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

INTRODUCTION

Following the widely publicized paper by Case and Deaton (2015) coining "deaths of despair," a growing body of research investigates drug- and alcohol-related (substance abuse) mortality. The US opioid crisis should serve as a cautionary tale for other high-income countries to dodge such an epidemic. Substance abuse is having a detrimental impact on overall life expectancy in many high-income countries, as they are the leading risk factor for mortality among people at younger ages (Shield and Rehm 2015). As a result of this, substance abuse mortality is discussed extensively in this context (Ho 2019; Westman et al. 2015). Eastern Europe is considered the most jeopardized when it comes to alcohol-related deaths (Jasilionis, Leon, and Pechholdová 2020), meanwhile, the US is known to be in peril when it comes to drug-related deaths (Ho 2019). However, it is on good authority that substance abuse mortality is becoming a global crisis. In most high-income countries, alcohol-related mortality is considerable, and drug-related mortality has shown an unprecedented and rapid increase (Rehm et al. 2019). Our study aims to situate substance abuse mortality internationally by studying deaths from drugs and alcohol together for three reasons: (1) the alarming rates of substance abuse mortality are not a localized phenomenon but rather a global issue (2) there could be a possible association between the consumption behavior of drugs and alcohol. Our study will update previous comparisons of mortality trends due to substance abuse, meanwhile ushering in macro-level similarities and differences amongst high-income countries.

Substance abuse mortality has, conventionally, been studied as a period effect, .i.e, it affects all age groups and cohorts uniformly. Though many countries are going through the worst period crises for substance abuse mortality in their history (Case and Deaton 2015), nevertheless there is evidence that specific cohorts experience a sustained higher risk of substance abuse deaths than others during their life course (Acosta et al. 2020). Easterlin's hypothesis argues that the size of one's cohort profoundly impacts their overall life chances due to the subsequent differentials in relative income (Easterlin 1968). This hypothesis is considered one of the most viable explanations for the poor performance in mortality among baby boomers, also predicting the implications of cohort size on criminal behavior including substance abuse (Easterlin 1978). It is therefore important to study substance abuse mortality from a cohort perspective. However, it is impossible to isolate cohort effects on a population as they are logically confounded with age and period effects, otherwise known as the "APC identification problem" (Bell and Jones 2013). Hence, to explore temporal trends in substance abuse mortality, we reposition ourselves to quantify deviations from linear cohort trends rather than estimating the point effects, which we will refer to as "non-linear APC trends" from here on. We hope to uncover existing patterns in excess mortality due to substance abuse among birth cohorts that will open potential paths toward understanding substance abuse behavior in a demographic context. Although many studies have followed this method of studying cohort behavior, to our knowledge, this is the first study looking at the temporal patterns of drug and alcohol-related mortality together across several high-income countries.

DATA AND RESEARCH METHODS

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

- Data for death counts in the WHO mortality database are available, using 3-digit ICD codes for identifying the underlying cause of death between the years 1999 and 2016.
- The population of the country is 5 million or more.

Data from the World Health Organization Mortality Database (WHO) on death counts by cause, age, and sex are extracted for the countries starting with the year in which each country first adopted the 10th revision of International Classification of Diseases (ICD-10) coding and ending with the most recent year data are available. All-cause death counts and exposures by age and sex were obtained from the Human Mortality Database (HMD) to obtain age-, sex-, and cause-specific death rates. Table T1 presents the ICD-10 codes we employed to identify alcohol- and drug-related deaths. Substance abuse mortality has three broad facets: mental or behavioral disorders, acute intoxication, and 100% attributable chronic diseases. However, only alcohol-related deaths can be classified into 100% attributable diseases.

We use the 2010 US population as the reference to standardize our rates. Based on the age-standardized cause-specific mortality rates by sex, we sort out a list of the top five countries by substance type for further analysis (see Table T2). We construct lexis surfaces of mortality change to explore temporal trends due to substance abuse. Lexis surfaces we use here are visualizations designed to show how a given value changes over a period and cohort in each age group (Rau et al. 2017). However, the lexis surface of observed mortality rates can be noisy due to the low frequency of events. Hence, we use a two-dimensional penalized composite link model to smoothly redistribute the grouped observations to make them more readable (Rizzi, Gampe, and Eilers 2015). These plots show patterns of mortality change over period/cohort (see Figure A2(a)).

