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Trends of Liver Cirrhosis Mortality in Europe, 1970–1989: Age-Period-Cohort Analysis and Changing Alcohol' Consumption

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Background. Since the mid 1970s, a striking reduction in alcohol-related problems has been observed in many Western countries. Liver cirrhosis mortality is considered to be a major indicator of alcohol-related problems in the general population. The aim of the present study is to describe liver cirrhosis mortality trends in European countries between 1970 and 1989.

Methods. This is a descriptive study on liver cirrhosis mortality in 25 European countries, and in four grouped European regions. A Poisson log-linear age-period-cohort model is used to clarify whether the recent trend in mortality represents a short-term fluctuation or an emerging long-term trend. In addition, a descriptive comparison between trends in *per capita* alcohol consumption and liver cirrhosis mortality is conducted.

Results. In the whole European population and in that of Western and Southern Europe increasing period effects were observed until the second half of the 1970s followed by a decline in the next periods. In Eastern Europe the decline in period effects started in the first half of the 1980s, whereas in Northern Europe an increasing period effect was observed until the second half of the 1970s, followed by a stabilization. Similar trends were observed for *per capita* alcohol consumption. The age effect analysis showed a continuously rising effect in Eastern Europe, whereas an attenuation of the effect at around age 65 years was observed in Western Europe. Intermediate patterns were observed in Southern and Northern Europe. The birth cohort effect suggested that in the Western and Southern populations mortality could continue to decrease over the next decade, while in Eastern and Northern Europe mortality is still rising and this will probably continue for the next decade.

Conclusions. The age-period-cohort analysis allows targeting of health care and prevention programmes based on future trends. Aetiological and prognostic factors act differently in Europe. A better understanding of the trends would require more detailed information on alcoholism treatment rates, alcohol habits, viral hepatitic infections and other factors involved in the aetiopathogenesis of the disease.

Keywords: age effect, alcohol consumption, cohort effect, liver cirrhosis, mortality, period effect

In developed western countries, cirrhosis of the liver is one of the 10 leading causes of death[1] and almost 150 000 subjects die every year from this disease.[2] Since the mid 1970s, a striking reduction in alcohol-related problems has been observed in many Western countries.[3–8] A strong positive association between *per capita* alcohol consumption and alcohol-related problems has been reported.[9–14] It might therefore be expected that the recent declines in cirrhosis mortality rates are accompanied by a corresponding reduction in *per capita* alcohol consumption. However, other factors, such as alcoholism treatment rate[7,15–17] and cohort effects involving reduced exposure to hepatotropic viruses,[18] could affect the trends in liver cirrhosis mortality.

Total cirrhosis mortality has been the preferred indicator of mortality from alcoholic cirrhosis, in part because of deficiencies in recording alcohol as the cause on death certificates.[19]

The object of our study was to describe liver cirrhosis mortality in European countries between 1970

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and 1989. We used an age-period-cohort log-linear Poisson model[20] to assess the effect of early environmental exposure on the geographical distribution and on the temporal pattern of mortality rates. In particular, we have attempted to clarify whether the recent trend in mortality data represents a short-term fluctuation or an emerging long-term trend, possibly related to the changes in alcohol consumption.

METHODS

Deaths from cirrhosis were obtained for 25 European countries from the 'World Health Statistics Annual' published by the World Health Organization (WHO).[21] Cirrhosis of the liver was identified as code 571 (International Classification of Diseases, 8th Revision from 1970 to 1978, 9th Revision from 1979 to 1989).[22,23]

Data on the resident populations at 1970, 1975, 1980, 1985 and 1990 were obtained for the considered countries from 'The Sex and Age Distribution of World Population' published by the United Nations.[24]

Estimates of the annual *per capita* alcohol consumption from 1961 to 1989 by the population of each country for individuals aged over 15 years were derived from the 'World Drink Trends' published by the Produktschap Voor Gedistillerde Dranken.[25]

