

Excess mortality across countries in the Western World since the COVID-19 pandemic: 'Our World in Data' estimates of January 2020 to December 2022

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ABSTRACT

Introduction Excess mortality during the COVID-19 pandemic has been substantial. Insight into excess death rates in years following WHO's pandemic declaration is crucial for government leaders and policymakers to evaluate their health crisis policies. This study explores excess mortality in the Western World from 2020 until 2022.

Methods All-cause mortality reports were abstracted for countries using the 'Our World in Data' database. Excess mortality is assessed as a deviation between the reported number of deaths in a country during a certain week or month in 2020 until 2022 and the expected number of deaths in a country for that period under normal conditions. For the baseline of expected deaths, Karlinsky and Kobak's estimate model was used. This model uses historical death data in a country from 2015 until 2019 and accounts for seasonal variation and year-to-year trends in mortality.

Results The total number of excess deaths in 47 countries of the Western World was 3 098 456 from 1 January 2020 until 31 December 2022. Excess mortality was documented in 41 countries (87%) in 2020, 42 countries (89%) in 2021 and 43 countries (91%) in 2022. In 2020, the year of the COVID-19 pandemic onset and implementation of containment measures, records present 1 033 122 excess deaths (P-score 11.4%). In 2021, the year in which both containment measures and COVID-19 vaccines were used to address virus spread and infection, the highest number of excess deaths was reported: 1 256 942 excess deaths (P-score 13.8%). In 2022, when most containment measures were lifted and COVID-19 vaccines were continued, preliminary data present 808 392 excess deaths (P-score 8.8%).

Conclusions Excess mortality has remained high in the Western World for three consecutive years, despite the implementation of containment measures and COVID-19 vaccines. This raises serious concerns. Government leaders and policymakers need to thoroughly investigate underlying causes of persistent excess mortality.

INTRODUCTION

Excess mortality is internationally recognised as an accurate measure for monitoring

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Excess mortality during the COVID-19 pandemic has been substantial. Insight into excess death rates in years following WHO's pandemic declaration is crucial for government leaders and policymakers to evaluate their health crisis policies.

WHAT THIS STUDY ADDS

⇒ Excess mortality has remained high in the Western World for three consecutive years, despite the implementation of containment measures and COVID-19 vaccines. This raises serious concerns.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

Government leaders and policymakers need to thoroughly investigate the underlying causes of persistent excess mortality.

and comparing health crisis policies across geographic regions. Lecess mortality concerns the number of deaths from all causes during a humanitarian emergency, such as the COVID-19 pandemic, above the expected number of deaths under normal circumstances.^{5–7} Since the outbreak of the COVID-19 pandemic, excess mortality thus includes not only deaths from SARS-CoV-2 infection but also deaths related to the indirect effects of the health strategies to address the virus spread and infection. \tilde{l}^{-4} The burden of the COVID-19 pandemic on disease and death has been investigated from its beginning. Numerous studies expressed that SARS-CoV-2 infection was likely a leading cause of death among older patients with pre-existing comorbidities and obesity in the early phase of the pandemic, that various containment measures were effective in reducing viral transmission and that COVID-19 vaccines prevented severe disease, especially among the elderly population. Although COVID-19 containment measures

COVID-19 vaccines were thus implemented to protect citizens from suffering morbidity and mortality by the COVID-19 virus, they may have detrimental effects that cause inferior outcomes as well. It is noteworthy that excess mortality during a crisis points to a more extensive underlying burden of disease, disablement and human suffering. If

On 11 March 2020, WHO declared the COVID-19 pandemic.¹⁷ Countries in the Western World promptly implemented COVID-19 containment measures (such as lockdowns, school closures, physical distancing, travel restrictions, business closures, stay-at-home orders, curfews and quarantine measures with contact tracing) to limit virus spread and shield its residents from morbidity and mortality.¹⁸ These non-pharmaceutical interventions however had adverse indirect effects (such as economic damage, limited access to education, food insecurity, child abuse, limited access to healthcare, disrupted health programmes and mental health challenges) that increased morbidity and mortality from other causes. 19 Vulnerable populations in need of acute or complex medical treatment, such as patients with cardiovascular disease, cerebrovascular conditions, diabetes and cancer, were hurt by these interventions due to the limited access to and delivery of medical services. Shortage of staff, reduced screening, delayed diagnostics, disrupted imaging, limited availability of medicines, postponed surgery, modified radiotherapy and restricted supportive care hindered protocol adherence and worsened the condition and prognosis of patients. 19-26 A recent study investigated excess mortality from some major non-COVID causes across 30 countries in 2020. Significant excess deaths were reported from ischaemic heart diseases (in 10 countries), cerebrovascular diseases (in 10 countries) and diabetes (in 19 countries).²⁷ On 14 October 2020, Professor Ioannidis from Stanford University published an overall Infection Fatality Rate of COVID-19 of 0.23%, and for people aged <70 years, the Infection Fatality Rate was 0.05%. Governments in the Western World continued to impose lockdowns until the end of 2021.

In December 2020, the UK, the USA and Canada were the first countries in the Western World that started with the roll-out of the COVID-19 vaccines under emergency authorisation.^{29–31} At the end of December 2020, a large randomised and placebo-controlled trial with 43548 participants was published in the New England Journal of Medicine, which showed that a two-dose mRNA COVID-19 vaccine regimen provided an absolute risk reduction of 0.88% and relative risk reduction of 95% against laboratory-confirmed COVID-19 in the vaccinated group (8 COVID-19 cases/17411 vaccine recipients) versus the placebo group (162 COVID-19 cases/17511 placebo recipients). 32 33 At the beginning of 2021, most other Western countries followed with rolling out massive vaccination campaigns. 34-36 On 9 April 2021, the overall COVID-19 Infection Fatality Rate was reduced to 0.15% and expected to further decline with the widespread use

of vaccinations, prior infections and the evolution of new and milder variants. ³⁷ 38