We fit a detrended Age-Period-Cohort (dAPC) model (Holford 1983) in Poisson specification using B-splines, with slopes constrained to zero on age, period, and cohort (APC) effects. The fitted model provides deviations from linear APC trends, also known as nonlinear effects, which can be expressed in terms of relative risk (RR) (see Appendix 3). We classify cohorts as "advantaged" or "disadvantaged" based on their RR values. RR for a given birth cohort is the likelihood of dying of drug or alcohol abuse compared to the expected overall cohort average. *Disadvantaged* cohorts are those in which the RR reaches a local maximum greater than one, whereas *advantaged* cohorts have RR reaching a local minimum less than one (see Figure A2(b)). In other words, disadvantaged and advantaged cohorts have a higher and lower risk of death than their neighboring cohorts once we account for the linear changes in mortality. Regarding periods, we identify period crises when their nonlinear effects peak above the overall period average.

PRELIMINARY RESULTS

Figure 1 shows drug-related *age-standardized death rates* (ASDRs) in selected high-income countries for both men and women. The highlighted countries showed high cause-specific mortality rates on average from 2012-2016. The results show that alarming drug-related mortality rates are not exclusive to the USA. Since 2006, Scotland has been posting consistently high rates of drug-related deaths, which can only be observed by separating it from the rest of the UK. Many Nordic and anglophone (i.e., Canada and Australia) countries also show rising drug mortality rates. Although the magnitude of drug-related mortality in women is comparatively lower than that in men, the pattern of increasing rate is consistent in both genders, i.e., it appears to be trending upwards for most high-income countries.

Figure 2 presents alcohol-related ASDRs in selected high-income countries by sex. Non-anglophone European countries show the highest ASDRs due to alcohol, with Hungary leading the charts for both men and women. When compared to drugs, the ASDRs are exceptionally high in the case of alcohol. The only cases in which average levels of ASDRs from drugs are higher than alcohol are in Scotland and the US, for both males and females. A clear downward trend in ASDRs can be observed in many countries for males, with Poland being an exception. In contrast, female mortality rates due to alcohol abuse are rising in several high-income countries.

Figure 3 shows the RR-values in terms of relative risk for disadvantaged cohorts by sex. For example, the bubble corresponding to the USA for drug-related mortality shows that US males born in 1956 are 45% (RR=1.45) more likely to die of drug abuse than the overall average of US cohorts born between 1930 and

2002. Irrespective of substance type, we observe an agglomeration of disadvantaged cohorts between 1945 and 1964, especially in alcohol-related deaths. We find highly disadvantaged drug abuse cohorts from the 1970s and the 1980s, which have been rarely discussed. The figure shows disadvantaged female cohorts closely trailing disadvantaged male cohorts for drugs and alcohol-related mortality in most countries, with a few exceptions in Germany, Austria, and Denmark.

Figure 4 shows the RR-values in terms of relative risk for period crises by sex. For example, the bubble corresponding to the USA for drug-related mortality depicts that the US males in 2005 and 2017 were 11 (RR=1.11) and 14 (RR=1.14) percent, respectively, more likely to die of drug abuse than the overall average. This result implies that between 1999 and 2020, US males have gone through two periods of crises of mortality due to drug abuse. Unlike nonlinear cohort effects, period fluctuations do not show much variation in substance abuse mortality. However, we observe period crises for many high-income countries around the mid-2000s in alcohol-related deaths, whereas disadvantaged periods due to drug-related deaths exist for several countries beyond 2010. For most countries, the period crises for drugs and alcohol do not happen simultaneously, Scottish and Hungarian males being the exception.

POTENTIAL DISCUSSION

The results of our study make it very apparent that a comprehensive investigation of both alcohol- and drug-related mortality is necessary to identify a possible association between them. We show that the drug epidemic in the USA is not an isolated phenomenon. Several countries like Australia, Canada, Norway, Scotland and Sweden are going through unprecedented times of drug-related mortality. We also show the necessity to study Scotland separately from the rest of the United Kingdom. Our study raises questions about drug abuse mortality among Millennials which has been surprisingly under the radar.

