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Trends in death rates from Liver diseases in the US for all ages and detailed analysis for age groups 75-84 and 35-44

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ABSTRACT

Using data from the US CDC (Centers for Disease Control and Prevention), we investigate trends in death rates from liver diseases (ICD-10 codes K70-K76). As we find a different pattern of excess mortality during the pandemic and post-pandemic years for different age groups, we perform a detailed analysis for older individuals, aged 75 to 84, and for younger individuals, aged 35 to 44. We also compare excess death rates from 2020 to 2023 from liver diseases for all 10-year age groups in the US. We analyze trends in death rates from liver diseases where these appear on the death certificate under multiple causes (MC) of death, or as the underlying cause (UC), as well as the trends in the ratio of multiple cause to underlying cause death rates (MC/UC).

For individuals aged 75 to 84, our results show that the excess UC death rates from liver diseases (K70-K76) were 2.4% (Z-Score of 3.9) in 2020, then rose to 8.8% (Z-Score of 14.4) in 2021, 7.3% (Z-Score of 11.9) in 2022 and 11.1% (Z-Score of 18.2) in 2023. We also observe that the rises of excess MC* death rates (where COVID-19-related deaths are excluded) from liver diseases in 2020, 2021, 2022 and 2023 mirror the excess UC death rates, suggests that a common underlying factor is at play.

For individuals aged 35 to 44, our results show that the excess UC death rates from liver diseases (K70-K76) were 38.5% (Z-Score of 16.2) in 2020, then rose to 54.2% (Z-Score of 22.8) in 2021, 38.7% (Z-Score of 16.3) in 2022 and 22.1% (Z-Score of 9.3) in 2023.

When investigating liver diseases as underlying cause for all age groups we observe that the rise in excess deaths occurred for all age groups, however, suggesting different patterns for younger and older individuals. For younger individuals, aged 65 or less, excess death rates from liver diseases appear to be related to rises in all-cause mortality in 2020, peaking in 2021 and subsequent normalization in 2022 and 2023. For older individuals, excess death rates rose from 2020 to 2023. The results indicate that from 2020 a novel phenomenon leading to increased liver disease death rates appears to be present which is driven by alcoholic liver disease in younger individuals while for older individuals, cirrhosis and fibrosis of the liver is the pathology driving excess death rates. From 2021 onwards, excess death rates for older individuals could be explained by adverse effects from COVID-19 vaccinations or lingering effects of multiple SARS-CoV-2 exposures, which requires further research.

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Keywords: Liver disease mortality, ICD-10 codes K70-K76, COVID-19 pandemic impact

1 INTRODUCTION

Context:

The COVID-19 pandemic was a societal paradigm-changing event. The US suffered particularly high excess mortality during 2020 and 2021 and persisted in 2022 and 2023, which merit a deeper understanding of the phenomenon and its persistent collateral damage. There are still a number of unanswered questions regarding the SARS-CoV-2 pandemic, from the effects of the SARS-CoV-2 virus itself (through its symptomatic manifestations of COVID and Long-COVID), the impacts of the pandemic control measures (lockdowns, masking, social distancing), the COVID-19 treatment protocols, and the introduction of COVID-19 vaccines based upon novel mRNA technology.

To answer these questions, we produced several research papers that analyze trends in death rates from different diseases comparing pre and post COVID-19 pandemic death rates for different diseases. Excess neoplasm death rates are shown by (Alegria, et al., 2024)[1] for younger individuals aged 15-44 and by (Alegria, et al., 2024)[2] for older individuals aged 75-84. Excess deaths from neurological diseases for younger individuals aged 15-44 in 2020 to 2023 are also shown by (Alegria, et al., 2024)[3]. These papers show that from 2020 there was a series break in the data that points to a novel phenomenon that is leading to excess death rates, which is impacting different body systems.

These papers show that excess death rates rose in 2020 but accelerated in 2021 and 2022, which is difficult to reconcile with excess deaths originating from COVID-19, but instead appear associated with the COVID-19 vaccinations roll out from 2021 onwards. A recent publication from Alessandria et. al. that compares all-cause mortality in COVID-19 vaccinated versus unvaccinated individuals in a province in Italy provides support for this hypothesis by showing about 20% higher all-cause mortality (computed as a hazard ratio) for vaccinated individuals.

In this paper, we investigate trends in death rates from liver diseases in the US which is complementary to our previous research.

Liver Disease and the COVID-19 Pandemic:

Early on during the SARS-CoV-2 pandemic, autoimmune hepatitis (AIP) was associated with adverse events following both COVID-19 disease and COVID-19 vaccinations, as shown in the different case reports (Durazo, et al., 2022)[4], (Zheng, et al., 2022)[5], (Roy, et al., 2022)[6], (Trontzas, et al., 2022)[7] and (Ueno, et al., 2023)[8], among others. These conditions tend to resolve in most cases, but merit further investigation and monitoring (Trontzas, et al., 2022)[7]. The number of cases found in the literature merited that the condition being classified as an adverse event of special interest (AESI) following COVID-19 vaccination, which led to Brighton Collaboration case definition for AIP (Kochhar, et al., 2024)[9].

Non-alcoholic fatty liver disease (NAFLD) also denominated as metabolic-associated fatty liver disease (MAFLD) is a known risk factor towards bad COVID-19 outcomes (Rivera-Esteban, et al., 2022)[10]. Additionally, a recent literature review finds several case studies of the liver damage associated with acute COVID-19 disease, but with few studies on the effect of COVID-19 vaccinations (Nowroozi, et al., 2023)[11].

Current study:

In this study, we provide a detailed analysis of excess deaths in 2020, 2021, 2022 and 2023 of the older 75-84 age group and the younger 35-44 age group. We do so because we observed that there is a distinct pattern of excess mortality for older individuals when compared to younger individuals. The selected age group cohorts represent typical cases for the pattern of behavior in younger and older individuals. We observe that younger individuals' excess mortality trends from 2020 onwards are driven by alcoholic liver disease (ICD-10 code: K70), while for older individuals' mortality trends are driven by fibrosis and cirrhosis of liver (ICD-10 code: K74), which becomes clear by

investigating trends in death rates for the most relevant sub-categories within the liver disease classification codes (ICD-10 codes: K70-K76).

We analyze trends in liver diseases where these appear on death certificates as multiple causes (MC) of death, or as the underlying cause (UC), as well as the trends in the ratio of multiple cause to underlying cause death rates. Additionally, we also analyze trends in MC death rates where COVID-19-related deaths are excluded.

After the detailed analysis of older individuals aged 75-84 and of younger individuals aged 35-44, we analyze excess death trends from liver diseases (K70-K76) for all ages, in ten-year age groups, as provided by the CDC (US Centers for Diseases Control and Prevention) WONDER system.

2 DATA

2.1 Cause of Death Data

The data used in this analysis are the number of deaths that occurred in the USA between 2000 and 2023, by underlying cause code (ICD-10), sex, and 10-year age groups, obtained using the CDC WONDER[1] system provided by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC). The mortality data is final up to 2021 but provisional from 2022 onwards. Additionally, for comparing multiple cause (MC)[2] of death trends from musculoskeletal diseases with underlying cause (UC)[3] of death trends, we download data from both the multiple cause of death databases and underlying cause of death databases.

Query parameters:

For underlying cause of death data, select variable grouped by: *1. Ten-year-age-groups, 2. Gender, 3. Year, 4. UCD – ICD Chapter*

(Link to the underlying cause of death databases).

For multiple cause of death data, select variable grouped by: *1. Ten-year-age-groups, 2. Gender, 3. Year, 4. MCD – ICD Chapter*

(Link to the multiple cause of death databases)

2.2 Definition of MC of Death and UC of Death

The Centers for Disease Control and Prevention (CDC) classifies deaths based on cause into two primary categories: ”Underlying Cause of Death” and ”Multiple Causes of Death.” These classifications are useful for epidemiological studies, public health, and understanding different mortality patterns. The definitions are:

Underlying Cause (UC) of Death: The underlying cause of death is defined as ”the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury,” according to the World Health Organization (WHO).

Multiple Causes (MC) of Death: Multiple causes of death include all causes and conditions reported on the death certificate that contributed to death, not just the underlying cause. This includes the underlying cause, immediate cause, and any other significant conditions contributing to death. Each death certificate contains a single underlying cause of death, and up to twenty additional multiple causes.

2.3 Data Use Restrictions

In this research paper we abide by the CDC’s restrictions on data use which are[4]:

“The Public Health Service Act (42 U.S.C. 242m(d)) provides that the data collected by the National Center for Health Statistics (NCHS) may be used only for the purpose for which they were obtained; any effort to determine the identity of any reported cases, or to use the information for any purpose other than for health statistical reporting and analysis, is against the law. Therefore, users will:

[1] CDC Wonder

[2] CDC Wonder Multiple Cause of Death

[3] CDC Wonder Underliyng Cause of Death

[4] CDC Wonder - Data Use Restrictions

- *Use these data for health statistical reporting and analysis only.*
- *Do not present or publish death counts of 9 or fewer or death rates based on counts of nine or fewer (in figures, graphs, maps, tables, etc.).*
- *Make no attempt to learn the identity of any person or establishment included in these data.*
- *Make no disclosure or other use of the identity of any person or establishment discovered inadvertently and advise the NCHS Confidentiality Officer of any such discovery."*

2.4 Population Data

The source for the population data that are used for computing death rates (deaths per 100,000) are the data retrieved from the CDC queries. We chose to use the CDC population data instead of data from the US Census Bureau for consistency with other researchers' analyses.

2.5 All-Cause Deaths Data

All cause deaths were retrieved from CDC WONDER, by using the following query parameters:

1.Ten-year-age-groups, 2. Gender, 3. Year. The ten-year-age-groups are: 1, 1-4, 5-14, 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, 85+.

