Royal Netherlands Academy of Arts and Sciences (KNAW)

The role of birth cohorts in long-term trends in liver cirrhosis mortality across eight European countries

Sergi Trias-Llimós[1], Maarten J. Bijlsma[2], Fanny Janssen[1,3]

1. Population Research Centre, Faculty of Spatial Sciences, University of Groningen, Landleven 1, 9747 AD Groningen, The Netherlands.

2. Max Planck Institute for Demographic Research, Konrad-Zuse-Straße 1, 18057 Rostock, Germany.

3. Netherlands Interdisciplinary Demographic Institute, Lange Houtstraat 19, 2511 CV The Hague, The Netherlands.

Running head: Birth cohort and liver cirrhosis mortality

Word count: 3,486

Declarations of competing interests: None

Corresponding author:

Sergi Trias-Llimós, Population Research Centre, Faculty of Spatial Sciences, University of Groningen, Landleven 1, 9747 AD Groningen, The Netherlands. Tel: 0031 (0)50 363 86 52; e-mail: s.trias.llimos@rug.nl

Abstract

Background and aims: Understanding why inequalities in alcohol-related mortality trends by sex and country exist, is essential for developing health policies. Birth cohort effects, indicative of differences by generation in drinking, have rarely been studied. This study estimated the relative contributions of birth cohorts to liver cirrhosis mortality trends and compared sex- and country-specific cohort patterns across eight European countries.

Design: Time-series analysis of population-level mortality data.

Setting: Austria, Finland, Hungary, Italy, the Netherlands, Poland, Spain and Sweden; 1950-2011.

Participants: National populations aged 15-94.

Measurements: We modelled country- and sex-specific liver cirrhosis mortality (from national vital registers) adjusting for age, period and birth cohort.

Findings: Birth cohorts (adjusted for age and period) made statistically significant contributions to liver cirrhosis mortality in all countries and for both sexes (p-values < 0.001), and more so among women (average contribution to deviance reduction of 38.8%) than among men (17.4%). The observed cohort patterns were statistically different between all but two country pairs (p-values < 0.001). Sex differences existed overall (p-value < 0.001), but not in the majority of countries (p-values > 0.999). Visual inspection of birth cohort patterns reveals birth cohorts at higher risk of liver cirrhosis mortality.

Conclusions: The inclusion of the birth cohort dimension improves the understanding of alcohol-attributable mortality trends in Europe. Birth cohorts at higher risk of liver cirrhosis mortality were born around 1935-1949 in Sweden and Finland, around 1950 in Austria and the Netherlands, and around 1960 or later in Hungary, Italy, Poland and Spain.

Introduction

Alcohol-attributable mortality, or the share of overall mortality attributable to alcohol, is higher in Europe than elsewhere in the world because of the high prevalence of alcohol consumption (1). However, the levels of and the trends in alcohol prevalence and subsequent alcohol-related mortality differ substantially across European countries and between the sexes (2-5). Understanding the long-term trends in alcohol-related mortality, the differences in these trends across countries and between the sexes, and the factors that explain these trends, is essential for developing health policies.

Previous studies that assessed the long-term trends in alcohol-related mortality mainly focused on calendar time as the time component, and on liver cirrhosis mortality as the indicator of alcohol-attributable mortality (6-10). However, the inclusion of another time dimension, such as birth cohort, has been crucial to understanding mortality (11) and cancer incidence trends (12, 13). Individuals who were born in the same period, and thus belong to the same birth cohort, have similar experiences at the same age, and are likely to adopt similar behaviours. In the particular case of alcohol, restrictions,

prices, and advertisements related to alcohol directly influence drinking behaviour at younger ages (14), which tends to predict patterns of alcohol use over the life course (15, 16). In addition, individuals who started drinking at younger ages are more prone to suffer from alcohol dependence (17) and to develop other alcohol-related problems, such as alcohol use disorders or injuries (18, 19). Therefore, in studying trends in alcohol prevalence and subsequent mortality, it is necessary to not only look at changes over age (= age effects)—increasing mortality with age—and calendar time (= period effects)—mortality change over subsequent years—, but also to examine the role of birth cohorts (= birth cohort effects), i.e. differences in mortality between those born in 1950 and those born in 1960. Indeed, recent studies on alcohol consumption trends have found that birth cohorts are significant explanatory factors (20, 21). These findings indicate that drinking habits are formed not just collectively (= period effects), as Skog posited (22), but also by generation (= birth cohort effects).

The relevance of birth cohorts has been also proved in the few studies that have assessed alcohol-attributable mortality. Analysing data for the period 1970-1989, Corrao et al. (23) found increasing liver cirrhosis mortality risks for cohorts born in the first half of the 20th century in Northern and Eastern Europe. Recent studies at the country-specific level found a decline in alcohol-related mortality risks for birth cohorts born after WWII in Sweden (24); and in Nordic countries, Germany, and France, based on data from 1980 to 2009 (25).

However, these previous studies did not examine trends over a long historical period, nor did they make pan-European country comparisons. Longer time series make it possible to compare more birth cohorts at the same age, and are therefore likely to provide more precise cohort estimates. In addition, because alcohol consumption and liver cirrhosis mortality trends are not always similar across European countries (5, 10), it is important to examine the country-specific role of birth cohorts across European countries.

Objectives

First, we estimate the extent to which birth cohorts explain liver cirrhosis mortality trends in countries across different European regions by simultaneously examining the age, period and birth cohort effects. Second, we compare the birth cohort patterns across countries and between sexes.

