DEVIATING TEMPORAL TRENDS OF SUBSTANCE ABUSE MORTALITY IN HIGH-INCOME COUNTRIES

INTRODUCTION

After almost a century of sustained increases, life expectancy improvements started to slow down in several high-income countries before the COVID-19 pandemic, with a few even experiencing a reversal of this trend(Crimmins and Zhang 2019; Ho and Hendi 2018; Hiam et al. 2017). This deceleration of improvements has been partly attributed to behavioral risk factors such as smoking, obesity, and drug abuse (Preston et al. 2014; Preston, Glei, and Wilmoth 2011; Ho and Hendi 2018; Gispert et al. 2008).

Since the start of the opioid overdose epidemic in the US and the publication of the influential paper by Case and Deaton (2015) on "deaths of despair," researchers have been investigating US drug- and alcohol-related deaths, also known as substance abuse (SA) mortality, in conjunction with suicides (Case and Deaton 2017; Ruhm 2018; Tilstra, Simon, and Masters 2021). Similar unprecedented increases in opioid overdoses have been observed in Australia and Canada (Lisa and Jessica 2018; Larance et al. 2018). Eastern Europe has also been grappling with its own epidemic of alcohol-related mortality (Rehm et al. 2007; Trias-Llimós and Janssen 2018; Trias-Llimós et al. 2018). These trends suggest that most high-income countries are currently experiencing a crisis in SA mortality, with levels of alcohol-related mortality being a significant issue and drug-related mortality showing rapid and unprecedented rises(Rehm et al. 2019).

Most research on drug- and alcohol-related mortality have predominantly focused on changes over age and period. For instance, the unprecedented increase in drug overdose mortality in the US has been extensively linked to a mid-life crisis (Carroll et al. 2022; J. B. Dowd et al. 2022; Currie and Schwandt 2021; Tilstra, Simon, and Masters 2021; Ruhm 2018; Infurna et al. 2021; King, Scheiring, and Nosrati 2022), although increases have been observed among all ages (Shield and Rehm 2015; Johnell et al. 2017), and considerable risk differences across cohorts have been identified (Jalal et al. 2020; W. Hall, Degenhardt, and Hickman 2020; Acosta et al. 2020). Similarly, there is evidence of cohort differences in alcohol-related mortality risks in several European countries (Trias-Llimós, Bijlsma, and Janssen 2017). Because of the conjunction of period crises and substantial cohort risk differentials in SA mortality, analyzing these trends requires accounting for temporal variations among the three demographic temporal dimensions: age, period, and cohort.

Despite the recent increase in both drug- and alcohol-related mortality, much research focuses on analyzing deaths from each substance separately, with little discussion about the association between the two. Different factors modulate alcohol- and drug-related mortality, including biological, behavioral, and structural factors(Garcia 2022). However, in recent years, researchers have acknowledged structural causes have foregone biological and behavioral factors behind them (Wu and Evangelist 2022). Birth cohorts have been found to share structural causes that drive SA mortality via various social determinants of health, including social support, cohesion, and organization (Ryder 1985). For instance, birth cohorts born or during economic recessions may suffer long-term consequences in mental health and are prone to SA as a coping mechanism. Studies have identified specific stressors incentivizing addiction to both drugs and alcohol(Zaleski, Levey-Thors, and Schiaffino 1998; Keyes, Hatzenbuehler, and Hasin 2011). Hence, it is plausible that changes in both risky behaviors are not completely independent, and important insights can be obtained by analyzing these causes of death simultaneously. This study addresses this gap by comparing age-period-cohort temporal trends in drug- and alcohol-related mortality among high-income countries.

BACKGROUND

Drugs- and alcohol-related mortality

In most high-income countries, drug-related mortality is mainly due to drug poisoning/overdose (Bargagli et al. 2006). Deaths from drug overdose in the US, mainly driven by synthetic opioids, have increased almost fivefold between 1999 and 2020 (Rates 2020). Most high-income anglophone countries, including Australia, Canada, Scotland, and England & Wales, have also seen increased drug-related mortality and are experiencing the worst drug-related epidemic since records began (Canada 2022; Breen and Manders 2021; Scotland 2021; Health and Welfare 2022). However, the upward trend in drug-related deaths is not limited to English-speaking countries. Several Nordic countries, including Denmark, Finland, Norway, and Sweden, have also seen substantial increases in recent years (Edvardsen and Clausen 2022; Simonsen et al. 2020). In most of these countries, drug-related mortality increases have occurred at a slower rate and considerably smaller magnitudes than those seen in the US (Ho 2019). Scotland, however, is an exception, having reached mortality rates comparable to the US in recent years (J. B. Dowd et al. 2022). Drug-related mortality trends are similar for both sexes, although the magnitude is considerably higher for males.

Unlike drugs, the largest contributor to alcohol-related deaths is not acute intoxication but degenerative diseases. The main contributor to alcohol-induced deaths is alcoholic liver diseases, followed by mental and behavioral disorders, and poisoning. Before the COVID-19 pandemic, for the past two decades, trends in alcohol-related mortality were believed to be declining in several high-income countries (Organization et al. 2013 ; Shield, Rylett, and Rehm 2016; Organization 2019). Nevertheless, several researchers have highlighted a turnaround in alcohol-related mortality since the beginning of the pandemic. Canada, Finland, Germany, Scotland, and the US saw a recent increase in alcohol-related mortality (White et al. 2022). Mortality trends due to alcohol vary greatly by geographic location and sex (Grigoriev et al. 2020). The levels of alcohol-related deaths in Central and Eastern Europe are vastly superior compared to other high-income countries (Rehm et al. 2007, 2019; Shield, Rylett, and Rehm 2016; Organization 2019). Irrespective of the trends, the levels of alcohol mortality in countries like Hungary, Estonia, Poland, Lithuania, Latvia, and the Czech Republic have been historically higher compared to the rest of Europe (Jasilionis, Leon, and Pechholdová 2020). But, some western European countries, including Finland, Germany, Denmark, and Austria, are approaching levels of eastern and central Europe (Mackenbach et al. 2015). Regarding gender differences in alcohol abuse, although alcohol-related mortality is predominant among males (Trias-Llimós and Janssen 2018), the gap has narrowed in recent years. In central and eastern Europe, it has been hypothesized that alcohol has been one of the main contributors to gender differences in life expectancy (McCartney et al. 2011; Trias-Llimós and Janssen 2018). However, the narrowing of the gap has not resulted from improvements in alcohol-related mortality among males but from deterioration among females (White 2020).

Several researchers have studied trends in SA mortality for different sets of high-income countries, including cross-national comparisons and their impact on life expectancy (Ho 2019; Barbieri 2019). This study aims to update existing cross-national studies on SA mortality trends for drugs and alcohol in the "worst performers," a group of high-income countries showing consistently high levels of SA mortality for each sex between 2012 and 2016.

Age-Period-Cohort Perspective in SA mortality

From an Age-Period-Cohort perspective, changes in SA mortality have been studied conventionally as a period shock that affects most or specific age groups (Case and Deaton 2015). However, there is evidence of sustained cohort differences in mortality risk from SA during the life course, even during period crises (Acosta et al. 2020; Keyes et al. 2011; Miech, Koester, and Dorsey-Holliman 2011; Rao and Roche 2017). According to (Ryder 1985), particularities of the births cohort, such as its size, profoundly impact several dimensions of life, including fertility, well-being, labor force participation, and mortality. Easterlin's

hypothesis advanced this approach by explaining the poor performance in mortality among baby boomer cohorts due to the mismatch in their early life expectations and later life experiences due to the large size of the cohort (Easterlin 1968, 1976). On the basis of this, Easterlin predicted rises in criminal behaviors and SA among members of the boomer cohorts (Easterlin 1978, 1987; Easterlin, Schaeffer, and Macunovich 1993). It is, therefore, important to study SA mortality from an age-period-cohort (APC) perspective. Additionally, social relations are an important determinant of SA behavior. The influence of peers during adolescence and the duration of this influence during the life course can substantially change mortality risks in certain cohorts (Bishop 2022; Keyes et al. 2011).

To study any demographic trend from an APC perspective, one must disentangle the individual contributions of age, period, and cohorts to the temporal variations. An important limitation of such analysis is the impossibility of isolating age, period, and cohort effects as they are logically confounded, otherwise known as the "APC identification problem" (Bell and Jones 2013). It is, however, possible to obtain valuable insights by focusing on the analysis of periods and cohorts in which mortality performance deviates from the linear trends, which are referred to in the literature as "non-linear APC trends." Uncovering existing patterns in mortality risk from SA differences across birth cohorts will open potential paths toward understanding SA behavior in a demographic context. Although some studies have followed this method of studying age-period-cohort components of variations in mortality from either drugs or alcohol abuse (Acosta et al. 2020; Miech, Koester, and Dorsey-Holliman 2011; Trias-Llimós, Bijlsma, and Janssen 2017), to our knowledge, this is the first study analyzing the temporal patterns of drug and alcohol-related mortality simultaneously across several high-income countries.

