Relationship between COVID-19 cases and monthly mortality from all causes, cancer, cardiovascular diseases and diabetes in 16 countries, 2020-2021

Margherita Pizzato [1], Claudia Santucci [1], Nazrul Islam [2,3], Carlo La Vecchia [1], Gianfranco Alicandro [4,5] *

[1] Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy.

[2] Nuffield Department of Population Health, University of Oxford, Oxford, UK.

[3] School of Primary Care, Population Sciences and Medical Education, University of Southampton, Southampton, UK.

[4] Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy.

[5] Department of Pediatric, Cystic Fibrosis Centre, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

* Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Via Francesco Sforza 35, 20122, Milano, Italy. e-mail: gianfranco.alicandro@unimi.it

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Abstract

Background. During the COVID-19 pandemic, mortality from some chronic diseases has increased. In this study, we evaluated monthly excess mortality from all causes, cancer, cardiovascular diseases (CVD), and diabetes during the months of 2020 and 2021, examining its relationship with COVID-19 cases.

Methods. Monthly cause-specific mortality data were downloaded from public repositories of national statistics offices or directly requested from them, while population data were obtained from the United Nations archives. Excess deaths were estimated as the difference between observed and expected deaths. Monthly expected deaths for 2020 and 2021 were calculated using a quasi-Poisson regression model trained on 2010-2019 data (or a shorter timespan if the full decade of data was not available). To quantify the correlation between COVID-19 cases and monthly excess mortality, we used the Spearman's coefficient of correlation (r_s).

Results. The study included 16 countries that provided monthly national data on causes of death (Argentina, Austria, Brazil, Switzerland, Chile, the Czech Republic, Germany, Georgia, Hungary, Italy, Latvia, Lithuania, Mexico, Serbia, Slovakia, and the USA). A positive correlation was found between COVID-19 cases and monthly excess mortality from all causes in all countries (r_s ranging from 0.61 to 0.91), from CVD in 11 countries (r_s ranging from 0.45 to 0.85), and for diabetes in 13 countries (r_s ranging from 0.42 to 0.79). Excess mortality above 5% was estimated from all causes in 14 countries for 2020 and 2021, from CVD in seven countries for 2020 and in nine countries for 2021, and from diabetes in 10 countries for 2020 and in 11 countries for 2021. No excesses were estimated for cancer mortality in all countries considered.

Conclusions. Excess mortality from CVD and diabetes persisted in several countries throughout 2021. These increases coincide with COVID-19 peaks, supporting the short-term impact of the COVID-19 pandemic on mortality from these causes.

Keywords: COVID-19; SARS-CoV-2; pandemic; excess mortality; excess deaths; causes of death; cancer; cardiovascular diseases; diabetes.

Key Messages

- We evaluated the monthly cause-specific excess mortality from cardiovascular diseases, diabetes, and cancer in 16 countries during 2020 and 2021, in relation to COVID-19 peaks.
- Excess mortality from cardiovascular diseases and diabetes persisted through 2021 in several countries, while no excess from cancer was observed.
- Excess mortality from cardiovascular diseases and diabetes coincided with COVID-19 peaks, suggesting an immediate effect of the pandemic on these causes of death.

Introduction

Our prior analysis of cause-specific excess mortality in 30 countries using data from the World Health Organization (WHO) revealed a rise in mortality from diabetes and cardiovascular diseases (CVD) in the first year of the pandemic, with no increase in cancer mortality [1]. These findings were later confirmed by other research groups in 2021 in some countries [2–5].

While these studies provided estimates on an annual basis, a more detailed evaluation of cause-specific excess mortality over shorter timeframes could offer new insights into the timing of COVID-19 peaks and mortality from other conditions. Specifically, such analysis allows for a deeper understanding of the pandemic's impact on cause-specific mortality by assessing both its immediate and later effects.

Immediate pandemic effects are expected to manifest during COVID-19 peaks and may include direct effects of SARS-CoV-2 infection on the cardiovascular system and glycaemic control, as well as increased mortality among clinically vulnerable individuals who did not access healthcare or did not receive adequate treatment during these periods. Later effects may manifest outside of COVID-19 peaks and encompass health complications among COVID-19 survivors, such as respiratory or cardiovascular sequelae, and increased mortality from other conditions due to delayed or deferred healthcare [6,7].

In this study, we collected cause-specific mortality data from 16 European and American countries to evaluate the relationship between monthly excess mortality from all causes, cancer, CVD, and diabetes and peaks in COVID-19 cases in 2020 and 2021.

Methods

Data source

At the end of 2023, we searched public repositories of national statistics offices to obtain monthly cause-specific mortality data for countries with completeness of cause-of-death data above 90% [8], disaggregated by sex, age category and cause of death for the period 2010-2021. When data were not publicly available, we sent requests to the national statistics offices to obtain data either free of charge or for a fee covering processing costs. We obtained data from 16 countries, i.e., Argentina, Austria, Brazil, Chile, Switzerland, the Czech Republic, Germany, Georgia, Hungary, Italy, Lithuania, Latvia, Mexico, Serbia, Slovakia, and the USA.

The first available calendar year varied by country: 2011 for most countries, 2010 for Lithuania, 2014 for Georgia, and 2015 for Argentina, Italy, and Serbia. Data were available through 2021 for all selected countries except Chile, which had data only through 2020. Different age groups were provided (**Supplementary Table S1**).

Causes of death were grouped by the national statistical offices using the code of the 10th Revision of the International Statistical Classification of Causes of Death and Related Health Problems (ICD-10): C00-C99 for cancers, I00-I99 for CVD, and E10-E14 for diabetes. For Slovakia, information on diabetes was not available. We evaluated mortality from CVD and diabetes since in a previous work we documented excess mortality for these conditions in several countries in 2020 [1]. Although, in our earlier study we did not find any excess in cancer mortality, we included it in the current analysis to investigate whether disruptions in screening and care during the first year of the pandemic affected cancer outcomes in 2021. We chose not to evaluate other causes of death due to anticipated large fluctuations in monthly mortality data for less common causes, which could complicate their interpretation.

Mid-year population data disaggregated by sex, age group, and calendar year were obtained from the United Nations Archive [9]. COVID-19 cases registered over the months of 2020 and 2021 were obtained from Our World in Data [10]. This dataset contains actual confirmed cases based on official reports from national health agencies.