Alcohol-related mortality is on the decline in several countries, and at the same time, drug-related mortality is increasing. The results suggest potential substitution behavior. i.e., substituting alcohol consumption with some form of drugs in younger cohorts. This assumption is further reinforced by the number of period crises for drugs compared to alcohol-related deaths in later years, implying that the population is becoming more and more susceptible to mortality from drugs than alcohol abuse with time.

The study's primary limitation is the lack of consistent data on substance abuse mortality for all the high-income countries. Ideally, we would have liked to do a separate analysis for acute intoxication, mental and behavioral disorders, and chronic diseases. However, we found instances of mortality trends suggesting a shift in classification between these categories, as it is the case in Scotland (see Appendix 4). Secondly, ICD-10 was implemented at different times in different countries, limiting our observation period significantly. Most high-income countries under observation transitioned from ICD-9 to ICD-10 by 2000. Our study requires 3-digit ICD codes for alcohol-related chronic diseases, which is not available for Finland, a country showing very high drug abuse death rates. Hence, for consistency, Finland was excluded from our analysis. Lastly, we would like to examine all broad classifications of substance abuse separately over a more extended period to observe temporal changes. However, the transitions through the ICD series are not seamless. The only standard classification from ICD-9 to ICD-10 is drug-related accidental poisoning, a minimal subset of substance abuse deaths.

Apart from the preliminary results, we will extend the current research by introducing contextual variables, such as cohort size and birth order based on Easterlin's hypothesis. Furthermore, we will conduct a statistical test to analyze the stability of these non-linear trends over time using an Age-Period-Cohort Hysteresis model (Chauvel, Leist, and Ponomarenko 2016). A hysteresis model tests the temporal stability of cohort effects and can inform us whether our claims of cohort fluctuations can hold over time or what proportion of the disproportional cohort mortality due to substance abuse is absorbed over the life course.