2.6 Data verification and limitations

The CDC WONDER system provides two separate databases from which to query underlying cause of death data and multiple causes of death data. Additionally, each is separated into two datasets comprising different time periods, so that in order to obtain time series from 2000 to 2023, multiple queries were performed.

Within the multiple causes of death databases, it is also possible to obtain the underlying cause of death data. We downloaded all the available yearly data (for MC of death and UC of death) and compared the different datasets for consistency, whenever the time periods overlapped.

From 2010 to 2021 the MC and UC of death data is final, while for 2022 and 2023 it is provisional. Details on provisional CDC deaths data can be found here[5].

3 METHODOLOGY

In this study, we analyze the trends in death rates for musculoskeletal diseases. We investigate these trends using yearly data and therefore a seasonal adjustment to the data is unnecessary.

In general terms, to estimate trends in these variables we use a methodology of computing excess death rates, which is the difference between the actual observed rates and a given baseline (expected rates). Because we want to describe the impact of the COVID-19 pandemic and post-pandemic periods relative to the prior state of the world, our baselines are based upon the estimation of the trend for a period prior to the pandemic.

In this study we will use method 2C, as described in our report on methodologies for measuring excess deaths in the population (Alegria, et al., 2024)[12]. Method 2C is based on computing the trends in death rates (deaths adjusted by the population) instead of deaths, as the baseline for estimating excess mortality. This method significantly reduces the noise of the estimation as it adjusts for population growth or decline, and by also providing different rates for each age category, we adjust for changes in population age distribution. The method also considers the prior trend in death rates, which tend to decline over time as the population grows healthier and risk factors are better managed.

3.1 Method 2C for Estimating Excess Death Rates

$$\begin{bmatrix} Excess \\ Deaths \end{bmatrix}_{t_i}^{AG} = Deaths_{t_i}^{AG} - Baseline_{t_i}^{AG} \quad (1)$$

[5] CDC Wonder Technical Notes for Provisional Mortality

Equation 1 is a general expression for estimating the excess absence rates relative to a given baseline. We use the superscript AG to indicate a given population age range, as this is the primary focus of the current analysis. Other cohorts which this equation could apply to include a specific region, sex, or underlying cause of death. The subscript t_i refers to time, that is, the corresponding year for which the excess deaths are computed.

For estimating the baseline for "normal or expected" death rates we use a simple linear fit:

$$Baseline(t_i) = \hat{b} + \hat{a}(t_i - t_0) \tag{2}$$

Where $\hat{a}$ and $\hat{b}$ are the estimated coefficients of the death rate trendline from 2013 to 2019. We also compute a Z-score that estimates the normalized deviation from trend:

$$Z = \frac{\Big[Deaths\Big]_{t_i}^{AG} - \Big[Baseline\Big]_{t_i}^{AG}}{\sigma_{2013-2019}} \tag{3}$$

Where σ is the standard deviation of the excess deaths during the pre-pandemic period 2013-2019.

3.2 ICD-10 Code List of Selected Causes of Death for: Liver diseases

For this analysis we selected all the ICD-10 codes from the CDC aggregated chapter lists (Letters K70 to K76), which refer to deaths attributed to liver diseases, within the wider category of digestive system diseases. We also compare death rates from the major sub-categories within the K70-K76 codes, in order to investigate the most common liver diseases that lead or contribute towards death.

4 ANALYSIS OF EXCESS DEATH RATES FOR AGE GROUPS 75-84 AND 35-44

In this section we perform an analysis of the trend in yearly death rates from liver diseases for two different age cohorts: a) for older individuals aged 75 to 84; b) for younger individuals, aged 35-44. In this analysis we use the 2013-2019 trend in deaths per 100,000 (death rates) as the baseline estimate for excess death rates. Excess death rates for the 2013-2019 period are in-sample while the rates for 2020, 2021, 2022 and 2023 are out of sample computations. We investigate trends in MC (multiple-cause) and UC (underlying cause) deaths rates from liver diseases, and also, trends in MC* death rates (MC deaths where COVID-19-related death are removed).

To contextualize trends in death rates from liver diseases, we first analyze the trends in all-cause death rates for the 35-44 and 75-84 age groups. We also analyze overall trends in death rates from liver diseases (ICD-10 codes: K70-K76) and the main sub-categories within, namely, alcoholic liver disease (ICD-10 code: K70), Hepatic Failure, Not Elsewhere Classified (ICD-10 code: K72) and Fibrosis and Cirrhosis of Liver (ICD-10 code: K74) in order to understand the relative contribution of each sub-category towards liver disease mortality for the 35-44 and 75-84 age groups.

We do not plot death rates for the sub-categories of Toxic Liver Disease (ICD-10 code: K71), Chronic Hepatitis, Not Elsewhere Classified (ICD-10 code: K73), Other Inflammatory Liver Diseases (ICD-10 code: K75) as they represent a negligible contribution towards total deaths from liver disease.

4.1 Deaths from All Causes

The analysis of the deaths from all causes allows us to contextualize the trends in death rates from liver diseases. Figure 1 shows the death rate per 100,000 individuals for all deaths in the US from 2010 to 2023, for the 75 to 84 age group (top) and for the 35-44 age group (bottom).

The all-cause death rate for individuals aged 75 to 84 was 5666.5 per 100,000 in 2000, decreasing monotonically to 4308.2 per 100,000 in 2019, corresponding to a 24.0% decline over the period (a 1.2% drop per annum during the period). The death rate rose in 2020 to 4997 per 100,000 and then again in 2021 to 5119 per 100,000. In 2022 the death rate dropped slightly to 4708 per 100,000

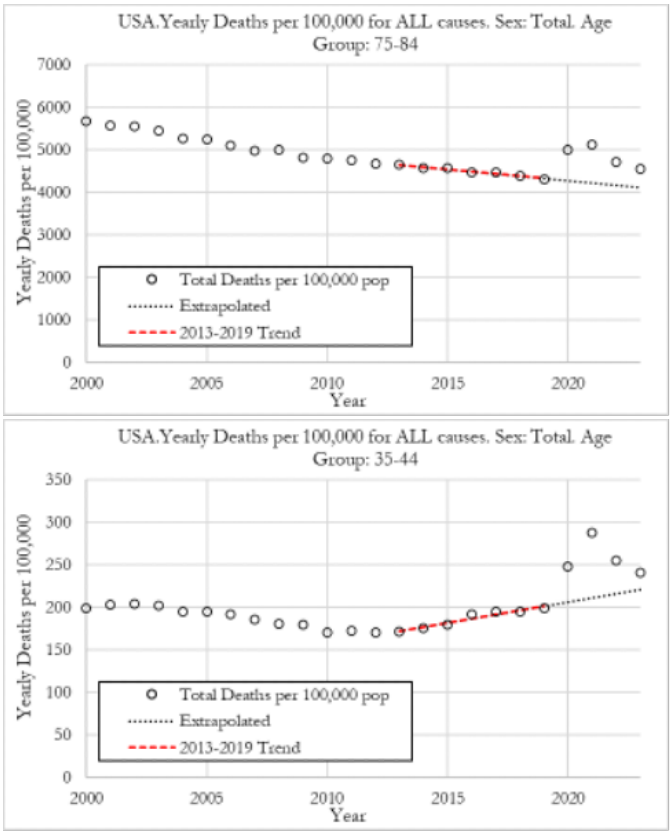


Figure 1. All-cause death rate (per 100,000) for the US from 2000 to 2023. The red dashed line shows the trend from 2013 to 2019. The dotted line shows the extrapolation of the trend from 2020 until 2023. Top: Age group: 75-84. Bottom: Age group: 35-44.

and in 2023 the death rate dropped again to 4555 per 100,000 (still above the 2013-2019 extrapolated trend).

For individuals aged 35 to 44, the all-cause death rate was 198.9 per 100,000 in 2000, which declined slightly until 2010 and subsequently rose steadily to 199.2 per 100,000 in 2019, a death rate close to observed in 2000. In 2020, the death rate increased to 248.0 per 100,000 and then again in 2021 to 287.9 per 100,000. In 2022 the death rate dropped slightly to 255.4 per 100,000 and in 2023 the death rate dropped further to 240.8 per 100,000 (still above the 2013-2019 extrapolated trend). We should note that the 2013-2019 extrapolated trend is likely to overstate expected future death rates as it extrapolates from a period of rising death rates.

4.1.1 Excess All-Cause Death Rates

Figure 2 shows the excess death rate for registered deaths (all-cause) in the US from 2010 to 2023 for the 75-84 age group (top) and for the 35-44 age group (bottom). The columns in Figure 2 refer to relative deviations from the 2013-2019 trend while the dashed line refers to the respective Z-Scores.

Figure 2 (top) shows that for the 75-84 age group, excess deaths in 2020 were 16.8%, with a Z-Score of 28.1, indicating a very high level of statistical significance, being considered an extreme occurrence. In 2021 excess deaths further increased to around 21.1% with a Z-Score above 35.4. Excess deaths in 2022 were 12.8% with a Z-Score of 21.4, again indicating an extreme occurrence. Excess death levels peaked in 2021, and in 2022 dropped to below excess deaths levels calculated in 2020. In 2023 excess deaths were 10.5%, with a Z-Score of 17.6, pointing to persistently high excess all-cause mortality in the 75-84 age group following the pandemic.

Figure 2 (bottom) shows that for the 35-44 age group, excess deaths in 2020 were 20.2%, with a Z-Score of 12.4, indicating a very high level of statistical significance, being considered an extreme occurrence. In 2021 excess deaths further increased to around 36.3% with a Z-Score above 22.2. Excess deaths in 2022 were 18.2% with a Z-Score of 11.2, again indicating an extreme occurrence. In 2023 excess deaths were 9.0%, with a Z-Score of 5.5.

