Trends in death rates from Neurological diseases in the US for all ages and detailed analysis for 15–44

2 authors:

Carlos Alegria
Riskmath lda
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Yuri Nunes
Universidade NOVA de Lisboa
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Trends in death rates from Neurological diseases in the US for all ages and detailed analysis for 15-44

C. Alegria [1,*] **and Y. Nunes** [1,2]

[1] *RiskMath Lda.*,* *Portugal*
[2] *LibPhys*,† *Department of Physics, FCT-NOVA, Portugal*

Correspondence*:
Corresponding Author
calegria@phinancetech.com

ABSTRACT

We investigate trends in death rates from neurological diseases (ICD-10 codes G00-G98) for all age groups in the US using data from the CDC (Centers for Disease Control and Prevention). We also perform a detailed analysis for younger individuals aged 15 to 44. We investigate trends in neurological 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.

For individuals aged 15 to 44 we show a rise in excess mortality from neurological diseases reported as the underlying cause of death, with a 4.4% increase in 2020, 10.0% in 2021, 9.9% in 2022 and 8.1% in 2023, with Z-Scores of 4.9, 11.1, 11.0 and 9.0 in 2020, 2021, 2022 and 2023, respectively, indicating highly statistically significant changes, particularly in 2021, 2022 and 2023. When looking at excess neurological disease deaths reported as multiple cause (MC) of death, we observe that these track all-cause mortality rises, registering excess mortality of 11.2% in 2020, 20.6% in 2021, 14.7% in 2022 and 7.1% in 2023, which were also highly statistically significant. However, for excess neurological disease deaths reported as multiple cause of death, once deaths where COVID-19 was also reported are removed, we observe that these follow a very similar pattern of excess deaths to that observed for neurological deaths when reported as underlying cause.

We also show that excess deaths from neurological diseases as underlying cause occurred for most age groups, with the strongest effect in ages 15-44. For individuals 65 and older there appears to be no statistically significant rise in excess mortality. The larger rise of excess death rates from neurological diseases reported as one of multiple causes compared to the underlying cause indicates that some deaths from these diseases are being brought forward by other causes, such as COVID-19-related deaths. Consequently, the rise in neurological disease deaths as underlying cause we report in the paper likely under-reports the described effect, particularly for older individuals.

The results indicate that from 2020 a novel phenomenon leading to increased neurological deaths appears to be present particularly in younger, working age individuals aged 15 to 44, which requires further investigation.

*Phinance Technologies - Humanity Projects

†LibPhys

1   INTRODUCTION

There are still a large number of unanswered questions regarding the COVID-19 pandemic, ranging from the effects of the SARS-CoV-2 virus itself to the impacts of the lockdowns, social distancing, COVID-19 treatment protocols, and the introduction of COVID-19 vaccines based upon novel mRNA technology. One of the aspects that is still not well recognized is the impact of the pandemic on neurological diseases and in particular the increase in neurological disease-related death rates, which we address in this paper.

A paper using data from the Global COVID Vaccine Data Network (GVDN) examining over 99 million vaccine recipients showed an increase in risk of neurological conditions such as Guillain-Barré syndrome (GBS), Transverse myelitis (TM), Bell's palsy (BP), Acute disseminated encephalomyelitis (ADEM), febrile seizures (FSZ) and generalized seizures (GSZ), for a 42-day period following vaccination (Faksova, et al., 2024)[1]. The results show for example that the AstraZeneca (ChAdOx1) vaccine was associated with a 2.49 increased risk of GBS, a 1.91 increased risk of TM, and a 2.23 increased risk of ADEM, in the 42-day period after the first dose. The Pfizer/BioNTech (BNT162b2) had a safer profile for neurological conditions, showing only a slightly concerning 1.05 increased risk of BP after the first dose.

A paper from Italy that reviews neurological complication following COVID-19 vaccines in the 18 months following the start of the vaccinations concludes that these complications are usually mild, of short duration and self-limiting but also admit that severe unexpected post-vaccination events are rare but possible (Tondo, G. et al., 2022)[2]. A review of serious neurological adverse events following vaccinations (Eslait-Olaciregui, et al., 2023)[3] also finds that these tend to be rare.

A more recent Italian population-based study of mild neurological complications following COVID-19 vaccinations estimates that about a third of the sampled individuals manifested neurological symptoms following the vaccinations. For the Pfizer/BioNTech (BNT162b2) vaccine the incidence rate was 30.2%. The most common neurological symptoms reported were headache (51.4%), sleepiness (37.8%), vertigo (13.4%), paraesthesia (10.4%) and cognitive fog (6.1%). The clinical onset of the symptoms tended to occur within a week from vaccination date and be short-lived.

Some observational data has implicated COVID-19 itself in the development of neurological symptoms, such as the observations of a study on US Veterans that spanned throughout 2021 (Xu, E. et al., 2022)[4], which reported that the relative risk of any neurological condition after COVID-19 was 1.42. The unfortunate need to rely on observational data to investigate these effects means that doing a risk/benefit analysis can produce wildly varying results depending on the methodology. For example, studies associating risk of a particular condition after COVID-19 compared to after vaccination rarely differentiate between long term conditions vs acute effects that are self-resolving in a short period of time (Patone, M. et al., 2021)[5]. In this case, the researchers for the Veterans study began tracking subjects before the rollout of the vaccine and failed to adjust for exposure to the vaccine during the follow-up period. As such, we cannot properly determine whether these neurological associations were affected by administering COVID-19 vaccination shortly after COVID infection, a practice which has been shown to increase the risk of systemic side effects (Menni, C. et al., 2021)[6], (Krammer, F. et al., 2021)[7] but was nevertheless encouraged by public health authorities. Furthermore, because the study uses a population with a significant amount of selection bias (United States Veterans), the exact relative risk ratios cannot be easily compared with other studies that calculated these same ratios after exposure to the vaccine.

In this paper, we investigate trends in death rates from neurological diseases (ICD-10 codes: G00 to G98) in the US to investigate if the studies referenced above, which focus on milder conditions and of shorter duration, are reflected in increased death rates from these conditions. We investigate trends in

neurological 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. We first provide a detailed analysis of the younger 15-44 age group as these individuals were found to be the most affected by neurological disease excess deaths, with statistically significant excess deaths starting in 2020 and then increasing substantially in 2021, 2022 and 2023. Later, we analyze excess death trends 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) of death trends from neurological diseases with underlying cause (UC) 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:[2]:

"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:

- *Use these data for health statistical reporting and analysis only.*

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[1] CDC Wonder

[2] CDC Wonder - Data Use Restrictions

- *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:

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 cause 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 cause 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[3].

3 METHODOLOGY

In this study, we analyze the trends in death rates for neurological 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, C. et al., 2024)[8]. 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

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

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[3] https://wonder.cdc.gov/wonder/help/mcd-provisional.html#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:

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

Where $\hat{a}$ and $\hat{b}$ are the estimated coefficients of the death rate trendline from 2010 to 2019. We also compute a Z-Score that estimates the normalized deviation from trend:

$$Z = \frac{\left[Deaths\right]_{t_i}^{AG} - \left[Baseline\right]_{t_i}^{AG}}{\sigma_{2010-2019}} \qquad (3)$$

Where σ is the standard deviation of the excess deaths during the pre-pandemic period 2010-2019.

3.2 ICD-10 Code List of Selected Causes of Death for: Neurological Diseases

For this analysis we selected all the ICD-10 codes from the CDC aggregated chapter lists (Letters G00 to G98), which refer to deaths attributed to Diseases of the nervous system (Neurological Diseases).