Estimates of excess mortality

Excess deaths for 2020 and 2021 were calculated as the difference between the observed number of deaths and the counterfactual expected number of deaths. The expected number of deaths for each country and cause of death was obtained by extrapolating the terms of a quasi-Poisson regression model, fitted on total and cause-specific mortality and population data of a reference pre-pandemic period, to the 2020 and 2021 data:

$$Log\left(\mathbb{E}(deaths_{i,j,k,l})\right) = \alpha + \beta_1 sex_i + f(\beta_2, age_j) + f(\beta_3, sex_i, age_j) + \beta_4 year_k + \beta_5(sex_i \cdot year_k) + f(\beta_6, month_l) + \log(pop_{i,j,k})$$

Where:

- $\mathbb{E}[deaths_{i,j,k,l}]$ is the expected number of deaths for sex i, age group j, year k and month l
- α is the intercept
- $\beta_1,\ldots,\beta_6$ are the coefficients associated with each term in the model
- $f(\beta_2, age_j)$ denotes the natural spline function $\beta_2 \cdot$ ns(age, df=3)
- $f(\beta_3, sex_i, age_j)$ denotes the natural spline function $\beta_3 \cdot$ ns(sex · age, df=3)

- $(sex_i \cdot year_k)$ is the interaction term between sex and year
- $f(\beta_6, month_l)$ denotes the natural spline function $\beta_6 \cdot ns(sex \cdot age, df=3)$
- $log(pop_{i,j,k})$ represents the natural logarithm of the population size, used as an offset term to control for differences in population size and age distribution over time

The reference period varied across countries depending on the available data. Age was included in the model as the midpoint of age classes, computed by averaging the lower and upper boundaries. For open-ended age classes (e.g., "85+"), we used a weighted mean based on available population data for older age classes. We replaced the original age categorizations with the midpoint in order to avoid over-parameterization. Due to the limited number of categories in the mortality data from Germany and Hungary, age was included as a categorical variable for these countries.

Empirical 95% confidence intervals (CIs) for the point estimate of excess deaths were derived via Monte Carlo simulation. We generated 1000 realizations of the regression coefficients from a multivariate normal distribution using their point estimates and the variance-covariance matrix. For each realization, we calculated the difference between observed and expected deaths and obtained the 95% CI using the normal approximation. Relative excess mortality was calculated as (observed deaths - expected deaths) / expected deaths * 100.

All statistical analyses were performed using software R version 4.3.0. No ethical committee approval was required since we used anonymized, aggregated data.

Correlation between COVID-19 cases and excess mortality

To evaluate whether the cause-specific excess mortality estimated for each month was related to the number of COVID-19 cases registered in the same month, we computed Spearman's correlation coefficient (r_s). This metric ranges from -1 to 1, with values close to -1 indicating a negative correlation and values close to 1 indicating a positive correlation. Values ≥ 0.7 were considered indicative of a strong correlation.

Sensitivity analysis

To account for the sensitivity of excess mortality estimates to the chosen baseline period for modelling expected deaths [11,12], we estimated excess mortality using all possible combinations of calendar years preceding the pandemic. These results were presented graphically, showing the distribution of the obtained estimates, and as extreme quantiles (2.5^{th} and 97.5^{th} percentiles).

To evaluate whether the estimated excess mortality was an exceptional event limited to the pandemic period, we used the same methodology to estimate the difference between observed and expected deaths in 2019. These results were then compared to those obtained for the pandemic years.

To mitigate the potential effect of undercounting during the initial phase of the pandemic [13], the correlation analysis was conducted separately for 2020 and 2021.

Results

This study included 16 countries that provided monthly data on causes of death: 11 from Europe (Austria, the Czech Republic, Germany, Georgia, Hungary, Italy, Latvia, Lithuania, Serbia, Slovakia, Switzerland), 4 from Central and Latin America (Argentina, Brazil, Chile, Mexico), and the USA.

Table 1 shows the estimates of excess deaths during 2020 and 2021 from all causes, cancer, CVD, and diabetes, by country. In 2020, Mexico had the highest excess mortality from all causes (+45.9%), while Germany (+3.2%), Latvia (+3.8%), and Austria (+8.2%) had the lowest ones. Other countries reported excess deaths ranging from 10% to 17%. In 2021, 12 countries experienced higher excess mortality from all causes compared to 2020. Mexico again had the highest excess (+48%), followed by Serbia (+40.3%), Slovakia (+36.7%), Georgia (+35.2%), and Brazil (+30.9%).

Cancer mortality was lower than expected in 11 countries, with most estimates being less than 5% except for Brazil (-5.3% in 2020 and -5.1% in 2021), Georgia (-13.9% in 2021) and Slovakia (-8.8% in 2021).

Excess mortality above 5% from CVD was observed in 2020 in seven countries (the Czech Republic, Georgia, Hungary, Lithuania, Mexico, Serbia, and Slovakia) and in 2021 in nine countries (Argentina, the Czech Republic, Georgia, Hungary, Lithuania, Latvia, Mexico, Serbia, and Slovakia), with excesses up to 32.3% estimated for Mexico. For diabetes, excesses above 5% were estimated in 2020 in 10 countries (Argentina, Brazil, Georgia, Hungary, Italy, Lithuania, Latvia, Mexico, Serbia, and the USA) and in 2021 in 11 countries (Argentina, Austria, Brazil, Georgia, Hungary, Italy, Lithuania, Latvia, Mexico, Serbia, and the USA), with excesses in 2021 of 25% in Mexico, 33% in Hungary and up to 58% in Georgia.

Figure 1 shows COVID-19 cases and estimates of excess mortality by month from January 2020 to December 2021 by country. Peaks in COVID-19 cases align with a concurrent rise in excess mortality from all causes in all countries. This pattern was partly observed also for excess mortality from CVD and diabetes.

Figure 2 presents the correlation coefficients between monthly cause-specific excess mortality and reported COVID-19 cases across 16 countries. COVID-19 cases showed a positive correlation with excess mortality in all

countries, except in Austria, Brazil, Chile, and Italy and the USA for CVD mortality, and Lithuania and Latvia for diabetes mortality. The correlation was strong ($r_s \geq 0.7$) for all-cause mortality in 14 countries, for CVD mortality in two countries, and for diabetes mortality in five countries. Negative correlations were found between COVID-19 cases and estimates of excess mortality from cancer in Georgia and Slovakia. Results of the analysis conducted separately for 2020 and 2021 are reported in **Supplementary Figure S1**.