4.2 Trends in UC and MC Death Rates for Different Sub-Categories of Deaths from Liver Disease

In this section we investigate the trends in MC and UC death rates from 2000 to 2023 from liver diseases (ICD-10 codes K70 to K76), for the age groups 35-44 and 75-84. We also investigate different sub-categories within liver diseases to understand the relative contribution towards death rates of the different types of categories of liver disease. We compare trends in death rates for alcoholic liver disease (K70), hepatic failure, not elsewhere classified (K72) and fibrosis and cirrhosis

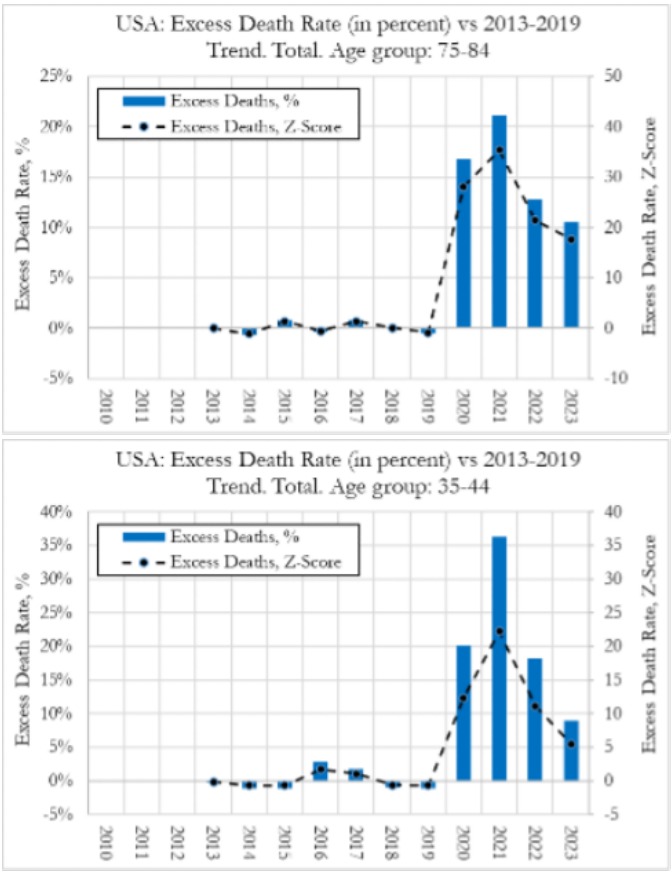


Figure 2. Excess all-cause death rates for both sexes in the US. The columns refer to percent deviations from 2013-2019 trend while the dashed line refers to the respective Z-Scores. Top: Age group 75-84. Bottom: Age group 35-44.

of liver (K74). The other sub-categories within liver disease deaths are not shown as they are negligible towards contributing to overall liver disease deaths.

4.2.1 UC and MC Death Rates

Figure 3 shows the death rate per 100,000 individuals from liver diseases (and selected sub-categories) in the US, for individuals aged 75-84, from 2000 to 2023. The figure on the top refers to UC (underlying-cause) deaths rates while the figure on the bottom shows trends in MC (multiple-causes) death rates.

For the 75-84 age group, we observe that both UC and MC death rates from liver diseases (ICD-10 codes: K70-K76) trended lower from 2000 to 2009 but then started trending upwards from 2010 to 2019. From 2020, deaths rates rose substantially.

We also note that the most important sub-category within liver-related deaths are fibrosis and cirrhosis of liver (K74). These account for more than half of liver deaths for older individuals aged 75-84, and as shown in Figure 3 are the main drivers of excess death rates from 2020 onwards.

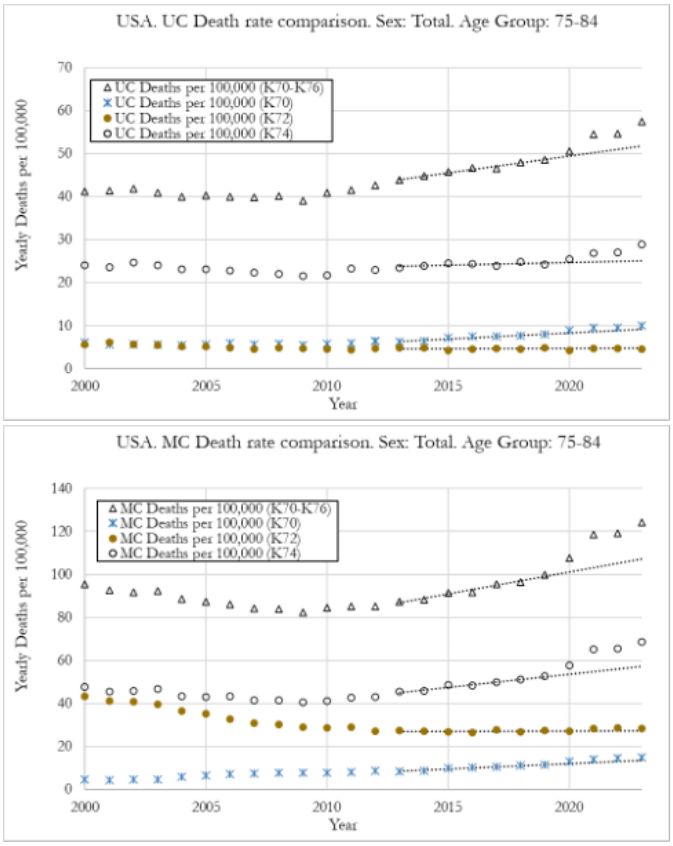


Figure 3. UC and MC death rates (per 100,000) from Liver diseases (K70-K76) and relevant sub-categories in the US for ages 75 to 84. The red dashed line shows the trend from 2013 to 2019. The dotted line shows the extrapolation of the trend from 2020 until 2023. Top: UC death rates. Bottom: MC death rates.

Figure 3 also illustrates that from 2020 (for MC death rates) there was a clear break from the prior 2013-2019 trend in death rates, while for UC death rates the break in trend appears to have occurred from 2021 onwards. These aspects will be also investigated in detail in the following sections.

Figure 4 shows the death rate per 100,000 individuals from liver diseases (and selected sub-categories) in the US, for individuals aged 35-44,

from 2000 to 2023. The figure on the top refers to UC (underlying-cause) deaths rates while the figure on the bottom shows trends in MC (multiple-causes) death rates.

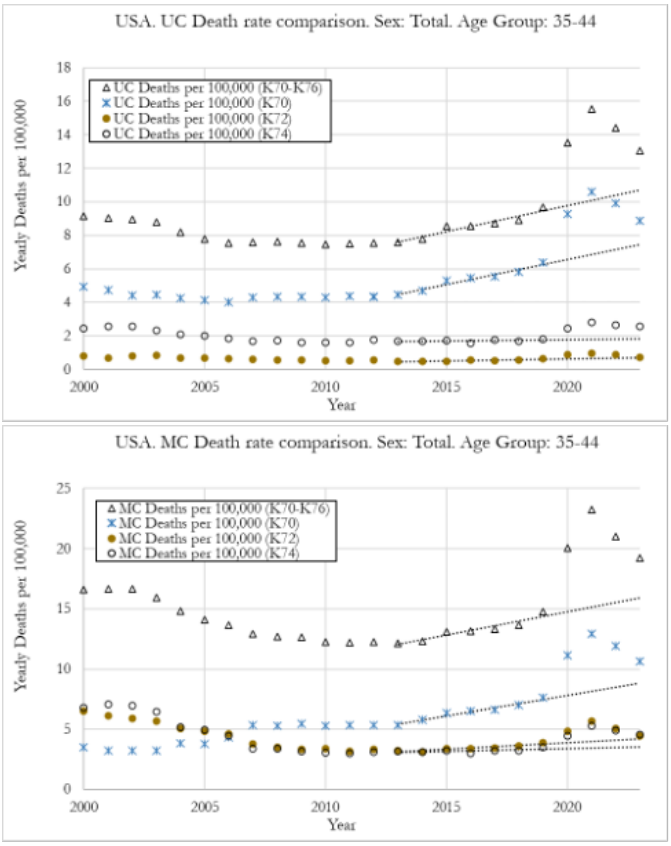


Figure 4. UC and MC death rates (per 100,000) from liver diseases (K70-K76) and relevant sub-categories in the US for ages 35 to 44. The red dashed line shows the trend from 2013 to 2019. The dotted line shows the extrapolation of the trend from 2020 until 2023. Top: UC death rates. Bottom: MC death rates.

For the 35-44 age group, we observe that both UC and MC death rates from liver diseases (K70-K76) trended lower from 2000 to 2013 but then started trending upwards from 2013 to 2019. Figure 4 also illustrates that from 2020 (both for UC and MC death rates) there was a clear break from the prior 2013-2019 trend in death rates.

We also note that the most important sub-category within liver-related deaths were from alcoholic liver disease (K70). These account for close to half the liver deaths for younger individuals aged 35-44, and as shown in Figure 4 are the main drivers of excess death rates from 2020 onwards.

4.3 Analysis of K70-K76 for Older Individuals, aged 75-84

We now investigate in detail the trends in MC, MC* (except COVID-19-related deaths) and UC death rates from 2000 to 2023 from liver diseases (ICD-10 codes: K70 to K76), for the 75-84 age group of both sexes. By analyzing both MC death rates and UC death rates, we can have a better understanding of the underlying phenomenon that leads to liver-related deaths. MC death rates need to be analyzed with caution as they refer to death rates for a given disease where it is either the underlying cause or a contributing factor towards death.

Figure 5 (top) shows that MC death rates from liver diseases for the 75-84 age group trended higher from 2000 to 2009 but then trended upwards from 2010 to 2019. From 2020 onwards we observe that both MC and UC death rates from liver disease rose substantially, with a clear break from the prior 2013-2019 trend. We also observe in Figure 5 (bottom) that the ratio of MC* to UC deaths trended lower from 2000 to 2019, from a value of 2.35 in 2000 to close to 2 in 2019. In 2020, 2021, 2022 and 2023 the ratio of MC* to UC deaths rose quickly, which means that MC* deaths (except COVID-19) from liver disease increased at a higher rate than UC deaths. It should be noted that MC and MC* death rates were the same from 2000 to 2019 as COVID-19 deaths only started in 2020.