4 YEARLY ANALYSIS OF EXCESS DEATH RATES FOR AGES 15-44

In this section we perform an analysis of the trend in yearly death rates for individuals aged 15 to 44 in the US, using the data from CDC WONDER. In this analysis we use the 2010-2019 trend in deaths per 100,000 (death rates) as the baseline estimate for excess death rates. Excess death rates for the 2010-2019 period are in-sample while the rates for 2020, 2021, 2022 and 2023 are out of sample computations.

In our study we investigate trends in MC (multiple-cause) and UC (underlying cause) deaths rates from neurological diseases, and also, trends in MC* death rates (MC deaths where COVID-19-related death are removed).

To contextualize trends in death rates from neurological diseases, we first analyze the trends in all-cause death rates.

4.1 Deaths from All Causes

The analysis of the deaths from all causes allows us to have a context by which we can then compare the death rates from neurological diseases. Figure 1 (top) shows the death rate per 100,000 individuals for all deaths in the US from 2010 to 2023, for the 15 to 44 age group. Figure 1 (bottom) shows the actual number of deaths during the period.

The all-cause death rate for individuals aged 15 to 44 was 112.8 per 100,000 in 2010, increasing slowly to 131.9 per 100,000 in 2019, corresponding to a 16.9% rise over the period. The death rate increased in 2020 to 163.5 per 100,000 and then again in 2021 to 186.0 per 100,000. In 2022 the death rate dropped slightly to 165.6 per 100,000 and in 2023 the death rate "normalized" to 139.1 (below the 2010-2019 extrapolated trend). Even though the changes in death rates are not age adjusted and could be due to ageing populations within the 15-44 age group, when looking at individuals 10-year age groups 15-24, 25-34 and 35-44, we observe a similar pattern 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 15-44 age group. The columns in Figure 2 refer to relative deviations from the 2010-2019 trend while the dashed line refers to the respective Z-Scores.

Figure 2 shows that excess deaths in 2020 were around 19.9%, with a Z-Score of 6.5. These values indicate a very high level of statistical significance, being considered an extreme occurrence. In 2021 excess deaths further increased to around 33.8%
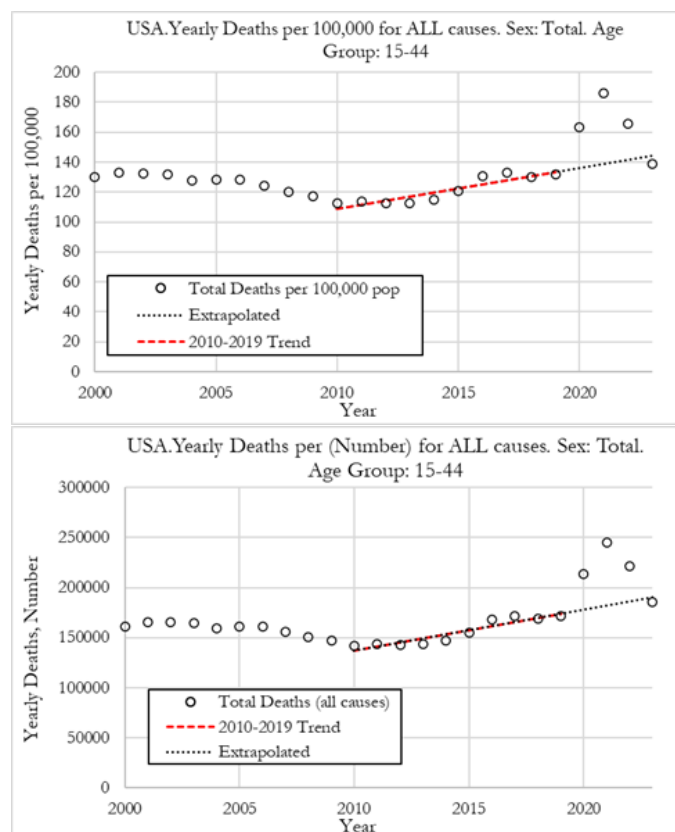
Figure 1. Yearly all-cause deaths for the US for individuals aged 15 to 44. The red dashed line shows the trend from 2010 to 2019. The dotted line shows the extrapolation of the trend from 2020 until 2023. Top: Death rate (per 100,000). Bottom: Deaths (Number).

with a Z-Score above 11.0. Excess deaths in 2022 were 16.8% with a Z-Score of 5.5, again indicating very high statistical significance. Excess death levels peaked in 2021, and in 2022 dropped to similar excess deaths to those calculated in 2020. In 2023 excess deaths were negative (-3.7%), pointing to a normalization of excess all-cause mortality in the 15-44 age group following the pandemic.

4.2 Trends in UC Death Rates for ICD-10 Codes G00 to G98 (Neurological Diseases)

In this section we investigate the trends in death rates from 2010 to 2023 where neurological diseases (ICD-10 codes G00 to G98) were classified as the underlying cause of death, for the 15-44 age group of both sexes.
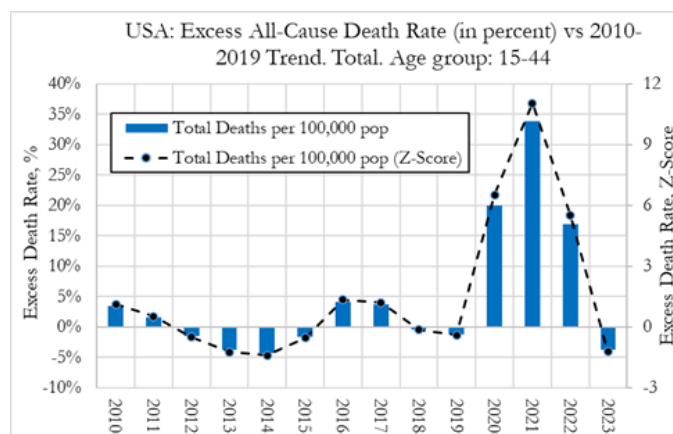
Figure 2. Excess all-cause death rates for both sexes aged 15 to 44 in the US. Top: Relative deviation from trend, percent. Bottom: Deviation from trend Z-Score.

4.2.1 UC Death Rates

Figure 3 (top) shows the death rate per 100,000 individuals for deaths from neurological diseases in the US from 2010 to 2023. We can observe that deaths per year from neurological diseases in the 15-44 age group have been trending higher from 2010 to 2019. In 2010 the death rate was 2.94 per 100,000 and in 2019 it was 3.31 per 100,000, a 12.6% rise.

The death rate rose in 2020 to 3.52 per 100,000, and then rose again to 3.76 per 100,000 in 2021. In 2022 the death rate rose further to 3.81 per 100,000 and in 2023 it was 3.80 per 100,000.

When presenting these numbers as the absolute number of deaths for diseases from neurological diseases, shown in Figure 3 (bottom), we can observe that in 2020 there were 4602 deaths, while in 2021 there were 4963 deaths, 5085 in 2022, and 5070 in 2023.

