuscript.

Response to Peer Review by John P.A. Ioannidis

[A] The data were uploaded from the official homepage on May 29, 2024, which is approximately one year after the latest time point described in the table. That is why we think it is rather unlikely that one year later data were updated. That the analyses were exploratory without a pre-registered protocol is now stated in the method section. Data from England were used because the dataset only included data from England. Other sources or data from other parts of the UK were not available at that time. The first 4 months of the UK vaccination were not included by the Office for National Statistics. That is why it was not possible to include in the analyses.

[B] The aspect of a possible healthy vaccine bias has been added to the discussion.

[C] That is correct. Other risk factors are not described, neither in the manuscript nor in the underlying datasets, so that an adjustment to the comorbidities and socioeconomic and other risk factors could not be done by us. This is certainly a relevant limitation of the analyses. At the same time, however, the COVID-19 age-adjusted mortality did not show major deviations according to the vaccination status although the same limitations apply such as lack of adjustment to the comorbidities and socioeconomic and other risk factors. If we assume that the higher non-COVID-19 age-adjusted mortality among the vaccinated is primarily explained by comorbidities and socioeconomic and other risk factors, would it not be plausible to assume that a similar finding is observed for the COVID-19 age-adjusted mortality? But this was not the case. Nevertheless, we included a paragraph in the discussion to explain the major and relevant limitations as suggested by the respected reviewer.

[D] The official data do not provide additional information on the nursing home status. That is why it was not possible to stratify the data accordingly.

[E] These are certainly interesting aspects of relevance. We have added them in the discussion to expand the discussion to other possible explanations for the non-COVID-19 morality rates.

[F] Many thanks for the comment. We have added a short paragraph to the discussion. The last two paragraphs of the discussion about other vaccines have been deleted.

[G] Misclassification is always possible, that is correct. We have added this aspect to the discussion.

[H] Unfortunately, this type of analysis was not possible based on the available data.

[I] We have added this relevant aspect briefly at the end of the discussion including the suggested reference.

[J] We agree. It is not the intention to speculate that COVID-19 vaccines could have killed millions of people. However, in many countries, it seems to be unmentionable in public that the vaccines may have contributed to even a little to the overall excess mortality observed in many countries in recent years. No possible cause should be excluded per se when looking for explanations for excess mortality.

Response to Peer Review by Martin Kulldorff

We agree that there is enormous uncertainty in estimates of post-pandemic excess mortality. The possible explanations for our findings are now included in the discussion, as suggested by both reviewers. We agree that causality remains unknown, as now clearly described at the end of the discussion. We also agree that further stratified analyses are warranted.

Reviewer Closure

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Reviewer Closure: Age-adjusted non-COVID-19 mortality rates according to the COVID-19 vaccination status

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Kampf and Fornerod have made several revisions based on my previous comments and I thank them for these changes. However, they have been unable to address any of the fundamental concerns that I had. They have not performed any new, substantive analyses, since they are limited by the lack of availability of relevant data. Despite a most welcome addition of limitations in the Discussion, their analysis continues to be a very crude probe with extremely limited ability to perform any proper adjustments. Its credibility therefore in making any causal inferences is close to zero. I continue to disagree strongly with the overall discussion offered by the authors on their findings. Their use and reading of the literature are extremely selective. They try to imply that their data suggest that vaccines may have been responsible for a considerable portion of the observed excess deaths, which is a fundamentally unfounded conclusion. I dissect here their Discussion, because even though it is egregiously biased, these points are useful to highlight as they represent popular false arguments that are often raised especially in social media and sadly inappropriately undermine vaccines.

1. It is not correct that “rates were expected to be in a similar range in each age group, assuming that there is no association between the vaccination status and the non-COVID-19 mortality rates.” Uncorrected, unadjusted group data are almost certain to show some association, which is almost certainly bias, this is a basic expectation in this type of data. The next couple of paragraphs of the Discussion are then trying to read signals out of what is probably pure noise and bias.

2. The study from Norway did raise some genuine concern early on. Based on this and other similar observations, vaccination in moribund nursing home individuals was probably reduced. However, even if you take these results literally, the total number of expected deaths at a global level from that reason are likely to be in the range of 15,000 [1]. This is a miniscule number compared to the supposedly many millions of deaths that are unexplained according to Kampf and Fornerod. Moreover, the life-time lost would be a few days or weeks for these people, even if we were to accept that their demise was accelerated by vaccination. The same applies to the alluded observations from Germany.