Substitution and Concomitance of SA

Although most research on SA mortality has focused on individual substances separately (for example, drug poisonings or alcoholic liver diseases), many drug users engage in polysubstance use. The analysis of polysubstance use is crucial because it has been demonstrated to significantly increase the risk of dying. Although the term 'polysubstance use' usually refers to the consumption of two or more drugs over a short period of time, we broaden this definition in this study to analyze the convergence of drug and alcohol abuse. Furthermore, it is generally recognized that combining drugs with alcohol greatly increases the risk of overdose and eventual death (Coffin et al. 2003; Polettini, Groppi, and Montagna 1999; Poulin, Stein, and Butt 1998; Gossop et al. 1996). Then, it is pertinent to analyze the extent to which higher susceptibilities to die from alcohol and drug abuse converge on the same population (i.e., concomitance) or affect different population segments sequentially (i.e., substitution). These two dynamics of substance use should be analyzed from period and cohort perspectives. Period shocks of mortality from drug and alcohol abuse affecting most age groups may or may not coincide. Similarly, sustained disadvantages towards mortality from drug and alcohol abuse can converge on the same birth cohorts or can alternate among successive cohorts. However, studies have yet to identify any possible link between cohort membership and the change in mortality risk due to the interaction of both SA patterns.

Several studies have analyzed SA from the APC perspective (Huang, Keyes, and Li 2018; Kraus et al. 2015; W. D. Hall, Degenhardt, and Lynskey 1999). However, most of these studies focus on either a single etiological mechanism of SA mortality (mainly drug overdose or alcoholic liver disease) or indistinguishably combining drugs and alcohol together. In order to determine how the risk of death from SA (both drugs and alcohol) varies depending on cohort membership, this study set out to investigate whether simultaneous or alternate abuse of drugs and alcohol has a generational influence on mortality in high-income countries.

DATA AND RESEARCH METHODS

Data

We select the high-income countries for our analysis based on the following criteria:

- Available data by cause of death in the WHO mortality database between 1994 and 2020.
- Cause of death in 3-digit codes (ICD-10).
- The population of the country is five million or more.

We extract data from the World Health Organization (WHO) Mortality Database (**WHOref?**) on death counts by cause, five-year age groups, and sex for high-income countries, starting in 1994, the year in which the 10th revision of the International Classification of Diseases (ICD-10) coding was first adopted in one of the "worst performers," and ending with the most recent data available. Furthermore, we analyze UK subnational divisions (i.e., Scotland, England & Wales, and Northern Ireland) separately due to substantial differences in drug- and alcohol-related mortality.

Table 1 presents the ICD-10 codes we employ to identify alcohol- and drug-related deaths. According to the structure of ICD-10 codes, SA mortality has three etiological mechanisms conducing in death: mental or behavioral disorders, acute intoxication, and the progressive development of chronic diseases. In the case of drug-related mortality, there are no chronic diseases that can be fully attributed to its abuse in the current literature. For this reason, mortality from drug abuse only includes causes related to behavioral disorders and acute intoxications. It is possible to identify certain chronic diseases that are, by definition, caused by alcohol abuse, also denoted as fully alcohol-attributable chronic diseases. Because identifying fully alcohol-attributable chronic diseases requires at least 3-digit ICD codes, we could not include countries with less granularity in cause classification, as was the case of Finland, despite showing very high SA death rates. We obtain population exposures by age and sex from the Human Mortality Database (HMD) (**HMDref?**) to derive age-, sex-, and cause-specific death rates.

Selection of countries under analysis based on SA mortality levels

To compare SA mortality across the countries under analysis, we compute age-standardized death rates using the 2010 US population as the reference. We conduct separate analyses by sex because of previously identified considerable differences in SA mortality in timing and intensity for men and women (Gelman and Auerbach 2016). Based on the age-standardized cause-specific mortality rates by sex, we select for our analysis a set of "worst performers," which includes the five countries with the highest age-standardized mortality rates from either alcohol or drug abuse between 2012 and 2016, and those with higher SA mortality levels after 2016 (for example, England & Wales surpassing Norway in Figure 1, Panel B) (see Table 2).

Smoothing of mortality rates over time and age

We smooth mortality rates from SA over time and age to avoid the noise of random variations and smoothly redistribute the grouped observations into single-year age groups. For this smoothing and age ungrouping simultaneous step, we apply a two-dimensional penalized composite link model (PCLM-2D) (Rizzi, Gampe, and Eilers 2015), using the 'ungroup' R package (Pascariu et al. 2021).

Contribution of Age-Period-Cohort temporal components to mortality changes

To determine the statistical contribution of each temporal component to explain the observed changes in mortality rates, we measure their respective contribution in reducing model deviance. Using the deviance statistic, a measure of unexplained variance, we compare the outcomes of intermediate models adding consecutively each temporal component. These percentage reductions show the contribution of model

additions and enable comparison between countries by sex. Estimates from this analysis would not only inform the relative importance of variations in each temporal dimension but also evaluate the relevance of analyzing SA mortality trends from an APC perspective.

Detrended Age-Period-Cohort (dAPC) Analysis

We fit a detrended Age-Period-Cohort (dAPC) model (Holford 1983) in Poisson specification using B-splines, with cohort slopes constrained to zero. The fitted model provides a trend of secular change in mortality, denoted in APC literature as the drift, and the deviations from linear age, period, and cohort trends, also known as nonlinear APC effects. Whereas the identification problem makes it impossible to decompose the drift into age, period, and cohort contributions (i.e., linear trends), nonlinear trends are fully identifiable (Holford 1983; Clayton and Schifflers 1987; Carstensen 2007) and are expressed in terms of relative risks (RR)(see Appendix 2). RR for a given period or birth cohort is the likelihood of dying of drug or alcohol abuse compared to the overall average period or cohort. We identify *advantaged* and *disadvantaged* cohorts and period crises for this study based on nonlinear period and cohort effects estimates. Disadvantaged cohorts are those in which the RR reaches a local maximum greater than the average, whereas advantaged cohorts have a RR reaching a local minimum lower than the average. In other words, disadvantaged and advantaged cohorts have a higher and lower risk of death than their neighboring cohorts once we account for the secular changes in mortality. Regarding periods, we identify period crises when their nonlinear effects are combined with the drift, and peak above the overall period average. We do this variation to account for any ongoing period crisis that might have been normalized by detrending. For example, Figure A2 depicts how deviations from trends are utilized in the study. While plotting the RR as a function of birth cohorts, the abscissa values corresponding to local maxima are identified as **disadvantaged cohorts**. In this example, an individual born in 1956 is 39 percent (RR=1.39) **more** likely to die of SA mortality than the overall average. Similarly, an individual born in 1940 is 28 percent (RR=0.725) **less** likely to die of SA mortality compared to the overall average. Hence, the cohort of 1940 would be known as an **advantaged** cohort having a lower risk advantage over its neighboring cohorts.

Trends in risk change over cohorts

To establish the link between drug and alcohol consumption over time and among cohorts, we analyze the temporal dynamics of 'polysubstance use' over time and across cohorts. We define two types of polysubstance use dynamics: 'concomitance' and 'substitution' of SA. The concomitance of substance use indicates that trends in mortality risk change over cohorts from both substances have the same direction, i.e., the risk is increasing or decreasing for both drug and alcohol-related mortality. In contrast, the substitution of SA occurs when the change in mortality risk for both substances moves in opposite directions. To identify concomitance and substitution dynamics, first, we perform a visual analysis of the cohort RR trends obtained from the dAPC model (a detailed example can be found in Appendix 3). Second, we measure the statistical association between risk mortality change over cohorts from each substance using Kendall's tau coefficient method(Kendall 1938). The tau summarise the overall polysubstance use dynamics over all the cohorts for each country and sex.

RESULTS

Trends in SA mortality across high-income countries

In Figure 1, we present *age-standardized death rates* (ASDRs) related to drug (Panel A) and alcohol (Panel B) -related mortality by sex. The highlighted countries exhibited the five highest mortality rates during 2012-2016. For drug-related deaths, the US and Scotland stand out because of extremely high drug-related mortality rates that have dramatically increased since 2006, with ASDRs well over double that of any other high-income country under study. Several Nordic and anglophone countries, including Canada, Sweden, Norway, and England & Wales, also demonstrate an increasing trend in drug mortality rates. Although the

rate of drug-related mortality in women is lower than that in men, rates are increasing in both genders across most high-income countries.