4.2.2 Excess UC Death Rates

Figure 4 shows the excess death rate from neurological diseases in the US, for the 15 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 2010-2019 trend, while Figure 4 (bottom) shows the Z-Score (signal strength) for the deviations from trend.
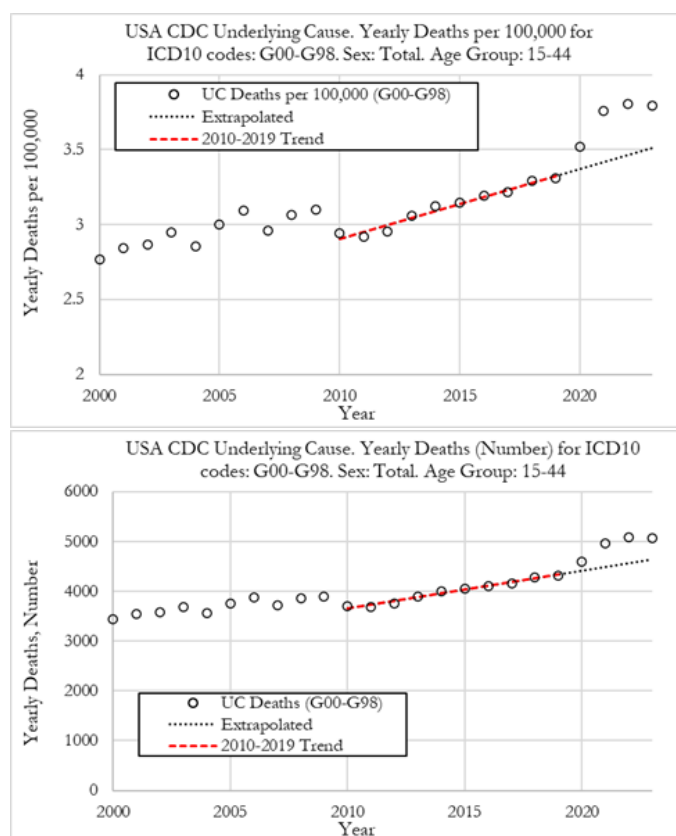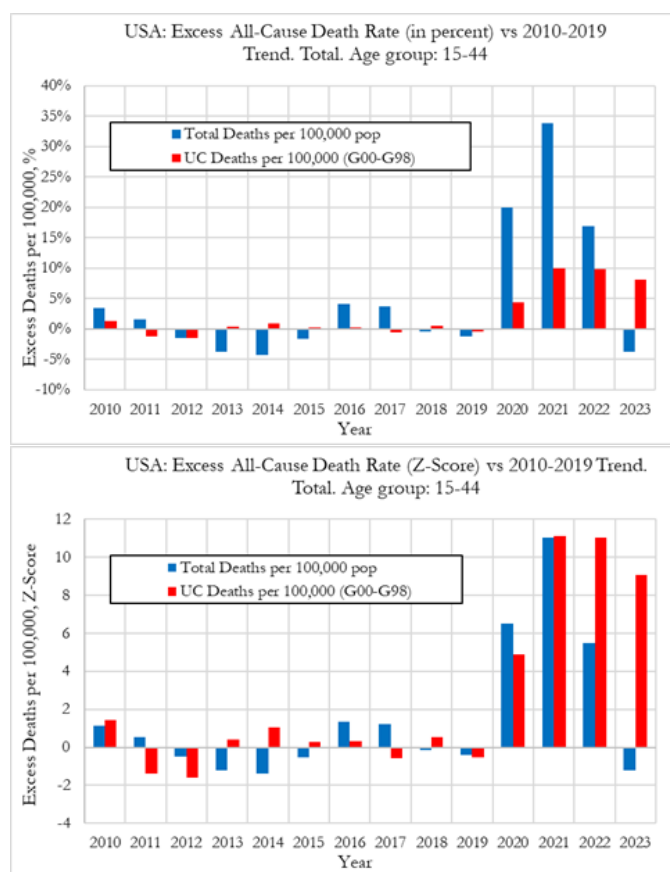
Figure 3. Yearly deaths from neurological diseases as underlying cause in the US for ages 15 to 44. The red dashed line shows the trend from 2010 to 2019. The dotted line shows the extrapolation of the trend from 2020 until 2023. Top: Deaths per 100,000. Bottom: Deaths (Number).

Figure 4. Excess UC death rates from neurological diseases from 2010 to 2023 for both sexes of ages 15 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.

In Figure 4 (top) we can observe that the excess death rates from neurological diseases as the underlying cause (UC) were 4.4% in 2020, then rose to 10.0% in 2021, 9.9% in 2022 and 8.1% in 2023. By comparison, the excess mortality for all-cause deaths was 19.9% in 2020, 33.8% in 2021, 16.8% in 2022, and -3.7% in 2023. Noteworthy is that while excess mortality for all-cause deaths dropped substantially from 2021 to 2022, excess deaths from neurological diseases as the underlying cause remained stable. This trend continued in 2023, with excess neurological deaths remaining high while all-cause excess deaths were negative.

In terms of the statistical significance of the excess deaths, we observe from Figure 4 (bottom) that the Z-Scores for neurological disease death rate deviations from trend were 4.9 in 2020, 11.1 in 2021,

11.0 in 2022 and 9.0 in 2023. The strength of the statistical significance of the excess deaths from neurological diseases was very high, being considered extreme events, indicating a clear change from the prior 2010-2019 trend.

4.3 Trends in MC Death Rates for ICD-10 Codes G00 to G98 (Neurological Diseases)

In this section we investigate the trends in death rates from 2010 to 2023 where neurological diseases (ICD-10 codes G00 to G98) were reported in one of the multiple causes of death (either underlying or secondary cause of death), for the 15-44 age group of both sexes.

MC deaths rates need to be analyzed with a degree of caution as they refer to death rates for a given disease where it is either the underlying cause or a contributing factor towards death. Neurological diseases tend to be contributing causes of death instead of underlying cause which means that MC death rates from neurological diseases could amount to several times the UC death rate. Nonetheless, by analyzing both MC death rates and UC death rates, we can have a better understanding of the underlying phenomena that lead to neurological-related deaths.

This analysis provides additional information in understanding the phenomenon of increased deaths from neurological diseases during the pandemic years, for this age group.

4.3.1 Deaths MC (Multiple cause) from ICD-10 Codes G00 to G98 (Neurological Diseases)

Figure 5 (top) shows the death rate per 100,000 individuals for deaths from neurological disease in the US from 2010 to 2023, where neurological diseases appear as one of multiple causes of death (either underlying or contributing). The figure also shows the MC* death rates from neurological diseases, which is death rates with neurological diseases as a multiple cause, except where COVID-19 is also reported as the underlying or a contributing cause.

We can observe that MC deaths per year from neurological diseases have been trending upwards from 2010 to 2019. In 2010 the death rate was 6.85 per 100,000 and in 2019 it was 8.32 per 100,000, a 21.5% rise.

MC death rates from neurological diseases rose substantially in 2020 to 9.54 per 100,000 and then rose to 10.57 per 100,000 in 2021 and then dropped slightly to 10.26 per 100,000 in 2022 and to 9.78 per 100,000 in 2023. When deaths where COVID-19 was also reported as a cause of death were removed, we observe that the MC* death rates (per 100,000) from neurological diseases were 9.07 in 2020, 9.53 in 2021 and 9.63 in 2022 and 9.61 in 2023. Even