Methods

Design

We estimated liver cirrhosis mortality trends from 1950 to 2011 for the national populations aged 15 to 94 of eight European countries belonging to different regions and with different alcohol

consumption levels, patterns and trends: Austria, Finland, Hungary, Italy, the Netherlands, Poland, Spain and Sweden.

Data

Liver cirrhosis mortality data by calendar year, five-year age groups, and sex from national vital registration systems were retrieved from the WHO Mortality database (26). These data were complete and of medium or high quality for all countries except Poland, because of a more substantial proportion of ill-defined causes (27). Because only a small share of ill-defined causes of death can be attributed to liver cirrhosis ((28), the potential underestimation of liver cirrhosis mortality in Poland is small. We used International Classification of Diseases (ICD) codes 581 in ICD-7, 571 in ICD-8 and ICD-9, and K70, K73, and K74 in ICD-10 (7). We redistributed the deaths in the open-ended age group 85+ in ICD-7, ICD-8 and ICD-9 to the age groups 85-89 and 90-94 by means of their average relative share in ICD-10 by country and sex. The mortality rates were obtained by dividing the deaths by the age-, sex-, and year-specific exposure population which we obtained from the Human Mortality Database (29). These five-year age group mortality rates were subsequently turned into one-year age group mortality rates by applying two-dimensional P-splines smoothing (30). The combination of ages 15-94 and years 1950-2011 resulted in the inclusion of the two-year overlapping birth cohorts (1855/56, …, 1995/1996). Because of missing data, in some countries different years and birth cohorts were included (see Supporting information, Table S1).

Statistical analysis

- *Descriptive analysis*

All analyses were done separately for men and women. To compare liver cirrhosis mortality across countries, the liver cirrhosis mortality rates were directly age-standardised using the European population of 2011 from Eurostat (31) as the standard. Age-standardised and age-specific liver cirrhosis mortality trends were plotted and visually inspected.

- *Age-period-cohort (APC) modelling*

Liver cirrhosis mortality rates were modelled as a function of age, period, and birth cohort. We fitted four different Poisson regression models for each country-sex combination (see Box 1), with the natural logarithm of population at risk as the offset term. To deal with the identification problem in APC modelling that results from the linear dependency between age, period, and birth cohort (age = calendar year (period) minus year of birth (cohort)), we applied the standard Clayton and Schifflers approach (32, 33). This approach distinguishes the shared linearity between period and birth cohort by means of identifying the drift, next to age, period and cohort. Drift represents the linear change in the outcome that is shared between period and birth cohort. By constraining two categories in the variable of interest (birth cohort), we can estimate and visualize non-linear birth cohort effects unaffected by

linear time-trend changes. We used as reference categories age 50, calendar year 1980, and birth cohorts 1900 and 1960. We examined country differences (in the full data set and between pairs of countries) and sex differences (in the full data set and in each country) by performing likelihood ratio tests comparing an APC model with sex-APC interactions or country-APC interactions with the same model excluding the sex-cohort or country-cohort interactions, respectively.

Box 1. APC modelling

Model parameters   Statistical notation

Age (A) $\ln[\lambda_a] = \mu + \alpha_a$

Age + drift (AD) $\ln[\lambda_{ad}] = \mu + \alpha_a + \delta$

Age + period (AP) $\ln[\lambda_{ap}] = \mu + \alpha_a + \beta_p$

Age + period + cohort (APC) $\ln[\lambda_{ap}] = \mu + \alpha_a + \beta_p + \gamma_c$

Where λ is the liver cirrhosis mortality rate. μ is the intercept, α, β and γ represent the age, period and birth cohort effects, and δ represents the drift.

To assess the relative contributions of birth cohorts to the model fit, we calculated the percentage of scaled deviance between the models A and APC that is attributed to the drift, to the non-linear period, and to the non-linear birth cohort components. We also assessed the fit of the different models to the data with likelihood ratio tests. Because of the observations for the extreme cohorts were less complete, we limited our graphs to cohorts born between 1900 and 1980. All data analyses were performed using R 3.2.5 in R studio 0.99.451.

Results

Descriptive results

Age-standardised liver cirrhosis mortality rates—higher for men than for women and at different levels for the different countries—seem to exhibit different patterns over time across the analysed countries (Figure 1). In Austria, Italy, Spain and Sweden the decline in liver cirrhosis mortality rates started around 1975, whereas in Hungary in the 1990s and only very recently in Finland.

<Figure 1 about here>

Examining the age-specific graphs (see Supporting Information, Figure S2) reveals that for some populations the age-specific period patterns are clearly parallel (i.e., Italian men), which suggests the predominance of period effects; whereas in other populations (i.e., Polish and Dutch women) different

period patterns can be observed for different age groups, which suggests the predominance of cohort effects.

APC modelling: the contribution of birth cohorts

Birth cohorts made statistically significantly contributions to the fit of the liver cirrhosis mortality model (p-values < 0.01), as compared with the AP models. These contributions were larger for women (unweighted average of 38.8%) than for men (unweighted average of 17.4%) in all countries except in Spain, and differed across countries (Figure 2). The contributions of birth cohorts were larger than the contributions of period and drift effects for Dutch and Polish women. In addition, the contributions of birth cohorts exceeded 20% for women in all of the other analysed countries except Spain. The APC models for all country-sex combinations provided a good fit to the data (p-values > 0.05).