The mean annual mortality rates were separately calculated for the 25 countries, for four large geographical Regions (Eastern, Northern, Western and Southern Europe) and for the whole European population. Rates were standardized (direct method) according to the European population.[26]

Mortality data were subsequently stratified into nine 5-year age groups (30–34; 35–39;...; 70–74), four 5-year time periods (1970–1974; 1975–1979; 1980–1984; 1985–1989) and 12 10-year birth cohorts (1895–1904; 1900–1909;...; 1950–1959). From this matrix, the effects of age and of period of death and the effect of the birth cohort on the observed number of deaths were estimated using a log-linear Poisson model, modified from that reported by Osmond and Gardner[27] and described in detail elsewhere.[28] In brief, the estimates were derived from the three-factors (age, period and cohort) model that minimizes the sum of the Euclidean distances from the three possible two-factor models (age/period; age/cohort; period/cohort). The effects of the period of death and of the birth cohort were expressed as relative risks, meaning that for each period, or cohort, the risk of death was referred to the weighted average of all the period, or cohort, effects made equal to one. The age effects can be considered as the mean age-specific mortality rates in the period considered. The model was used for the whole European population and after stratification for the four European Regions.

TABLE 1 *Trends in age-adjusted mortality rates from liver cirrhosis (per 100 000 per year). Data are shown for the whole European population and for the population of 25 countries and four regions of Europe. Males*

	Periods			
	1970–1974	1975–1979	1980–1984	1985–1989
Bulgaria	10.39	14.21	19.45	26.87
Czechoslovakia	27.19	30.85	33.50	33.99
German Democratic Republic	15.14	18.91	21.78	25.47
Hungary	20.91	31.53	53.10	68.45
Poland	16.98	20.91	19.37	18.28
Romania	34.35	39.27	48.54	51.02
EASTERN EUROPE	21.20	26.01	31.12	33.47
Denmark	12.06	13.82	15.95	18.39
Finland	8.06	9.99	10.52	13.94
Iceland	3.05	2.44	1.50	2.06
Ireland	4.53	4.96	4.73	4.22
Norway	5.32	6.42	7.51	9.14
Sweden	12.84	16.96	12.33	9.01
United Kingdom	3.88	4.74	5.19	6.29
NORTHERN EUROPE	5.72	7.03	7.04	7.83
Austria	50.09	51.76	48.90	44.30
Belgium	16.62	18.27	17.51	15.88
Federal Republic of Germany	39.40	42.38	37.57	31.28
France	55.80	52.75	43.04	32.35
Luxembourg	41.72	42.20	36.50	28.75
Netherlands	6.67	7.49	7.85	7.60
Switzerland	27.49	22.21	20.56	16.46
WESTERN EUROPE	40.75	40.95	35.33	28.48
Greece	24.24	19.79	16.09	13.87
Italy	51.86	55.48	50.41	42.37
Portugal	56.62	65.96	57.54	47.37
Spain	38.91	41.62	38.15	34.01
Yugoslavia	25.83	31.35	41.84	32.33
SOUTHERN EUROPE	43.20	46.50	43.84	36.62
EUROPE	30.49	32.70	31.39	27.58

RESULTS

Trends in Mortality Rates

A total of 1827 550 deaths from liver cirrhosis were accounted during the period 1970–1989 and were used in the analysis.

Table 1 shows the age-adjusted mortality rate trends in males. Increasing rates were observed in the whole

European population from 1970–1974 to 1975–1979, corresponding to a 7.2% increase; followed by a steady decrease in the next periods (from 1975–1979 to 1985–1989 corresponding to a 15.7% decline). A trend similar to that of the whole European population was observed for Western and Southern Europe populations, whereas in Eastern and Northern Europe mortality rates steadily increased over the considered period. On the whole, a 30.1% and a 15.2% decline in rates in Western and Southern Europe were observed respectively. The countries in which the decline was more evident were Greece (–42.8%) and France (–42.0%). Increasing rates of 61.3% and 39.4% were observed in Eastern and Northern Europe respectively. The countries in which the increase was more evident were Hungary (+227.4%) and Bulgaria (+158.6%). Although in Eastern Europe the mortality rate was about half the Southern European rate in the first half of the 1970s, similar mortality rates were observed in the two Regions in the second half of the 1980s. Mortality rates in Northern Europe were far lower than in other regions, even if they have steadily increased in recent years.