after removing COVID-19 related deaths, we observe an increase in MC* neurological deaths in 2020, 2021 and 2022, and a stabilization in 2023 rather than a reversion to trend.
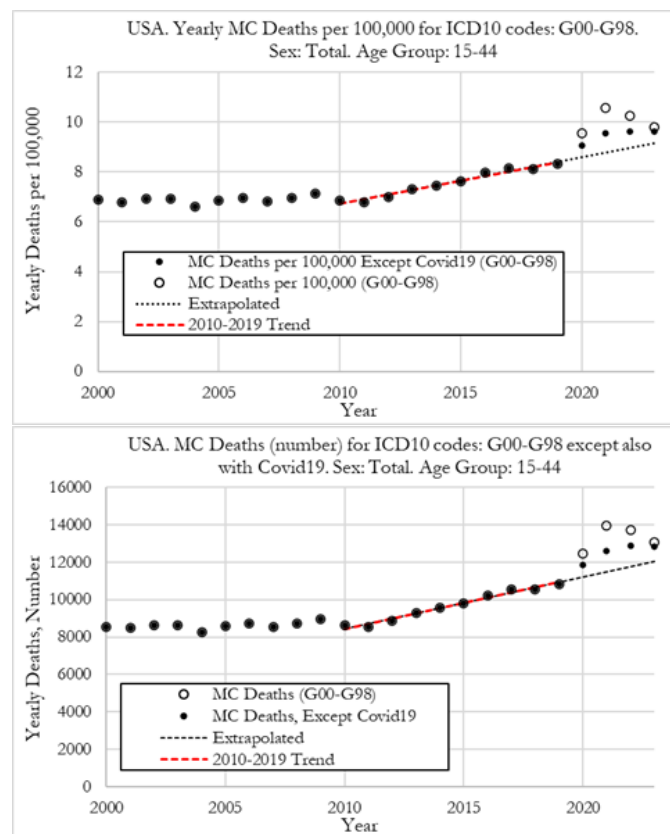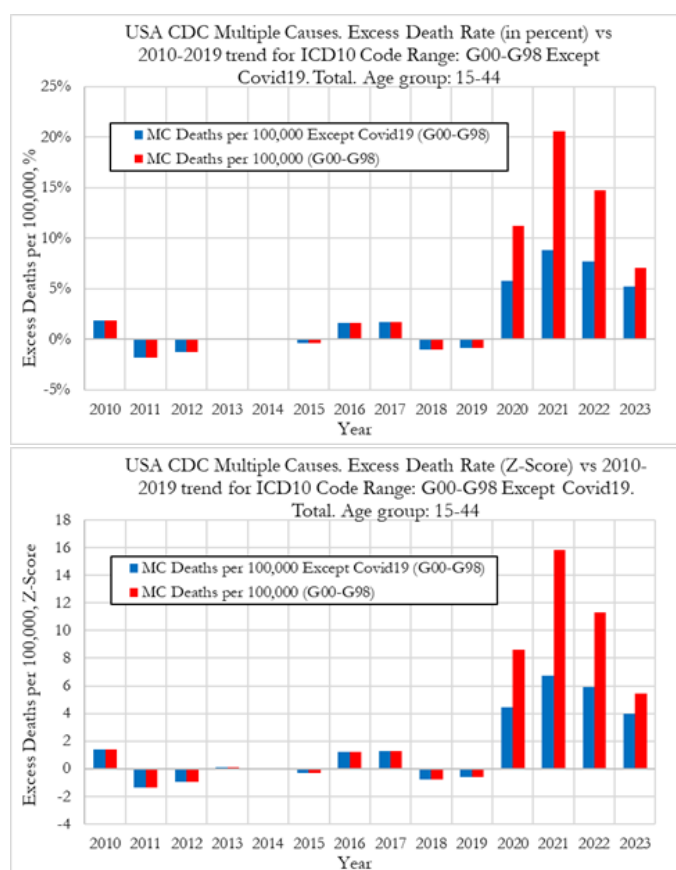

Figure 5. Yearly deaths from neurological diseases as one of multiple causes (underlying or contributing factor) in the US, for ages 15 to 44. The red dashed line shows the trend from 2010 to 2019. The dotted line shows the extrapolation of the trend from 2020 until 2023. Top: Deaths per 100,000. Bottom: Deaths (Number).

4.3.2 Excess MC Deaths Rates

Figure 6 compares the excess MC death rates from neurological diseases from 2010 to 2023, while also showing, for comparison, the excess from MC deaths from neurological diseases where COVID-19-related deaths were not counted, for ages 15 to 44 in the US. The figure on the top refers to relative deviations from the 2010-2019 trend, while Figure 6 (bottom) shows the Z-Score (signal strength) for the deviations from trend.

It should be noted that the way excess death rates (either MC death rates or UC cause death rates) are computed, they adjust for prior trends in deaths rates and are also scale-adjusted when relative deviation from trends are computed. We also compute volatility-adjusted (dispersion around the trend) excess death rates which allows us to have an idea of the signal strengths, and which also allows for a direct comparison of excess MC death rates with excess UC death rates.

Figure 6. Excess MC death rates from neurological diseases from 2010 to 2023 for both sexes of ages 15 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.

In Figure 6 (top) we can observe that the excess MC death rates from neurological diseases were 11.2% in 2020, then rose to 20.6% in 2021, before declining to 14.7% in 2022, and 7.1% in 2023. These numbers track the rises in all-cause mortality

which we mentioned in Figure 4, and are closely associated with COVID-19-related deaths.

By comparison, the excess MC death rates from neurological diseases where COVID-19-related deaths were removed, were 5.8% in 2020, 8.8% in 2021, 7.7% in 2022 and 5.2% in 2023. Of note is that the rise in excess mortality for MC deaths from neurological diseases where COVID-19-related deaths were removed, exhibited a similar pattern to UC excess death rates from neurological diseases.

In terms of the statistical significance of the excess deaths, when looking at excess MC deaths from neurological diseases, the Z-Score in 2020 was 8.6, 15.8 in 2021, 11.3 in 2022 and 5.4 in 2023. These are extreme events.

In terms of the statistical significance of the excess deaths, when looking at excess MC* deaths from neurological diseases (where COVID-19-related deaths are not counted), the Z-Score in 2020 was 4.5, 6.7 in 2021, 5.9 in 2022 and 4.0 in 2023. These values show high statistical significance.

4.4 Comparison of MC* and UC Death Rates from Neurological Diseases

We now compare the trends in MC*[4] death rates and UC death rates from neurological diseases (ICD-10 codes G00 to G98), from 2010 to 2023 for the 15-44 age group of both sexes.

Figure 7 (top) shows the MC* deaths rates and UC death rates from neurological diseases for ages 15 to 44 in the US, from 2010 to 2023. When comparing UC and MC* death rates, we observe that both have been trending higher from 2010 to 2019. We also observe that MC* death rates are substantially higher than UC death rates from neurological diseases, as illustrated by the ratio of MC*/UC death rates, Figure 7 (bottom)), which is close to 2.5 across the 2010-2023 period. The ratio did not vary significantly during the pandemic years, 2020, 2021, 2022 and 2023, indicating that both MC* and UC

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[4] MC* death rates refer from MC death rates from neurological diseases where COVID-19-related deaths were removed