The MC death rate was 99.81 per 100,000 in 2019 and then rose in 2020 to 107.56 per 100,000, and then to 118.46 per 100,000 in 2021, to 119.23 per 100,000 in 2022 and to 124.19 per 100,000 in 2023.

After removing COVID-19-related deaths, the MC* death rate rose in 2020 to 102.41 per 100,000, and then rose again to 111.70 per 100,000 in 2021, to 112.95 per 100,000 in 2022 and in 2023 it rose again to 121.95 per 100,000. Even after removing COVID-19 related deaths, we observe an increase in MC* liver deaths in 2020, 2021, 2022 and 2023.

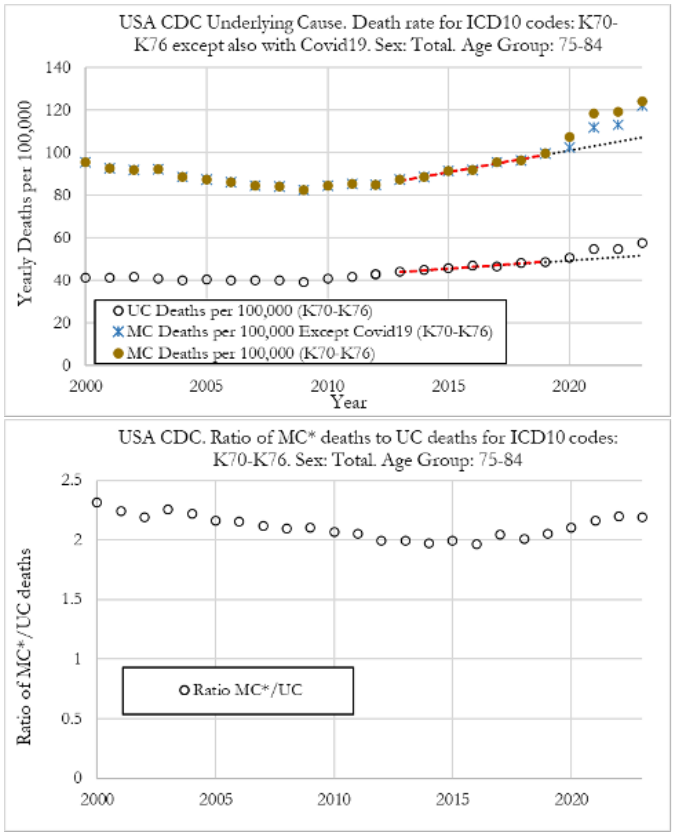


Figure 5. Death rates from liver diseases in the US for ages 75 to 84. The red dashed line shows the trend from 2013 to 2019. The dotted line shows the extrapolation of the trend from 2020 until 2023. Top: Death Rates per 100,000. Bottom: Ratio of MC* to UC deaths.

As for UC death rates, from a value of 48.58 per 100,000 in 2019, they rose to 50.57 per 100,000 in 2020, and then to 54.56 per 100,000 in 2021, to 54.64 per 100,000 in 2022 and to 57.43 per 100,000 in 2023.

The ratio of MC* to UC deaths remained stable at around 2.2 in 2021, 2022 and 2023, after a slight rise in 2020 and 2021.

4.3.1 Excess UC Death Rates for Age Group 75-84

Figure 6 shows the excess death rate from liver diseases in the US (ICD-10 codes: K70-K76), for the 75 to 84 age group from 2010 to 2023. The plots also show the excess all-cause deaths for comparison. The figure on the top refers to relative deviations from the 2013-2019 trend, while Figure 6 (bottom) shows the Z-Score (signal strength) for the deviations from trend.

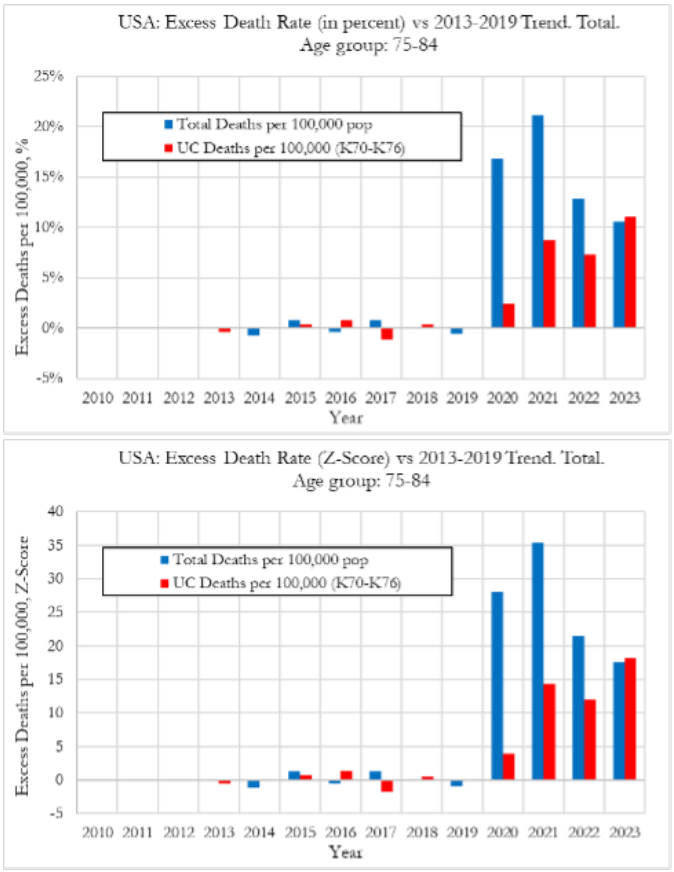


Figure 6. Excess UC death rates from liver diseases (K70-K76) from 2010 to 2023 for both sexes of ages 75 to 84 in the US. Top: Relative deviation from trend, percent. Bottom: Deviation from trend Z-Score. Excess deaths from all causes are shown for comparison.

In Figure 6 (top) we can observe that the excess death rates from liver diseases as the underlying cause (UC) were 2.4% (Z-Score of 3.9) in 2020, then rose to 8.8% (Z-Score of 14.4) in 2021, 7.3% (Z-Score of 11.9) in 2022 and 11.1% (Z-Score of 18.2) in 2023. By comparison, the excess mortality for all-cause deaths was 16.8% in 2020, 21.1% in 2021, 12.8% in 2022, and 10.5% in 2023.

It is noteworthy that while excess all-cause mortality peaked in 2021 and then dropped in 2022 and 2023, excess deaths from liver diseases as the underlying cause rose consecutively in 2021, 2022 and 2023. Additionally, while excess all-cause

deaths suffered an extreme rise of 16.8% in 2020, excess death rates from liver diseases were subdued at 2.4%.

4.3.2 Excess MC Deaths Rates for Age Group 75-84

We now analyze excess MC deaths rates and excess MC* death rates (by excluding COVID-19 related deaths) from liver diseases (K70-K76), for ages 75 to 84 in the US, as shown in Figure 7. The figure on the top refers to relative deviations from the 2013-2019 trend, while figure on the bottom shows the Z-Score (signal strength) for the deviations from trend.

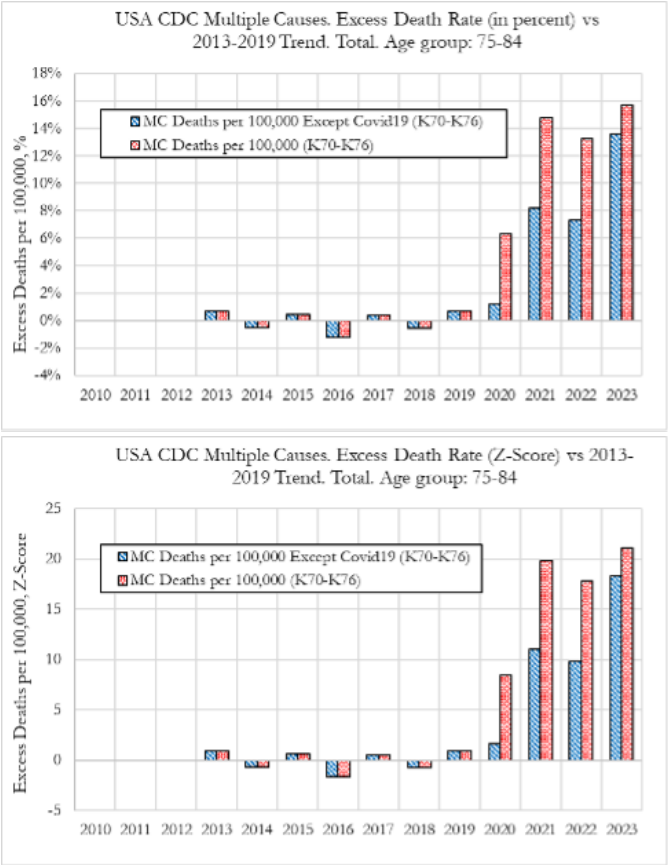


Figure 7. Excess MC death rates from liver diseases (K70-K76) from 2010 to 2023 for both sexes of ages 75 to 84 in the USA. Top: Relative deviation from trend, percent. Bottom: Deviation from trend Z-Score. Excess MC* death rates (where COVID-19-related deaths are removed) are shown for comparison.

In Figure 7 (top) we can observe that the excess MC death rates from liver diseases were 6.3% (Z-Score of 8.5) in 2020, then rose to 14.8% (Z-Score of 19.8) in 2021, and to 13.3% (Z-Score of 17.8) in 2022, and 15.7% (Z-Score of 21.1) in 2023. In terms of the statistical significance of the excess deaths, these can be considered extreme events.