Overall, estimates using different combinations of baseline periods were close to each other, with a few exceptions, such as Germany for total and CVD mortality and the USA for cancer mortality (**Supplementary Figure S2 and Table S2**). For example, in Mexico, 95% of the estimates of CVD excess deaths for 2021 fell between 63,047 and 65,475 deaths. In Germany, there was higher uncertainty, with 95% of the estimates for the same year ranging between -18,346 and 36,982 excess deaths. In the USA, 95% of the estimates of excess deaths from diabetes in 2021 were between 11,099 and 14,232 deaths.

The majority of the estimates obtained for 2019 were close to 0, with some indicating lower-than-expected mortality. However, the excess mortality we estimated in 2020 and 2021 was not observed in 2019 (**Supplementary Figure S3**).

Discussion

The novelty of our study lies in presenting new estimates of excess mortality from CVD and diabetes during 2020 and 2021 using monthly data that are not currently available in public repositories. These data allowed for a better understanding of the temporal relationship between COVID-19 waves and cause-specific excess mortality.

We found persisting excess mortality from all causes in 2021 across all 16 countries, with important excess mortality from CVD in nine countries and from diabetes in 11 countries. Cancer mortality was lower than expected in 11 countries. Our study also shows that peaks in COVID-19 cases and excess mortality are closely aligned in time, indicating immediate effects of COVID-19 waves on mortality from CVD and diabetes.

SARS-CoV-2 infection may be directly responsible for the excess mortality from CVD and diabetes. The virus causes cardiovascular dysfunction through multiple pathways. Endothelial damage associated with COVID-19 increases the risk of clot formation, while hypoxia forces cells into anaerobic metabolism, producing harmful metabolic byproducts that cause further cellular damage [14]. SARS-CoV-2 invades cardiac cells via ACE2 receptors, leading to cardiomyocyte necrosis, releasing cytotoxic contents that weaken the heart muscle and impair its contractility [15]. The immune response to infection triggers inflammation within cardiac tissues, further compromising heart function and disrupting electrical conduction.

SARS-CoV-2 infection has been associated with new-onset diabetes and severe hyperglycemia, as well as worsening of glycemic control in pre-existing diabetes[16]. SARS-CoV-2 replicates in pancreatic β-cells, inducing morphological and functional changes that disrupt insulin production [17,18]. The viral entry and replication within β-cells can trigger apoptosis, diminishing the number of functional β-cells. The systemic inflammation associated with COVID-19 exacerbates this problem by increasing insulin resistance through cytokine-mediated pathways [19]. Moreover, corticosteroids have been largely used in the management of severe COVID-19 cases, potentially leading to severe hyperglycemia in patients with undiagnosed diabetes or pre-diabetes [20].

The COVID-19 pandemic has posed important challenges for healthcare systems, impacting the management of chronic diseases. Hospitals and healthcare facilities reallocated resources, including ICU beds and medical staff, to manage COVID-19 patients, resulting in the deferral or cancellation of routine care for non-COVID conditions [21]. Many patients, fearful of virus exposure, avoided seeking medical assistance. Lockdown measures further restricted physical access to healthcare services, disproportionately affecting vulnerable populations reliant on regular medical support.

The availability of COVID-19 vaccines had only a partial impact on excess mortality in 2021. Despite vaccine campaigns starting in early 2021, by the end of the first half of the year, less than 50% of the population in most countries had been fully vaccinated [22]. In addition, the Omicron variant caused a massive increase in COVID-19 cases in December 2021, superimposed to the still prevalent Delta variant.

The excess mortality from CVD and diabetes we found in our study was previously reported in studies using annual data. In Mexico, a study based on death certificates reported excess mortality of 32.5% for ischemic heart diseases and 36.8% for diabetes [5]. These estimates were obtained using a regression model trained on 2015-2019 data to estimate the expected number of deaths in 2020-2021. A comparison of death rates from CVD and diabetes in 2021 with the average figure of 2015-2019 in Brazil resulted in estimates of 23% for CVD and +60% for diabetes, considerably higher than our estimates (+2.9% for CVD and +14.8% for diabetes) [3]. A study based on multiple causes-of-death data reported an +18% excess mortality in an Italian region (Veneto) in 2021, an estimate close to the one we found for the whole country (+14%) [23]. The 14% excess mortality from diabetes we estimated in 2021 in the USA is consistent with the 18% excess mortality reported in a recent study covering the period from March 2020 to March 2022 [24].

Regarding cancer mortality, other studies found no excess or even decreasing mortality in pandemic years, indicating that COVID-19 had no short-term impact on cancer mortality.[2] The decreased mortality can be partly attributed to COVID-19 acting as a competing cause of death in patients with cancer [25].

When interpreting our results, some important factors need to be considered. Estimates of excess mortality are subject to different methodological choices, including the statistical model, the baseline pre-pandemic period used to derive the model for the expected deaths and the age categorization.

Among these, the choice of baseline period emerged as a critical subjective choice in estimating excess deaths during the pandemic [26,27]. To address this, we tried different baseline periods and found consistent excesses not only for total mortality, but also for mortality from CVD and diabetes. However, some exceptions were noted such as Germany (for all causes and CVD mortality) and the USA (for cancer mortality), where estimates showed higher uncertainty.

Our model to estimate expected deaths included a linear term for the year, assuming that the pre-pandemic trend would have continued unchanged in the absence of the pandemic.

Cross-country comparisons, however, may be somewhat limited by the varying age categorizations in the data sets used for the analysis. While data from six countries (Austria, Brazil, Switzerland, Chile, Lithuania, and the USA) were available in five-year intervals up to 100+ years, other countries provided less detailed data. For example, in Germany and Hungary, the oldest open-ended age groups were 65+ and 60+, respectively.

Although all the countries in our study followed WHO guidelines for coding causes of death, differences in diagnostic and certification practices, inadequate training of the certifying physicians, and lack of understanding of the importance of accurate certification may compromise between-country comparisons. Even in high-income countries with well-established vital statistics systems, some deaths are classified in "ill-defined" causes, which include broad, uninformative diagnoses, such as heart failure and senility. The frequency of these causes varies greatly between countries, with WHO reporting estimates in the countries considered in our study ranging between 3 to 65%, with the highest rates observed in Georgia and Argentina [28].