death rates from neurological diseases had similar trends during those years.
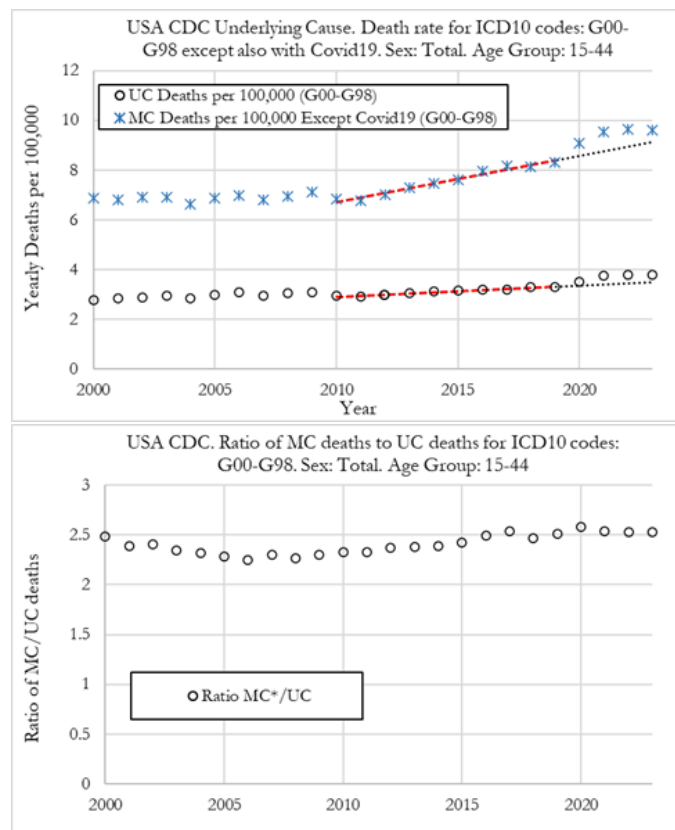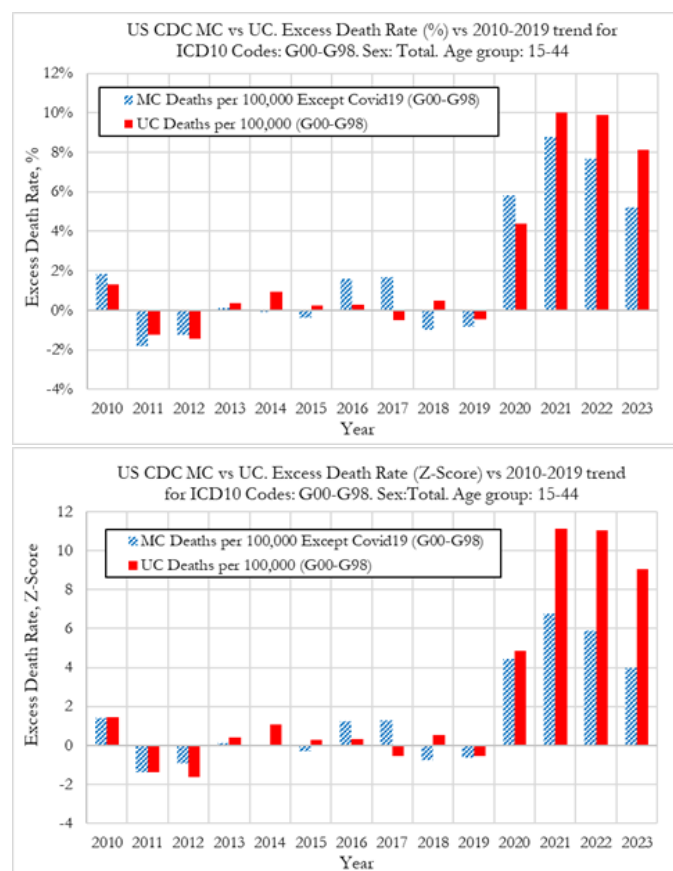

Figure 7. Yearly deaths from neurological diseases as multiple cause (underlying or contributing factor) in the US, for ages 15 to 44, with COVID-19-related deaths removed. The red dashed line shows the trend from 2010 to 2019. The dotted line shows the extrapolation of the trend from 2020 until 2023. Top: Deaths per 100,000. Bottom: Ratio MC*/UC.

This is confirmed in Figure 8 that illustrates the excess MC* and UC deaths rates from neurological diseases, which overall show similar pattern of excess death rates in 2020, 2021, 2022 and 2023. In 2020, the excess UC death rate from neurological diseases was 4.4%, while 5.8% for MC* death rate, both having high Z-Scores of 4.9 and 4.5, respectively (as shown in Figure 8 bottom).

In 2021, the excess UC death rate was 10.0% with a Z-Score of 11.1, while for MC*, the excess death rate was 8.8% with a Z-Score of 6.7. In 2022, the UC excess death rate was 9.9%, while 7.7% for MC*, with respective Z-Scores of 11.0 and 5.9. In

2023, the UC excess death rate was 8.1%, while 5.2% for MC*, with respective Z-Scores of 9.0 and 4.0.

Figure 8. Excess MC* and UC deaths rates from neurological diseases for ages 15 to 44, in the US. Top: Relative deviation from trend, percent. Bottom: Deviation from trend Z-Score.

Interestingly, for comparison, the excess UC death rates from neoplasms for individuals aged 15 to 44 in the US were 1.7% in 2020, 5.6% in 2021, and 7.9% in 2022, with Z-Scores of 3.5, 11.8 and 16.5, respectively, as reported in our previous paper showing an equivalent analysis for neoplasm deaths (Alegria, et al., 2024)[9].

We conclude that UC neurological disease deaths show a similar pattern of excess death rates as previously reported for neoplasms, with the main difference being that neurological death rates showed larger rises in 2020, a rise that already represented a signal with high statistical significance.

Possible explanations for the change from the historical trend in neurological deaths in 2020, include the collateral effects of the lockdowns on the lifestyle habits of individuals aged 15 to 44, such as alcohol consumption, fentanyl, or other drugs. Other explanations could include COVID-19 side effects that were not recognized or recorded on the death certificates. From 2021 onwards, lockdowns likely played a smaller role in the continued rising excess death rates from neurological diseases, while a new factor was introduced in the form of the novel COVID-19 vaccinations which could have played a significant role, together with enduring effects from multiple SARS-CoV-2 exposures.

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

In this chapter we generalize the previous analysis for all age groups. We compute the excess deaths (deviation from trend) from neurological diseases, for the different age groups in the US.

5.1 Excess UC Deaths from Neurological Diseases for Different Age Groups

Here we compute, for all age groups, the excess UC death rates from neurological diseases in 2020, 2021, 2022 and 2023, shown in Figure 9. The detailed results are also shown in the appendix.

In Figure 9 (top) we plot the excess UC death rate (in percent) while Figure 9 (bottom) shows the respective Z-Scores. Each data-point on the graphs is obtained by performing the analysis described in the methodology section where the extrapolated 2010-2019 trendline in death rates is subtracted from the death rates in 2020, 2021, 2022 and 2023, for each of the age groups. The highlighted region corresponds to the results for the detailed analysis shown previously for the 15 to 44 age group.

Figure 9 shows that the excess UC death rates from neurological diseases seem to have impacted mostly younger individuals aged 15 to 44 and also new-born below 1 year of age. For age groups 45-54

and older we do not notice outstanding excess death rates, similarly for age groups 1-4 and 5-14. For a more detailed analysis, the appendix tables shows all the individual values that are plotted in Figure 9.

For age groups 15-24, 25-34 and 35-44 we observe statistically significant excess death rates, particularly in 2021, 2022 and 2023. The signal strengths in 2020 were weak for 15-24 and 25-34 age groups, likely due to small sample sizes, while for age group 35-44 there was already a statistically significant increase in death rates starting in 2020.

The largest percentage of excess deaths were observed in the younger 15-24 age group, where excess death rates were 6.8% (Z-Score: 2.3) in 2020, 14.5% (Z-Score: 4.9) in 2021, 16.5% (Z-Score: 5.6) in 2022 and 20.9% (Z-Score: 7.1) in 2023. Excess death rates rose consecutively in 2020, 2021, 2022 and 2023, with the rises in 2021, 2022 and 2023 showing very high statistical significance (extreme occurrences), while in 2020 the excess death rates had lower statistical significance.

For age group 35-44, excess death rates were 3.8% (Z-Score: 3.7) in 2020, 8.3% (Z-Score: 8.1) in 2021, 6.5% (Z-Score: 6.4) in 2022 and 4.6% (Z-Score: 4.5) in 2023. This age group already showed a clear signal in excess death rates from 2020, albeit with a lower percentage change when compared with the 15-24 age group. As with most causes of death, death rates from neurological diseases tend to increase exponentially with age for individuals over 10 years old, leading to larger sample sizes in the older age groups, and therefore any change in death rates is more likely to reach statistical significance compared with younger age groups.