The countries in non-anglophone Europe exhibit high levels of ASDRs caused by alcohol, with Hungary having the highest rates for both males and females, well above the rest of the countries. In general, alcohol-related death rates are considerably higher than drug-related, except for the US and Scotland, the only countries with comparable higher levels of ASDRs for drug abuse. For males, there is a clear declining trend in ASDRs in many countries, except for Poland and the Czech Republic. Conversely, female mortality rates due to alcohol misuse are increasing in several high-income countries.

Relevance of Cohort Analysis

Figure 2 shows the contribution of the drift and non-linear period and cohort effects to deviance reduction when modeling mortality trends from drug (Panel A) and alcohol (Panel B) abuse by sex and country. In the case of drug-related mortality, the contributions of the nonlinear cohort effects and drift to the model fit are considerable for males (mean contribution of 55 and 37 percent, respectively) and females (41 and 48 percent). The contribution of non-linear period effects is considerably lower for males and females (mean contribution of 8 and 11 percent, respectively). The largest contribution of the nonlinear birth cohort effects was among German males (98 percent). In general, nonlinear cohort effects contributed more than 25 percent to the deviance reduction in all cases, except for both sexes in the US and Canada, and females in Denmark, where the drift contribution was the highest, explaining more than 75 percent of the deviance reduction.

The analysis of temporal contributions to changes in alcohol-related mortality shows that similar to drug-related trends, the contributions of non-linear cohort effects and drift are substantial for both males and females, with non-linear cohort effects being the largest contributor in many cases. The contribution of non-linear period effects is relatively small for both genders. Swedish females have the largest contribution of non-linear birth cohort effects (89 percent), while these effects account for more than 25 percent of the deviance reduction in most countries for both males (9 out of 11) and females (7 out of 11). However, unlike drug-related deaths, the drift considerably impacts the deviance reduction for the Czech Republic and Norway, with lower contributions in Canada and Denmark for both sexes.

In general, non-linear birth cohort effects have a larger impact than non-linear period effects. To further validate our results regarding the relevance of the cohort component, we perform a robustness check on our estimates by applying an alternate method in the appendix Appendix 4. The findings from this sensitivity analysis are consistent with the results presented here.

Non-Linear APC trends

Cohort risk inequalities

Figure 3, we identify disadvantaged cohorts by substance type and gender, indicating their RR. As an illustration, the bubble related to drug-related mortality in the US reveals that males born in 1956 have a 39% higher risk (RR=1.39) of dying from drug abuse than the average of all US cohorts born between 1930 and 2002. We observe a concentration of disadvantaged cohorts between 1950 and 1965 from both drugs and alcohol for most countries. While the alcohol-disadvantaged cohorts are mostly concentrated around the 1950s, drug-disadvantaged cohorts are more spread out. We identify several older, pre-world war II, drug-disadvantaged cohorts (Canada, Sweden, Scotland, and England & Wales) and relatively younger cohorts from the 1970s and 1980s that are substantially disadvantaged. In most countries, the figure depicts female cohorts closely following or overlapping male cohorts regarding drugs (8 out of 11) and alcohol-related mortality (9 out of 11) among disadvantaged groups.

Period Crisis

In Figure 4, we present the RR values for period crises by substance type and sex, showing the percentage difference in the likelihood of dying from drug or alcohol abuse compared to the overall average. For example, the empty bubble for the US for drug-related mortality in 2019 indicates that US males are 18 percent more likely to die from drug abuse compared to the overall average. The results suggest that US males are currently experiencing a period crisis in drug-related mortality. Unlike nonlinear cohort effects, period fluctuations show less synchronicity in SA mortality across countries, suggesting that period crises are not simultaneous across the observed countries. However, most countries (8 out of 11) face ongoing crises of SA mortality, with disadvantaged periods observed beyond 2010. The period crises for drugs and alcohol do not happen simultaneously for all countries, but it is possible (US, Czech Republic, Canada, and England & Wales).

'Polysubstance' use dynamics between cohorts

Figure 5 shows patterns of concurrent changes in mortality risk due to drugs and alcohol obtained from the dAPC model. Although concomitance is more pronounced in most countries, there are still considerable differences. For the US and Canada, a considerable portion of cohorts shows a concomitance of SA (ranging from 83-91 percent of the cohorts). Other countries, including England & Wales, the Czech Republic, Hungary, Denmark, Norway, and Sweden, also show SA concomitance to a lesser degree (ranging from 53-79 percent of the cohorts). Scotland is the only country where substance substitution is predominant for both sexes, with more than 60 percent of its cohorts showing alternation in the abuse of drugs and alcohol. Germany and Poland show sex differences, with German males and Polish females showing substance concomitance contrary to their sexual counterparts, where substitution seems more prevalent. The study also observes variations in substitution. For example, younger cohorts (born in 1980 and after) in the US, Canada, and England & Wales mostly realize concomitance. Still, there is a substitution in mortality risk trends in Norway, Poland, and Scotland.

Table 3 summarizes the correlation estimates between nonlinear cohort effects slopes from the dAPC model by substance type. In general, there is a positive association between changes in the risk of drug-related deaths and those of alcohol-related deaths over cohorts, meaning that an increase in the risk of one is associated with an increase in the other, implying a concomitance of increased risks on members of the same birth cohorts. However, Scottish cohorts are an exception, suggesting a substance substitution with a negative association between the RR of dying from drugs and alcohol across birth cohorts, although this correlation is not statistically significant. There is a positive association in all other cases, with significant values of Kendall's τ ranging from 0.24 (Polish females) to 0.82 (Canadian males). On average, there is a pattern of simultaneous disadvantage in cohorts toward mortality risks from drugs and alcohol abuse.

DISCUSSION

Our study reveals that Scotland and the US have experienced the most severe drug crises to date in magnitude and intensity over the past two decades, without signs of improvements in the short term. In the rest of the countries, drug-related mortality is also increasing but with levels and rates of change well below those in Scotland and the US. Alcohol-related mortality improvements have stagnated for most high-income countries, with Poland and the Czech Republic even showing upward trends. Most high-income countries under study are currently experiencing period crises (7 out of 11). While in the US, Canada, Czech Republic, and England & Wales, this crisis involves both substances, in Sweden and Scotland, it is limited to drugs, and in Poland to alcohol.

Visual inspection of birth cohort patterns reveals that birth cohorts at higher risk of SA mortality were born around 1950–1964 in most selected countries (8 out of 11). This pattern is more pronounced for alcohol compared to drugs, as we see a larger number of more recent birth cohorts (1965+) at higher risk for drug-related mortality. In general, polysubstance use dynamics among cohorts is of concomitance, i.e., the cohort

disadvantage converges for both substances. Scotland is the only country where substance substitution is predominant over cohorts for both sexes.

During the 27 years of observation, many selected high-income countries experienced period mortality crises due to substance abuse. The most widely discussed among them is the ongoing US drug crisis. While prescription opioids have been blamed for the significant rise in drug-related deaths in the USA (Jalal et al. 2018) and Canada (Lisa and Jessica 2018; Imtiaz and Rehm 2016), the underlying reasons for the crisis in other high-income countries, including the Czech Republic, Scotland, Sweden, and England & Wales, may differ due to differences in the pharmaceutical companies' influence on prescribing practices, in healthcare systems and utilization, and in policy responses to the initial breakthrough in drug-related deaths (Ho 2019; J. B. Dowd et al. 2022). However, we cannot distinguish specific drug types involved in these deaths with the available data. Further analyses in this regard are suggested to understand better the differences across countries and the dynamics of polysubstance use.

Our results show that alcohol-related mortality peaked before 2005 in several countries under analysis, including Hungary, Sweden, Scotland, Norway, Germany, and Denmark. The declining trend of alcohol-related mortality in males is suggested to be due to a decline in pure alcohol consumption. Our findings on alcohol mortality in females partially support previous evidence that more and more women are drinking more (Moinuddin et al. 2016) in half of the countries where we observe an increasing trend in alcohol mortality. Although pure alcohol consumption decreased in most EU countries in recent years, including in Hungary (Kurshed et al. 2022), our study highlights that alcohol-related mortality remains an issue for both sexes. There are three possible explanations for this. First, in some Eastern European countries, pure alcohol consumption is more than twice the global average (Organization 2019). Second, it has been previously found that alcohol abuse does not always predict mortality perfectly (Jasilionis, Leon, and Pechholdová 2020). Lastly, the information about consumption levels is not always reliable because of unreported homemade alcohol consumption in countries like Poland and Hungary (Popova et al. 2007). Moreover, the conflicting trajectories for males and females shown in our study support the results of narrowing the gender gap in alcohol-related mortality trends in many high-income countries(White 2020; Slade et al. 2016; Keyes, Li, and Hasin 2011).