<Figure 2 about here>

APC modelling: the effects of age, period, and birth cohort

Liver cirrhosis mortality rates increased with age for men until around ages 60-75 in all countries except Italy, where they kept increasing along the analysed age groups (Figure 3). Liver cirrhosis mortality generally peaked at slightly older ages for women than for men. In Hungary, however, the pattern among women looked similar to that of men, while in Italy no decline was observed. Compared to the reference category (age 50), age effects were largest for women and in the Southern European countries.

<Figure 3 about here>

The period effects (including drift) logically showed the same pattern as the age-standardised liver cirrhosis mortality trends described above (see Supporting Information, Figure S1).

Overall, the non-linear birth cohort patterns were statistically different across countries and between sex (Table 1). Although sex-differences were found in Italy, Spain and Hungary (p-values < 0.001), they were insignificant in all other analysed countries (p-values > 0.999). Birth cohort patterns were statistically different between all pairs of countries except for Netherlands-Finland (p-value = 0.932) and Netherlands-Austria (p-value > 0.999). The graphs of the birth cohort effects (Figure 4) suggest that the statistical difference in cohort patterns between most countries, and between sexes in some countries, is mostly due to differences in timing. Mortality started to decline for birth cohorts born around the 1940s and 1950s in Sweden and Finland, and for cohorts born around the 1960s in Spain and Hungary. In Italy (men) and in Poland the onset of the decline was five to 10 years later.

<Table 1 about here>

<Figure 4 about here>

Discussion

Summary of results

Birth cohorts contributed significantly to liver cirrhosis mortality trends in all eight European countries studied, and for both sexes. The relative contributions of birth cohorts differed across countries, and were larger for women than for men. The observed cohort patterns were statistically different between all, but two, country pairs. Sex differences in the patterns existed overall, but not in the majority of countries. Visual inspection of birth cohort patterns reveals that birth cohorts at higher risk of liver cirrhosis mortality were born around 1935-1949 in Sweden and Finland, around 1950 in Austria and the Netherlands, and around 1960 or later in the other analysed countries.

Evaluation of data and methods

In all of the APC analyses an important methodological issue that arose was the treatment of the identification problem (birth cohort = period - age). Like previous demographic (11) and epidemiological studies (12, 34), we applied the standard Clayton and Schifflers approach (32, 33) because it detects drift, or the co-linear pattern of period and cohort. Using this approach enabled us to identify cohort effects that could not be ascribed to period, although the total cohort effect was underestimated when the share of drift was large. However, because the contribution of drift for many countries (the Netherlands, Austria, Finland, Sweden, and Poland) appears to have been relatively small, our estimated cohort effects—and, consequently, age and period effects as well—are likely close to the real effects.

In our analyses, we compare countries across different European regions. Instead, we could have considered countries as nested in regions, which enables the comparison of cohort trends between regions by modelling country-level random effects and fixed-effect regional indicators (35). We focus on the comparison of individual countries because it was as yet unknown to what extent cohort trends between individual countries within a region differ. Indeed, the evidence generated by this study (significant differences between pairs of countries within each region), indicates important within-regional variation. Therefore, we recommend that if a hierarchical (i.e. country-level random effect) approach is taken, more than two countries per region are selected so that regional effects can be precisely estimated despite potentially large within-regional variation.

In assessing the long-term trends in alcohol-related mortality in several European countries, we used liver cirrhosis mortality as a proxy, as was done in previous studies (6-10), which enabled us to avoid having to cope with ICD revisions for more specific causes of death. Note, however, that liver

cirrhosis mortality is a good indicator of alcohol-related chronic diseases, but not of acute conditions. Yet because most of mortality attributed to alcohol is from chronic diseases (i.e., (2, 36)), this is unlikely to have affected the results much. Furthermore, although viral hepatitis (37) and, to a lesser extent, obesity (i.e., (38)) are risk factors that sometimes accompany liver cirrhosis, their low prevalence (viral hepatitis) (39) and different patterns over time (general increase in obesity) (40) suggest that they were of minimal importance. At the population level, liver cirrhosis mortality trends over calendar time generally seem to follow the patterns of per capita alcohol consumption in most European countries (8, 9), which indicates that alcohol was both the main contributor to and the driver of liver cirrhosis mortality trends (10).

Comparison of results with previous APC studies on alcohol-related mortality

Our birth cohort patterns estimates are directly comparable to those of two studies that assessed mortality from a few major diseases attributed to alcohol in Sweden (24) and in the Nordic countries, Germany, and France (25). The birth cohort patterns we observed appear to be similar to the birth cohort patterns in alcohol-attributable mortality found in previous studies for Finland and Sweden, which again supports the use of liver cirrhosis mortality as a proxy for alcohol-related mortality. By including countries with different alcohol consumption levels, patterns and trends, we were able to observe important timing differences between and across countries in the birth cohort effects on liver cirrhosis mortality. Unlike for alcohol-related period trends, Sweden and Finland are forerunners in the cohort decline in alcohol-attributable mortality, whereas Poland seem to lag behind.

Our formal assessment of the actual contributions of birth cohorts to liver cirrhosis mortality trends by country, which was not done before, provided us with additional information about the relative importance of cohort and period patterns.