Similar trends were observed in females (Table 2). Increasing rates were observed in the whole European population from 1970–1974 to 1975–1979, corresponding to a 2.3% increase, followed by a steady decrease from 1975–1979 to 1985–1989, corresponding to a 8.6% decline. Similarly, declining rates of 23.3% and 15.7% in Western and Southern Europe were observed. Also for females, the countries with the more evident decline were Greece (–45.0%) and France (–41.0%). Increasing rates of 44.3% in Eastern Europe were observed, with more evident increases in Hungary (+171.5%) and Bulgaria (+69.5%). Although in the first half of the 1970s the mortality rate in Eastern Europe was about half of the Southern European rate, similar mortality rates in the two Regions were observed in the second half of the 1980s. Finally, although Northern Europe mortality rates increased by 34.8%, the figures were far lower than in other Regions.

TABLE 2 *Trends in age-adjusted mortality rates from liver cirrhosis (per 100 000 per year). Data are shown for the whole European population and for the population of 25 countries and four regions of Europe. Females*

	Periods			
	1970–1974	1975–1979	1980–1984	1985–1989
Bulgaria	4.63	5.17	6.50	7.85
Czechoslovakia	9.28	9.71	11.69	10.23
German Democratic Republic	6.20	7.10	8.20	9.53
Hungary	9.06	13.08	19.69	24.60
Poland	8.52	8.62	7.91	7.34
Romania	17.37	19.73	24.76	26.97
EASTERN EUROPE	9.40	10.63	12.60	13.07
Denmark	7.86	6.69	6.63	8.05
Finland	3.18	3.28	3.64	4.86
Iceland	3.05	0.63	1.53	1.86
Ireland	2.78	3.17	3.05	2.79
Norway	2.63	3.32	3.40	3.77
Sweden	5.19	6.54	5.09	4.05
United Kingdom	2.76	3.20	3.75	4.27
NORTHERN EUROPE	3.30	3.76	4.02	4.45
Austria	13.35	14.16	14.06	13.12
Belgium	8.45	9.00	8.70	8.57
Federal Republic of Germany	13.83	14.10	13.63	12.42
France	20.16	18.50	16.11	11.89
Luxembourg	16.70	14.20	13.00	12.39
Netherlands	3.64	3.71	3.71	3.90
Switzerland	6.56	5.95	5.73	5.46
WESTERN EUROPE	14.36	14.01	12.99	11.02
Greece	8.66	7.16	5.36	4.76
Italy	17.42	18.71	17.69	16.20
Portugal	23.47	21.07	18.64	15.40
Spain	15.79	14.23	12.33	11.35
Yugoslavia	9.60	11.20	14.05	11.17
SOUTHERN EUROPE	15.75	15.84	14.98	13.27
EUROPE	11.48	11.74	11.70	10.73

Period Effects

Figure 1 shows that in the whole European population and in Western and Southern Europe the period effects followed the trends of the mortality rates already described in Tables 1 and 2. In these areas, increasing rates were observed from the first to the second time period, followed by a steady decrease in the next periods. For Eastern and Northern Europe, on the other hand, some disagreement between age-adjusted mortality rates and period effects was observed. A decline in the last period in Eastern Europe and a stabilization starting from the second period in Northern Europe were observed in this analysis. These trends were similar in males and females.