Although COVID-19 vaccines were provided to guard civilians from suffering morbidity and mortality by the COVID-19 virus, suspected adverse events have been documented as well. 15 The secondary analysis of the placebo-controlled, phase III randomised clinical trials of mRNA COVID-19 vaccines showed that the Pfizer trial had a 36% higher risk of serious adverse events in the vaccine group. The risk difference was 18.0 per 10000 vaccinated (95% CI 1.2 to 34.9), and the risk ratio was 1.36 (95% CI 1.02 to 1.83). The Moderna trial had a 6% higher risk of serious adverse events among vaccine recipients. The risk difference was 7.1 per 10 000 vaccinated (95% CI -23.2 to 37.4), and the risk ratio was 1.06 (95% CI 0.84 to 1.33). 39 By definition, these serious adverse events lead to either death, are life-threatening, require inpatient (prolongation of) hospitalisation, cause persistent/significant disability/incapacity, concern a congenital anomaly/ birth defect or include a medically important event according to medical judgement. The authors of the secondary analysis point out that most of these serious adverse events concern common clinical conditions, for example, ischaemic stroke, acute coronary syndrome and brain haemorrhage. This commonality hinders clinical suspicion and consequently its detection as adverse vaccine reactions.³⁹ Both medical professionals and citizens have reported serious injuries and deaths following vaccination to various official databases in the Western World, such as VAERS in the USA, EudraVigilance in the European Union and Yellow Card Scheme in the UK. 42-48 A study comparing adverse event reports to VAERS and EudraVigilance following mRNA COVID-19 vaccines versus influenza vaccines observed a higher risk of serious adverse reactions for COVID-19 vaccines. These reactions included cardiovascular diseases, coagulation, haemorrhages, gastrointestinal events and thromboses.^{39 49} Numerous studies reported that COVID-19 vaccination may induce myocarditis, pericarditis and autoimmune diseases. 50-57 Postmortem examinations have also ascribed myocarditis, encephalitis, immune thrombotic thrombocytopenia, intracranial haemorrhage and diffuse thrombosis to COVID-19 vaccinations. 58-67 The Food and Drug Administration noted in July 2021 that the following potentially serious adverse events of Pfizer vaccines deserve further monitoring and investigation: pulmonary embolism, acute myocardial infarction, immune thrombocytopenia and disseminated intravascular coagulation. 39 68

Insight into the excess death rates in the years following the declaration of the pandemic by WHO is crucial for government leaders and policymakers to evaluate their health crisis policies.¹⁻⁴ This study therefore explores excess mortality in the Western World from 1 January 2020 until 31 December 2022.

MATERIALS AND METHODS

Setting

The Western World is primarily defined by culture rather than geography. It refers to various countries in Europe and to countries in Australasia (Australia, New Zealand) and North America (the USA, Canada) that are based on European cultural heritage. The latter countries were once British colonies that acquired Christianity and the Latin alphabet and whose populations comprised numerous descendants from European colonists or migrants. ⁶⁹

Study design

All-cause mortality reports were abstracted for countries of the Western World using the 'Our World in Data' database. ¹² Only countries that had all-cause mortality reports available for all three consecutive years (2020–2022) were included. If coverage of one of these years was missing, the country was excluded from the analysis.

The 'Our World in Data' database retrieves their reported number of deaths from both the Human Mortality Database (HMD) and the World Mortality Dataset (WMD). ⁵ HMD is sustained by research teams of both the University of California in the USA and the Max Planck Institute for Demographic Research in Germany. HMD recovers its data from Eurostat and national statistical agencies on a weekly basis. ⁵ The 'Our World in Data' database used HMD as their only data source until February 2021. ⁵ WMD is sustained by the researchers Karlinsky and Kobak. WMD recovers its data from HMD, Eurostat and national statistical agencies on a weekly basis. ⁵ The 'Our World in Data' database started to use WMD as a data source next to HMD since February 2021. ⁵

'Excess mortality' is assessed as the deviation between the reported number of deaths in a country during a certain week or month in 2020 until 2022 and the expected or projected number of deaths in a country for that period under normal conditions.⁵ For the baseline of expected deaths, the estimate model of Karlinsky and Kobak was used. This linear regression model uses historical death data in a country from 2015 until 2019 and accounts for seasonal variation in mortality and year-to-year trends due to changing population structure or socioeconomic factors.^{5 7}

Karlinsky and Kobak fit their regression model separately for every country: $D_{t,Y} = \alpha_t + \beta \cdot Y + \epsilon$. In this formula, $D_{t,Y}$ is the number of deaths observed on week (or month) t in year Y, β is a linear slope across years, α_t are separate intercepts (fixed effects) for each week (month/quarter) and $\epsilon \sim N(0,\sigma^2)$ is the Gaussian noise. The model prediction for 2020 is taken as the baseline for the excess mortality calculations: $\widehat{B}_t = \widehat{\alpha}_t + \widehat{\beta} \cdot 2020$. The final excess mortality estimate is as follows: $\sum_{t \geq t_1} \left(D_{t,2020} - \widehat{B}_t \right) + \sum_t \left(D_{t,2021} - \widehat{B}_t \right)$, where t_1 indicates the summation onset in 2020. The variance V are t_2 of estimator Δ is computed as follows: X is the predictor matrix in the regression, Y is the response vector, $\widehat{\beta} = \left(X^T X \right)^{-1} X^T Y$ is the vector of estimated regression coefficients, and

 $\hat{\sigma}^2 = \|y - X\hat{\beta}\|^2/(n-p)$ is the unbiased estimate of noise variance, in which n is the sample size and P is the number of predictors. $\operatorname{cov}[\hat{\beta}] = \widehat{\sigma}^2 (\mathbf{x}^T \mathbf{x})^{-1}$ is the covariance matrix of $\hat{\beta}$. $S = \operatorname{Cov}[\hat{\beta}_t] = \operatorname{Cov}[X_{2020}\hat{\beta}] = \widehat{\sigma}^2 X_{2020} (X^T X)^{-1} X_{2020}^T$ is the covariance matrix of predicted baseline values $\hat{\beta}_t$, where X_{9090} is the predictor matrix for 2020. Karlinsky and Kobak depict vector w with elements w, of length equal to the number of rows in X_{9090} . They set all elements before t, to zero, all elements from t, forward to 1, and raise by one all elements corresponding to 2021 data.⁷ The predictive variance of Δ is denoted as follows: $\operatorname{Var}[\Delta] = \operatorname{Var}\left[\sum_{t} w_{t} \widehat{B}_{t}\right] + \sum_{t} w_{t} \widehat{\sigma}^{2} = w^{T} S w + \widehat{\sigma}^{2} \|w\|_{1}$ which the first term represents the uncertainty of $\hat{\beta}_t$ and the second term represents the additive Gaussian noise. The square root of Var $[\Delta]$ is regarded as the standard error of Δ . When the fraction $z = |\Delta| / \sqrt{var[\Delta]}$ is below 2, the excess mortality of that country is considered not significantly different from zero.