Explanation of results

We observed potential differences between the sexes and across countries in the contributions of birth cohorts to the liver cirrhosis mortality trends. Although different contributions of drift can affect the comparison of the contributions of birth cohorts, we can be certain that the cohort contributions in Poland and the Netherlands were larger for women than for men. These potential sex and country differences in the contributions of birth cohorts can be linked to differences between the sexes and countries in the abruptness of changes in alcohol consumption over time, and subsequent changes in alcohol-attributable mortality over calendar time versus cohort. For example, the small contributions of birth cohorts to liver cirrhosis mortality that we observed in Italy and Spain can be linked to the rapid decline in alcohol consumption over calendar time in those countries (1). This is reflected in the clear bell-shaped curve in liver cirrhosis mortality across all age groups (Figure 1), and, more importantly, for the separate age groups (Figure S2), which could indicate that the economic factors and policy changes have affected drinking behaviour of the population more equally. Similarly, in

Hungary the rapid changes in liver cirrhosis mortality over calendar time (Figure 1) are well reflected in a relatively low contribution of birth cohorts as compared to period (Figure 2). For the Netherlands and Poland, on the other hand, the period changes in liver cirrhosis mortality were much less pronounced and varied for the different age groups (see Supporting information, Figure S2), which made room for larger contributions of the birth cohort dimension relative to the period dimension. Because women tend to drink less than men (5), variation in alcohol consumption over calendar time due to contextual effects (such as policy and cultural changes) is likely to have been smaller as well. Indeed, our results showed more level period trends in liver cirrhosis mortality for women than for men, combined with less parallel age-specific trends for women; which again resulted in cohort effects making stronger contributions for women than for men.

Birth cohort effects are larger when changes in mortality over time are observed for a few, rather than for all age groups. As young drinkers are expected to be more prone to change their drinking behaviour than older drinkers with well-established patterns (21), they may be more likely to alter their patterns not only in response to changes in alcohol policy, but also to changes in levels of social awareness of alcohol damage. Therefore, it is plausible that changes of this kind have affected the drinking behaviour of the younger age groups in particular, and therefore resulted in cohort effects.

The observed differences in the timing of the increase and the subsequent decline in the risk of dying from liver cirrhosis for the subsequent cohorts—which occurred earlier in Sweden and later in Poland—seem to be very much in line with the assumption that economic progress led to contextual changes, especially for young people. Indeed, positive changes in alcohol policies and increased social awareness of alcohol damage generally occurred earlier in more economically advanced countries than in less economically advanced countries (41). This hypothesis is also in line with the existing literature for Sweden, as the early peak in the cohort pattern has been linked to alcohol policies and social awareness (21, 24).

The birth cohorts at higher risk of liver cirrhosis mortality can also be linked with country-specific alcohol consumption when those generations were young adults. In most Southern European countries, the decline in alcohol consumption started around 1975 (1), and was mostly driven by economic factors and policy changes (42). This is in line with our observation for Spain that cohorts born around 1960 (aged around 15 in 1975) had higher risk of liver cirrhosis mortality. Similar links between the observed patterns for liver cirrhosis mortality and alcohol consumption can be made for Austria and the Netherlands, as alcohol consumption started to moderately decline in the late 1970s while the cohorts at higher risk of liver cirrhosis mortality were born in the 1950s. In Finland, by contrast, alcohol consumption did not decline during the 20th century (1); however a decline in cohort liver cirrhosis mortality for birth cohorts born after 1950 could be observed. The cohorts at higher risk of liver cirrhosis mortality in Finland were adolescents and younger adults between the mid-1960s and the mid-1970s, when a dramatic increase in alcohol consumption in the country occurred (from

2.5 to 6.5 litres per person per year) in response to changes in alcohol policies (43). For Poland and Hungary information about consumption levels is less reliable because of a large share of underreported home-made alcohol consumption (5), which tends to be more toxic (44); however, the late peak in the cohort pattern certainly is in line with the observation that the change in context (and decline in alcohol sales data) occurred later in these countries than in most of the other analysed countries.

Further research should assess whether the decline in alcohol-related mortality risks along generational lines will continue for younger generations, given that in some European countries binge drinking has increased among recent generations (45, 46).

Conclusions

Overall, the inclusion of the birth cohort dimension significantly adds to our ability to describe and understand alcohol-attributable mortality trends in Europe. We observed clear differences across countries and between the sexes in the effects of birth cohorts on liver cirrhosis mortality trends, which could be linked to differences in the abruptness of changes in alcohol consumption over time. Also, differences in the timing of the birth cohorts experiencing smaller risks than their predecessors showed, with Sweden as a forerunner and Poland lagging behind all other analysed countries.

The cohort dimension should not be ignored in future studies, as it can not only provide information to health policy-makers about the age-specific impact of their health policies and other contextual changes; it can also provide information about which birth cohorts are at elevated risk of alcohol-attributable mortality, and will therefore affect future mortality levels.

Acknowledgements

References

1. World Health Organization. *Global status report on alcohol and health-2014.* World Health Organization; 2014.

2. Rehm J., Sulkowska U., Manczuk M., Boffetta P., Powles J., Popova S.*, et al*. Alcohol accounts for a high proportion of premature mortality in central and eastern Europe. *Int J Epidemiol* 2007; 36: 458-67.

3. Rehm J., Zatonksi W., Taylor B., Anderson P. Epidemiology and alcohol policy in Europe. *Addiction* 2011; 106 Suppl 1: 11-9.

4. Simpura J., Karlsson T. Trends in drinking patterns in fifteen European countries, 1950-2000. A collection of country reports. Helsinki, Finland: STAKES. 2001 18:31-53.

5. Popova S., Rehm J., Patra J., Zatonski W. Comparing alcohol consumption in central and eastern Europe to other European countries. *Alcohol Alcohol* 2007; 42: 465-73.