Additionally, we may have underestimated the overall impact of COVID-19 on diabetes-related mortality, as diabetes is often considered a contributing factor rather than a cause of death. This was clearly demonstrated in a study on death certificates in the USA, which found 47.6% excess mortality when diabetes was considered as a contributing cause and only 18.4% when it was considered as an underlying cause of death [24].

In the early stages of the pandemic, the true impact of COVID-19 was not fully captured by national institutions, particularly in countries with a severe first wave and limited testing capacity. For example, in Italy, about 44,000 excess deaths were estimated in March-May 2020, while only 33,000 COVID-19 deaths were officially recorded [29]. As the pandemic progressed, countries with robust healthcare systems and intensive testing protocols were better able to capture cases compared to those with limited resources [30]. This variation complicates international

comparisons and may have influenced our assessment of the correlation between COVID-19 cases and excess mortality. To account for this, we provided separate estimates for 2020 and 2021, which confirmed a direct correlation between COVID-19 cases and excess mortality associated with CVD and diabetes in several countries. Finally, our analysis is limited to 2020 and 2021, as no data are available for more recent years. However, recent data indicate that excess total mortality has substantially decreased in 2023 [31]. Further studies are needed to evaluate potential long-term effects on cause-specific mortality, particularly cancer mortality.

In conclusion, our findings indicate that the excess mortality from CVD and diabetes, documented by previous studies in 2020, persisted in several countries through 2021. Additionally, the monthly analysis reveals that excess mortality from these causes coincides with COVID-19 peaks, suggesting the immediate effects of the pandemic on mortality from these conditions.

Ethics approval: Ethics approval was not required for this study as the data utilized were obtained from public repositories or provided by national statistical institutes in aggregated, non-identifiable form.

Data availability: The data underlying this article were partly available in public repositories of the offices of statistics of Argentina, Brazil, Chile, Hungary, Lithuania, Mexico, Slovakia and USA. For other countries (Austria, Switzerland , Czech Republic, Germany, Georgia, Italy, Latvia, and Serbia), the data were provided by their respective national statistics offices and require permission for access. Data will be shared upon request to the corresponding author, pending approval from the national statistics offices of the respective countries.

Supplementary data: Supplementary data are available at IJE online.

Author contributions: Margherita Pizzato: Conceptualization, Visualization, Writing - original draft. Claudia Santucci: Writing - review & editing. Nazrul Islam: Writing - review & editing. Carlo La Vecchia: Writing - review & editing, Project administration, Funding acquisition. Gianfranco Alicandro: Data curation, Formal Analysis, Investigation, Methodology, Visualization, Writing - original draft, Supervision. All authors had full access to the data in the study, verified them, and accepted responsibility for submitting the manuscript for publication.

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Figure captions:

Figure 1. Monthly trends in COVID-19 cases (dotted line) and excess mortality (% difference from the expected number of deaths) from all causes, cancer, cardiovascular diseases and diabetes (continuous lines), by country, 2020-2021. Country abbreviations (ISO 3166 - Country code): ARG: Argentina; AUT: Austria; BRA: Brazil; CHE: Switzerland; CHL: Chile; CZE: Czech Republic; DEU: Germany; GEO: Georgia; HUN: Hungary; ITA: Italy; LTU: Lithuania; LVA: Latvia; MEX: Mexico; SRB: Serbia; SVK: Slovakia; USA: United States of America.

Figure 2. Correlation between COVID-19 cases and monthly excess mortality from all causes, cancer, cardiovascular diseases and diabetes by country, 2020-2021. ALL: All causes. CAN: Cancer. CVD: Cardiovascular disease. DIA: Diabetes. rs= Spearman's coefficient of correlation. Country abbreviations (ISO 3166 - Country code): ARG: Argentina; AUT: Austria; BRA: Brazil; CHE: Switzerland; CHL: Chile; CZE: Czech Republic; DEU: Germany; GEO: Georgia; HUN: Hungary; ITA: Italy; LTU: Lithuania; LVA: Latvia; MEX: Mexico; SRB: Serbia; SVK: Slovakia; USA: United States of America.