The model regards excess mortality during the COVID-19 pandemic as the sum of the following factors: (a) deaths directly generated by SARS-CoV-2 infection, (b) deaths generated by medical system overload owing to the pandemic, (c) excess deaths from other natural causes (eg, influenza and other infectious respiratory diseases during winter seasons), (d) excess deaths from unnatural causes (eg, traffic accidents, homicides, suicides, deaths from drug overdoses and unintentional injuries) and (e) excess deaths from extreme events (such as heat waves, wars, power outages and natural disasters). Karlinsky and Kobak's model expressly takes factor (e) into account and acknowledges that the contribution of factors (b), (c) and (d) is in general minor for the majority of nations compared with factor (a). The researchers have used the officially reported national COVID-19 death counts from the WHO dataset.⁷² In their model, common seasonal influenza during 2015 and 2019 contributes to the projected baseline of expected deaths.' In addition, the model corrects for peaks of excess deaths during heat waves. Because the number of excess deaths is impacted by the population size of a nation, the excess mortality estimates have been normalised by the population size. Population size estimates of the United Nations World Population Prospect dataset have been used to estimate excess deaths per 100 000 population for 2020 until 2022.^{7 73} Because the Infection Fatality Rate of SARS-CoV-2 is age dependent and nations have different age structures, the excess mortality estimates have been normalised by the yearly sum of the baseline mortality to account for the nation's age structure.⁷ Because the projected baseline uses a linear trend, the model can also reckon for ameliorations in death registration across recent years.⁷ For each country separately, Karlinsky and Kobak have taken these various factors into account when predicting the baseline mortality for 2020 until 2022. If required, adjustments have been made accordingly. For example, in the USA, the weekly death data (R^2 =0.89, F=31.7) give rise to the following: $\hat{\beta}=773\pm57$. This implies that every year, the number of weekly deaths rises on average by ~800. The predicted weekly deaths for 2020 are thus higher than the 2015–2019 average. Regarding the strong and statistically significant annual trend, it is therefore not accurate to employ the 2015–2019 data as a baseline. Another example of correction concerns Belgium, the Netherlands, France, Luxembourg and Germany. In August 2020, a peak of excess deaths was observed during a heat wave in these countries. To account for this, weeks 32-34 were excluded from the excess mortality calculation in these nations. This decreased the excess mortality estimates for these countries by 1500 for Belgium, 660 for the Netherlands, 1600 for France, 35 for Luxembourg and 3700 for Germany. Karlinsky and Kobak present more details about the used method in their joint publication.

'Excess mortality P-score' concerns the percentage difference between the reported number of deaths and the projected number of deaths in a country.⁵ This measure permits comparisons between various countries. Although presenting the raw number of excess deaths provides insight into the scale, it is less useful to compare countries because of their large population size variations.⁵ The 'Our World in Data' database presents P-scores in a country during a certain week or month in 2020 until 2022.⁵ These P-scores are calculated from both the reported number of deaths in HMD and WMD and the projected number of deaths using the estimate model of Karlinsky and Kobak in WMD.^{5 7 70 71}

For correct interpretation of excess mortality provided by the 'Our World in Data' database, the following needs to be taken into consideration: the reported number of deaths may not represent all deaths, as countries may lack the infrastructure and capacity to document and account for all deaths.⁵ In addition, death reports may be incomplete due to delays. It may take weeks, months or years before a death is actually reported. The date of a reported death may refer to the actual death date or to its registration date. Sometimes, a death may be recorded but not the date of death. Countries that provide weekly death reports may use different start and end dates of the week. Most countries define the week from Monday until Sunday, but not all countries do. Weekly and monthly reported deaths may not be completely comparable, as excess mortality derived from monthly calculations inclines to be lower.⁵⁷

For our analysis, weekly all-cause mortality reports from the 'Our World in Data' database were converted to monthly reports. Subsequently, the monthly reports were converted to annual reports.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

The 'Our World in Data' database contained all-cause mortality reports of 47 countries (96%) in the Western World for the years 2020, 2021 and 2022. Only Andorra and Gibraltar were excluded. Both countries lacked all-cause mortality reports for the year 2022. Most countries (n=36, 77%) present weekly all-cause mortality reports, whereas 11 countries (23%) report monthly. The latter countries include the following: Albania, Bosnia Herzegovina, Faeroe Islands, Greenland, Kosovo, Liechtenstein, Moldova, Monaco, North Macedonia, San Marino and Serbia.

The all-cause mortality reports were abstracted from the 'Our World in Data' database on 20 May 2023. At this date, four countries (9%) still lacked all-cause mortality reports for various periods: Canada (1 month), Liechtenstein (3 months), Monaco (3 months) and Montenegro (4 months). It is noteworthy that all-cause mortality reports are also still being updated for the other countries due to registration delays which may take weeks, months or even years.

Excess mortality

Online supplemental table 1 illustrates that the total number of excess deaths in the 47 countries of the Western World was 3 098 456 from 1 January 2020 until 31 December 2022. Excess mortality was documented in 41 countries (87%) in 2020, in 42 countries (89%) in 2021 and in 43 countries (91%) in 2022.

In 2020, the year of the COVID-19 pandemic and implementation of the containment measures, 1033 122 excess deaths (P-score 11.4%) were recorded. In 2021, the year in which both COVID-19 containment measures and COVID-19 vaccines were used to address virus spread and infection, a total of 1256 942 excess deaths (P-score 13.8%) were reported. In 2022, the year in which most containment measures were lifted and COVID-19 vaccines were continued, preliminary available data counts 808 392 excess deaths (P-score 8.8%).

Figure 1 presents the excess mortality and cumulative excess mortality in 47 countries of the Western World over the years 2020, 2021 and 2022. The linear excess mortality trendline is almost horizontal.

Excess mortality P-scores

Figure 2 shows the excess mortality P-scores per country in the Western World. Only Greenland had no excess deaths between 2020 and 2022. Among the other 46 countries with reported excess mortality, the percentage difference between the reported and projected number of deaths was highest in 13 countries (28%) during 2020, in 21 countries (46%) during 2021 and in 12 countries (26%) during 2022. Figure 3 exemplifies excess mortality P-score curves of the highest-populated country of North America (the USA), the four highest-populated countries of Europe (Germany, France, the UK and Italy) and the highest-populated country of Australasia (Australia).

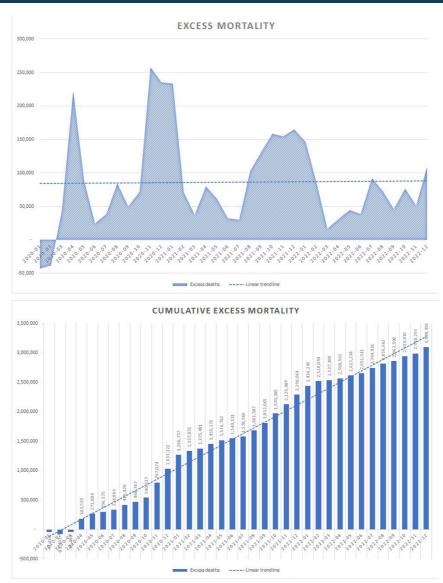


Figure 1 Excess mortality and cumulative excess mortality in the Western World (n=47 countries). Preliminary and incomplete all-cause mortality reports are available for 2022.