6. Munoz-Perez F., Nizard A. Alcohol consumption and cirrhosis mortality in the industrialised countries since 1950. *European Journal of Population/Revue européenne de Démographie* 1999; 14: 367-86.

7. Leon D.A., McCambridge J. Liver cirrhosis mortality rates in Britain from 1950 to 2002: an analysis of routine data. *Lancet* 2006; 367: 52-6.

8. Ramstedt M. Per capita alcohol consumption and liver cirrhosis mortality in 14 European countries. *Addiction* 2001; 96 Suppl 1: S19-33.

9. Ramstedt M. Population drinking and liver cirrhosis mortality: is there a link in eastern Europe? *Addiction* 2007; 102: 1212-23.

10. Zatonski W.A., Sulkowska U., Manczuk M., Rehm J., Boffetta P., Lowenfels A.B.*, et al*. Liver cirrhosis mortality in Europe, with special attention to Central and Eastern Europe. *Eur Addict Res* 2010; 16: 193-201.

11. Janssen F., Kunst A.E., Netherlands Epidemiology and Demography Compression of Morbidity research group. Cohort patterns in mortality trends among the elderly in seven European countries, 1950-99. *Int J Epidemiol* 2005; 34: 1149-59.

12. Dhillon P.K., Yeole B.B., Dikshit R., Kurkure A.P., Bray F. Trends in breast, ovarian and cervical cancer incidence in Mumbai, India over a 30-year period, 1976-2005: an age-period-cohort analysis. *Br J Cancer* 2011; 105: 723-30.

13. McNally R.J., Blakey K., James P.W., Gomez Pozo B., Basta N.O., Hale J. Increasing incidence of thyroid cancer in Great Britain, 1976-2005: age-period-cohort analysis. *Eur J Epidemiol* 2012; 27: 615-22.

14. Paschall M.J., Grube J.W., Kypri K. Alcohol control policies and alcohol consumption by youth: a multi-national study. *Addiction* 2009; 104: 1849-55.

15. Pitkanen T., Lyyra A.L., Pulkkinen L. Age of onset of drinking and the use of alcohol in adulthood: a follow-up study from age 8-42 for females and males. *Addiction* 2005; 100: 652-61.

16. Eliasen M., Kaer S.K., Munk C., Nygard M., Sparen P., Tryggvadottir L.*, et al*. The relationship between age at drinking onset and subsequent binge drinking among women. *Eur J Public Health* 2009; 19: 378-82.

17. Hingson R.W., Heeren T., Winter M.R. Age at drinking onset and alcohol dependence: age at onset, duration, and severity. *Arch Pediatr Adolesc Med* 2006; 160: 739-46.

18. Dawson D.A., Goldstein R.B., Chou S.P., Ruan W.J., Grant B.F. Age at first drink and the first incidence of adult-onset DSM-IV alcohol use disorders. *Alcohol Clin Exp Res* 2008; 32: 2149-60.

19. Hingson R.W., Zha W. Age of drinking onset, alcohol use disorders, frequent heavy drinking, and unintentionally injuring oneself and others after drinking. *Pediatrics* 2009; 123: 1477-84.

20. Meng Y., Holmes J., Hill-McManus D., Brennan A., Meier P.S. Trend analysis and modelling of gender-specific age, period and birth cohort effects on alcohol abstention and consumption level for drinkers in Great Britain using the General Lifestyle Survey 1984-2009. *Addiction* 2014; 109: 206-15.

21. Kraus L., Tinghog M.E., Lindell A., Pabst A., Piontek D., Room R. Age, period and cohort effects on time trends in alcohol consumption in the Swedish adult population 1979-2011. *Alcohol Alcohol* 2015; 50: 319-27.

22. Skog O.J. The collectivity of drinking cultures: a theory of the distribution of alcohol consumption. *Br J Addict* 1985; 80: 83-99.

23. Corrao G., Ferrari P., Zambon A., Torchio P., Arico S., Decarli A. Trends of liver cirrhosis mortality in Europe, 1970-1989: age-period-cohort analysis and changing alcohol consumption. *Int J Epidemiol* 1997; 26: 100-9.

24. Rosen M., Haglund B. Trends in alcohol-related mortality in Sweden 1969-2002: an age-period-cohort analysis. *Addiction* 2006; 101: 835-40.

25. Kraus L., Osthus S., Amundsen E.J., Piontek D., Harkonen J., Legleye S.*, et al*. Changes in mortality due to major alcohol-related diseases in four Nordic countries, France and Germany between 1980 and 2009: a comparative age-period-cohort analysis. *Addiction* 2015; 110: 1443-52.

26. World Health Organization. WHO Mortality Database Available at http://www.who.int/healthinfo/statistics/mortality_rawdata/en/ (data downloaded on October 30th, 2014).

27. Mathers C.D., Fat D.M., Inoue M., Rao C., Lopez A.D. Counting the dead and what they died from: an assessment of the global status of cause of death data. *Bull World Health Organ* 2005; 83: 171-7.

28. Mokdad A.A., Lopez A.D., Shahraz S., Lozano R., Mokdad A.H., Stanaway J*., et al*. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. *BMC Med* 2014; 12: 145,014-0145-y.

29. Human Mortality Database. University of California, Berkeley (USA), and Max Planck Institute for Demographic Research (Germany). Available at http://www.mortality.org (data downloaded on December 4th, 2014).

30. Camarda C.G. MortalitySmooth: an R package for smoothing Poisson counts with P-Splines. *Journal of Statistical Software* 2012; 50: 1-24.