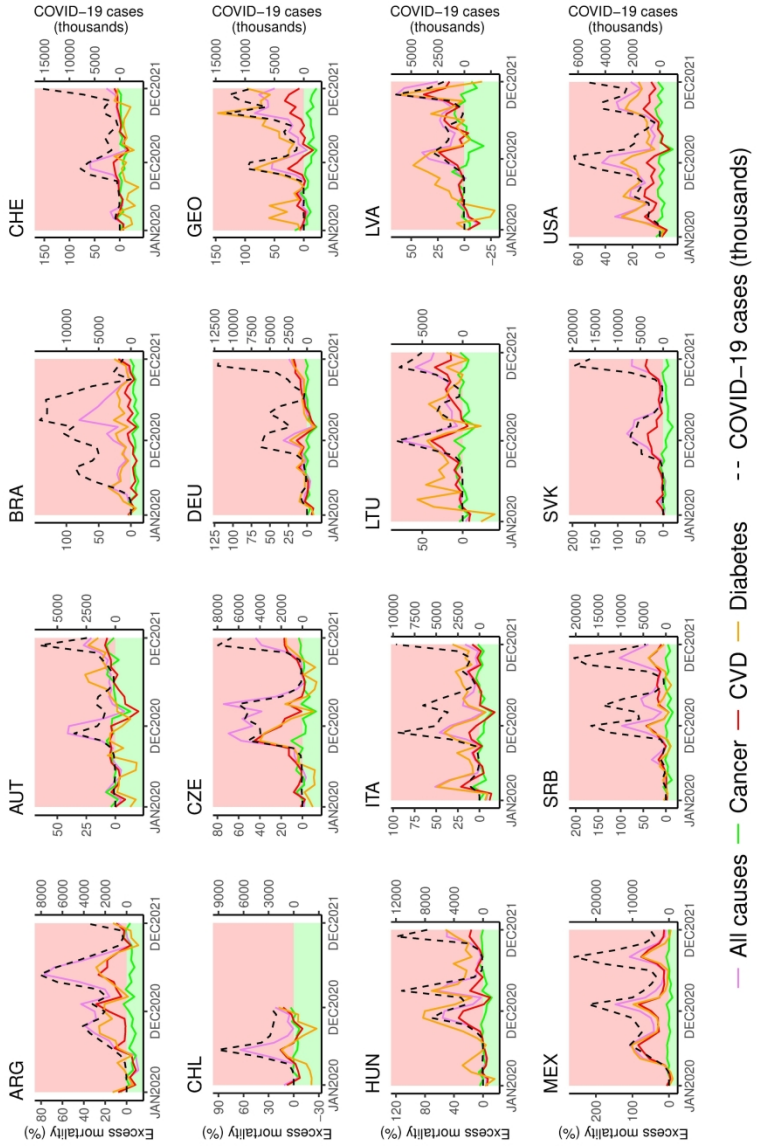

Figure 1. Monthly trends in COVID-19 cases (dotted line) and excess mortality (% difference from the expected number of deaths) from all causes, cancer, cardiovascular diseases and diabetes (continuous lines), by country, 2020-2021. Country abbreviations (ISO 3166 - Country code): ARG: Argentina; AUT: Austria; BRA: Brazil; CHE: Switzerland; CHL: Chile; CZE: Czech Republic; DEU: Germany; GEO: Georgia; HUN: Hungary; ITA: Italy; LTU: Lithuania; LVA: Latvia; MEX: Mexico; SRB: Serbia; SVK: Slovakia; USA: United States of America.

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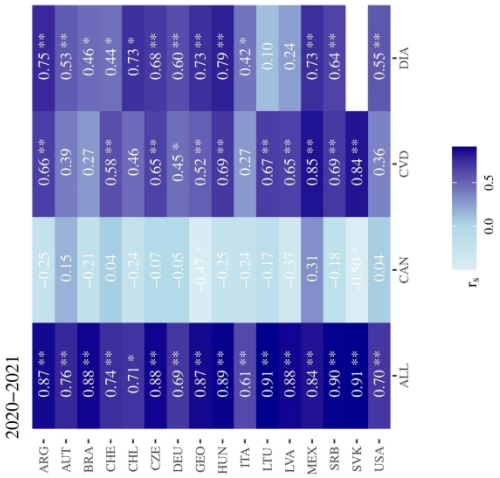

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Table 1. Excess mortality and corresponding 95% confidence interval (CI) from all causes, cancer, cardiovascular diseases, and diabetes in 16 countries in 2020 and 2021.