Despite important period SA mortality crises, we found that nonlinear cohort effects explain more variations in SA mortality than nonlinear period effects in all observed countries. In other words, cohort differences explain more SA mortality variations than period shocks. This finding corroborates the adequacy of employing APC approaches when analyzing trends in SA mortality. However, we must be careful when interpreting these results. When a crisis is unfolding linearly and has not reached a peak, or it is decreasing without having reached the minimum, these linear changes in mortality are captured by the drift. As described earlier in the methods section, the linear trend captured by the drift cannot be decomposed into its period and cohort components due to the identification problem. Only when SA mortality changes nonlinearly again, will we be able to identify if the observed crises result from period or cohort variations. This seems to be the reason for the larger drift contribution for drugs in Canada and the US, and for alcohol in Hungary.

We found a clear pattern of disadvantaged cohorts for SA mortality among cohorts born between 1950-1964, consistent with previous research (Acosta et al. 2020; Miech, Koester, and Dorsey-Holliman 2011; Trias-Llimós, Bijlsma, and Janssen 2017). However, the cohort patterns across countries are more distinct for alcohol-related than drug-related mortality. One of the possible explanations is the latency period for a SA death and the stability of cohort effects over the life course. Young members of a birth cohort can change their SA behavior over their life course, and the cohort effects can diminish or exacerbate over time. Whereas drug-related mortality is primarily driven by acute drug poisonings, which occur suddenly, alcohol-related mortality is mainly driven by alcoholic liver disease, which takes years to develop and kill. Therefore, cohort disadvantages in alcohol-related diseases result from well-sustained alcohol abuse but may not reflect the current abuse behaviors. Whereas cohort patterns of drug-related mortality are less likely

to diminish and reflect the current drug abuse scenario. However, these explanations are speculative and require further analyses to test the stability of cohort effects over the life course.

Studies have proposed several mechanisms that drive cohort behavior with empirical examples (Vaupel, Manton, and Stallard 1979; Ryder 1985; Easterlin 1987; Mannheim 1952; Barclay and Kolk 2015; Kandel 1980). We can discuss the mechanisms driven by cohort size based on our results. It has been hypothesized that the cohort disadvantage in mortality among US boomers results from the mismatch between early life expectations and later life experiences in boomers stemming from their larger cohort size (Easterlin 1987). On the contrary, our findings do not support this hypothesis because steep rises in births were not simultaneous in all the selected countries (Van Bavel and Reher 2013). However, these mechanisms share underlying structural causes that eventually are responsible for dissimilar cohort behavior. And if social policies counterbalance these structural causes, subsequent cohort behavior will respond poorly to this mechanism. For example, many researchers have identified education attainment as crucial in differential mortality trends (Ho 2017). The US education system was caught off-guard by the boomers due to a lack of school infrastructure to mitigate this steep rise in population. Nonetheless, once the structure is in place to account for such a steep increase, an upsurge in cohort size will have a negligible effect on mortality risk via education. This approach can be expanded to other contextual factors, including welfare state and family characteristics. Therefore, we hypothesize that it is the change in cohort size concerning current infrastructure rather than the size of the cohort itself. Our study also highlights SA mortality in US millennials (cohorts 1981-1996). It encourages further research into the SA mortality trends for changes in cohort size and its impact on generational experiences.

We found that most UK cohorts born in the 1970s are disadvantaged towards SA mortality. One possible explanation for this behavior in Scotland and England & Wales is the de-industrialization and civil unrest in the UK in the late 1970s. It is often the case that distinct cohort effects originate from distinguishable period effects (historical events). The UK was among the first to suffer from the sickness of the post-industrial age (Keeble and Walker 1994; Walkerdine et al. 2012). Simultaneously, there was widespread civil unrest due to the oil and energy crises (Schumacher 1985; Warlouzet 2017). Some researchers have hypothesized that the UK underwent enormous societal changes during this period (Jenkins 1995; Purcell 2005; Harkness and Evans 2011). Combined with the widening socio-economic gradient, these societal changes resulted in a unique generational experience for newborns. Children born in the late 1970s UK shared a generational rift in an otherwise prosperous and wealthy society. However, this may explain the cohort behavior simply, and further research is required.

Temporal trends in SA mortality have been studied, focusing on an individual drug risk in isolation or generalizing substances together without distinction (Crummy et al. 2020). Limiting studies to this approach often overlooks interactions between substances and can impede understanding the underlying behavioral patterns. By studying temporal trends (nonlinear cohort effects in our case) in drugs and alcohol, our study enables us to observe changes in mortality risk due to the interaction between SA patterns. The study shows that the concomitance of elevated mortality risk due to both substances in cohorts is a recurring theme for several countries. However, the widespread substitution in the youngest and oldest cohorts in several countries, including Germany, Hungary, Scotland, and Sweden, shows these cohorts' changing dynamics of SA behavior.

We identify several limitations in our analysis. First, our study was limited by the lack of consistent data on SA mortality among all high-income countries. Ideally, deaths classified as resulting from acute intoxication, mental and behavioral disorders, and chronic diseases should be analyzed separately. However, we found mortality trends suggesting shifts in cause attribution across these categories. One example is Scotland, where drug-related deaths were mainly classified as drug disorders during the first half of the observation period and then shifted to drug poisonings in 2010 (see Appendix 5). We overcame this classification issue by grouping all SA mortality categories together within each substance.

The major point of contention in any APC analysis is the solution to the "APC identification problem." It has been established in the literature that it is impossible to identify linear trends in APC without making strong assumptions (@ Bell and Jones 2013). Many studies sidestep this problem by analyzing nonlinear trends which are identifiable (Holford 1983; Clayton and Schifflers 1987; Carstensen 2007). This approach enables us to account for the contribution of drift and the nonlinear APC effects in model fit. Although nonlinear trends can be deceiving without the knowledge of the linear trends around which they vary (@ Bell and Jones 2013), we show the share of drift was relatively small for many countries compared to the share of nonlinear period and cohort effects. This suggests that the trends in nonlinear period and cohort effects estimates shown in our model are close to the overall period and cohort effects, as the contribution of linear trends was relatively low in most cases.

We were also limited in the observation period (27 years, between 1994 and 2020) due to changes in ICD classification. Ideally, we would like to examine SA mortality over a more extended period to observe temporal changes and identify temporal factors modulating mortality crises. However, the harmonization of SA mortality between the transitions through the ICD versions is not seamless, because the only cause related to substance abuse that is fully harmonizable from ICD-9 to ICD-10 is drug-related accidental poisoning deaths, which is only a subset of SA mortality.

Notably, the study has two future implications pertaining to both academic as well as public health policy audiences. First, the study emphasizes the importance of including cohort parameters while forecasting SA mortality. Although, several studies have developed mortality forecasting models based on an APC structure (Cairns et al. 2011; Jarner and Kryger 2011; K. Dowd et al. 2011), most applications summarize mortality by age and period while ignoring cohort effects (Janssen, Wissen, and Kunst 2013). Second, our findings provide vital information for policymakers. While designing intervention programs for a foreseeable rise in the burden of SA mortality, understanding better the substances toward which each cohort is susceptible to abuse is crucial. For instance, if a cohort shows a substitution of mortality risk, resources can be allocated efficiently for the specific SA instead of a more general approach.

Based on our findings, we consider that further research should be conducted in the following areas. First, future studies should test for the stability of cohort inequalities over the life course to verify whether mortality disadvantages are sustained over the life course. Second, future studies should identify causal mechanisms that originate from sudden changes in cohort size rather than the size of the cohort itself. Third, future studies should address the Scottish discrepancy with the rest of the UK in SA mortality and its remarkable resemblance to the US patterns. Finally, future studies should assess the impact of substance substitution and concomitance on mortality, either in terms of within cohort loss of years of life or life expectancy. This assessment will bring valuable insights for analyzing cohort inequalities that originate from shifting the abuse from one substance to another or keeping them both together.

CONCLUSIONS

We analyzed SA mortality trends in high-income countries from an Age-Period-Cohort perspective. We found that cohort membership is a decisive factor in modulating mortality risks related to drug and alcohol abuse in the observed countries. We show that mortality disadvantages related to the abuse of drugs and alcohol converge on the same birth cohorts in most cases. We identify that Scotland is exceptional in this regard, as birth cohorts seem to alternate abuse susceptibility between both substances over time. Our findings are relevant in determining which birth cohorts are at elevated risk due to SA mortality, thus foreseeing potential mortality perturbations in the future. This information is also precious for policymakers in designing more targeted rather than generic interventions. Overall, this study lays the groundwork for future research on SA abuse mortality to explain better its determinants as well as cohort inequalities.

Supplementary materials, including lexis surfaces, can be found here.