Figure 4 highlights a map of excess mortality P-scores in the Western World over the years 2020, 2021 and 2022. ⁷⁴ Table 1 presents a classification of excess mortality P-scores in the Western World.

DISCUSSION

This study explored the excess all-cause mortality in 47 countries of the Western World from 2020 until 2022. The overall number of excess deaths was 3098456. Excess mortality was registered in 87% of countries in 2020, in 89% of countries in 2021 and in 91% of countries in 2022. During 2020, which was marked by the COVID-19 pandemic and the onset of mitigation measures, 1033122 excess deaths (P-score 11.4%) were to be regretted. ^{17 18} A recent analysis of seroprevalence studies in this prevaccination era illustrates that the Infection

Fatality Rate estimates in non-elderly populations were even lower than prior calculations suggested.³⁷ At a global level, the prevaccination Infection Fatality Rate was 0.03% for people aged <60 years and 0.07% for people aged <70 years. ³⁸ For children aged 0–19 years, the Infection Fatality Rate was set at 0.0003%. 38 This implies that children are rarely harmed by the COVID-19 virus. 19 38 During 2021, when not only containment measures but also COVID-19 vaccines were used to tackle virus spread and infection, the highest number of excess deaths was recorded: 1256942 excess deaths (P-score 13.8%).^{26 37} Scientific consensus regarding the effectiveness of nonpharmaceutical interventions in reducing viral transmission is currently lacking. ⁷⁵ Touring 2022, when most mitigation measures were negated and COVID-19 vaccines were sustained, preliminary available data count 808 392

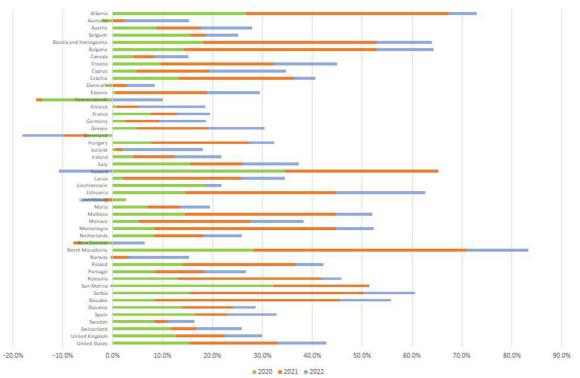


Figure 2 Excess mortality P-scores per country in the Western World (n=47 countries). Preliminary and incomplete all-cause mortality reports are available for 2022.

excess deaths (P-score 8.8%). ³⁹ The percentage difference between the documented and projected number of deaths was highest in 28% of countries during 2020, in 46% of countries during 2021, and in 26% of countries during 2022.

This insight into the overall all-cause excess mortality since the start of the COVID-19 pandemic is an important first step for future health crisis policy decision-making.¹⁻⁴

The next step concerns distinguishing between the various potential contributors to excess mortality, including COVID-19 infection, indirect effects of containment measures and COVID-19 vaccination programmes. Differentiating between the various causes is challenging. National mortality registries not only vary in quality and thoroughness but may also not accurately document the cause of death. The usage of different models to

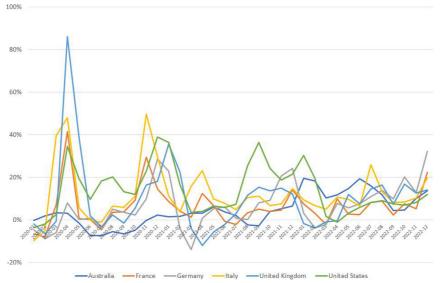


Figure 3 Excess mortality P-score curves of six countries in the Western World. Preliminary and incomplete all-cause mortality reports are available for 2022.

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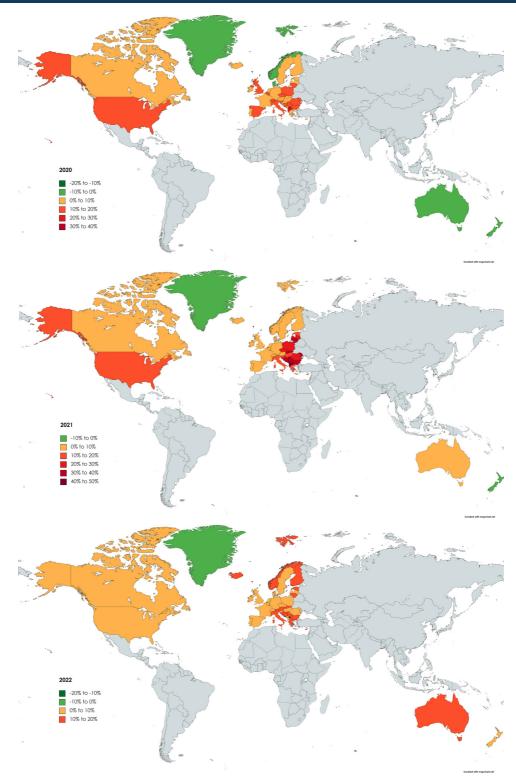


Figure 4 Map of excess mortality P-scores in the Western World (n=47 countries). ⁷⁴ Preliminary and incomplete all-cause mortality reports are available for 2022.

investigate cause-specific excess mortality within certain countries or subregions during variable phases of the pandemic complicates elaborate cross-country comparative analysis. $^{1\ 2\ 16}$ Not all countries provide mortality

reports categorised per age group. ² ¹² Also testing policies for COVID-19 infection differ between countries. ¹ ² Interpretation of a positive COVID-19 test can be intricate. ⁷⁷ Consensus is lacking in the medical community

Table 1 Classification of excess mortality P-scores in the Western World (n=47 countries)