Age Effects

Figure 2 shows the patterns of the age effects in the considered Regions. For both males and females, Eastern and Western Europe populations presented the two extreme conditions. The age effects in the Eastern population showed a continuously rising trend, whereas an attenuation of the effects around age 65 years was observed for the Western population. Moreover, while

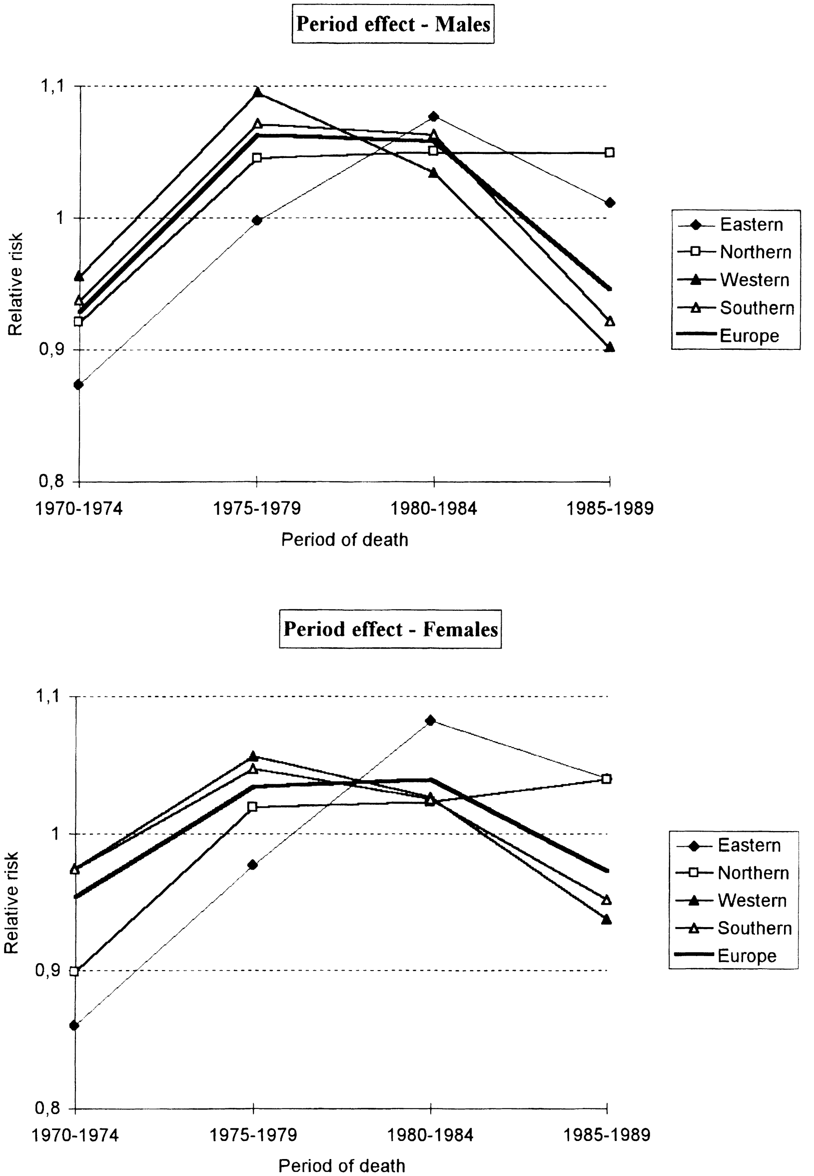

FIGURE 1 *Period effects on the mortality rates from liver cirrhosis in males and females of the whole European population and of the population of the four European Regions. The effects were expressed as relative risk of death, considering one as reference value for their weighted average*

in Western Europe higher age effects were observed up to 60–64 (males) and 55–59 (females) age groups, higher age effects in older populations of Eastern Europe were observed. Intermediate patterns were observed for Southern and Northern Europe.

Cohort Effects

Figure 3 shows the cohort effects both for males and females. In Western and Southern Europe, a decreasing relative risk was observed throughout the period, paralleling the pattern of the whole European population.