For newborns below the age of 1, the excess death rates were 8.9% (Z-Score: 1.5) in 2020, 21.8% (Z-Score: 3.7) in 2021, 10.8% (Z-Score: 1.9) in 2022 and 21.6% (Z-Score: 3.7) in 2023. In 2020 the increase in death rates was not statistically significant. However, in 2021 and 2023 excess death rates exhibited a high degree of statistical significance while in 2022 excess death rates were somewhat statistically significant. These signals merit further investigation in our opinion. In particular, the excess
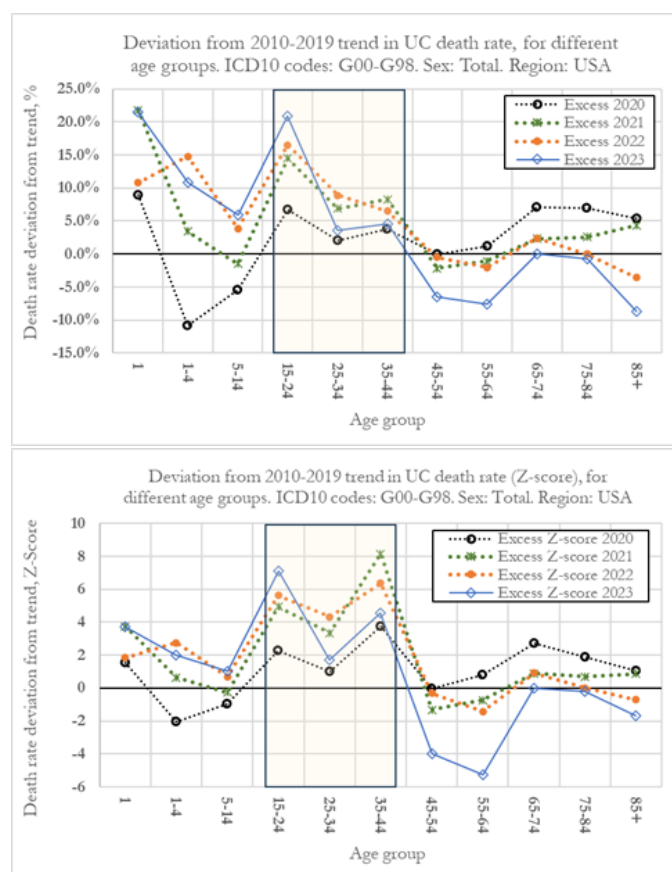
Figure 9. Excess UC death rates from neurological diseases for 2020, 2021, 2022 and 2023 for different age groups of both sexes in the US. Top: Relative deviation from trend, percent. Bottom: Deviation from trend Z-Score.

deaths signal in 2021 coincided with the vaccination of pregnant women for COVID-19, which could have played a role in the effect on newborns, in addition to other more common factors.

For older age groups from 45 upwards, we see negative excess deaths from neurological diseases in 2023, most marked for the 45-64 age groups and individuals over 85. This may be the first year that we see the reversal of a previous 'pull forward' effect whereby fragile individuals with neurological diseases were more likely to die during the pandemic years due to the added impact of lockdowns, reduced access to healthcare provision, COVID-19 infection and its sequelae, and vaccination effects. As some of these individuals have died sooner than would otherwise have been expected, this results in a negative excess death rate for the year(s)

they would have died without the impact of the pandemic.

5.2 Excess MC Deaths from Neurological Diseases for Different Age Groups

In this section we compute, for all 10-year age groups, the excess MC death rates from neurological diseases in 2020, 2021, 2022 and 2023, shown in Figure 10. For a detailed view of the results refer to the appendix.

In Figure 10 (top) we plot the excess MC death rate (in percent) while Figure 10 (bottom) shows the respective Z-Scores. As mentioned previously, each data-point on the charts corresponds to the excess death rate for a given year, which is obtained by performing the analysis described in the methodology section where the extrapolated 2010-2019 trendline in death rates is subtracted from the MC death rates in 2020, 2021, 2022 and 2023, for each of the age groups. The highlighted region corresponds to the results for the detailed analysis shown previously for the 15 to 44 age group.

In Figure 10 we can observe that in general, excess MC death rates from neurological diseases were higher than for excess UC death rates in 2020, 2021, 2022 and 2023, for age groups 15-24 and older, despite the fact that multiple-cause neurological deaths are multiple times underlying-cause deaths (as shown in Figure 7 – bottom). However, this and can be explained by MC neurological death rates increasing due to the impact of COVID-19 and the rise in all-cause mortality during the pandemic years. Consequently, in the next section we analyze excess MC neurological deaths where COVID-19-related deaths are excluded.

We also notice from Figure 10 that MC excess death rates from neurological diseases were highest in 2020 for older age groups (around 15%), from ages 55 and older, while for younger age groups, the inverse occurred with the highest death rates occurring in 2021 and 2022. Additionally, MC death rates are significantly higher values than for equivalent excess UC death rates, for example for age group 35-44 MC excess death rates were 12.0% (Z-Score:

7.7) in 2020, 22.3% (Z-Score: 14.3) in 2021, 15.1% (Z-Score: 9.7) in 2022 and 7.4% (Z-Score: 4.8) in 2023. Consequently, we would expect that the larger increase in MC death rates from neurological diseases would lead to lower UC death rates in the following year, due to a pull-forward effect of fragile individuals suffering from neurological diseases. The opposite occurs for those aged 44 and under. However, as previously described, the older age groups are exhibiting negative excess UC death rates in 2023, indicating that the pull forward effect may be ending for these age groups.
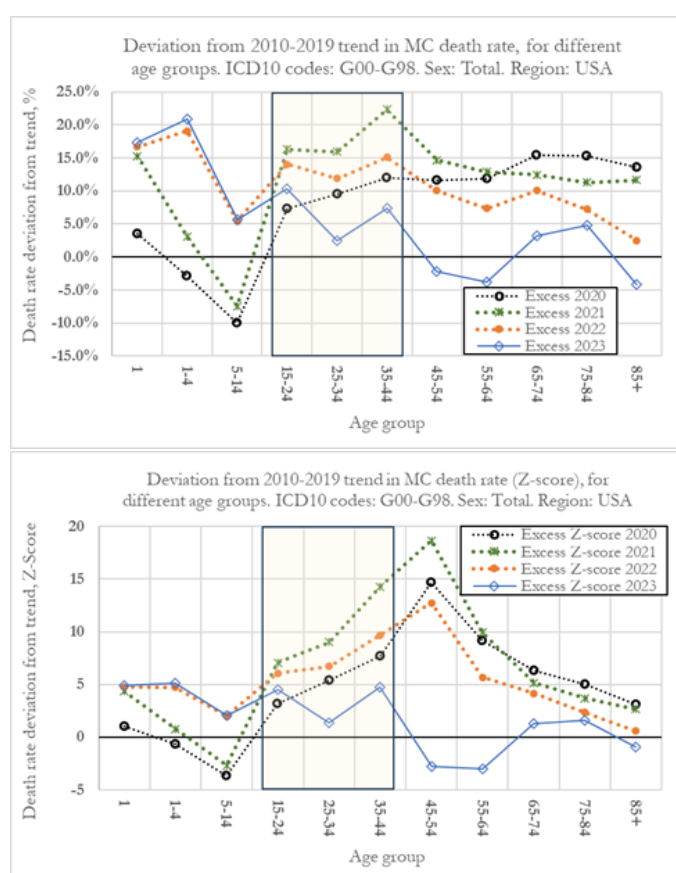
Figure 10. Excess MC death rates from neurological diseases for 2020, 2021, 2022 and 2023 for different age groups of both sexes in the US. Top: Relative deviation from trend, percent. Bottom: Deviation from trend Z-Score.