Excess mortality P-scores	2020		2021		2022*	
	Number of countries	Excess deaths	Number of countries	Excess deaths	Number of countries	Excess deaths
–20% to –10%	1 (2%)	-60	0 (0%)	0	1 (2%)	-1,112
–10% to 0%	5 (11%)	-6,583	5 (11%)	-660	3 (6%)	-256
0% to 10%	21 (45%)	149276	18 (38%)	249 071	25 (53%)	631 094
10% to 20%	16 (34%)	875 598	8 (17%)	639757	18 (38%)	178 666
20% to 30%	2 (4%)	11478	6 (13%)	215497	0 (0%)	0
30% to 40%	2 (4%)	3414	8 (17%)	135905	0 (0%)	0
40% to 50%	0 (0%)	0	2 (4%)	17373	0 (0%)	0

regarding when a deceased infected with COVID-19 should be registered as a COVID-19 death. 177 Indirect effects of containment measures have likely altered the scale and nature of disease burden for numerous causes of death since the pandemic. However, deaths caused by restricted healthcare utilisation and socioeconomic turmoil are difficult to prove. 178-81 A study assessing excess mortality in the USA observed a substantial increase in excess mortality attributed to non-COVID causes during the first 2 years of the pandemic. The highest number of excess deaths was caused by heart disease, 6% above baseline during both years. Diabetes mortality was 17% over baseline during the first year and 13% above it during the second year. Alzheimer's disease mortality was 19% higher in year 1 and 15% higher in year 2. In terms of percentage, large increases were recorded for alcoholrelated fatalities (28% over baseline during the first year and 33% during the second year) and drug-related fatalities (33% above baseline in year 1 and 54% in year 2).⁸² Previous research confirmed profound under-reporting of adverse events, including deaths, after immunisation. 83 84 Consensus is also lacking in the medical community regarding concerns that mRNA vaccines might cause more harm than initially forecasted.⁸⁵ French studies suggest that COVID-19 mRNA vaccines are gene therapy products requiring long-term stringent adverse events monitoring. 85 86 Although the desired immunisation through vaccination occurs in immune cells, some studies report a broad biodistribution and persistence of mRNA in many organs for weeks. 85 87-90 Batch-dependent heterogeneity in the toxicity of mRNA vaccines was found in Denmark. 48 Simultaneous onset of excess mortality and COVID-19 vaccination in Germany provides a safety signal warranting further investigation. 91 Despite these concerns, clinical trial data required to further investigate these associations are not shared with the public. 92 Autopsies to confirm actual death causes are seldom done. 58 60 90 93-95 Governments may be unable to release their death data with detailed stratification by cause, although this information could help indicate whether COVID-19 infection, indirect effects of containment

measures, COVID-19 vaccines or other overlooked factors play an underpinning role. ¹ ⁸⁻¹⁴ ²⁰⁻²⁵ ³⁹⁻⁶⁰ ⁶⁸ ⁹⁰ This absence of detailed cause-of-death data for certain Western nations derives from the time-consuming procedure involved, which entails assembling death certificates, coding diagnoses and adjudicating the underlying origin of death. Consequently, some nations with restricted resources assigned to this procedure may encounter delays in rendering prompt and punctual cause-of-death data. This situation existed even prior to the outbreak of the pandemic. ¹⁵

A critical challenge in excess mortality research is choosing an appropriate statistical method for calculating the projected baseline of expected deaths to which the observed deaths are compared. 96 Although the analyses and estimates in general are similar, the method can vary, for instance, per length of the investigated period, nature of available data, scale of geographic area, inclusion or exclusion of past influenza outbreaks, accounting for changes in population ageing and size and modelling trend over years or not. 796 Our analysis of excess mortality using the linear regression model of Karlinsky and Kobak varies thus to some extent from previous attempts to estimate excess deaths. For example, Islam et al conducted an age- and sex-disaggregated time series analysis of weekly mortality data in 29 high-income countries during 2020. 97 They used a more elaborate statistical approach, an overdispersed Poisson regression model, for estimating the baseline of expected deaths on historical death data from 2016 to 2019. In contrast to the model of Karlinsky and Kobak, their baseline is weighing down prior influenza outbreaks so that every novel outbreak evolves in positive excess mortality.⁷⁹⁷ Islam's study found that age-standardised excess death rates were higher in men than in women in nearly all nations. 97 Alicandro et al investigated sex- and age-specific excess total mortality in Italy during 2020 and 2021, using an overdispersed Poisson regression model that accounts for temporal trends and seasonal variability. Historical death data from 2011 to 2019 were used for the projected baseline. When comparing 2020 and 2021, an increased share of the total

excess mortality was attributed to the working-age population in 2021. Excess deaths were higher in men than in women during both periods. 98 Msemburi et al provided WHO estimates of the global excess mortality for its 194 member states during 2020 and 2021. For most countries, the historical period 2015-2019 was used to determine the expected baseline of excess deaths. In locations missing comprehensive data, the all-cause deaths were forecasted employing an overdispersed Poisson framework that uses Bayesian inference techniques to measure incertitude. This study describes huge differences in excess mortality between the six WHO regions. 99 Paglino et al used a Bayesian hierarchical model trained on historical death data from 2015 to 2019 and provided spatially and temporally granular estimates of monthly excess mortality across counties in the USA during the first 2 years of the pandemic. The authors found that excess mortality decreased in large metropolitan counties but increased in non-metropolitan counties. 100 Ruhm examined the appropriateness of reported excess death estimates in the USA by four previous studies and concluded that these investigations have likely understated the projected baseline of excess deaths and therewith overestimated excess mortality and its attribution to non-COVID causes. Ruhm explains that the overstatement of excess deaths may partially be explained by the fact that the studies did not adequately take population growth and age structure into account. 96 101-104 Although all the above-mentioned studies used more elaborate statistical approaches for estimating baseline mortality, Karlinsky and Kobak argue that their method is a trade-off between suppleness and chasteness.⁷ It is the simplest method to captivate seasonal fluctuation and annual trends and more transparent than extensive approaches.

This study has various significant limitations. Death reports may be incomplete due to delays. It may take weeks, months or years before a death is registered.⁵ Four nations still lack all-cause mortality reports for 1-4 months. Some nations issue complete data with profound arrears, whereas other nations publish prompt, yet incomplete data.⁵⁷ The presented data, especially for 2022, are thus preliminary and subject to backward revisions. The more recent data are usually more incomplete and therefore can undergo upward revisions over time. This implies that several of the reported excess mortality estimates can be underestimations.⁷ The completeness and reliability of death registration data can also differ per nation for other reasons. The recorded number of deaths may not depict all deaths accurately, as the resources, infrastructure and registration capacity may be limited in some nations.⁵⁷ Most countries report per week, but some per month. Weekly reports generally provide the date of death, whereas monthly reports often provide the date of registration. Weekly and monthly reports may not be entirely comparable. ^{5 7} Our data are collected at a country level and provide no detailed stratification for sociodemographic characteristics, such as age or gender.⁵⁷

In conclusion, excess mortality has remained high in the Western World for three consecutive years, despite the implementation of COVID-19 containment measures and COVID-19 vaccines. This is unprecedented and raises serious concerns. During the pandemic, it was emphasised by politicians and the media on a daily basis that every COVID-19 death mattered and every life deserved protection through containment measures and COVID-19 vaccines. In the aftermath of the pandemic, the same morale should apply. Every death needs to be acknowledged and accounted for, irrespective of its origin. Transparency towards potential lethal drivers is warranted. Cause-specific mortality data therefore need to be made available to allow more detailed, direct and robust analyses to determine the underlying contributors. Postmortem examinations need to be facilitated to allot the exact reason for death. Government leaders and policymakers need to thoroughly investigate underlying causes of persistent excess mortality and evaluate their health crisis policies. Pdf by: https://www.pro-memoria.info

Dissemination to participants and related patient and public communities

We will disseminate findings through a press release on publication and contact government leaders and policymakers to raise awareness about the need to investigate the underlying causes of persistent excess mortality.