31. Eurostat. Census data 2011.

32. Clayton D., Schifflers E. Models for temporal variation in cancer rates. I: Age-period and age-cohort models. *Stat Med* 1987; 6: 449-67.

33. Clayton D., Schifflers E. Models for temporal variation in cancer rates. II: Age-period-cohort models. *Stat Med* 1987; 6: 469-81.

34. Bijlsma M.J., Hak E., Bos J.H., de Jong-van den Berg L.T., Janssen F. Inclusion of the birth cohort dimension improved description and explanation of trends in statin use. *J Clin Epidemiol* 2012; 65: 1052-60.

35. Brown H., Prescott R. *Applied Mixed Models in Medicine.* John Wiley & Sons; 2006.

36. Rey G., Boniol M., Jougla E. Estimating the number of alcohol-attributable deaths: methodological issues and illustration with French data for 2006. *Addiction* 2010; 105: 1018-29.

37. Schuppan D., Afdhal N.H. Liver cirrhosis. *Lancet* 2008; 371: 838-51.

38. Ioannou G.N., Weiss N.S., Kowdley K.V., Dominitz J.A. Is obesity a risk factor for cirrhosis-related death or hospitalization? A population-based cohort study. *Gastroenterology* 2003; 125: 1053-9.

39. Esteban J.I., Sauleda S., Quer J. The changing epidemiology of hepatitis C virus infection in Europe. *J Hepatol* 2008; 48: 148-62.

40. OECD. Health at a glance: Europe 2012. OECD Publishing; 2012.

41. Österberg, E., & Karlsson, T. Alcohol policies in EU Member States and Norway in the second half of the twentieth century. In Österberg, E., & Karlsson, T., editors. Alcohol policies in EU member states and Norway. A collection of country reports. Helsinki, Finland: STAKES 2002; 433-60.

42. Gual A., Colom J. Why has alcohol consumption declined in countries of southern Europe? *Addiction* 1997; 92 Suppl 1: S21-31.

43. Karlsson, T., & Österberg, E. Finland. In Österberg, E., & Karlsson, T., editors. Alcohol policies in EU member states and Norway. A collection of country reports. Helsinki, Finland: STAKES 2002; 140-67.

44. Szucs S., Sarvary A., McKee M., Adany R. Could the high level of cirrhosis in central and eastern Europe be due partly to the quality of alcohol consumed? An exploratory investigation. *Addiction* 2005; 100: 536-42.

45. Harkonen J.T., Makela P. Age, period and cohort analysis of light and binge drinking in Finland, 1968-2008. *Alcohol Alcohol* 2011; 46: 349-56.