5.3 Excess MC* Deaths from Neurological Diseases for Different Age Groups

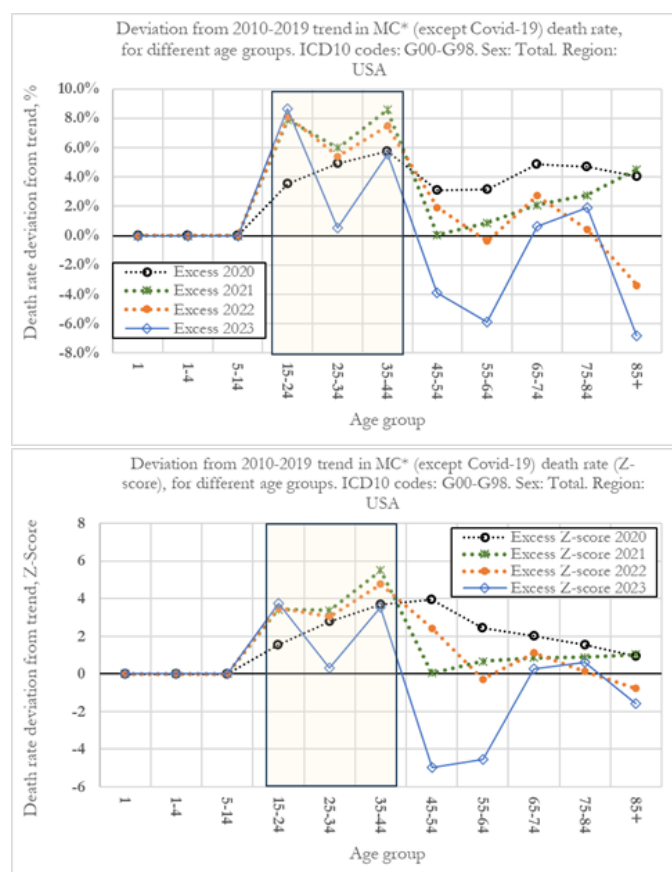Now we compute, for all age groups, the excess MC* death rates from neurological diseases in 2020,

2021, 2022 and 2023. As a reminder, MC* death rates refer to MC deaths from neurological diseases except for those where COVID-19 is also reported (either as underlying cause or a contributing cause).

In Figure 11 (top) we plot the excess MC* death rates (in percent) while Figure 11 (bottom) shows the respective Z-Scores. The results show that the excess MC* death rates exhibit a similar pattern to UC excess death rates for the different age groups. After removing deaths related from COVID-19, we can still observe excess MC death rates in 2021, 2022 and 2023 for the most affected age groups of 15 to 44. This is likely due to the rise in MC* death rates being driven by the rises in UC death rates.

When looking at the younger 15-24 age group, excess MC* death rates were 3.5% (Z-Score: 1.5) in 2020, 7.9% (Z-Score: 3.4) in 2021, 8.1% (Z-Score: 3.5) in 2022 and 8.7% (Z-Score: 3.7) in 2023. When comparing these values with the equivalent excess UC death rates which were 6.8% (Z-Score: 2.3) in 2020, 14.5% (Z-Score: 4.9) in 2021, 16.5% (Z-Score: 5.6) in 2022 and 20.9% (Z-Score: 7.1) in 2023, we observe that both follow a similar pattern where excess death rates rose consecutively in 2020, 2021, 2022 and 2023. Furthermore, in both cases, excess death rates seem to have impacted mostly in 2021, 2022 and 2023, exhibiting rises with very large Z-Scores. A similar pattern is found for age group 25-34 and 35-44.

Older individuals appear, in general, to be less impacted, particularly in 2021, 2022 and 2023, with lower Z-Scores for the excess MC* death rates, and negative MC* death rates for the 45-64 and 85+ age groups, with strong statistical significance for the negative excess death rates for those between 45 and 64.

For newborns below the age of 1 and age groups 1-4 and 5-14, the excess MC* death rates could not be computed due to data suppression rules by the CDC WONDER system which occur in small sample sizes.

Figure 11. Excess MC* death rates from neurological diseases (except COVID-19-related deaths) 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.

6   SUMMARY OF FINDINGS AND COMMENTARY

In this study we investigate trends in death rates from neurological diseases (ICD-10 codes G00-G98) for all age groups in the US using data from the CDC. We also perform a detailed analysis for younger individuals aged 15 to 44. We investigate trends in neurological diseases where these appear on 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. We also investigate trends in MC* neurological deaths, that is, multiple cause neurological deaths except those that are also COVID-19-related.

Excess neurological disease deaths for all ages

When investigating different age groups, Figure 9 shows (with more detail in the appendix) that the excess UC death rates from neurological diseases in 2020, 2021, 2022 and 2023 seem to have impacted mostly younger individuals aged 15 to 44, and also newborns below 1 year of age. For age groups 45-54 and older we do not notice significant excess death rates, similarly for age groups 1-4 and 5-14.

We show statistically significant excess death rates from neurological diseases for age groups 15-24, 25-34 and 35-44, particularly in 2021, 2022 and 2023. The consistency of excess death rates for the individual age groups within the broader 15-44 age group analysis points to the observed signals being a real effect and not an artifact of changing age-group proportions. The signal strengths in 2020 were weak for 15-24 and 25-34 age groups, likely due to small sample sizes, while for age group 35-44 there was already a statistically significant increase in death rates starting in 2020. The largest percentage of excess deaths were observed in the younger 15-24 age group, where excess death rates were 6.8% (Z-Score: 2.3) in 2020, 14.5% (Z-Score: 4.9) in 2021, 19.9% (Z-Score: 6.8) in 2022 and 20.9% (Z-Score: 7.1) in 2023. Excess death rates rose consecutively in 2020, 2021, 2022 and 2023 with the rises in 2021, 2022 and 2023 showing very high statistical significance (extreme occurrences), while in 2020 the excess death rates had lower statistical significance.

For newborns below the age of 1, the excess death rates were 8.9% (Z-Score: 1.5) in 2020, 21.8% (Z-Score: 3.7) in 2021, 14.5% (Z-Score: 2.5) in 2022 and 21.6% (Z-Score: 3.7) in 2023. In 2020 the increase in death rates was not statistically significant. However, in 2021 and 2023 excess death rates exhibited a high degree of statistical significance and in 2022 excess death rates were also statistically significant, albeit with lower strength. It should be noted that the excess deaths signal in 2021 coincided with the mass vaccination campaign for COVID-19 (which included pregnant women),

and that might have played a role in the observed signal, and we believe merits further investigation.

One must also explain why older individuals, who are subject to more COVID-19 vaccinations do not appear to be impacted so strongly as younger individuals in 2021, 2022 and 2023. One explanation could be that there was a larger pull-forward effect for older individuals that tracks the all-cause mortality increase caused by the COVID-19 pandemic, and subsequently lower excess death rates from neurological diseases (in 2021 and 2022). This is supported by the negative excess UC deaths from neurological diseases in older age groups in 2023, which could indicate the end of the pull-forward effect.

Excess deaths from neurological diseases for age group 15 to 44

Our results show that the excess UC death rates from neurological diseases for individuals aged 15 to 44 age were 4.4% (Z-Score 4.9) in 2020, then rose to 10.0% (Z-Score 11.1) in 2021, 11.2% (Z-Score 12.4) in 2022 and 8.1% (Z-Score 9.0) in 2023. In 2020 we already observe a significant deviation from the 2010-2019 trend in UC death rates, and the excess UC death rates in 2021, 2022 and 2023 can be considered extreme occurrences due to their very high statistical significance. The results show a clear break from the prior historical trend in death rates from neurological diseases, pointing to a new phenomenon in action, worsening in 2022 and persisting through 2023.

When analyzing excess MC death rates from neurological diseases we show that these were 11.2% in 2020, which then rose to 20.6% in 2021 before subsiding to 14.7% in 2022 and 7.1% in 2023. These numbers track closely the rises in all-cause mortality which we mentioned in Figure 4, and are closely associated with COVID-19-related deaths as was confirmed by the MC* analysis. When analyzing MC* death rates from neurological diseases (where COVID-19 deaths are excluded) we show that these followed a similar pattern to UC deaths rates, suggesting that the rises in excess MC* death rates were driven by the rises in excess UC death rates.