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Contributors SM, MH and GK conceived and designed the study. SM and MH acquired and analysed the data. All authors interpreted the results. SM wrote the first draft of the manuscript. All other authors provided feedback and approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. SM is responsible for the overall content as guarantor.

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REFERENCES

- 1 Wang H, Paulson KR, Pease SA, et al. COVID-19 excess mortality collaborators. estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. Lancet 2022;399:1513-36.
- Rossen LM, Nørgaard SK, Sutton PD, et al. Excess all-cause mortality in the USA and Europe during the COVID-19 pandemic,
- 2020 and 2021. *Sci Rep* 2022;12:18559.

 Beaney T, Clarke JM, Jain V, *et al.* Excess mortality: the gold standard in measuring the impact of COVID-19 worldwide? *J R Soc* led 2020;113:329-34.
- WHO. The true death toll of COVID-19: estimating global excess mortality. 2021. Available: https://www.who.int/data/stories/thetrue-death-toll-of-covid-19-estimating-global-excess-mortality
- Giattino C, Ritchie H, Ortiz-Ospina E, et al. Our world in data. Excess mortality during the Coronavirus pandemic (COVID-19). n.d. Available: https://ourworldindata.org/excess-mortality-covid#
- Checchi F, Roberts L. Interpreting and using mortality data in humanitarian emergencies. Humanitarian Practice Network; 2005. 52. Available: https://odihpn.org/publication/interpreting-andusing-mortality-data-in-humanitarian-emergencies/ Karlinsky A, Kobak D. Tracking excess mortality across countries
- during the COVID-19 pandemic with the world mortality dataset. Elife 2021;10:e69336.
- Rea IM, Alexander HD. Triple jeopardy in ageing: COVID-19, comorbidities and inflamm-ageing. Ageing Res Rev 2022;73:101494.
- Konstantinoudis G, Cameletti M, Gómez-Rubio V, et al. Regional excess mortality during the 2020 COVID-19 pandemic in five European countries. *Nat Commun* 2022;13:482.
- Zhang JJ, Dong X, Liu GH, et al. Risk and protective factors for COVID-19 morbidity, severity, and mortality. Clin Rev Allergy *mmunol* 2023;64:90–107.
- Talic S, Shah S, Wild H, et al. Effectiveness of public health measures in reducing the incidence of COVID-19, SARS-Cov-2 transmission, and COVID-19 mortality: systematic review and meta-analysis. *BMJ* 2021;375:e068302.
- Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the pfizer-biontech and oxford-astrazeneca vaccines on COVID-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ 2021:373:n1088.
- Tregoning JS, Flight KE, Higham SL, et al. Progress of the COVID-19 vaccine effort: viruses, vaccines and variants versus efficacy, effectiveness and escape. Nat Rev Immunol
- Graña C, Ghosn L, Evrenoglou T, et al. Efficacy and safety of COVID-19 vaccines. Cochrane Database Syst Rev 2022;2023. WHO. Vigiaccess. COVID-19 vaccine. Reported potential side
- effects. n.d. Available: https://www.vigiaccess.org
- 16 Ricoca Peixoto V, Vieira A, Aguiar P, et al. Excess mortality since COVID-19: what data do we need and what questions should we ask to understand its causes in Portugal? Acta Med Port 2022:35:783-5.
- World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. WHO directorgeneral's opening remarks at the media briefing on COVID-19, 11 March 2020. n.d. Available: https://who.int/director-general/ speeches/detail/who-director-general-s-opening-remarks-at-the
- media-briefing-on-covid-19---11-march-2020

 18 International Monetary Fund (IMF). Policy responses to COVID-19. IMF; 2021. Available: https://www.imf.org/en/Topics/imf-andcovid19/Policy-Responses-to-COVID-19
- El Salih I, Njuguna FM, Widjajanto PH, et al. Impact of COVID-19 measures on the health and healthcare of children in East-Africa: scoping review. Int J Health Plann Manage 2023;38:579-98.