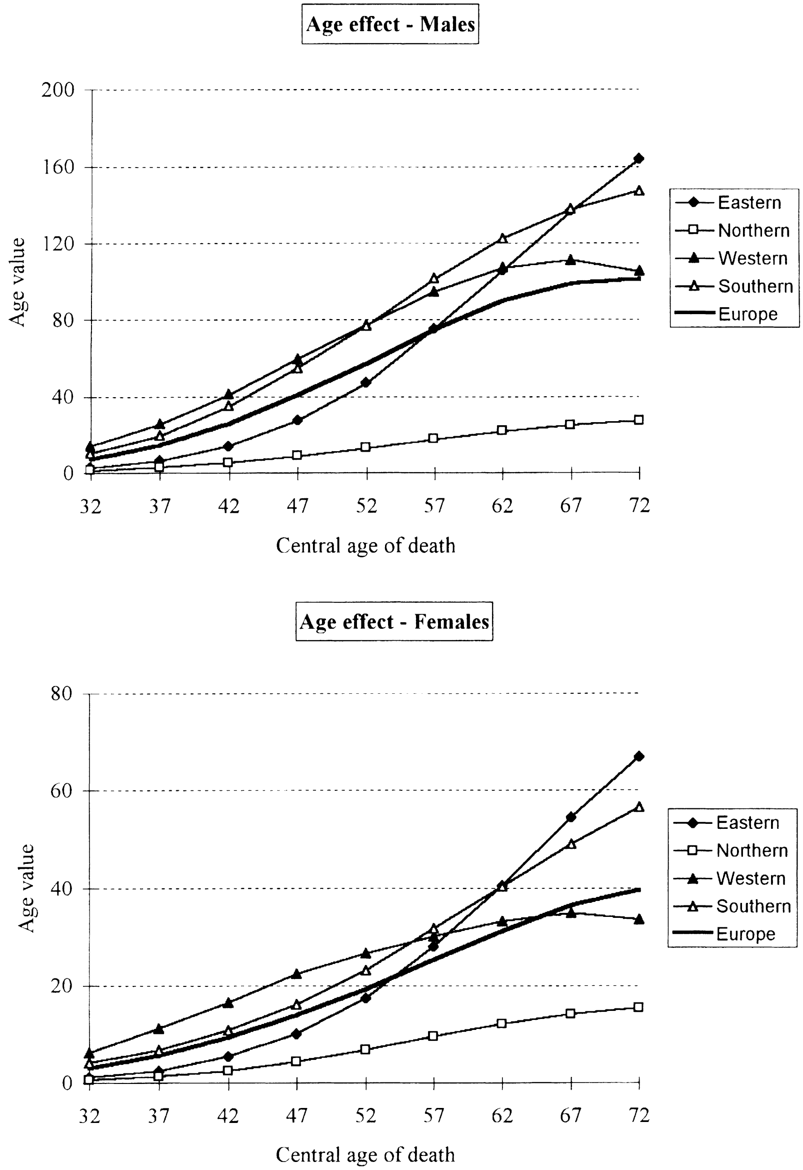

FIGURE 2 *Age effects on the mortality rates from liver cirrhosis in males and females of the whole European population and of the population of the four European Regions. The effects can be considered as mortality rates per 10^{-5} per $year^{-1}$ (age values)*

The opposite, with constantly increasing risk, was observed for Eastern and Northern populations. It must be noted that the Eastern cohort effects reached higher levels: in both males and females, the risk of death of the subjects born 1950–1959 was more than threefold that of the subjects born 1920–1929.

Alcohol Consumption

Figure 4 shows the *per capita* alcohol consumption across Europe between 1961 and 1989. Increasing consumption was observed in the whole European population in the 1960s (+15.8%) and 1970s (+6.9%), followed by a decrease in the 1980s (–11.3%). The