Of note, the larger rise in MC death rates from neurological diseases when compared with UC death rates implies that there was a pull forward effect due to the early deaths of the most fragile individuals of the 15-44 age group with neurological diseases. Consequently, we would expect that this would lead to lower (or even negative) excess UC death rates from neurological diseases in subsequent years, which was contrary to what has so far occurred.

How can we explain the excess UC deaths from neurological diseases in 2020, 2021, 2022 and 2023?

In 2020, this could be explained by deaths from health effects related to the pandemic management measures such lockdowns and lack of medical care, or other related factors such as stress, less exercise, worse food habits, or from under-diagnosed COVID-19 itself, or related side effects.

The acceleration in excess death rates from neurological diseases in 2021, 2022 and 2023 is more difficult to explain due to COVID-19 on its own. Given the case studies of neurological adverse events following COVID-19 vaccination cited in the literature, one possible factor could be adverse effects of the COVID-19 vaccines. Furthermore, one must also account for the possibility of continuous COVID-19 infections or Long COVID (Jangnin, et al., 2024)[10] or "Long COVID-19 vaccines" (Asadi-Pooya, et al., 2023)[11] being contributors towards an increased incidence or severity of neurological conditions, leading to increased neurological disease death rates.

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 (5th 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 when 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 the emergence of neurological diseases following COVID-19 vaccination cited above, future studies should focus on COVID-19 vaccinated and un-vaccinated individuals and whether the vaccination rollout or COVID-19-related conditions such as Long COVID are contributing factors to the ongoing rise in neurological-related deaths (Tindle, 2024)[12]

Future research should be aimed at disentangling the effects of each factor separately or in combination, stratified by age group, to better inform public health decisions in the future and lead towards effective therapeutic strategies for related conditions.

CONFLICT OF INTEREST STATEMENT

None that the authors are aware of.

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APPENDIX

Summary tables with MC, MC* and UC excess death rates from neurological diseases 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 Age Group	UC Excess Death Rate Deviation,%	UC Excess Death Rate Z-Score	MC Excess Death Rate Deviation,%	MC Excess Death Rate Z-Score	MC* Excess Death Rate Deviation,%	MC* Excess Death Rate Z-Score	Ratio MC/UC
1	8.9	1.5	3.5	1.0	n.a.	**n.a.**	2.45
1-4	-10.5	-2.0	-2.8	-0.7	n.a.	**n.a.**	2.74
5-14	-5.5	-1.0	-10.0	-.6	-11.6	-4.2	2.12
15-24	6.8	2.3	7.3	**3.2**	3.5	1.5	2.12
25-34	2.0	1.0	9.6	**5.4**	4.9	2.8	2.65
35-44	3.8	**3.7**	12.0	**7.7**	5.8	**3.7**	3.01
45-54	0.0	0.0	11.6	**14.7**	3.1	**3.9**	3.12
55-64	1.1	0.8	11.9	**9.2**	3.1	2.4	2.78
65-74	7.0	2.7	15.4	**6.4**	4.9	2.0	2.07
75-84	6.9	1.9	15.3	**5.0**	4.7	1.5	1.59
85+	5.3	1.0	13.6	**3.1**	4.0	0.9	1.40

Table 1. UC, MC and MC* excess death rates from neurological diseases for different age groups in 2020. Excess death rates refer to deviations from 2010-2019 trend. The ratio MC/UC is the ratio of MC deaths to UC deaths from neurological diseases.

2021 Age Group	UC Excess Death Rate Deviation,%	UC Excess Death Rate Z-Score	MC Excess Death Rate Deviation,%	MC Excess Death Rate Z-Score	MC* Excess Death Rate Deviation,%	MC* Excess Death Rate Z-Score	Ratio MC/UC
1	21.8	**3.7**	15.3	**4.4**	n.a.	**n.a.**	2.52
1-4	3.5	0.6	3.1	0.8	1.1	0.3	2.52
5-14	-1.5	-0.3	-7.4	-2.7	-10.4	-3.8	2.16
15-24	14.5	**4.9**	16.3	**7.1**	7.9	**3.4**	2.16
25-34	6.9	**3.3**	16.0	**9.0**	6.0	**3.4**	2.69
35-44	8.3	**8.1**	22.3	**14.3**	8.6	**5.5**	3.18
45-54	-2.2	-1.3	14.	**18.7**	0.0	0.0	3.30
55-64	-1.0	-0.7	12.9	**10.0**	0.9	0.7	2.87
65-74	2.3	0.9	12.5	5.1	2.1	0.9	1.59
75-84	2.5	0.7	11.3	3.7	2.7	0.9	1.59
85+	4.3	0.9	11.7	2.7	4.54	1.0	1.38

Table 2. UC, MC and MC* excess death rates from neurological diseases for different age groups in 2021. Excess death rates refer to deviations from 2010-2019 trend. The ratio MC/UC is the ratio of MC deaths to UC deaths from neurological diseases.

2022 Age Group	UC Excess Death Rate		MC Excess Death Rate		MC* Excess Death Rate		Ratio MC/UC
	Deviation,%	*Z*-Score	**Deviation,%**	*Z*-Score	**Deviation,%**	*Z*-Score	
1	10.8	1.9	16.7	**4.8**	14.6	**4.1**	2.89
1-4	14.8	2.8	19.1	**4.7**	14.0	**3.5**	2.65
5-14	3.9	0.7	5.5	2.0	0.1	0.0	2.29
15-24	16.5	**5.6**	14.0	**6.1**	8.1	**3.5**	2.10
25-34	8.9	**4.3**	11.9	**6.7**	5.4	**3.1**	2.55
35-44	6.5	**6.4**	15.1	**9.7**	7.5	**4.8**	3.07
45-54	-0.5	-0.3	10.0	**12.8**	1.9	2.4	3.14
55-64	-2.0	-1.4	7.4	**5.7**	-0.4	-0.3	2.77
65-74	2.4	0.9	10.1	**4.2**	2.7	1.1	2.05
75-84	0.0	0.0	7.2	2.4	0.4	0.1	1.56
85+	-3.6	-0.7	2.5	0.6	-3.4	-0.8	1.36

Table 3. UC, MC and MC* excess death rates from neurological diseases for different age groups in 2022. Excess death rates refer to deviations from 2010-2019 trend. The ratio MC/UC is the ratio of MC deaths to UC deaths from neurological diseases.

2023 Age Group	UC Excess Death Rate		MC Excess Death Rate		MC* Excess Death Rate		Ratio MC/UC
	Deviation,%	*Z*-Score	**Deviation,%**	*Z*-Score	**Deviation,%**	*Z*-Score	
1	21.6	**3.7**	17.3	**4.9**	n.a.	**n.a.**	2.75
1-4	10.9	2.0	20.9	**5.2**	18.7	**4.6**	2.81
5-14	5.9	1.0	5.7	2.1	4.1	1.5	2.27
15-24	20.9	**7.1**	10.4	**4.5**	8.7	**3.7**	1.97
25-34	3.6	1.7	2.5	1.4	0.5	0.3	2.47
35-44	4.6	**4.5**	7.4	**4.8**	5.5	**3.5**	2.94
45-54	-6.5	-4.0	-2.2	-2.8	-3.9	-5.0	3.00
55-64	-7.6	-5.3	-3.8	-3.0	-5.9	-4.5	2.64
65-74	0.0	0.0	3.2	1.3	0.6	0.3	1.96
75-84	-0.7	-0.2	4.8	1.6	1.9	0.6	1.53
85+	-8.6	-1.7	-4.2	-1.0	-6.8	-1.6	1.34

Table 4. UC, MC and MC* excess death rates from neurological diseases for different age groups in 2023. Excess death rates refer to deviations from 2010-2019 trend. The ratio MC/UC is the ratio of MC deaths to UC deaths from neurological diseases.