- 20 Pritchard-Jones K. de C V Abib S. Esiashvili N. et al. The threat of the COVID-19 pandemic on reversing global life-saving gains in the survival of childhood cancer: a call for collaborative action from SIOP. Ecancermedicalscience 2021;15:1187.
- Ferrara P, Dallagiacoma G, Alberti F, et al. Prevention, diagnosis and treatment of cervical cancer: a systematic review of the impact of COVID-19 on patient care. Prev Med 2022;164:107264.
- Walker MJ, Meggetto O, Gao J, et al. Measuring the impact of the COVID-19 pandemic on organized cancer screening and diagnostic follow-up care in Ontario, Canada: a provincial, population-based study. Prev Med 2021;151:106586.
- 23 Barrett R, Hodgkinson J. Impact of the COVID-19 pandemic on cardiovascular heart disease medication use: time-series analysis of England's prescription data during the COVID-19 pandemic. Ther Adv Cardiovasc Dis 2022;16:17539447221137170.
- 24 Nogueira RG, Etter K, Nguyen TN, et al. Changes in the care of acute cerebrovascular and cardiovascular conditions during the first year of the COVID-19 pandemic in 746 hospitals in the USA:
- retrospective analysis. *BMJ Med* 2023;2:e000207. Khunti K, Aroda VR, Aschner P, *et al*. The impact of the COVID-19 pandemic on diabetes services: planning for a global recovery. Lancet Diabetes Endocrinol 2022;10:890-900.
- Upamali S, Rathnayake S. Perspectives of older people with uncontrolled type 2 diabetes mellitus towards medication adherence: a qualitative study. PLoS One 2023;18:e0289834.
- Alicandro G, La Vecchia C, Islam N, et al. A comprehensive analysis of all-cause and cause-specific excess deaths in 30 countries during 2020. Eur J Epidemiol 2023;38:1153-64.
- Ioannidis JPA. Infection fatality rate of COVID-19 inferred from seroprevalence data. Bull World Health Organ 2021;99:19-33F.
- Baraniuk C. Covid-19: how the UK vaccine Rollout delivered success, so far. BMJ 2021;372:421.
- Mortiboy M, Zitta J-P, Carrico S, et al. Combating COVID-19 vaccine inequity during the early stages of the COVID-19 pandemic. J Racial Ethn Health Disparities 2024;11:621-30.
- Government of Canada. COVID-19 vaccination in Canada. n.d. Available: https://health-infobase.canada.ca/covid-19/vaccineadministration/
- Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020:383:2603-15.
- Brown RB. Relative risk reduction: misinformative measure in clinical trials and COVID-19 vaccine efficacy. Dialogues Health 2022:1:100074
- European Centre for Disease Prevention and Control. Overview of the implementation of COVID-19 vaccination strategies and deployment plans in the EU/Eea14 June 2021. Stockholm ECDC;
- Australian Government. Department of health and aged care. COVID-19 vaccine Rollout on track to begin 22 February. 2021. Available: https://www.health.gov.au/news/covid-19-vaccinerollout-on-track-to-begin-22-february
- Reuters. New zealand begins COVID-19 vaccinations programme, Australia starts Monday. 2021. Available: https://ww.reuters. com/article/us-health-coronavirus-newzealand-vaccineidUSKBN2AK02X
- loannidis JPA. Reconciling estimates of global spread and infection fatality rates of COVID-19: an overview of systematic evaluations. Eur J Clin Invest 2021;51:e13554.
- Pezzullo AM, Axfors C, Contopoulos-loannidis DG, et al. Agestratified infection fatality rate of COVID-19 in the non-elderly population. Environ Res 2023;216:114655.
- Fraiman J, Erviti J, Jones M, et al. Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults. *Vaccine* 2022;40:5798–805.
- 40 Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-Cov-2 vaccine. N Engl J Med 2021;384:403-16.
- Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against COVID-19. N Engl J Med 2021;384:2187-201.
- VAERS. Vaccine adverse event reporting system. n.d. Available: https://www.vaers.hhs.gov
- European Medicines Agency. Science medicines health. human regulatory. Eudravigilance. n.d. Available: https://www.ema.europa. eu/en/human-regulatory/research-development/pharmacovigilance/
- Medicines & healthcare products regulatory agency. The yellow card scheme. n.d. Available: https://yellowcard.mhra.gov.uk/ information

- Toriesen I. Covid-19: pfizer-biontech vaccine is "likely" responsible for deaths of some elderly patients, Norwegian review finds. BMJ 2021;373:1372.
- Oster ME, Shay DK, Su JR, et al. Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021. JAMA 2022;327:331.
- Karlstad Ø, Hovi P, Husby A, et al. SARS-Cov-2 vaccination and myocarditis in a Nordic cohort study of 23 million residents. JAMA Cardiol 2022;7:600-12.
- Schmeling M, Manniche V, Hansen PR. Batch-dependent safety of the BNT162b2 mRNA COVID-19 vaccine. Eur J Clin Invest 2023:53:e13998.
- Montano D. Frequency and associations of adverse reactions of COVID-19 vaccines reported to pharmacovigilance systems in the European Union and the United States. Front Public Health 2021:9:756633.
- Krug A, Stevenson J, Høeg TB. BNT162b2 vaccine-associated MYO/pericarditis in adolescents: a stratified risk-benefit analysis. Eur J Clin Invest 2022;52:e13759.
- Gao J, Feng L, Li Y, et al. A systematic review and meta-analysis of the association between SARS-Cov-2 vaccination and myocarditis or pericarditis. *Am J Prev Med* 2023;64:275–84. Wong HL, Hu M, Zhou CK, *et al.* Risk of myocarditis and
- pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases. Lancet 2022;399:2191-9.
- 53 Pillay J, Gaudet L, Wingert A, et al. Incidence, risk factors, natural history, and hypothesized mechanisms of myocarditis and pericarditis following COVID-19 vaccination: living evidence syntheses and review. *BMJ* 2022;378:e069445.
- Uversky VN, Redwan EM, Makis W, et al. IgG4 antibodies induced by repeated vaccination may generate immune tolerance to the SARS-Cov-2 spike protein. *Vaccines (Basel)* 2023;11:991.
- Chen Y, Xu Z, Wang P, et al. New-onset autoimmune phenomena post-COVID-19 vaccination. Immunology 2022;165:386-401.
- Rodríguez Y, Rojas M, Beltrán S, et al. Autoimmune and autoinflammatory conditions after COVID-19 vaccination. New case reports and updated literature review. J Autoimmun 2022;132:102898.
- Dotan A, Muller S, Kanduc D, et al. The SARS-Cov-2 as an instrumental trigger of autoimmunity. Autoimmun Rev
- Schwab C, Domke LM, Hartmann L, et al. Autopsy-based histopathological characterization of myocarditis after anti-SARS-Cov-2-vaccination. Clin Res Cardiol 2023;112:431-40.
- Chen J, Wu T, Zhang C, et al. Clinically suspected lethal viral myocarditis combined with encephalitis: a COVID-19 vaccine complication. ESC Heart Fail 2023;10:1422-5.
- Sessa F, Salerno M, Esposito M, et al. Autopsy findings and causality relationship between death and COVID-19 vaccination: a systematic review. J Clin Med 2021;10:5876.
- Choi J-K, Kim S, Kim SR, et al. Intracerebral hemorrhage due to thrombosis with thrombocytopenia syndrome after vaccination against COVID-19: the first fatal case in Korea. *J Korean Med Sci*
- 62 Aladdin Y, Algahtani H, Shirah B. Vaccine-induced immune thrombotic thrombocytopenia with disseminated Intravascular coagulation and death following the ChAdOx1 nCoV-19 vaccine.
- J Stroke Cerebrovasc Dis 2021;30:105938.
 Bjørnstad-Tuveng TH, Rudjord A, Anker P. Fatal cerebral haemorrhage after COVID-19 vaccine. Tidsskr Nor Laegeforen 2021;141:33928772.
- Wiedmann M, Skattør T, Stray-Pedersen A, et al. Vaccine induced immune thrombotic thrombocytopenia causing a severe form of cerebral venous thrombosis with high fatality rate: a case series. Front Neurol 2021;12:721146.
- See I, Su JR, Lale A, et al. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26.COV2.S vaccination. JAMA 2021;325:2448.
- Shazley O, Alshazley M. A COVID-positive 52-year-old man presented with venous thromboembolism and disseminated intravascular coagulation following johnson & johnson vaccination: a case-study. Cureus 2021;13:e16383.
- Sharifian-Dorche M, Bahmanyar M, Sharifian-Dorche A, et al. Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination; a systematic review. J Neurol Sci 2021;428:117607.
- Food and Drug Administration. Initial results of near real-time safety monitoring COVID-19 vaccines. 2021. Available: https://www. fda.gov/vaccines-blood-biologics/safety-availability-biologics/ initial-results-near-real-time-safety-monitoring-covid-19-vaccinespersons-aged-65-years-and-old