46. OECD. Tackling Harmful Alcohol Use: Economics and Public Health Policy. OECD Publishing; 2015.

Figure 1. Age-standardised liver cirrhosis mortality rate in 8 European countries, ages 15-94, 1950-2011, by sex
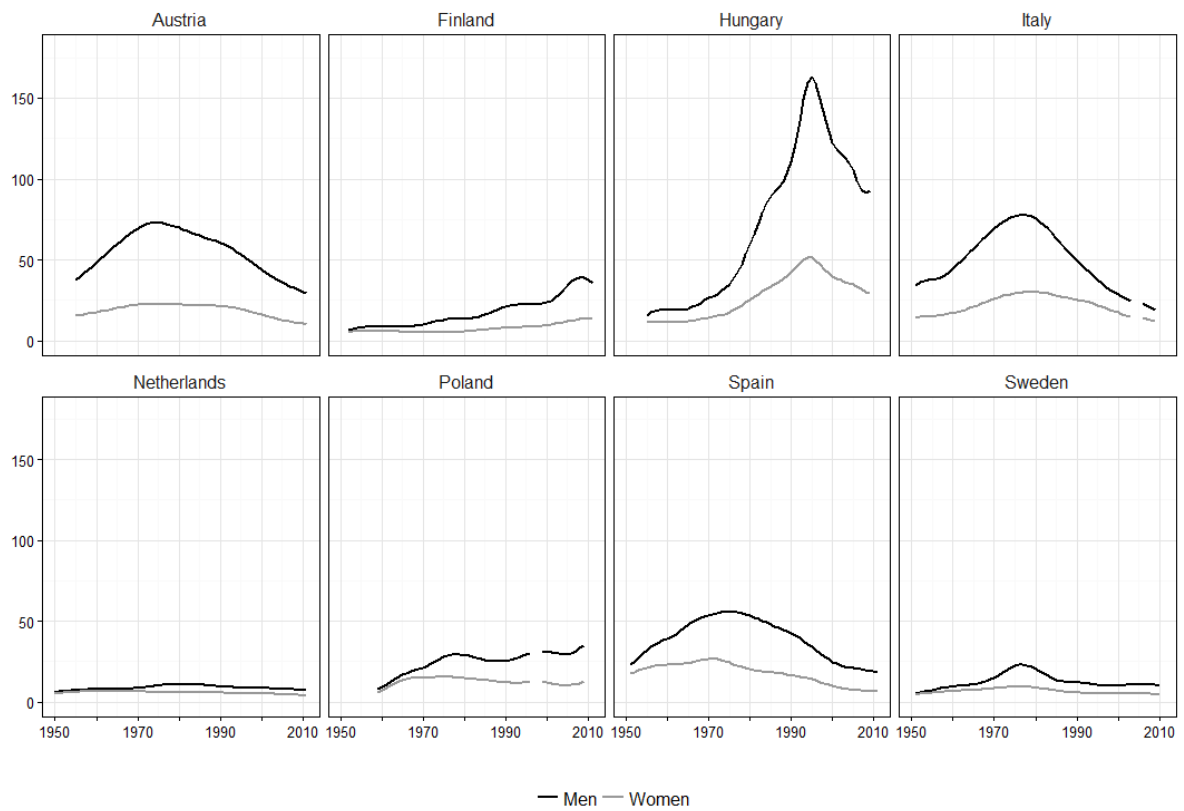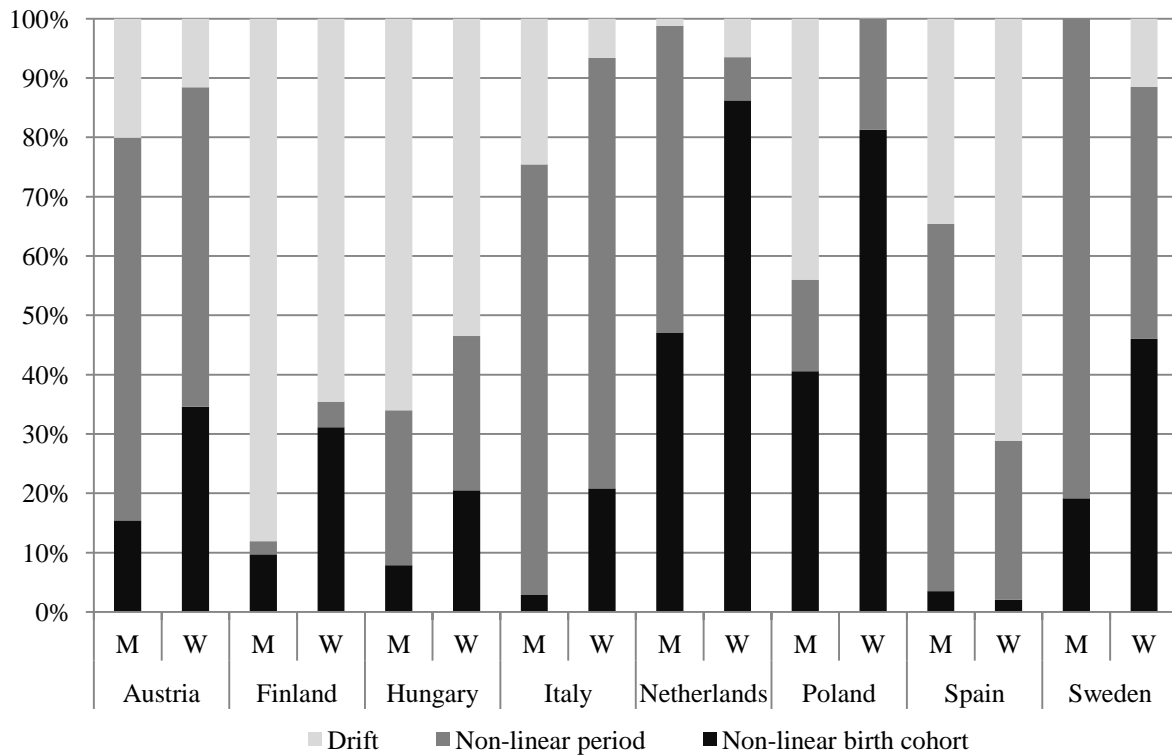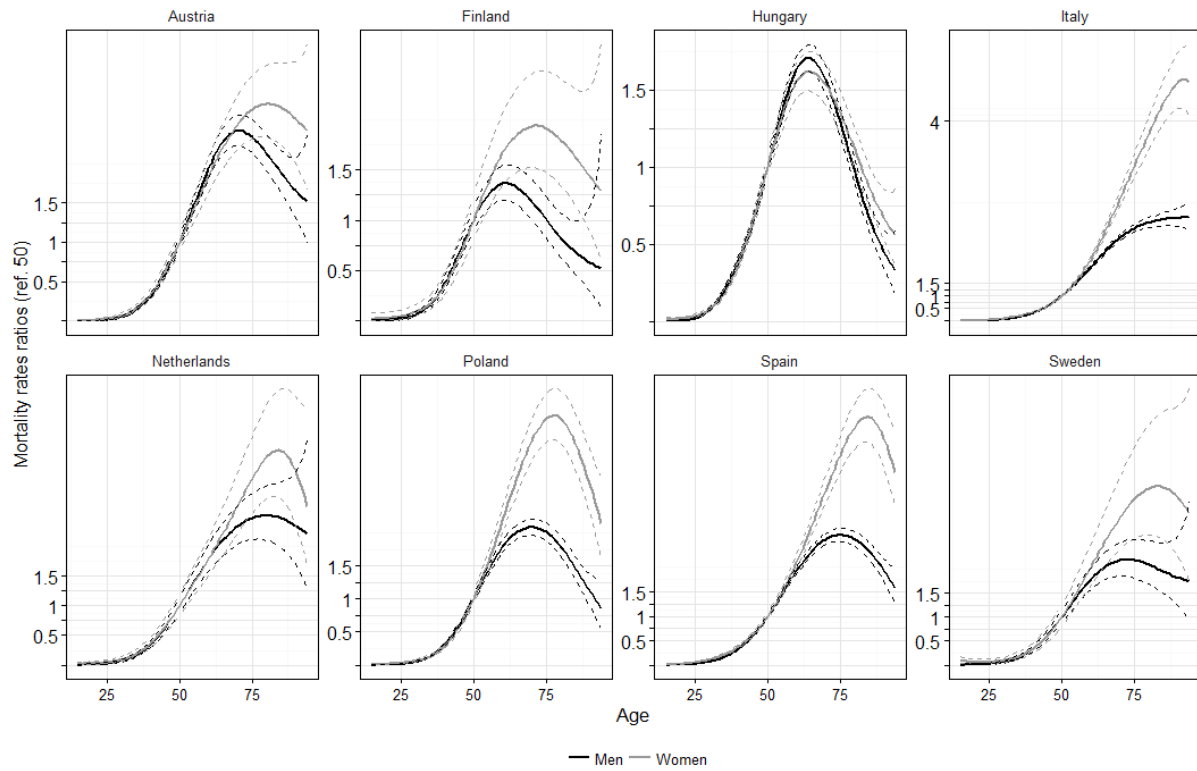
Figure 2. Contribution to the deviance reduction between models A and APC of liver cirrhosis mortality in 8 European countries 1950-2011, ages 15-94, by sex[a,b,c]
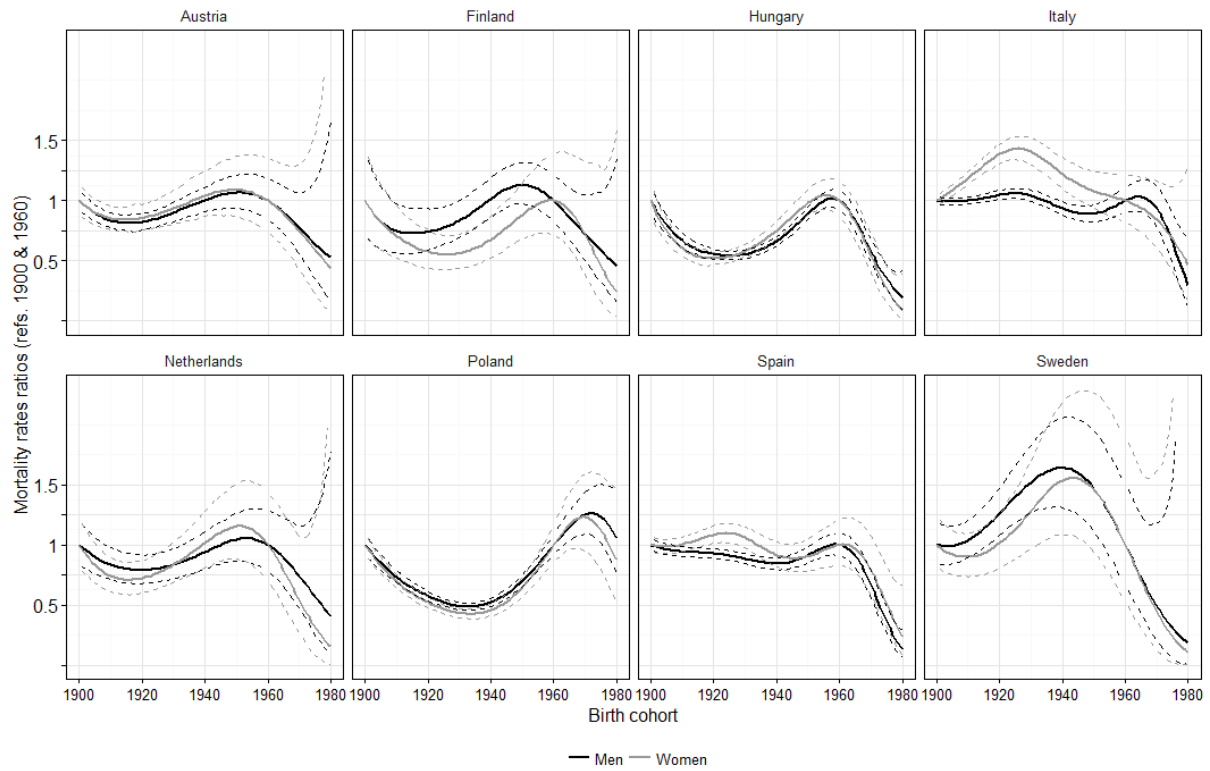