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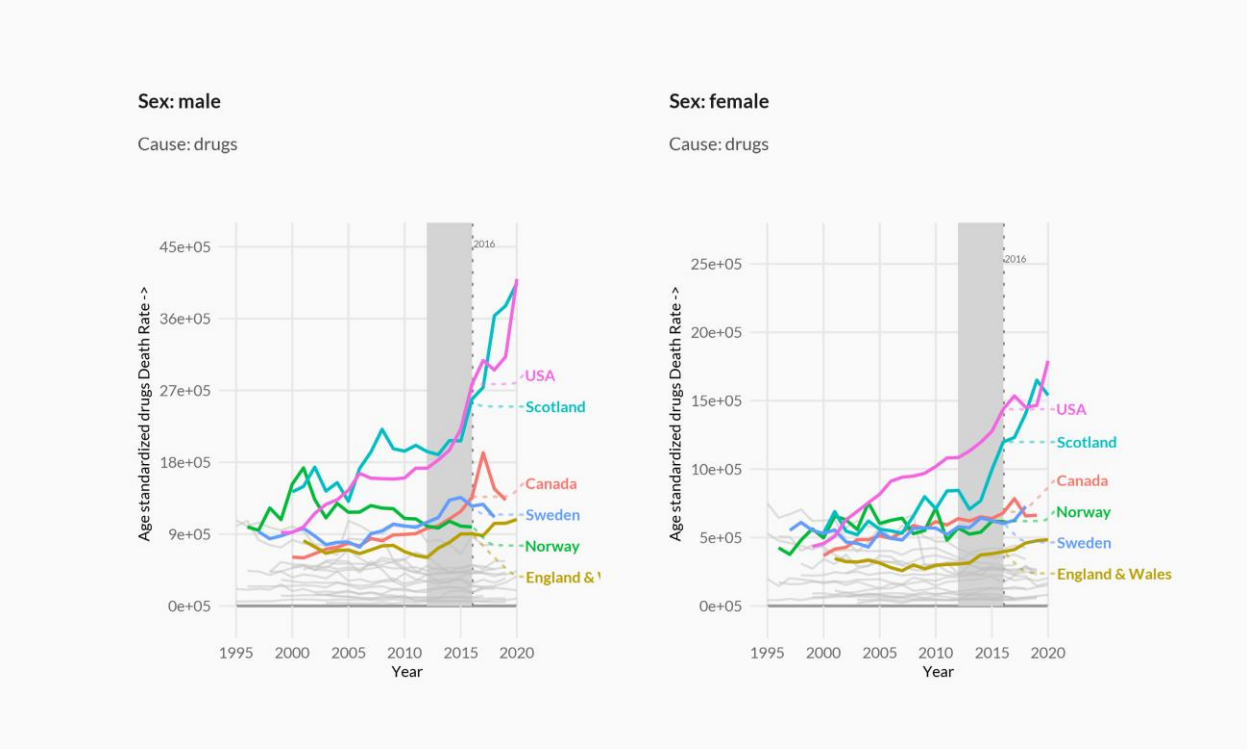
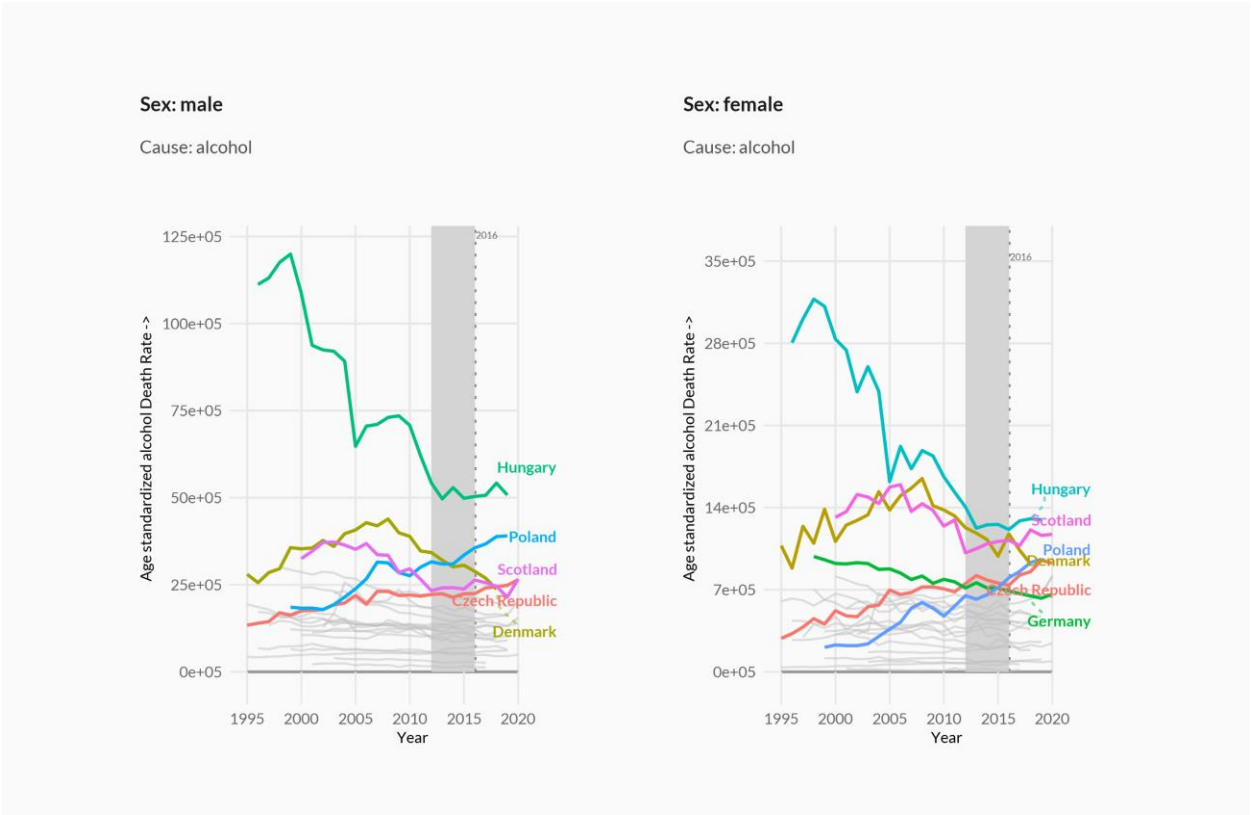
FIGURE LIST

Figure 1: Age-standardized death rates

Panel A



Panel B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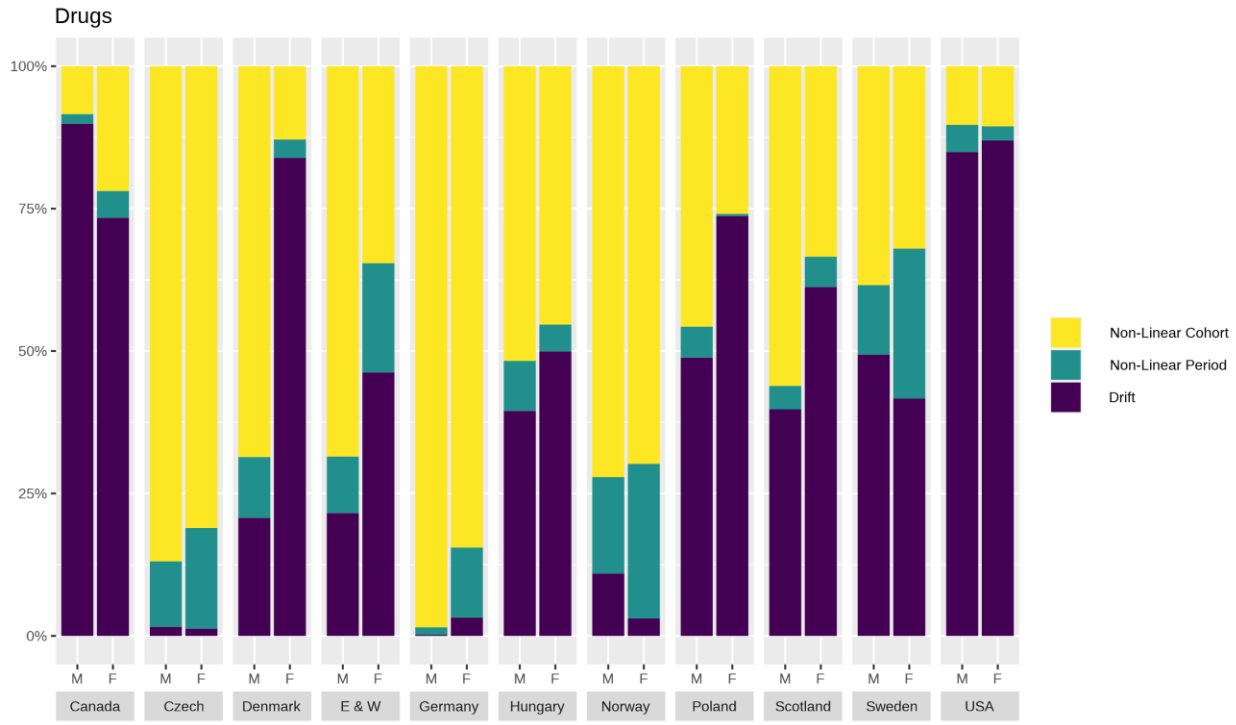
Cause: alcohol
125e+05
100e+05
75e+05
50e+05
25e+05
0e+05
Age standardized alcohol Death Rate -->
2016
Hungary
Poland
Scotland
Czech Republic
Denmark
1995
2000
2005
2010
2015
2020
Year
Sex: female
Cause: alcohol
35e+05
28e+05
21e+05
14e+05
7e+05
0e+05
Age standardized alcohol Death Rate -->
2016
Hungary
Scotland
Poland
Denmark
Czech Republic
Germany
1995
2000
2005
2010
2015
2020
Year