By comparison, the excess MC* death rates from liver diseases where COVID-19-related deaths were removed, were 1.2% (Z-Score of 1.7) in 2020, 8.2% (Z-Score of 11.0) in 2021, 7.3% (Z-Score of 9.8) in 2022 and 13.6% (Z-Score of 18.3) in 2023. Of note is that the rise in excess mortality for MC deaths from liver diseases where COVID-19-related deaths were removed, exhibited a similar pattern to UC excess death rates from liver diseases (shown in Figure 6).

We also observe that MC* death rates are about 2 times higher than UC death rates from liver diseases, as illustrated by the ratio of MC*/UC death rates (Figure 5 - bottom). The ratio did not vary significantly during the pandemic years, 2020, 2021, 2022 and 2023, indicating that both MC* and UC death rates from liver diseases had similar rises during those years.

4.4 Analysis of K70-K76 for Younger Individuals, aged 35-44

We now investigate in detail the trends in MC, MC* (except COVID-19-related deaths) and UC death rates from 2000 to 2023 for liver diseases (ICD-10 codes K70 to K76), for the 35-44 age group of both sexes.

Figure 8 (top) shows the death rate per 100,000 individuals for deaths from liver disease from 2000 to 2023, for individuals aged 35-44. We can observe that both UC and MC death rates from liver disease have been trending higher from 2013 to 2019.

Both MC and UC death rates from liver disease trended lower from 2000 to 2013 and thereafter trended upwards from 2013 to 2019. MC deaths rates were 12.14 per 100,000 and in 2013, rising to 14.75 per 100,000 in 2019, a 21% increase (which corresponds to a 3.1% rise per annum). As for

UC deaths, in 2013 the death rate was 7.60 per 100,000 and in 2019 it was 9.66 per 100,000, a 27.1% increase (which corresponds to a 3.9% rise per annum).

We also observe in Figure 8 (bottom) that the ratio of MC to UC deaths was on a stable downward trend from 2000 to 2019, from a value of 1.8 in 2000 to 1.55 in 2019, which is slightly lower than the equivalent ratio for individuals aged 75-84.

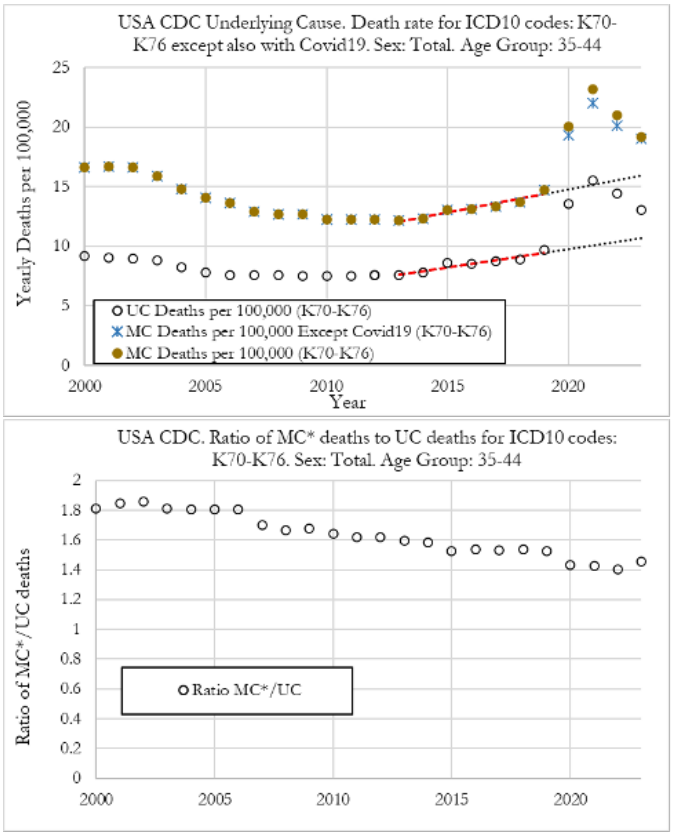


Figure 8. Death rates from liver diseases (K70-K76) in the US for ages 35 to 44. The red dashed line shows the trend from 2013 to 2019. The dotted line shows the extrapolation of the trend from 2020 until 2023. Top: Death Rates per 100,000. Bottom: Ratio of MC* to UC deaths.

The MC death rate was 14.75 per 100,000 in 2019 and then rose in 2020 to 20.05 per 100,000, and then to 23.22 per 100,000 in 2021. In 2022 death rates dropped to 20.99 per 100,000 and then to 19.20 per 100,000 in 2023.

MC* death rates (after removing COVID-19-related deaths) rose in 2020 to 19.33 per 100,000, and then to 22.02 per 100,000 in 2021. In 2022, death rates were 20.15 per 100,000 and 19.20 per 100,000 in 2023. Removing COVID-19 related deaths, does not have a significant impact on MC death rates (as shown in Figure 8).

As for UC death rates, these jumped from 9.66 per 100,000 in 2019 to 13.53 per 100,000 in 2020 and then to 15.53 per 100,000 in 2021. In 2022 the UC death rate was 14.4 per 100,000 and in 2023 it was 13.04 per 100,000.

The ratio of MC* to UC deaths remained stable in 2020, 2021, 2022 and 2023, after a slight drop in 2020.

4.4.1 Excess UC Death Rates for Age Group 35-44

Figure 9 shows the excess death rate from liver disease in the US (K70-K76), for the 35 to 44 age group from 2010 to 2023. The plots also show the excess all-cause deaths for comparison. The figure on the top refers to relative deviations from the 2013-2019 trend, while Figure 9 (bottom) shows the Z-Score (signal strength) for the deviations from trend.

In Figure 9 (top) we can observe that the excess death rates from liver disease as the underlying cause (UC) were 38.5% (Z-Score of 16.2) in 2020, then rose to 54.2% (Z-Score of 22.8) in 2021, 38.7% (Z-Score of 16.3) in 2022 and 22.1% (Z-Score of 9.3) in 2023. By comparison, the excess mortality for all-cause deaths was 20.2% (Z-Score of 12.4) in 2020, 36.3% (Z-Score of 22.2) in 2021, 18.2% (Z-Score of 11.2) in 2022, and 9.0% (Z-Score of 5.5) in 2023.

Of note is that while for 35 to 44 year-old UC excess death rates from liver disease scale with all-cause mortality (with a very high correlation) in 2020 to 2023, for 75 to 84 this was not the case, as shown in Figure 6, where excess UC death rates from liver diseases do not correlate highly with excess all-cause death rates. We will explore this in further detail further below as the underlying drivers for excess deaths are different for the 35-44 age group and the 75-84 age group.

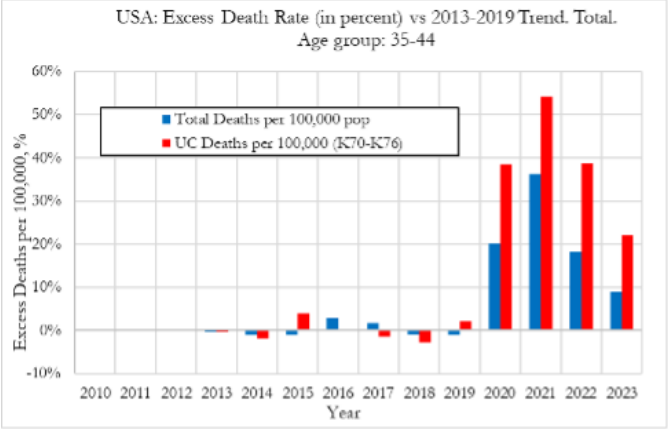


Figure 9. Excess UC death rates from liver diseases (K70-K76) from 2010 to 2023 for both sexes of ages 35 to 44 in the US. Top: Relative deviation from trend, percent. Bottom: Deviation from trend Z-Score. Excess deaths from all causes are shown for comparison.

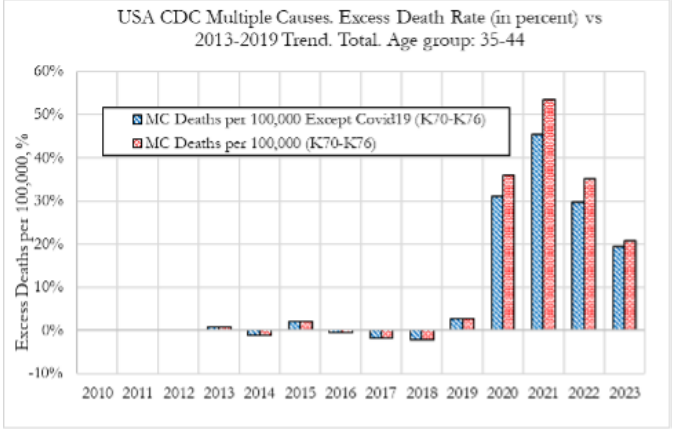


Figure 10. Excess MC death rates from liver diseases (K70-K76) from 2010 to 2023 for both sexes of ages 35 to 44 in the USA. Top: Relative deviation from trend, percent. Bottom: Deviation from trend Z-Score. Excess MC* death rates (where COVID-19-related deaths are removed) are shown for comparison.

4.4.2 Excess MC Deaths Rates for Age Group 35-44

We now analyze excess MC deaths rates and excess MC* death rates (by excluding COVID-19 related deaths) from liver disease (K70-K76), for ages 35 to 44 in the US, as shown in Figure 10. The figure on the top refers to relative deviations from the 2013-2019 trend, while figure on the bottom shows the Z-Score (signal strength) for the deviations from trend.

In Figure 10 (top) we can observe that the excess MC death rates from liver diseases were 35.9% (Z-Score of 19.0) in 2020, then rose to 53.4% (Z-Score of 28.2) in 2021, and to 35.2% (Z-Score of 18.6) in 2022, and 20.7% (Z-Score of 10.9) in 2023. In terms of the statistical significance of the excess deaths, these can be considered extreme events.