Country	Year	All causes		Cancers		Cardiovascular diseases		Diabetes	
		Excess deaths (95% CI)	% (95% CI)	Excess deaths (95% CI)	% (95% CI)	Excess deaths (95% CI)	% (95% CI)	Excess deaths (95% CI)	% (95% CI)
ARG	2020	35,149 (28,568; 41,729)	10.4 (8.4; 12.3)	-2466 (-3185; -1746)	-3.9 (-5.0; -2.7)	738 (-969; 2445)	0.8 (-1.0; 2.6)	868 (636; 1099)	9.7 (7.1; 12.2)
	2021	92,887 (84,532; 101,241)	27.6 (25.1; 30.1)	-1709 (-2617; -800)	-2.7 (-4.1; -1.3)	10,647 (8491; 12,802)	11.2 (9.0; 13.5)	847 (555; 1138)	9.5 (6.2; 12.8)
AUT	2020	6950 (6119; 7780)	8.2 (7.2; 9.2)	543 (270; 815)	2.6 (1.3; 3.8)	183 (-208; 574)	0.6 (-0.6; 1.8)	-193 (-272; -113)	-6.3 (-8.9; -3.7)
	2021	6994 (6025; 7962)	8.2 (7.1; 9.4)	280 (-35; 595)	1.3 (-0.2; 2.8)	-696 (-1144; -247)	-2.2 (-3.6; -0.8)	248 (156; 339)	8.2 (5.1; 11.2)
BRA	2020	174,504 (143,727; 205,280)	12.7 (10.4; 14.9)	-12,935 (-16,308; -9561)	-5.3 (-6.7; -3.9)	-11,972 (-18,602; -5341)	-3.2 (-5.0; -1.4)	8537 (7528; 9545)	12.7 (11.2; 14.2)
	2021	431,359 (395,105; 467,612)	30.9 (28.3; 33.5)	-12,578 (-16,595; -8560)	-5.1 (-6.7; -3.4)	10,821 (3081; 18,560)	2.9 (0.8; 5.0)	10,086 (8898; 11,273)	14.8 (13.1; 16.5)
CHE	2020	7868 (7190; 8545)	11.5 (10.5; 12.5)	-591 (-823; -358)	-3.3 (-4.5; -2.0)	302 (42; 561)	1.5 (0.2; 2.8)	-181 (-228; -133)	-15.2 (-19.1; -11.2)
	2021	2498 (1706; 3289)	3.6 (2.5; 4.8)	-728 (-999; -456)	-4.0 (-5.5; -2.5)	-317 (-614; -19)	-1.6 (-3.1; -0.1)	-84 (-138; -29)	-7.1 (-11.7; -2.5)
CHL	2020	15,568 (14,434; 16,701)	14.1 (13.1; 15.1)	-356 (-648; -63)	-1.2 (-2.2; -0.2)	351 (17; 684)	1.2 (0.1; 2.4)	-280 (-381; -178)	-7.1 (-9.7; -4.5)
CZE	2020	17,597 (16,638; 18,555)	15.8 (14.9; 16.6)	455 (191; 718)	1.6 (0.7; 2.5)	5362 (4917; 5806)	11.7 (10.7; 12.6)	232 (117; 346)	4.9 (2.5; 7.3)
	2021	28,575 (27,463; 29,686)	25.7 (24.7; 26.7)	-452 (-756; -147)	-1.6 (-2.7; -0.5)	3115 (2613; 3616)	7.0 (5.8; 8.1)	58 (-83; 199)	1.2 (-1.6; 4.0)
DEU	2020	30,874 (18,022; 43,725)	3.2 (1.9; 4.6)	-947 (-2818; 924)	-0.4 (-1.2; 0.4)	7496 (2644; 12347)	2.3 (0.8; 3.7)	1324 (857; 1790)	5.4 (3.5; 7.3)
	2021	63,831 (47,303; 80,358)	6.7 (4.9; 8.4)	-3846 (-6243; -1448)	-1.6 (-2.6; -0.6)	15,005 (8911; 21,098)	4.6 (2.7; 6.5)	1460 (864; 2055)	6.0 (3.5; 8.4)
GEO	2020	4995 (4209; 5780)	11.0 (9.2; 12.7)	-312 (-517; -106)	-3.7 (-6.2; -1.3)	1258 (872; 1643)	6.0 (4.2; 7.9)	227 (175; 278)	30.3 (23.3; 37.1)
	2021	15,600 (14,657; 16,542)	35.2 (33.1; 37.3)	-1230 (-1498; -961)	-13.9 (-16.9; -10.8)	1429 (956; 1901)	6.9 (4.6; 9.2)	412 (352; 471)	57.7 (49.3; 66.0)
HUN	2020	13,340 (10,576; 16,103)	10.5 (8.3; 12.6)	135 (-629; 899)	0.4 (-1.9; 2.8)	3221 (2385; 4056)	5.1 (3.8; 6.5)	730 (640; 819)	24.1 (21.1; 27.0)
	2021	29,841 (26,680; 33,001)	23.7 (21.2; 26.2)	-366 (-1233; 501)	-1.2 (-3.9; 1.6)	4233 (3279; 5186)	6.9 (5.3; 8.4)	1009 (904; 1113)	33.3 (29.8; 36.7)
ITA	2020	94,809 (86,709; 102,908)	14.7 (13.4; 15.9)	-2928 (-4618; -1237)	-1.6 (-2.6; -0.7)	4690 (1478; 7901)	2.1 (0.7; 3.6)	3822 (3399; 4244)	17.6 (15.7; 19.6)
	2021	55,071 (44,148; 65,993)	8.5 (6.8; 10.2)	-4752 (-7000; -2503)	-2.7 (-3.9; -1.4)	-1540 (-5793; 2713)	-0.7 (-2.7; 1.2)	3083 (2519; 3646)	14.3 (11.7; 16.9)
LTU	2020	4776 (4354; 5197)	12.3 (11.2; 13.4)	172 (17; 326)	2.1 (0.2; 4.0)	1682 (1390; 1973)	7.9 (6.5; 9.3)	107 (71; 142)	18.4 (12.2; 24.4)
	2021	9995 (9518; 10,471)	26.5 (25.3; 27.8)	-231 (-407; -54)	-2.8 (-5.0; -0.7)	2557 (2231; 2882)	12.5 (10.9; 14.1)	82 (36; 127)	13.0 (5.7; 20.1)
LVA	2020	988 (629; 1346)	3.8 (2.4; 5.1)	43 (-88; 174)	0.7 (-1.5; 3.0)	164 (-65; 393)	1.1 (-0.5; 2.7)	64 (23; 104)	10.6 (3.8; 17.2)
	2021	6835 (6420; 7249)	26.0 (24.5; 27.6)	-116 (-268; 36)	-2.0 (-4.6; 0.6)	1965 (1700; 2229)	13.6 (11.8; 15.4)	73 (23; 122)	11.5 (3.6; 19.2)
MEX	2020	341,657 (329,120; 354,193)	45.9 (44.2; 47.6)	1195 (367; 2022)	1.2 (0.4; 2.1)	64,261 (62,787; 65,734)	32.5 (31.8; 33.3)	41,698 (40,956; 42,439)	37.8 (37.1; 38.5)
	2021	360,257 (345,546; 374,967)	48.0 (46.0; 49.9)	-334 (-1304; 636)	-0.3 (-1.3; 0.7)	64,697 (62,959; 66,434)	32.3 (31.5; 33.2)	27,931 (27,058; 28,803)	25.0 (24.3; 25.8)
SRB	2020	16,660 (14,965; 18,354)	16.6 (14.9; 18.3)	-578 (-973; -182)	-2.6 (-4.4; -0.8)	4013 (2946; 5079)	7.8 (5.7; 9.9)	212 (57; 366)	6.7 (1.8; 11.5)
	2021	39,224 (37,117; 41,330)	40.3 (38.1; 42.5)	-1088 (-1587; -588)	-5.0 (-7.3; -2.7)	7196 (5886; 8505)	14.6 (11.9; 17.2)	237 (43; 430)	7.6 (1.4; 13.8)
SVK	2020	4971 (4364; 5577)	9.2 (8.1; 10.3)	-206 (-404; -7)	-1.4 (-2.8; 0.0)	2488 (2152; 2823)	10.1 (8.7; 11.4)		
	2021	19,734 (19,033; 20,434)	36.7 (35.4; 38.0)	-1265 (-1496; -1033)	-8.8 (-10.5; -7.2)	4262 (3883; 4640)	17.7 (16.1; 19.3)		
USA	2020	469,170 (439,275; 499,064)	16.1 (15.1; 17.1)	-2768 (-6166; 630)	-0.4 (-1.0; 0.1)	44,247 (35,996; 52,497)	5.0 (4.1; 5.9)	13,564 (12,944; 14,183)	15.3 (14.6; 16.0)
	2021	484,547 (449,048; 520,045)	16.3 (15.1; 17.5)	-3939 (-7901; 23)	-0.6 (-1.3; 0.0)	27,895 (18,103; 37,686)	3.1 (2.0; 4.2)	12,403 (11,664; 13,141)	13.6 (12.8; 14.5)

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SUPPLEMENTARY MATERIAL

Manuscript title: Temporal relationship between COVID-19 cases and monthly mortality from all causes, cardiovascular diseases and diabetes in 16 countries, 2020-2021.

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Table S1. Data availability (period, age categories and causes of death) by country.

Country	Period	Age categories	Causes of death
ARG	2015-2021	<20, 20-39, 40-49, …, 80+	ALL, CAN, CVD, DIA
AUT	2011-2022	<1, 1-4, 5-9, …, 100+	ALL, CAN, CVD, DIA
BRA	2011-2022	<1, 1-4, 5-9, …, 100+	ALL, CAN, CVD, DIA
CHE	2011-2021	<1, 1-4, 5-9, …, 100+	ALL, CAN, CVD, DIA
CHL	2011-2020	0-4, 5-9, … , 100+	ALL, CAN, CVD, DIA
CZE	2011-2021	<1, 1-4, 5-9, … , 85+	ALL, CAN, CVD, DIA
DEU	2011-2021	0-15, 15-45, 45-65, 65+	ALL, CAN, CVD, DIA
GEO	2014-2022	0-4, 5-9, … , 85+	ALL, CAN, CVD, DIA
HUN	2011-2022	0-14, 15-39, 40-59, 60+	ALL, CAN, CVD, DIA
ITA	2015-2021	<1, 1-4, 5-9, …, 95+	ALL, CAN, CVD, DIA
LIT	2010-2021	<1, 1-4, 5-9, …, 100+	ALL, CAN, CVD, DIA
LVA	2011-2021	0-4, 5-9, …, 85+	ALL, CAN, CVD, DIA
MEX	2011-2021	<1, 1-4, 5-9, … , 85+	ALL, CAN, CVD, DIA
SRB	2015-2022	<1, 1-4, 5-9, … , 85+	ALL, CAN, CVD, DIA
SVK	2011-2022	0-4, 5-9, … , 90+	ALL, CAN, CVD
USA	2011-2021	<1, 1-4, 5-9, …, 100+	ALL, CAN, CVD, DIA

ALL: All causes. CAN: Cancer. CVD: Cardiovascular diseases. DIA: Diabetes.