Figure 2: Deviance reduction

Panel A



Panel B

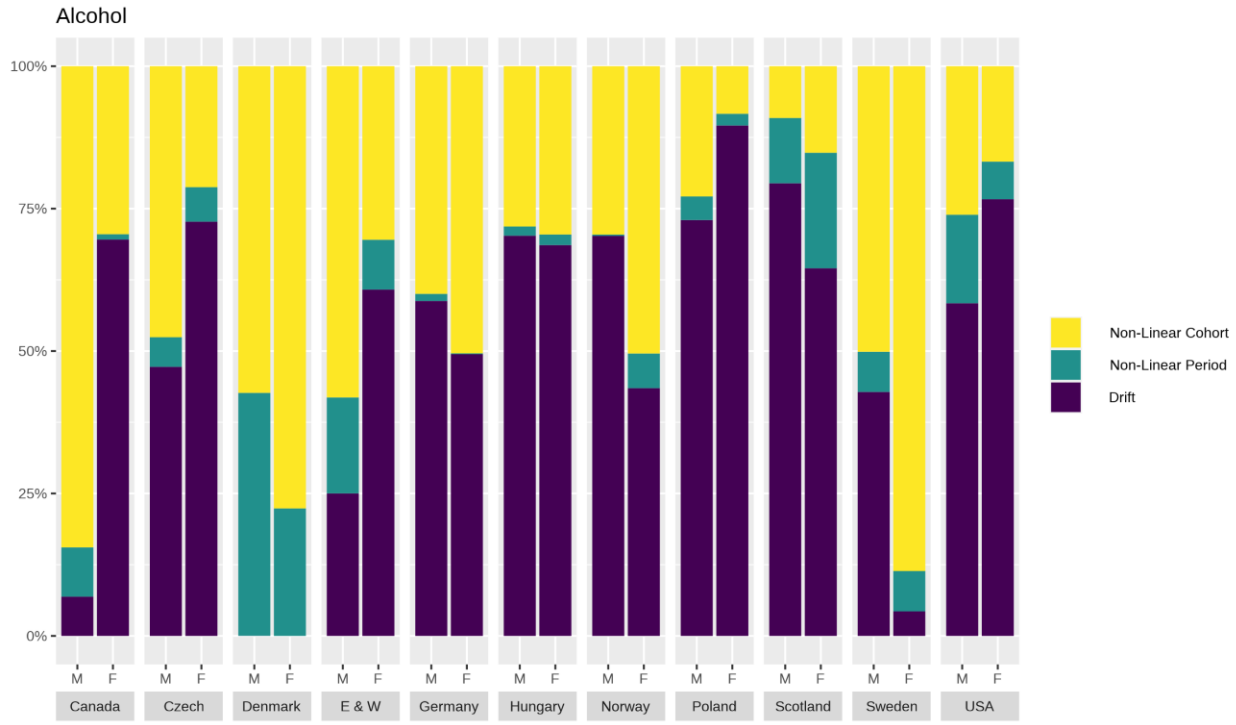


Figure 3: Disadvantaged cohorts by sex

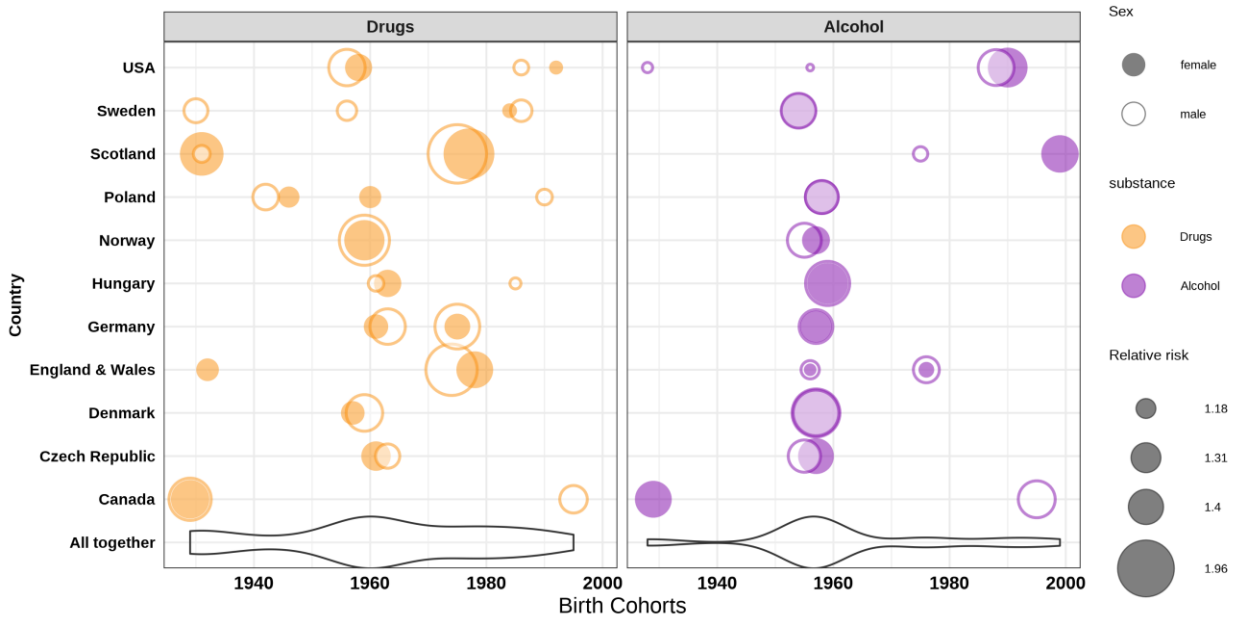


Figure 4: Period crises by sex

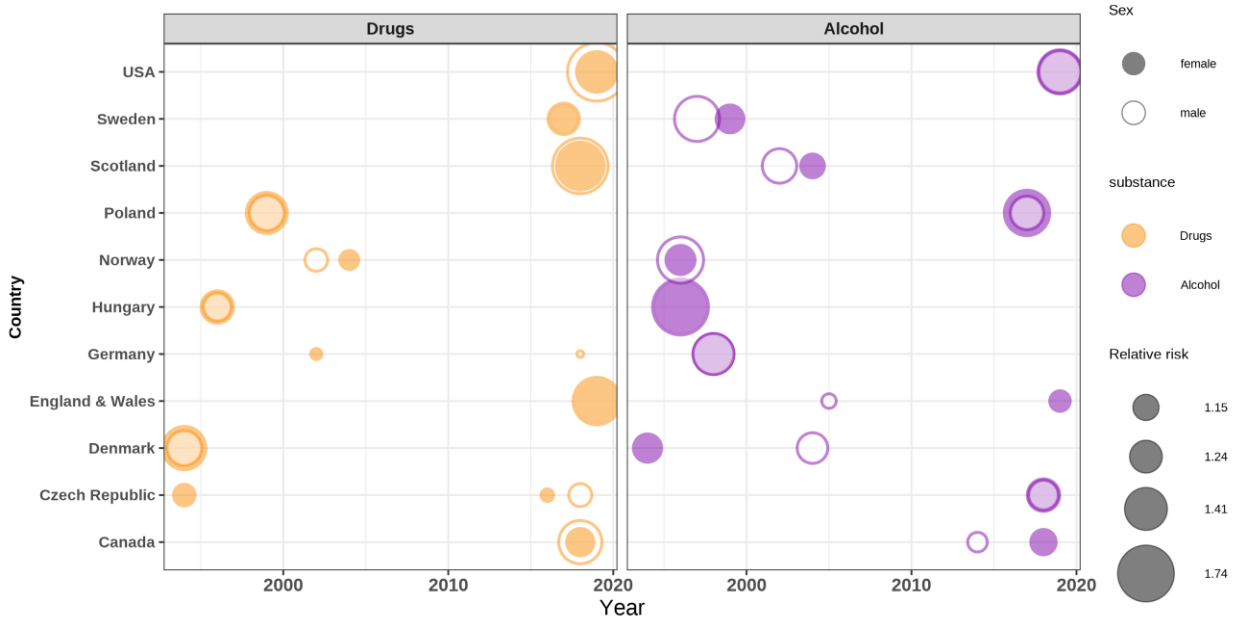


Figure 5: Mortality risk changes in cohorts

APPENDIX

Appendix 1: Table list

Table 1: ICD-10 codes used in the study

Cause of Death	ICD-10 codes
Drug-related:	
acute intoxication	X40-44, X60-64, Y10-14
mental and behavioral disorder	F11-16, F18-19
Alcohol-related:	
acute intoxication	X45, X65, Y15, Y90-91
mental and behavioral disorder	F10
100% attributable chronic diseases	K70,E244,G312,G621, G721,I426,K292, K852,K860,Q860,P043