3. Non-specific effects on death remain a speculative issue. The evidence for or against such non-specific effects for vaccines in general, and even more for COVID-19 vaccines, is even more thin and bias-prone that the evidence provided by Kampf and Fornerod in their study.

4. The Japanese paper cited by Kampf and Fornerod has been retracted. The retraction notice runs: “The Editors-in-Chief have retracted this article. Upon post-publication review, it has been determined that the correlation between mortality rates and vaccination status cannot be proven with the data presented in this article. As this invalidates the conclusions of the article, the decision has been made to retract. The authors disagree with this retraction.” I agree that the paper made unbelievable strong statements given the type of data that it had.

5. The study on rat cells has unknown relevance to humans, let alone to human deaths. The cited article on

vaccine-associated myocarditis mortality was also withdrawn by the previous journal where it had been published, and the retraction note runs: “This Article-in-Press has been withdrawn at the request of the Editors-in-Chief. Members of the scientific community raised concerns about this Article-in-Press following its posting online. The concerns encompassed. • Inappropriate citation of references. • Inappropriate design of methodology. • Errors, misrepresentation, and lack of factual support for the conclusions. • Failure to recognise and cite disconfirming evidence. The concerns were shared with the authors, who prepared a response and submitted a revised manuscript for consideration by the journal. In consideration of the extent of the concerns raised and the responses from the authors, the journal sent the revised manuscript to two independent peer-reviewers. The peer-reviewers concluded that the revised manuscript did not sufficiently address the concerns raised by the community and that it was not suitable for publication in the journal. The authors disagree with this withdrawal and dispute the grounds for it.” Myocarditis is indeed a recognized adverse event for mRNA vaccines, especially in young males and some deaths may have been caused by it. However, the best estimates would suggest roughly a few hundred deaths at a global level (or far fewer) over the entire pandemic: the risk of myocarditis seems to be less than 150 per million in children and adolescents and much lower in higher ages and among cases 1-4% may die [2-4] – in fact, these rates may also be inflated. At any rate, such cardiac deaths would account for an extremely miniscule portion of any observed excess deaths during the pandemic.

6. There is absolutely nothing striking about the age pattern; for this type of data, this (or more extreme even) patterns may easily occur without the vaccines having anything to do with it. Totally or partly different patterns have been seen in similar groupings/analyses in other countries, now cited by Kampf and Fornerod in their revised paper.

7. The meandering extrapolation used to suggest “an overall negative benefit-risk” is completely unfounded. It is very likely indeed that effectiveness against Omicron was less versus effectiveness for previous variants, this has been widely documented [5-7]. But the logical jump from reduced effectiveness to net harm is totally unjustified.

8. There is absolutely no way that one can account for 12.3 million deaths from vaccine adverse events, each of which seems likely to account for a few hundred or a few thousands of deaths globally at most, based on the incidence data we have [1]. Non-COVID-19 reasons like deaths from health care disruption, poor health care and limited access, overdose, deaths of despair, and many other problems that accompanied the pandemic and the often highly detrimental pandemic response can readily account for millions of deaths. Blaming these deaths to vaccines only shows bias and, worse, takes our efforts away from fixing major real problems that have plagued public health even before the pandemic and have decimated communities during the pandemic. The roots of these problems may continue unaddressed, while weird vaccine blame games are being played.

9. I am a strong supporter of the need for randomized trials, and it is a pity that we did not get more randomized evidence. However, extrapolating from 21 and 17 deaths with such short follow-up to millions of deaths from harms is among the most improbable extrapolations I have seen ever made in the medical literature.

10. A single case adds negligible weight to the claims made here. As above, it is indeed possible that some deaths occurred due to myocarditis, but the scale of numbers is 1000-fold or more lower than the phenomenon that Kampf and Fornerod try to explain.