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Figure S2. Effect of different choices of baseline periods on the estimates of excess deaths in 2020 and 2021. The estimates of excess deaths were derived from different combinations of available years preceding the COVID-19 pandemic.

For countries with five pre-pandemic years, we used all possible combinations of three to five years (16 combinations). For the countries with nine pre-pandemic years, we used all possible combinations of five to nine pre-pandemic years (256 combinations). For countries with ten pre-pandemic years, we used all possible combinations of five to ten years.

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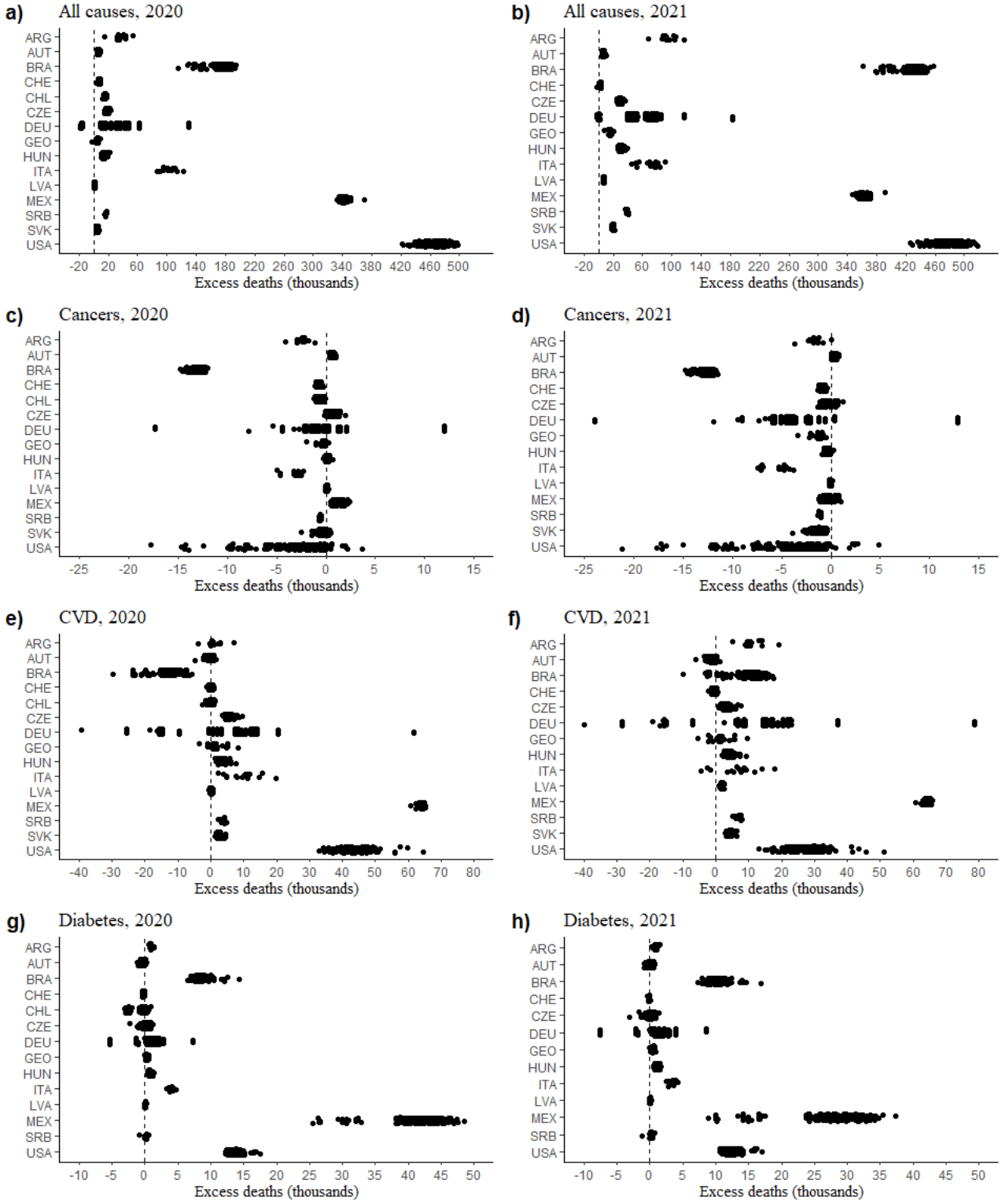

Table S2. Extreme percentiles (2.5^{th} and 97.5^{th}) of the excess death estimates obtained from different combinations of available years preceding the COVID-19 pandemic.