Table 2: Average ASDRs for the worst performers over 2012-2016 (per 100000)

Country	Drugs(M)	Drugs(F)	Alcohol(M)	Alcohol(F)
Canada	11.2	6.46	10.9	4.00
England & Wales	7.87	3.54	12.7	6.40
Norway	10.1	5.74	9.19	3.25
Scotland	21.1	9.02	24.3	10.8
Sweden	12.2	6.04	9.81	3.57
USA	21.0	12.3	14.1	5.15
Denmark	7.85	4.11	31.2	11.4
Hungary	3.23	2.91	51.4	12.7
Poland	1.03	0.54	32.5	6.89
Germany	4.22	2.24	21.6	7.18
Czech Republic	2.09	1.91	22.2	7.69

Table 3: Kendell's τ estimates for consumption effects

Country	τ (Male)	p-Val	τ (Female)	p-Val
Canada	0.819	0 ***	0.771	0 ***
England & Wales	0.422	0 ***	0.416	0 ***
Norway	0.298	0.01 **	0.337	0.004 **
Scotland	-0.178	0.131	-0.194	0.1
Sweden	0.147	0.206	0.216	0.061
USA	0.691	0 ***	0.517	0 ***
Czech Republic	0.32	0.004 **	0.547	0 ***
Denmark	0.166	0.146	0.343	0.002 **
Hungary	0.141	0.22	0.292	0.01 **
Poland	0.095	0.424	0.241	0.039 *
Germany	0.219	0.058	0.06	0.612

Appendix 2: Detrended APC (dAPC) model

The detrended A-P-C model is given by:

$$lny^{apc} = \alpha_a + \pi_p + \gamma_c + \alpha_o rescale(a) + \gamma_o rescale(c) + \beta_o + \sum_j \beta_j x_j + \epsilon_i$$

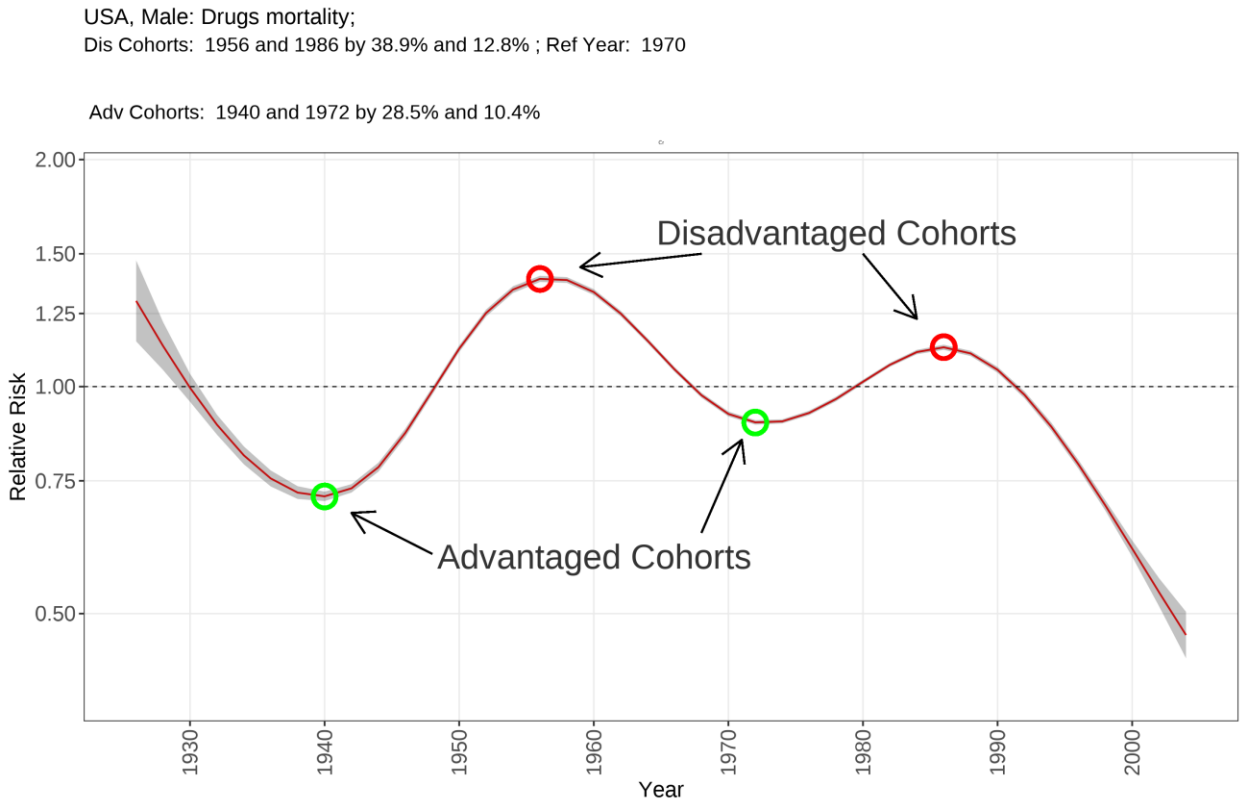
$$constraints: \begin{cases} p = c + a \\ \sum_a \alpha_a = \sum_p \pi_p = \sum_c \gamma_c = 0 \\ Slope_a(\alpha_a) = Slope_p(\pi_p) = Slope_c(\gamma_c) = 0 \\ min(c) < c < max(c) \end{cases}$$

Where, α_a:Age effect Vector; π_p:Period Vector; γ_c:Cohort Vector;

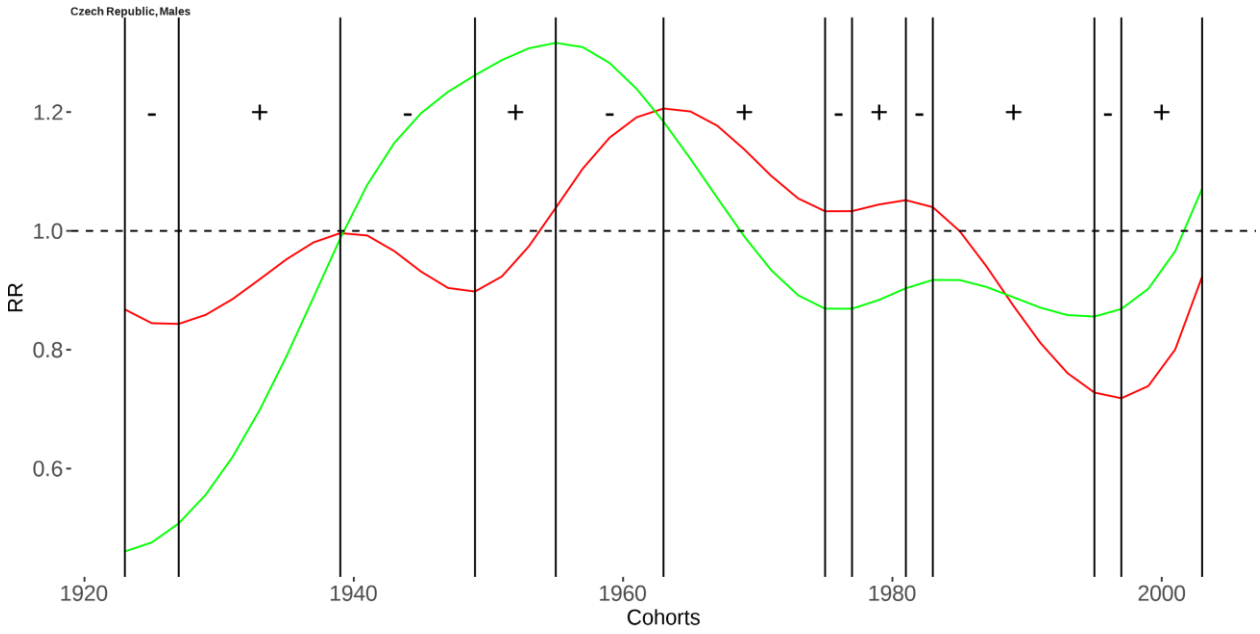
$\alpha_o rescale(a)$, $\gamma_o rescale(c)$: transformations to absorb linear trends;

β_o, β_j & ϵ_i: intercept, reg. coefficients & residuals respectively.