Excess MC* death rates from liver diseases (where COVID-19-related deaths were removed), were 31.1% (Z-Score of 16.4) in 2020, 45.4% (Z-Score of 24.0) in 2021, 29.8% (Z-Score of 15.8) in 2022 and 19.4% (Z-Score of 10.2) in 2023.

The rise in excess mortality for both MC and MC* deaths from liver diseases (where COVID-19-related deaths were excluded), exhibited a similar pattern to UC excess death rates, for individuals aged 35-44 (shown in Figure 9). The ratio of MC*/UC death rates (Figure 8 - bottom) dropped slightly in 2020 and then remained stable through 2021, 2022 and 2023, indicating that both MC*

and UC death rates from these diseases had similar behaviors during those years.

5 ANALYSIS OF EXCESS DEATH TRENDS FROM LIVER DISEASES FOR ALL AGES

In this chapter we generalize for all age groups the previous analysis of trends in death rates from liver diseases. We compute the excess deaths (deviation from 2013-2019 trend) from liver diseases (ICD-10 codes: K70-K76) for the different age groups in the US.

The data for age groups 1, 1-4 and 5-14 cannot be computed as the number of deaths in these age groups are very low, falling below CDC suppression limitations that do not allow for publication.

5.1 Excess UC Deaths from Liver Diseases for Different Age Groups

In this section, we compute for all age groups, the excess UC death rates from liver diseases in 2020, 2021, 2022 and 2023, shown in Figure 11. The detailed results are also shown in the tables of the appendix.

In Figure 11 (top) shows the excess UC death rate (in percent) and in Figure 11 (bottom) the respective Z-Scores are shown. Each datapoint on the graphs is obtained by performing the analysis described in the methodology section where the extrapolated 2013-2019 trendline in death rates is subtracted from the death rates in 2020, 2021, 2022 and 2023, for each of the age groups.

The results from Figure 11 show that the excess UC death rates from liver diseases had a higher impact (in percentage terms) on younger individuals when compared to older individuals. The results show that excess death rates tend to be higher the lower the age-group, with the 15-24 age group being the most impacted with increased liver disease death rates. As for older individuals, aged 75 and above, they experienced much lower excess death rates in 2020, 2021, 2022 and 2023.

For individuals aged 65 and younger, Figure 11 shows that we observe statistically significant excess death rates from liver diseases, that started in 2020, peaked in 2021 and then dropped in 2022 and 2023. The pattern of excess deaths from liver diseases for these age groups closely tracks changes in all-cause mortality from 2020 to 2023. For example, within these age groups, as shown in Figure 11, the largest percentage of excess deaths were observed in the 15-24 age group, where excess death rates were 45.4% (Z-Score: 5.7) in 2020, 55.1% (Z-Score: 6.9) in 2021, 70.9% (Z-Score: 8.9) in 2022 and 42.5% (Z-Score: 5.4) in 2023. For a more detailed analysis, the appendix tables shows all the individual values that are plotted in Figure 11.

As we've shown previously in Figure 4, for younger individuals, alcoholic liver disease was the main contributor to changes in death rates from liver diseases from 2020 to 2023. Consequently, increased levels of alcohol consumption during the pandemic years, could be a contributory factor towards increased liver disease deaths (Slater, et al., 2024)[13].

The pattern of excess deaths was different for individuals aged 75 and above, showing much lower excess death rates (in percentage terms) than those for younger age groups. Notwithstanding, the statistical significance of the excess deaths rates show very high statistical significance from 2021 onwards, due to the larger sample sizes for older individuals when compared to younger individuals. For older individuals, excess deaths rose consecutively from 2020 to 2023, with the main increase in excess mortality starting in 2021 and not in 2020 as was the case for younger individuals. As we've shown previously in Figure 3, for older individuals, cirrhosis and fibrosis of the liver was the main contributor to changes in deaths rates from liver diseases from 2020 to 2023. Consequently, increased levels of alcohol consumption during the pandemic years, are unlikely to be a significant contributory factor towards increased liver disease deaths for older individuals.

For the older age groups, excess deaths increased substantially in 2021, 2022 and 2023, showing extreme deviations from the prior 2013-2019 trend. Additionally, as illustrated by the detailed analysis of the 75-84 age group, in section 4.3, even as excess all-cause deaths declined in 2022 and 2023, excess death rates from liver diseases continued to rise. The results suggest that the COVID-19 disease, pandemic lockdowns, or increased alcohol consumption are unlikely explanations for the rise in excess liver disease death rates, for older individuals. The prioritization of older individuals to receive the COVID-19 inoculations or cumulative exposure to SARS-CoV2, might be better explanations for the observed pattern.

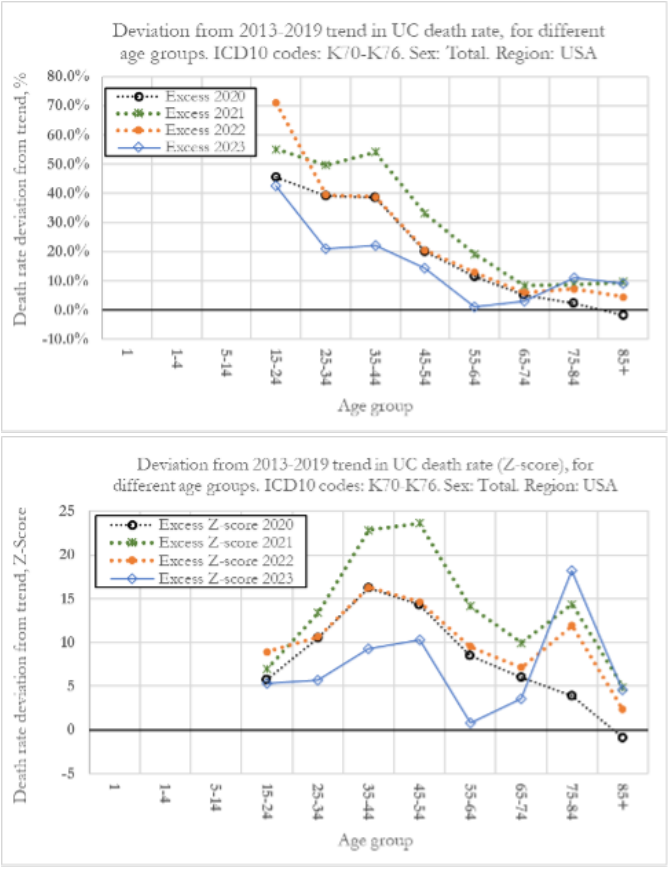


Figure 11. Excess UC death rates from liver diseases (K70-K76) for 2020, 2021, 2022 and 2023 for different age groups of both sexes in the US. Top: Relative deviation from trend, percent. Bottom: Deviation from trend Z-Score.

5.2 Excess MC and MC* Deaths from Liver Diseases for Different Age Groups

In this section we compute, for all 10-year age groups, the excess MC and MC* death rates from liver diseases (K70-K76) in 2020, 2021, 2022 and 2023, shown in Figure 12 (MC excess death rates) and Figure 13 (MC* excess death rates). For a detailed view of the results refer to the appendix tables. As a reminder, MC* death rates refer to MC deaths from liver diseases except for those where COVID-19 is also reported (either as underlying cause or a contributing cause). In Figure 12 (top) we plot the excess MC death rate (in percent) while Figure 12 (bottom) shows the respective Z-Scores.

The results in Figure 12 show that MC excess death rates from liver diseases already exhibited high statistical significance in 2020, for all age groups, except for the 15-24 age group. This can be understood as MC death rates tend to follow changes in all-cause mortality. The relatively low percent changes for the 15-24 age group can be explained by the low sample size for this age group, which leads to more noisy estimates (as illustrated by the respective Z-Scores, shown in Figure 12 (bottom)).

We also observe that for younger individuals, aged below 65 years old, excess death rates peaked in 2021 and then dropped in 2022 and 2023, mirroring changes in all-cause mortality. For older individuals (age groups 75-84 and 85+), excess deaths increased in 2021 and remained high in 2022 and 2023, pointing to a different pattern of behavior.

After removing COVID-19-related deaths, the results show that the excess MC* death rates exhibit a similar pattern to UC excess death rates for the different age groups. This is likely due to the rise in MC* death rates being driven by the rises in UC death rates.

For older individuals, aged 75-84 and 85+, after removing COVID-19-related deaths, we observe statistically insignificant excess MC* death rates in 2020, in similarity to observed for UC death rates. Excess death rates rose substantially from 2021,

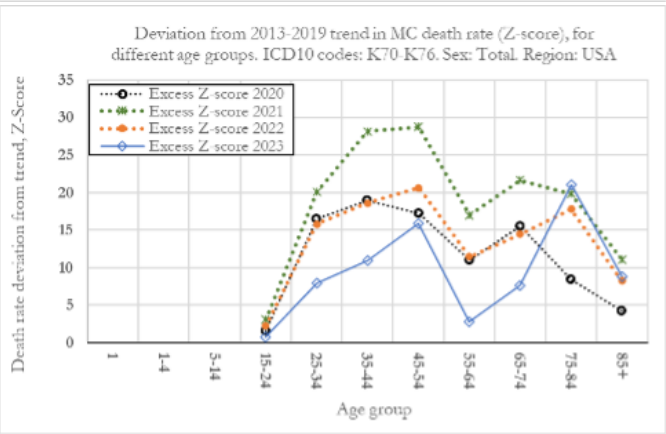
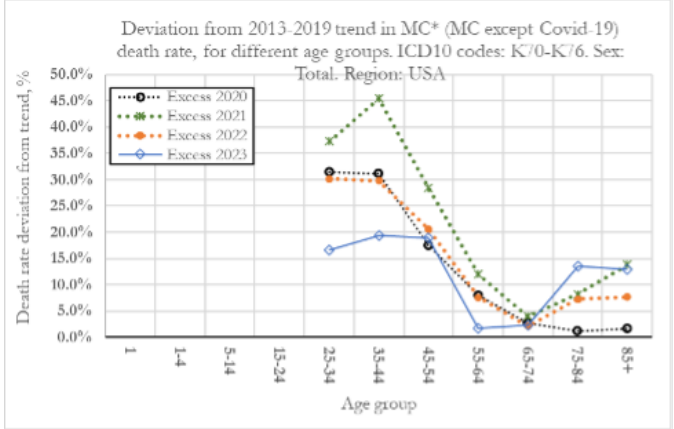


Figure 12. Excess MC death rates from liver diseases (K70-K76) for 2020, 2021, 2022 and 2023 for different age groups of both sexes in the US. Top: Relative deviation from trend, percent. Bottom: Deviation from trend Z-Score.