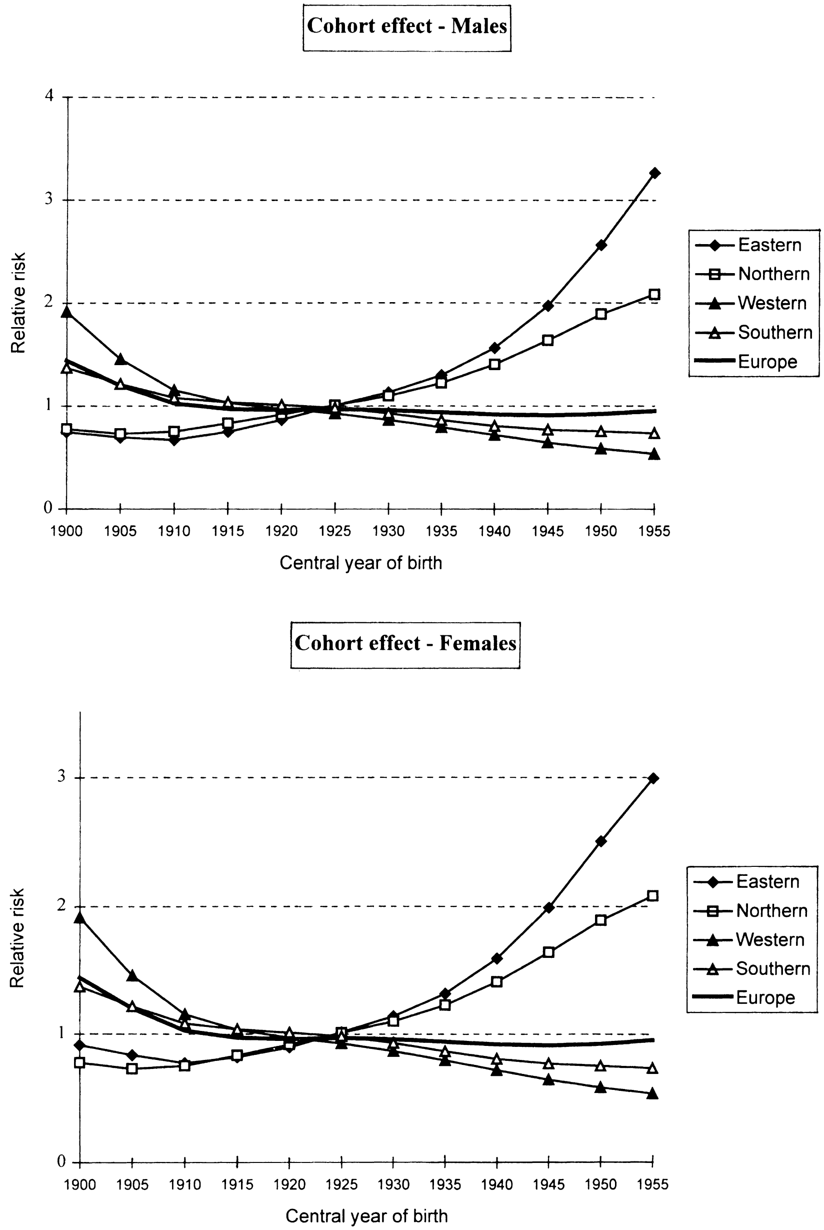

FIGURE 3 *Cohort effects on the mortality rates from liver cirrhosis in males and females of the whole European population and of the population of the four European Regions. The effects were expressed as relative risk of death, considering one as reference value for their weighted average*

highest increase in the first 20 years was observed in Eastern Europe. In this Region, from 1961 to 1980 alcohol consumption had a 95.3% increase, whereas smaller increases were observed over this period in Northern (+54.1%), Western (+5.3%) and Southern (+18.8%) Europe. Decreasing consumption was observed from 1981 to 1989 in Western (–10.6%) and Southern (–19.4%) Europe, while in Eastern and