11. Still a disservice, I think, to make the conclusion “that the COVID-19 vaccines may have contributed to the excess mortality”. Given that more than 13 billion doses of COVID-19 vaccines were given, some deaths due to adverse events are likely to have happened, but they are likely to be overall far fewer than the lives saved. Vaccines in the balance saved more lives, especially among the elderly and the most vulnerable. Of course, risk-benefits and cost-effectiveness need to be carefully studied for different age and risk profile strata and one size does not fit all. However, I am afraid that analyses that use such crude data to make such claims as Kampf and Fornerod did, do not help to advance our knowledge on this front.

References

1. Ioannidis JPA, Pezzullo AM, Cristiano A, Boccia S. Global estimates of lives and life-years saved by COVID-19 vaccination during 2020-2024. medRxiv 2024; doi: https://doi.org/10.1101/2024.11.03.24316673. JAMA Health forum (accepted).

2. Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, Watkinson P, Khunti K, Harnden A, Coupland CAC, Channon KM, Mills NL, Sheikh A, Hippisley-Cox J. Risk of Myocarditis After Sequential Doses of COVID-19 Vaccine and SARS-CoV-2 Infection by Age and Sex. Circulation. 146:743–754, 2022.

3. Pillay J, Gaudet L, Wingert A, Bialy L, Mackie AS, Paterson DI, Hartling L. Incidence, risk factors, natural history, and hypothesised mechanisms of myocarditis and pericarditis following covid-19 vaccination: living evidence syntheses and review. BMJ. 378:e069445, 2022.

4. Cho JY, Kim KH, Lee N, Cho SH, Kim SY, Kim EK, Park JH, Choi EY, Choi JO, Park H, Kim HY, Yoon HJ, Ahn Y, Jeong MH, Cho JG. COVID-19 vaccination-related myocarditis: a Korean nationwide study. European Heart Journal, 44:2234–2243, 2023.

5. Chalupka A, Richter L, Chakeri A, El-Khatib Z, Theiler-Schwetz V, Trummer C, Krause R, Willeit P, Benka B, Ioannidis JPA, Pilz S. Effectiveness of a fourth SARS-CoV-2 vaccine dose in previously infected individuals from Austria. European Journal of Clinical Investigation, 54:e14136, 2024. doi: 10.1111/eci.14136.

6. Chalupka A, Riedmann U, Richter L, Chakeri A, El-Khatib Z, Sprenger M, Theiler-Schwetz V, Trummer C, Willeit P, Schennach H, Benka B, Werber D, Høeg TB, Ioannidis JPA, Pilz S. Effectiveness of the First and Second Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine Dose: A Nationwide Cohort Study From Austria on Hybrid Versus Natural Immunity. Open Forum Infectious Diseases, 11:ofae547, 2024. doi: 10.1093/ofid/ofae547.

7. Ioannou GN, Berry K, Rajeevan N, Li Y, Yan L, Huang Y, Lin HM, Bui D, Hynes DM, Rowneki M, Bohnert A, Boyko EJ, Iwashyna TJ, Maciejewski ML, Smith VA, Berkowitz TSZ, O'Hare AM, Viglianti EM, Aslan M, Bajema KL. Effectiveness of the 2023-to-2024 XBB.1.5 COVID-19 Vaccines Over Long-Term Follow-up: A Target Trial Emulation. Annals of Internal Medicine, 2025;178:348-359. [Epub 4 February 2025]. doi:10.7326/ANNALS-24-01015

Reviewer Closure

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Closure: Age-adjusted non-COVID-19 mortality rates according to the COVID-19 vaccination status

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Descriptive epidemiology is useful for raising issues that need thorough investigation. Access to and adjustment for potential confounding variables are needed before conclusions can be made from these UK data. This article will hopefully open the access to the additional variables needed to conduct a thorough observational study. Until then, the authors have wisely concluded that “excess deaths are subject to many uncertainties”, that “causal explanations require great caution”, that “a causal relationship … has not been firmly established” and that the question “requires further research”.

The unfortunate failure to conduct randomized trials to evaluate whether the Covid vaccines reduce mortality has led to observational and modelling studies with widely divergent claims concerning the number of lives saved or caused by the vaccines. This requires open and honest scientific discussions about the strengths and weaknesses of both data and methods. With traditional publishing, this manuscript might have been rejected by some journals before eventually being published without the reader having access to any of the peer-reviews. The way forward is not to hide descriptive epidemiological studies but to openly and honestly discuss them.