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

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FIGURE LIST

Figure 1: Age-standardized drug abuse death rates

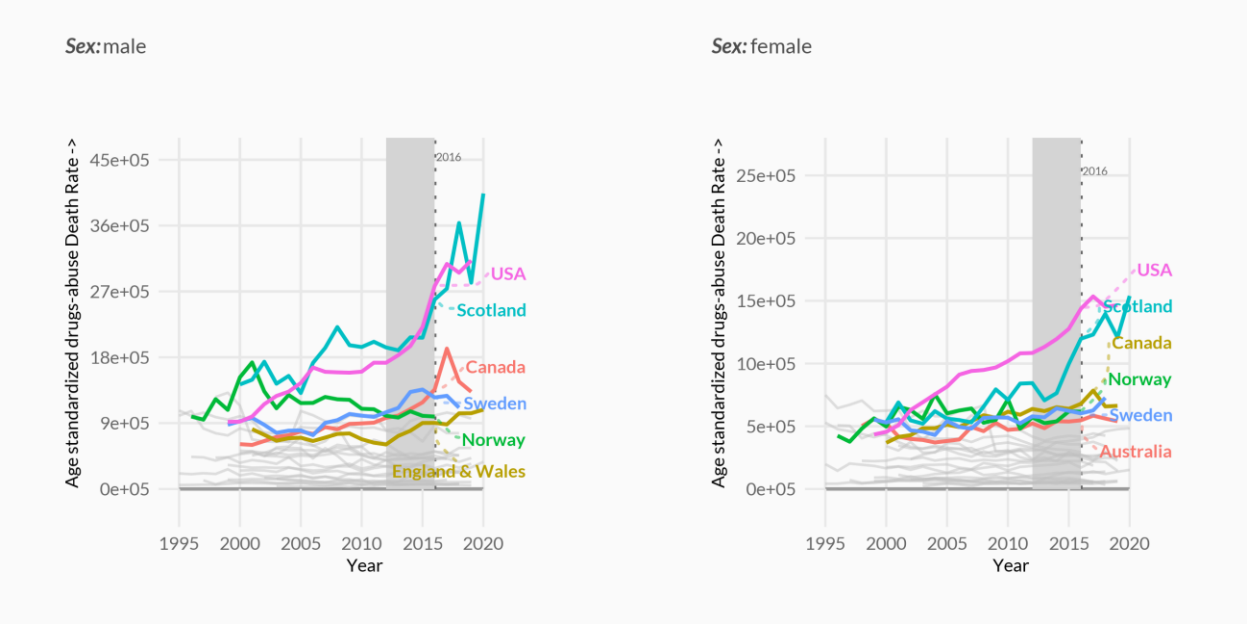