a. M and W refer to men and women, respectively.
b. Comparison between AP and APC models p-value (likelihood ratio test): p-values<0.01 in all countries and sexes.
c. Comparison of the APC models to the data (likelihood ratio test): p-values>0.05 in all countries and sexes.

Figure 3. Estimated age effects of liver cirrhosis mortality in 8 European countries, 1950-2011, by sex[a]

a. Dotted lines illustrate the 95% confidence intervals.

Figure 4. Estimated non-linear birth cohort effects of liver cirrhosis mortality in 8 European countries, 1950-2011[a]

a. Dotted lines illustrate the 95% confidence intervals.

Table 1. Tests for cohort effects differences[a] by sex (in each country)[b] and between countries[c] in liver cirrhosis mortality (p-values)

	Sex	Austria	Finland	Hungary	Italy	Netherlands	Poland	Spain	Sweden
Austria	>0.999								
Finland	>0.999	**<0.001**							
Hungary	**<0.001**	**<0.001**	**0.018**						
Italy	**<0.001**	**<0.001**	**<0.001**	**<0.001**					
Netherlands	>0.999	>0.999	0.932	**<0.001**	**<0.001**				
Poland	>0.999	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**			
Spain	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**		
Sweden	>0.999	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	

a. For the grouped data of 8 countries the p-values for both sex and country differences were <0.001.
b. Likelihood ratio test for sex-specific cohort effects in each country.
c. Likelihood ratio test for country-specific cohort effects between pairs of countries.