- World Population Review. The modern meaning of the Western world (the Latin West). n.d. Available: https://worldpopulationr eview.com/country-rankings/western-countries
- HMD. Reliability and accuracy matter. Human Mortality Database. n.d. Available: https://www.mortality.org
- World mortality dataset: international data on all-cause mortality, Available: https://github.com/akarlinsky/world_mortality
- WHO Coronavirus (COVID-19) dashboard. n.d. Available: https:// covid19.who.int
- United Nations, Department of Economic and Social Affairs. Population division. World population prospects. n.d. Available: https://population.un.org/wpp/
- MapChart. World map: simple. n.d. Available: https://:www. mapchart.net/world.html
- Lison A, Banholzer N, Sharma M, et al. Effectiveness assessment of non-pharmaceutical interventions; lessons learned from the COVID-19 pandemic. Lancet Public Health 2023;8:e311-7.
- Jefferson T, Dooley L, Ferroni E, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses. Cochrane Database Syst Rev 2023;1:CD006207.
- Surkova E, Nikolayevskyy V, Drobniewski F. False-positive COVID-19 results: hidden problems and costs. Lancet Respir Med 2020;8:1167-8.
- Uyl-de Groot CA, Schuurman MS, Huijgens PC, et al. Fewer cancer diagnoses during the COVID-19 epidemic according to diagnosis, age and region. TSG 2021;99:1-8.
- Schwarz V, Mahfoud F, Lauder L, et al. Decline of emergency admissions for cardiovascular and cerebrovascular events after the outbreak of COVID-19. *Clin Res Cardiol* 2020;109:1500–6. Causey K, Fullman N, Sorensen RJD, *et al.* Estimating global
- and regional disruptions to routine childhood vaccine coverage during the COVID-19 pandemic in 2020: a modelling study. Lancet 2021;398:522-34.
- Ezenwa BN, Fajolu IB, Nabwera H, et al. Impact of COVID-19 lockdown measures on institutional delivery, neonatal admissions and prematurity: a reflection from Lagos, Nigeria. BMJ Paediatr Open 2021;5:e001029.
- Ruhm CJ. The evolution of excess deaths in the United States during the first 2 years of the COVID-19 pandemic. Am J Epidemiol 2023;192:1949-59.
- Food and Drug Administration, Center for Drug Evaluation and Research, World of Drug Safety Module. The adverse event. n.d.
- Available: www.accessdata.fda.gov/scripts/cderworld/ Hazell L, Shakir SAW. Under-reporting of adverse drug reactions: a systematic review. *Drug Saf* 2006;29:385–96.
- Banoun H. mRNA: vaccine or gene therapy? The safety regulatory issues. Int J Mol Sci 2023;24:10514.
- Guerriaud M, Kohli E. RNA-based drugs and regulation: toward a necessary evolution of the definitions issued from the European Union legislation. Front Med 2022;9:1012497.
- Fertig TE, Chitoiu L, Marta DS, et al. Vaccine mRNA can be detected in blood at 15 days post-vaccination. Biomedicines 2022:10:1538.
- Röltgen K, Nielsen SCA, Silva O, et al. Immune imprinting, breadth of variant recognition, and germinal center response in human SARS-Cov-2 infection and vaccination. Cell 2022;185:1025-40.
- Magen E, Mukherjee S, Bhattacharya M, et al. Clinical and molecular characterization of a rare case of BNT162b2 mRNA COVID-19 vaccine-associated myositis. Vaccines 2022;10:1135.
- Mörz M. A case report: multifocal necrotizing encephalitis and myocarditis after BNT162b2 mRNA vaccination against COVID-19. /accines 2022;10:1651.
- Kuhbandner C, Reitzner M. Estimation of excess mortality in
- Germany during 2020-2022. *Cureus* 2023;15:e39371.

 Doshi P, Godlee F, Abbasi K. Covid-19 vaccines and treatments: we must have raw data, now. *BMJ* 2022;376:102.

 Sperhake JP. Autopsies of COVID-19 deceased? Absolutely. *Leg*
- Med (Tokyo) 2020;47:101769.
- Tzankov A, Jonigk D. Unlocking the lockdown of science and demystifying COVID-19: how autopsies contribute to our understanding of a deadly pandemic. Virchows Arch 2020:477:331-3.
- Schneider J, Sottmann L, Greinacher A, et al. Postmortem investigation of fatalities following vaccination with COVID-19 vaccines. Int J Legal Med 2021;135:2335-45.
- Ruhm CJ. Excess deaths in the United States during the first year of COVID-19. Prev Med 2022;162:107174.
- Islam N, Shkolnikov VM, Acosta RJ, et al. Excess deaths associated with COVID-19 pandemic in 2020: age and sex disaggregated time series analysis in 29 high income countries. BMJ 2021;373:n1137.

- 98 Alicandro G, Remuzzi G, Centanni S, et al. Excess total mortality in 2021 in Italy was about one third of that observed in 2020. Med Lav 2021:112:414-21
- 99 Msemburi W, Karlinsky A, Knutson V, et al. The WHO estimates of excess mortality associated with the COVID-19 pandemic. *Nature* 2023;613:130–7.
- 100 Paglino E, Lundberg DJ, Zhou Z, et al. Monthly excess mortality across counties in the United States during the COVID-19 pandemic. Sci Adv 2023;9:eadf9742.
 101 Woolf SH, Chapman DA, Sabo RT, et al. Excess deaths from
- 101 Woolf SH, Chapman DA, Sabo RT, et al. Excess deaths from COVID-19 and other causes in the US, March 1, 2020, to January 2, 2021. JAMA 2021;325:1786–9.
- 102 Rossen LM, Branum AM, Ahmad FB, et al. Notes from the field: update on excess deaths associated with the COVID-19 pandemic - United States, January 26, 2020-February 27, 2021. MMWR Morb Mortal Wkly Rep 2021;70:570–1.
- 103 Institute for Health Metrics and Evaluation. Estimation of total mortality due to COVID-19. 2021. Available: http://www.healthdata. org/special-analysis/estimation-excess-mortality-due-covid-19and-scalars-reported-covid-19-deaths
- 104 Sanmarchi F, Golinelli D, Lenzi J, et al. Exploring the gap between excess mortality and COVID-19 deaths in 67 countries. JAMA Netw Open 2021;4:e2117359.

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