Country	Year	All causes	Cancers	CVD	Diabetes
ARG	2020	21,100; 49,442	-3668; -1360	-2575; 5533	602; 1358
	2021	75,078; 112,846	-3180; -277	6515; 17,237	449; 1471
AUT	2020	5439; 8121	397; 859	-1417; 947	-711; 52
	2021	5257; 8375	119; 643	-2500; 272	-355; 549
BRA	2020	137,814; 187,881	-14,132; -12,274	-22,940; -7756	7177; 10,548
	2021	388,274; 446,162	-13,996; -11,722	-1969; 15,559	8248; 12,457
CHE	2020	6723; 8656	-957; -436	-541; 769	-307; -122
	2021	1134; 3558	-1152; -550	-1291; 255	-230; -11
CHL	2020	13,899; 16,784	-781; -182	-1107; 1059	-2543; 498
CZE	2020	16,107; 20,371	6; 1309	4468; 6938	-376; 811
	2021	26,769; 31,679	-1013; 524	1965; 4849	-731; 848
DEU	2020	-16,607; 61,913	-5029; 2116	-17,762; 20,505	-1363; 2850
	2021	-235; 117,649	-9267; 337	-18,346; 36,982	-2177; 3978
GEO	2020	3363; 6263	-1014; -11	-1098; 5053	20; 521
	2021	13,686; 17,425	-2147; -806	-2193; 5877	77; 732
HUN	2020	11,340; 16,363	-104; 364	2088; 4532	521; 1053
	2021	27,291; 33,221	-656; -107	2911; 5697	728; 1371
ITA	2020	88,728; 119,438	-4869; -2372	2818; 18235	3415; 4650
	2021	47,266; 88,537	-7263; -3931	-3799; 16372	2627; 4190
LVA	2020	531; 1433	-1; 131	-245; 497	25; 118
	2021	6315; 7354	-166; -17	1479; 2369	20; 138
MEX	2020	335,788; 350,439	597; 2051	62,847; 64,895	29,548; 46,378
	2021	352,973; 370,336	-1004; 640	63,047; 65,475	13,699; 33,708
SRB	2020	14,958; 17,733	-730; -497	2694; 4603	-554; 489
	2021	36,904; 40,633	-1280; -984	5357; 7902	-725; 645
SVN	2020	3909; 5888	-1124; 377	1749; 3437	NA
	2021	18,523; 20,768	-2327; -498	3307; 5297	NA
USA	2020	437,154; 489,771	-11,479; 594	36,944; 50,540	12,518; 15,093
	2021	445,159; 508,135	-13,943; 372	17,905; 35,196	11,099; 14,232

CVD, cardiovascular disease; NA, not available.

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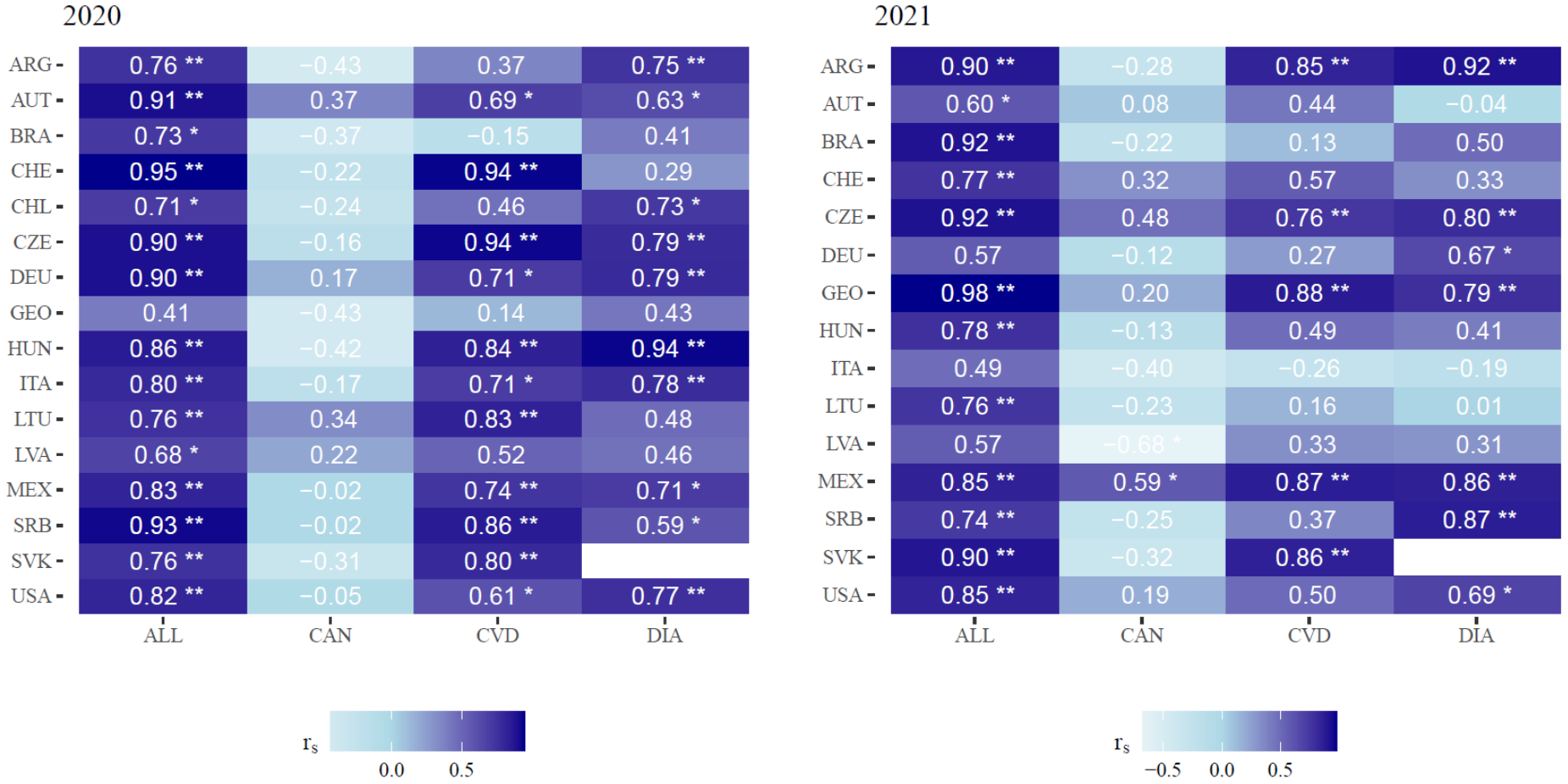
Figure S1. Correlation between COVID-19 cases and monthly excess mortality from all causes, cancer, cardiovascular diseases and diabetes by country in 2020 and 2021.



r_s: Spearman's correlation coefficient. *p<0.05, **P<0.01

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Figure S3. Comparison between the estimates of excess deaths (%) for 2020 and 2021 with those obtained for 2019, using previous years as baseline periods. Country abbreviations (ISO 3166 - Country code): ARG: Argentina; AUT: Austria; BRA: Brazil; CHE: Switzerland; CHL: Chile; CZE: Czech Republic; DEU: Germany; GEO: Georgia; HUN: Hungary; ITA: Italy; LTU: Lithuania; LVA: Latvia; MEX: Mexico; SRB: Serbia; SVK: Slovakia; USA: United States of America.