Figure 2: Age-standardized alcohol abuse death rates

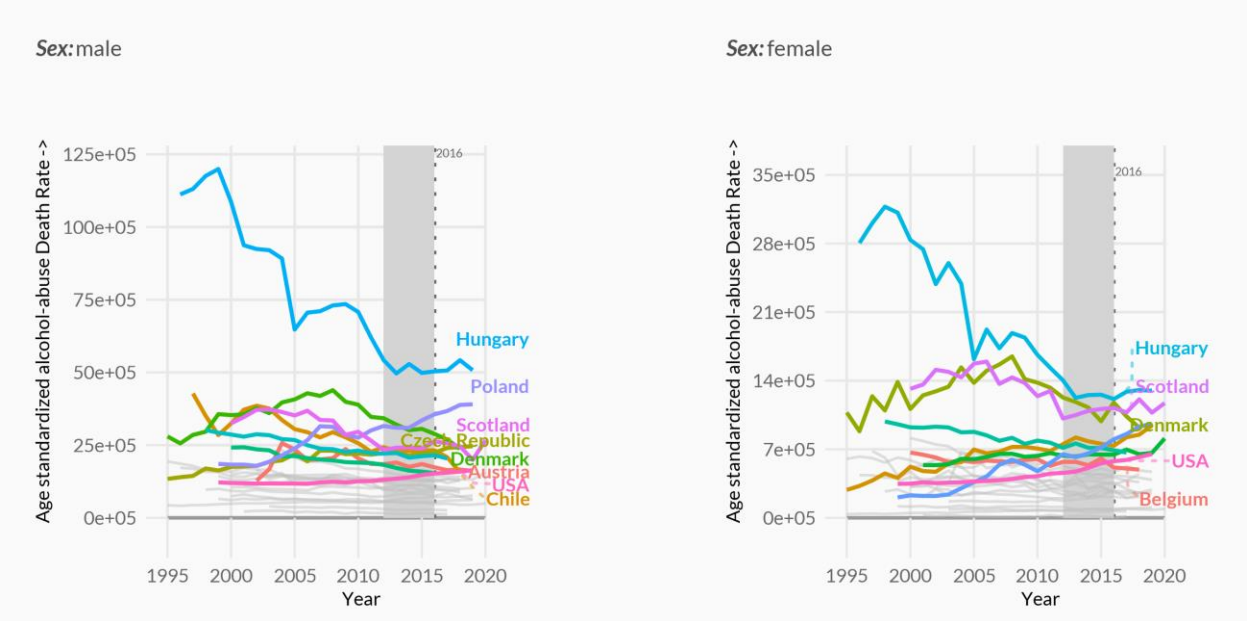


Figure 3: Disadvantaged cohorts by sex

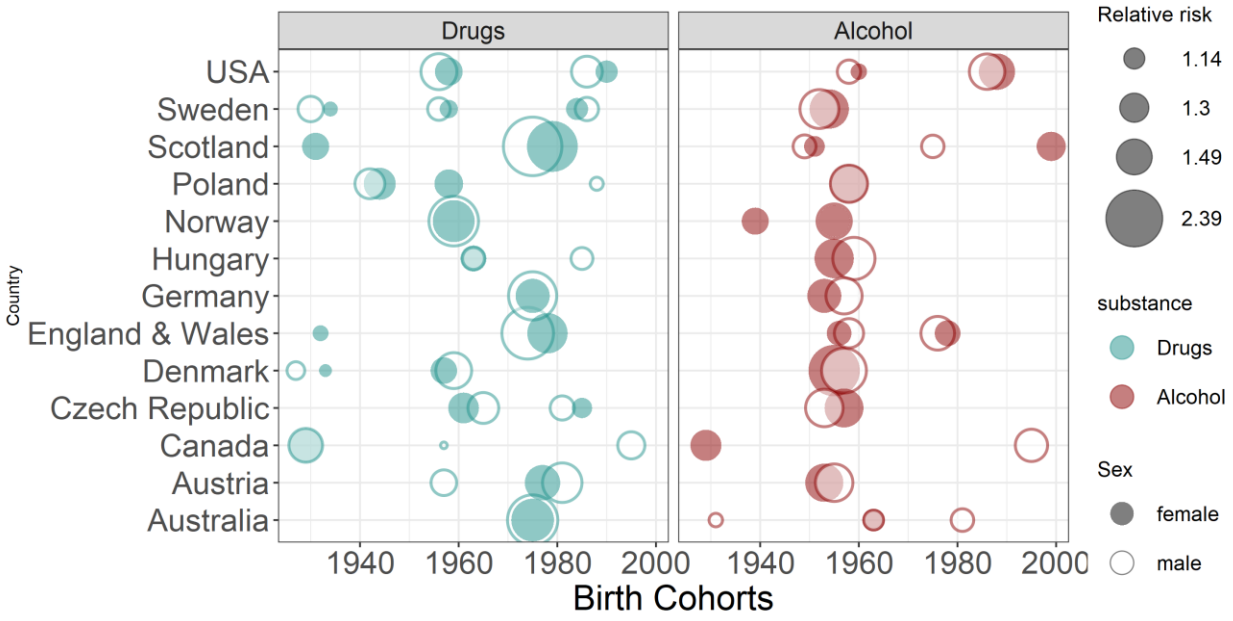
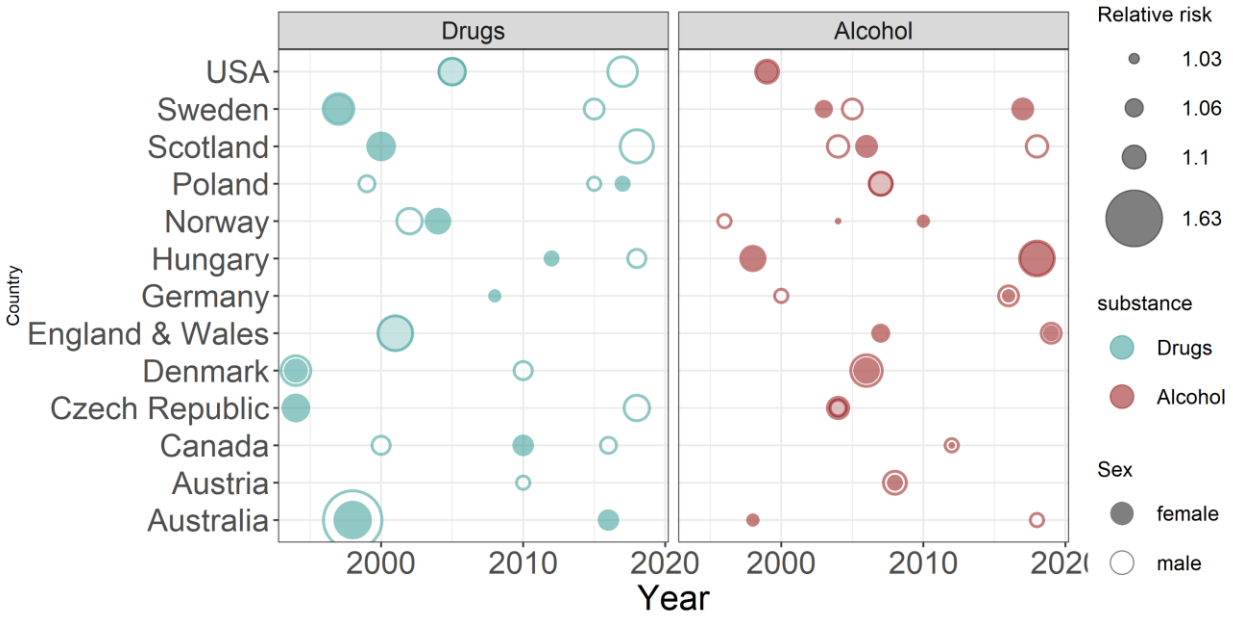