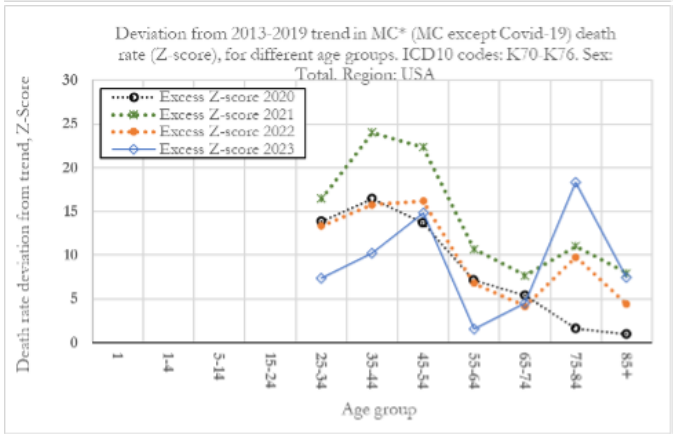


Figure 13. Excess MC* death rates (except COVID-19-related deaths) from liver diseases (K70-K76) for 2020, 2021, 2022 and 2023 for different age groups of both sexes in the US. Top: Relative deviation from trend, percent. Bottom: Deviation from trend Z-Score.

remaining high in 2022 and 2023, with very high statistical significance.

For individuals aged 65 and younger, excess death rates peaked in 2020 and 2021 and then declined in 2022 and 2023. The excess death rates in general show very high levels of statistical significance, as shown in Figure 13 - bottom. For younger individuals, the brunt of the effect was felt in 2020 and 2021, while for older individuals, the excess death rates peaked in 2023.

6 SUMMARY OF FINDINGS AND DISCUSSION

6.1 Excess Death Rates from Liver Diseases for Age Group 35 to 44

For individuals aged 35 to 44, our results (Figure 9) show that the excess UC death rates from liver diseases (ICD-10 codes: K70-K76) were 38.5% (Z-Score of 16.2) in 2020, then rose to 54.2% (Z-Score of 22.8) in 2021, 38.7% (Z-Score of 16.3) in 2022 and 22.1% (Z-Score of 9.3) in 2023. By comparison, the excess mortality for all-cause deaths was 20.2% (Z-Score of 12.4) in 2020, 36.3% (Z-Score of 22.2) in 2021, 18.2% (Z-Score of 11.2) in 2022, and 9.0% (Z-Score of 5.5) in 2023, which shows changes liver disease death rates mirrored

closely changes in all-cause death rates from 2020 to 2023, albeit with a scaling factor of close to 2.

Excess MC death rates from liver diseases (Figure 10) were 35.9% (Z-Score of 19.0) in 2020, then rose to 53.4% (Z-Score of 28.2) in 2021, and to 35.2% (Z-Score of 18.6) in 2022, and 20.7% (Z-Score of 10.9) in 2023. When analyzing MC death rates after removing COVID-19-related deaths, we observe MC* death rates from liver diseases, were 31.1% (Z-Score of 16.4) in 2020, 45.4% (Z-Score of 24.0) in 2021, 29.8% (Z-Score of 15.8) in 2022 and 19.4% (Z-Score of 10.2) in 2023.

The rise in excess mortality for both MC and MC* deaths from liver diseases (where COVID-19-related deaths were excluded), exhibited a similar pattern to UC excess death rates, for individuals aged 35-44, which are correlated to excess all-cause death rates.

Excess death rates from liver diseases from 2020 to 2023 for younger individuals, for which the 35-44 age group is a typical case, are driven by alcoholic liver disease and have a different pattern of behavior when compared to excess deaths rates from liver diseases for older individuals. We discuss these differences on the discussion of excess death rates for all age groups.

6.2 Excess deaths from liver diseases for age group 75 to 84

For individuals aged 75 to 84, the results plotted in Figure 6 show that the excess UC death rates from liver diseases (K70-K76) 2.4% (Z-Score of 3.9) in 2020, then rose to 8.8% (Z-Score of 14.4) in 2021, 7.3% (Z-Score of 11.9) in 2022 and 11.1% (Z-Score of 18.2) in 2023. By comparison, the excess mortality for all-cause deaths was 16.8% in 2020, 21.1% in 2021, 12.8% in 2022, and 10.5% in 2023.

Interestingly, for individuals aged 75-84, while excess all-cause mortality peaked in 2021 and then dropped in 2022 and 2023, excess deaths from liver diseases as the underlying cause rose consecutively in 2021, 2022 and 2023. Additionally, while excess all-cause deaths suffered an extreme rise of 16.8% in 2020, excess death rates from liver diseases were subdued at 2.4%.

Excess MC death rates from liver diseases (Figure 7) were 6.3% (Z-Score of 8.5) in 2020, then rose to 14.8% (Z-Score of 19.8) in 2021, and to 13.3% (Z-Score of 17.8) in 2022, and 15.7% (Z-Score of 21.1) in 2023. By comparison, the excess MC* death rates from liver diseases (where COVID-19-related deaths were removed), were 1.2% (Z-Score of 1.7) in 2020, 8.2% (Z-Score of 11.0) in 2021, 7.3% (Z-Score of 9.8) in 2022 and 13.6% (Z-Score of 18.3) in 2023. Of note is that the rise in excess mortality for MC* deaths with liver diseases (where COVID-19-related deaths were removed) exhibited a similar pattern to UC excess death rates from liver diseases.

Excess death rates from liver diseases from 2020 to 2023 for older individuals, for which the 75-84 age group is case study, are driven by cirrhosis and fibrosis of liver (ICD-10 code: K74) and exhibit a different pattern of behavior when compared to excess deaths rates from liver diseases for younger individuals. These differences are discussed in further detail in the next section.

6.3 Excess Liver Disease Deaths for All Ages

When investigating excess death rates from liver diseases (ICD-10 codes: K70-K76) from 2020 to 2023 for the distinct 10-year age groups, we observe two different patterns of behavior for individuals aged 65 and younger and for individuals aged 75 and older, with individuals aged 65-74 falling somewhere in the middle. The previously presented detailed analysis of excess death rates from liver diseases for younger individuals aged 35-44 and for older individuals aged 75-84 are case studies that exemplify each of these patterns of behavior.

We show in Figure 11 that for younger individuals, aged 65 and lower, excess death rates from liver diseases started in 2020 and peaked in 2021, subsequently dropping in 2022 and 2023. The pattern of excess deaths from liver diseases for younger individuals tracks changes in all-cause

mortality from 2020 to 2023. As we've shown in Figure 4, for younger individuals, the principal driver of changes in death rates from liver disease in 2020, 2021, 2022 and 2023 was alcoholic liver disease (ICD-10 code: K70).

Consequently, the increased levels of alcohol consumption per capita that was observed in 2020, 2021 and 2022 (Slater, et al., 2024)[13], was a likely contributory factor towards increased liver disease death rates during the period. Although not being within the scope of this paper, we performed a quick analysis of the changes in alcohol consumption per capita to see if it could fully explain the increases in death rates from alcoholic liver disease and our preliminary analysis suggested that it cannot. Interestingly, however, we observe that the increase in alcoholic liver disease death rates is mostly driven by increases in spirits consumption and less so by wine and beer. We noticed that accounting for increases in alcohol consumption per capita only explain a fraction of the increase in death rates, suggesting that other additional factors are at play. These factors could be either the societal lockdowns and pandemic-related changes in lifestyles (in 2020), sequalae from the COVID-19 disease (in 2020 through 2023), or COVID-19 vaccinations (from 2021 onwards).

In particular, a significant body of evidence is now pointing towards the COVID-19 vaccinations playing a significant role in contributing towards the excess all-cause mortality in 2021, 2022 and 2023 that is observed in developed countries with high COVID-19 vaccine intake. For example, a recent paper from Alexandria et al. (Alessandria, et al., 2024)[14], show that individuals with 2 or more vaccine doses experienced about 20% higher excess all-cause mortality (measured as all-cause death hazard ratios) when compared to unvaccinated individuals in a province in Italy. The paper confirms previous suspicions that were already present in the Pfizer clinical trials (Michels, et al., 2023)[15] where the authors show that of the 38 deaths reported in the 6-Month Interim Report of Adverse Events, 21 BNT162b2 vaccinated subjects died compared to 17 placebo subjects, which corresponds to 23.5% excess all-cause mortality. Even though the sample size was small and not possible to infer statistical significance, the recent paper from Italy provided confirmation of the signal at a population level. Furthermore, the analysis of serious adverse events (SAE) of special interest in the Moderna and Pfizer clinical trials (Fraiman, et al., 2022)[16] showed to the Pfizer trial exhibited a 57% higher risk of an SAE of special interest in vaccinated participants relative to the placebo control and 36% higher risk for the Moderna trial. The estimated rate of SAEs of special interest for both clinical trials combined was 1 in 800 for the recipients of these vaccines.