Figure A2



Appendix 3: Describing simultaneous or substitution effect



The above figure illustrates the non-linear cohort trends in RR due to substance abuse mortality for Czech males. To determine the change in mortality risk of alcohol and drugs concurrently, we overlay the non-linear cohort trends for drugs and alcohol on top of each other. At each inflection point, we divide the plots and analyze the slope in each in-between segment. We assign a positive sign when both slopes move in the same direction and a negative sign when moving in opposite directions. In accordance with our definition of polysubstance use dynamics, a positive sign indicates concomitance, while a negative sign suggests substitution. For instance, the cohorts born between 1939 and 1949 exhibit opposite slopes, indicating a substitution, where the mortality risk of one substance increases contrary to the other, i.e., substitution. While cohorts between 1949 to 1955 have concurrently increasing slopes, signifying concomitance of increasing mortality risk for both substances.

Appendix 4: 'Cohortality' coefficient

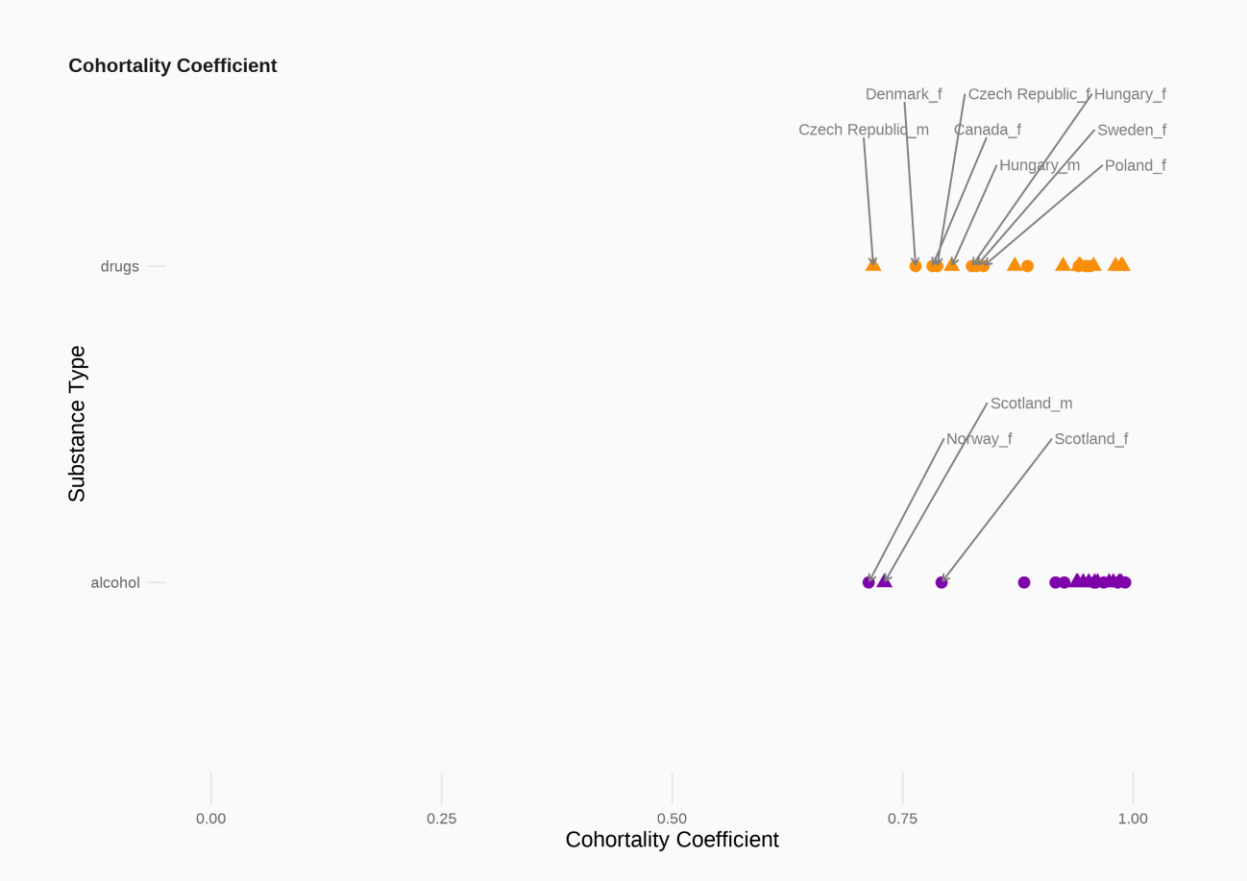
For the estimation and comparison of cohort mortality levels, we use the 'Cohortality' Coefficient (CC) suggested by Chauvel, Leist, and Ponomarenko (2016) as a measure to assess the degree to which the non-linear cohort effects absorb age-period interaction. In a Poisson specification, CC can be expressed as

$$CC = 1 - \frac{D(APC)}{D(AP)}$$

$$D(model) = 2\big(ln(L_{AxP}) - ln(L_{model})\big)$$

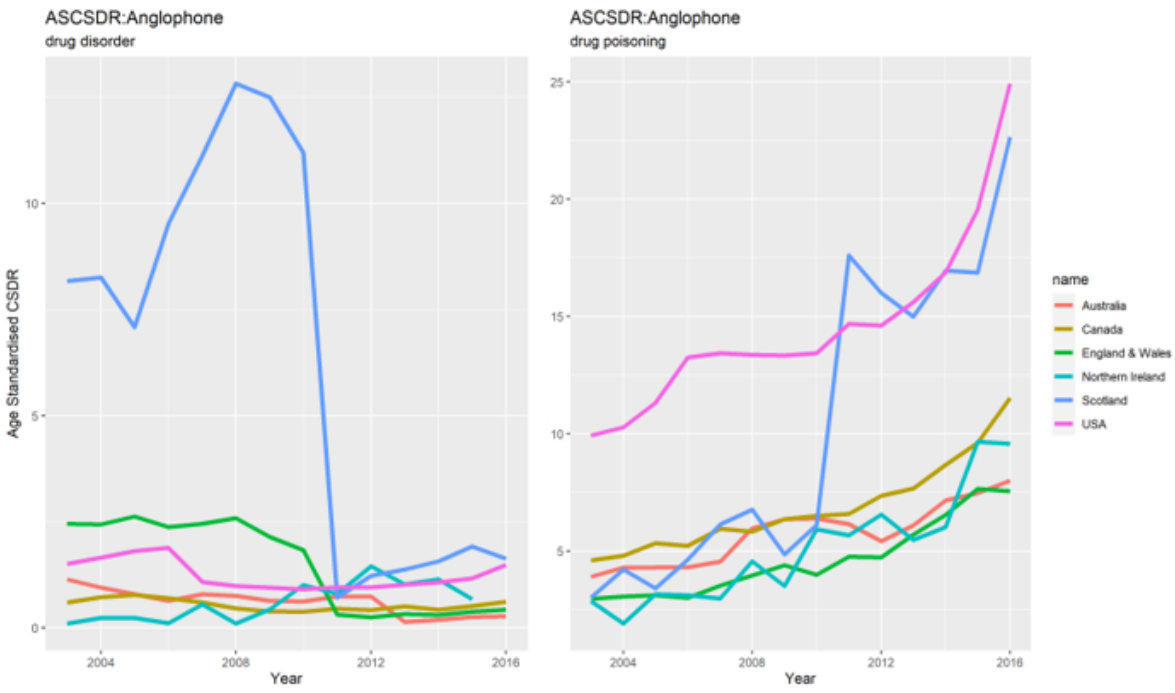
Where, D is the residual deviance statistics and L denotes the likelihood function for the corresponding model(Gelman and Hill 2006).

In other words, CC summarizes the extent to which the age-period interaction is due to cohort effects. When CC is close to one, the cohort term perfectly explains the age-period interaction. If CC is closer to zero, birth cohort is irrelevant in explaining the phenomenon.



The above figure shows the value of CC for each country by substance type. The results indicate that the cohort term is highly effective in summarizing the age-period interaction, with a mean value greater than 0.9 or 90 percent. Regardless of the substance type, the CC value varies from 0.71 (Norwegian females) to 0.99 (US females), implying that the cohort component can account for at least 70 percent of the age-period interaction.

Appendix 5: Suspected reporting error



The figure shows age-standardized cause-specific death rates for anglophone countries. It shows that in 2010, there was a steep decline in drug disorder (mental and behavioral) mortality in Scotland. Meanwhile, in the same year, there was also an increase of similar magnitude in the drug poisoning rate. This behavior suggests a shift in classification from drug disorder to drug poisoning. We cannot wholly rely on a specific cause of death like drug poisoning or drug disorder; instead, we combine both and analyze all drug-related mortality.