Figure 4: Period crises by sex



APPENDIX

Appendix 1: Table list

Table T1: 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	F11-19
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 T2: Average ASDRs for highlighted countries 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
Australia	8.96	5.26	7.86	2.64
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
Austria	5.12	2.51	18.2	4.93
Germany	4.22	2.24	21.6	7.18
Czech Republic	2.09	1.91	22.2	7.69

Appendix 2: From Lexis surfaces to identifying non-linearities

Lexis surface of mortality change: Figure A2(a) depicts a lexis surface of mortality change over a period in U.S males for alcohol-related deaths. Here, the yellow to red change indicates an increase in cause-specific mortality in the subsequent year in the same age. In contrast, a green to blue transition depicts a decline in cause-specific mortality in the subsequent year in the same age. The black contour lines depict the point of inflection in mortality rates for a given age. For example, at 45, the mortality rate increases yearly until 2006, after which it declines until 2013. Lexis surfaces by substance type and sex for all the countries included in the study can be found in the supplementary materials).

Non-linear APC trends: Figure A2(b) depicts how deviations from trends are utilized in the study. After fitting the dAPC model, we exponentiate the coefficients ($\exp^{coeff}$.) to obtain RR values. 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 45% (RR=1.45) **more** likely to die of substance abuse mortality compared to the overall sample average. Similarly, an individual born in 1940 is 31.1% (RR=0.699) **less** likely to die of substance abuse mortality compared to the overall sample average. Hence, the cohort of 1939 would be known as an **advantaged cohort** having a lower risk advantage over other cohorts.

figure A2(a): Lexis surface of mortality change

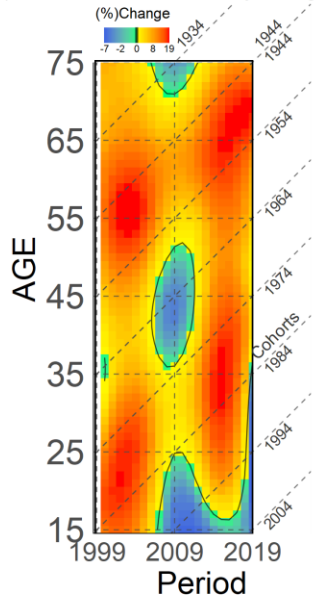
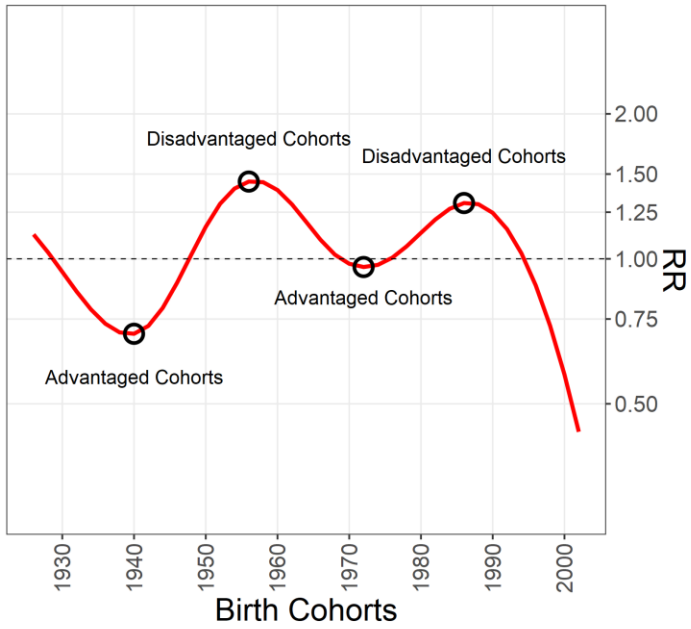


figure A2(b): Non-linear APC trends



Appendix 3: Detrended APC (dAPC) model

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

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

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

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.

Appendix 4: Suspected reporting error

The following graph 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.