Finally, the Nonclinical Evaluation Report BNT162b2 [mRNA] COVID-19 vaccine submitted to the Australian TGA (TGA - Health Safety Regulation, 2021)[17] show that the vaccine was not confined to the injection site but distributed across almost all important organs of the body with particular accumulation in the liver (page 45 of the report) as stated in the conclusions: "Slow but significant distribution of lipid nanoparticles from the site of injection with major uptake into liver", which could explain the liver being particularly impacted by production of the toxic spike protein.

The pattern of excess deaths was different for older individuals aged 75 and above, showing much lower excess death rates (in percentage terms) than those for younger age groups. For older individuals, excess deaths rose consecutively from 2020 to 2023, with the main increase in excess mortality starting in 2021 and not in 2020 as was the case for younger individuals. For the older age groups, excess deaths increased substantially in 2021, 2022 and 2023, showing extreme deviations from the prior 2013-2019 trend. Additionally, as illustrated by the detailed analysis of the 75-84 age group, in section 4.3, even as excess all-cause deaths declined in 2022 and 2023, excess death rates from liver diseases continued to rise.

As we've mentioned previously, for older individuals, cirrhosis and fibrosis of the liver was the main contributor to changes in deaths rates from

liver diseases from 2020 to 2023. Consequently, increased levels of alcohol consumption during the pandemic years, are unlikely to be a significant contributory factor towards increased liver disease deaths for older individuals.

The results suggest that COVID-19 pandemic lockdowns are also unlikely explanations for the rise in excess liver disease death rates, for older individuals, as excess death rates were subdued in 2020. As excess deaths continued to rise in 2022 and 2023, indicating a worsening of the phenomenon that is leading to excess liver disease deaths. As previously explained, there is more and more evidence that this could be related to continuous uptake of COVID-19 inoculations within the older age groups (Alessandria, Malatesta, et al., 2024)[14].

One cannot exclude other possible contributing factors such as pandemic-related changes in lifestyles, inflammatory processes due to cumulative exposures to SARS-CoV-2, "Long COVID" (Jangnin, et al., 2024)[18] or other factors.

Limitations of the study

The main limitations of this study are data-related:

One of the limitations of our analysis is that the 2022 and 2023 data from the CDC for the different causes of death is provisional, at the date of the data download (5^{th} April 2024), which signifies that it might be subject to change, particularly in the classification of underlying cause or when adding secondary causes of disease. This might lead to some discrepancies once the final data is released.

Furthermore, the CDC population denominator, used to compute the death rates, is also provisional in 2023, as the population values for 2023 are the same as 2022, for each of the age groups. This might lead to changes in the death rate calculations once final values for both MC death classification and the population denominator are released.

The second limitation is the data suppression that the CDC WONDER system imposes on deaths with fewer than 10 individuals. This suppression means that it is not possible to perform a more granular analysis, such as analyzing deaths that are conditional on several distinct causes (disaggregating MC deaths), and in particular for younger age groups.

Future work

Given the literature showing adverse effects following COVID-19 vaccination cited above, which include musculoskeletal diseases, future studies should focus on COVID-19 vaccinated and unvaccinated individuals and whether the vaccination roll out or COVID-19-related conditions such as Long COVID are contributing factors to the ongoing rise in musculoskeletal-related deaths shown in this paper.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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APPENDIX

Summary tables with MC, MC and UC excess death rates from liver diseases (K70-K76) in 2020, 2021, 2022 and 2023, for all age groups.*

MC* - *Refers to Multiple Cause Deaths with the exception of those with COVID-19 ICD-10 code U07.1*

n.a. - *Data not possible to calculate due to data suppression rules for CDC WONDER*

2020	UC Excess Death Rate		MC Excess Death Rate		MC* Excess Death Rate		Ratio MC/UC
Age Group	**Deviation**,%	Z**-Score**	**Deviation**,%	Z**-Score**	**Deviation**,%	Z**-Score**	
1	n.a.	**n.a.**	n.a.	**n.a.**	n.a.	**n.a.**	n.a.
1-4	n.a.	**n.a.**	n.a.	**n.a.**	n.a.	**n.a.**	n.a.
5-14	n.a.	**n.a.**	n.a.	**n.a.**	n.a.	**n.a.**	n.a.
15-24	45.4	**5.7**	13.2	1.6	n.a.	n.a.	2.75
25-34	39.0	**10.5**	37.5	**16.5**	31.5	**13.9**	1.56
35-44	38.5	**16.2**	35.9	**19.0**	31.5	**16.4**	1.48
45-54	20.0	**14.3**	21.9	**17.3**	17.4	**13.7**	1.58
55-64	11.5	**8.5**	12.4	**11.0**	8.0	**7.1**	1.81
65-74	5.1	**6.0**	8.1	**15.5**	2.8	**5.4**	2.07
75-84	2.4	**3.9**	6.3	**8.5**	1.2	1.7	2.13
85+	-1.8	-0.9	7.3	**4.2**	1.6	0.9	2.38

Table 1. UC, MC and MC* excess death rates from liver diseases (K70-K76) for different age groups in 2020. Excess death rates refer to deviations from 2013-2019 trend. The ratio MC/UC is the ratio of MC deaths to UC deaths from liver diseases.

2021	UC Excess Death Rate		MC Excess Death Rate		MC* Excess Death Rate		Ratio MC/UC
Age Group	**Deviation**,%	Z**-Score**	**Deviation**,%	Z**-Score**	**Deviation**,%	Z**-Score**	
1	n.a.	**n.a.**	n.a.	**n.a.**	n.a.	**n.a.**	n.a.
1-4	n.a.	**n.a.**	n.a.	**n.a.**	n.a.	**n.a.**	n.a.
5-14	n.a.	**n.a.**	n.a.	**n.a.**	n.a.	**n.a.**	n.a.
15-24	55.1	**6.9**	25.7	**3.1**	n.a.	**n.a.**	2.96
25-34	49.7	**13.4**	45.4	**20.0**	37.3	**16.5**	1.53
35-44	54.2	**22.8**	53.4	**28.2**	45.4	**24.0**	1.49
45-54	33.1	**23.6**	36.5	**28.8**	28.4	**22.4**	1.57
55-64	19.2	**14.1**	19.1	**17.0**	12.0	**10.7**	1.78
65-74	8.4	**9.9**	11.3	**21.7**	4.0	**7.7**	2.08
75-84	8.8	**14.4**	14.8	**19.8**	8.2	**11.0**	2.17
85+	9.6	**4.9**	19.3	**11.1**	13.9	**8.0**	2.39

Table 2. UC, MC and MC* excess death rates from liver diseases (K70-K76) for different age groups in 2021. Excess death rates refer to deviations from 2013-2019 trend. The ratio MC/UC is the ratio of MC deaths to UC deaths from liver diseases.

2022	UC Excess Death Rate		MC Excess Death Rate		MC* Excess Death Rate		Ratio MC/UC
Age Group	**Deviation**,%	Z**-Score**	**Deviation**,%	Z**-Score**	**Deviation**,%	Z**-Score**	
1	n.a.	**n.a.**	n.a.	**n.a.**	n.a.	**n.a.**	n.a.
1-4	n.a.	**n.a.**	n.a.	**n.a.**	n.a.	**n.a.**	n.a.
5-14	n.a.	**n.a.**	n.a.	**n.a.**	n.a.	**n.a.**	n.a.
15-24	70.9	**8.9**	18.8	2.2	n.a.	**n.a.**	2.63
25-34	39.4	**10.7**	35.8	**15.8**	30.2	**13.3**	1.52
35-44	38.7	**16.3**	35.2	**18.6**	29.8	**15.8**	1.46
45-54	20.5	**14.6**	26.3	**20.7**	20.6	**16.2**	1.58
55-64	12.9	**9.5**	12.9	**11.4**	7.6	**6.8**	1.77
65-74	6.0	**7.1**	7.5	**14.5**	2.2	**4.2**	2.06
75-84	7.3	**11.9**	13.3	**17.8**	7.3	**9.8**	2.18
85+	4.6	2.3	14.4	**8.3**	7.7	**4.4**	2.41

Table 3. UC, MC and MC* excess death rates from liver diseases (K70-K76) for different age groups in 2022. Excess death rates refer to deviations from 2013-2019 trend. The ratio MC/UC is the ratio of MC deaths to UC deaths from liver diseases.

2023	UC Excess Death Rate		MC Excess Death Rate		MC* Excess Death Rate		Ratio MC/UC
Age Group	**Deviation**,%	Z**-Score**	**Deviation**,%	Z**-Score**	**Deviation**,%	Z**-Score**	
1	n.a.	**n.a.**	n.a.	**n.a.**	n.a.	**n.a.**	n.a.
1-4	n.a.	**n.a.**	n.a.	**n.a.**	n.a.	**n.a.**	n.a.
5-14	n.a.	**n.a.**	n.a.	**n.a.**	n.a.	**n.a.**	n.a.
15-24	42.5	**5.4**	6.6	0.8	n.a.	**n.a.**	2.92
25-34	21.1	**5.7**	18.1	**8.0**	16.6	**7.3**	1.52
35-44	22.1	**9.3**	20.7	**10.9**	19.4	**10.2**	1.47
45-54	14.4	**10.3**	20.1	**15.9**	18.9	**14.9**	1.56
55-64	1.1	0.8	3.1	2.8	1.8	1.6	1.79
65-74	3.0	**3.6**	4.0	**7.7**	2.4	**4.5**	2.06
75-84	11.1	**18.2**	15.7	**21.1**	13.6	**18.3**	2.16
85+	9.1	**4.6**	15.3	**8.8**	12.9	**7.4**	2.34

Table 4. UC, MC and MC* excess death rates from liver diseases (K70-K76) for different age groups in 2023. Excess death rates refer to deviations from 2013-2019 trend. The ratio MC/UC is the ratio of MC deaths to UC deaths from liver diseases.