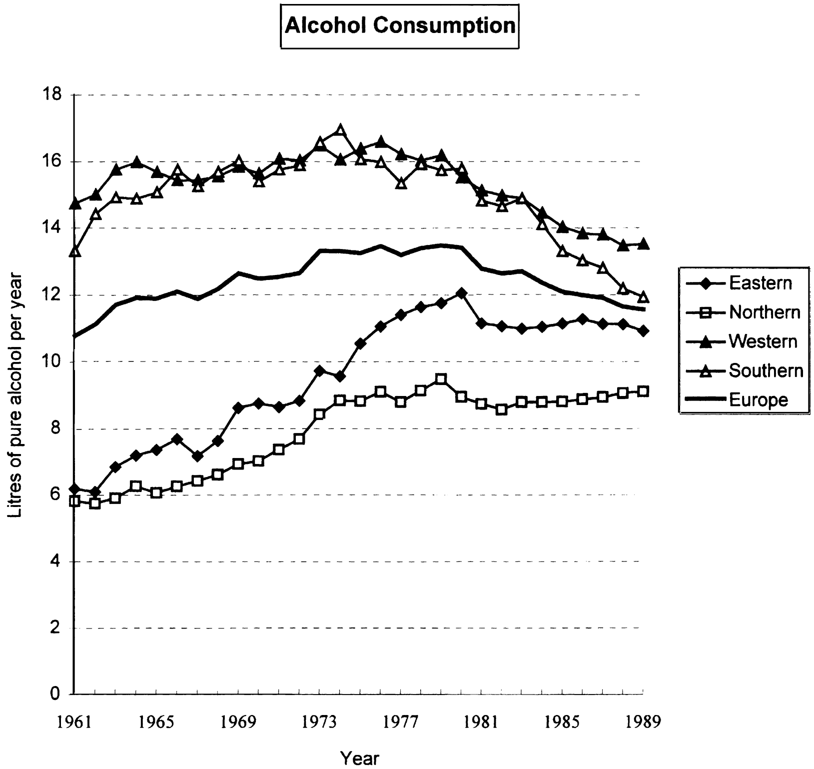

FIGURE 4 *Trends in mean annual alcohol consumption in the whole Europe and in the four European Regions. Data were expressed as per capita consumption in the population aged over 15 years*

Northern Europe lesser variations were observed throughout these years. Moreover, while a wide variability of alcohol consumption was evident at the beginning of the 1960s, with intakes in Western and Southern Europe being more than double those of Eastern and Northern Regions, weak differences between Regions were present at the end of the 1980s.

DISCUSSION

Cohort analysis, as a method for understanding the trend of mortality or of incidence for any disease, was introduced by Frost in his study on tuberculosis mortality.[29] Further developments in age-period-cohort (APC) analysis[20] provided a more appropriate approach for studying the effects on mortality of any disease due to early environmental exposure, contributing to a re-evaluation of descriptive epidemiology, especially for cancer mortality.[30–34]

The APC model used in this paper[28] has the advantage over other methods[35–37] of providing immediate information on the effects studied, although there are still some methodological and interpretative difficulties, discussion of which is outside the scope of this paper.[30,36,37]

We have used APC analysis in the European population in an attempt to understand the recently observed changing trend of mortality from liver cirrhosis in several countries.[6]

The period effects estimated by the log-linear Poisson model presented some differences with respect to the observed age-adjusted rates. In particular, in Eastern and Northern Europe, mortality rates steadily increased over the considered period, while the period effects showed a weak decline (Eastern Europe) or at least stabilization (Northern Europe) in the 1980s. These differences could be due to the temporal variations of the age distribution of those who died from liver cirrhosis, which could have affected the standardized mortality rates. Since our APC model is unable to evaluate interactions between effects, we cannot test this hypothesis.

Ledermann suggested that *per capita* alcohol consumption is a reliable indicator of the proportion of heavy drinkers in a given population, and that alcohol-related problems, such as liver cirrhosis, increase as *per capita* consumption increases.[38] Several epidemiological studies have confirmed the strong association between *per capita* alcohol consumption and cirrhosis mortality.[9–14] Our results suggest a relation between these variables. In Northern Europe, we observed lower levels both of alcohol consumption and of cirrhosis mortality, whereas Western and Southern European populations were characterized by higher levels of both. In these last regions, from the first half of the 1970s to the second half of the 1980s, *per capita* alcohol consumption decreased, and cirrhosis mortality strongly declined. Moreover, in Eastern European populations, from the beginning of the 1970s to the beginning of the 1980s, *per capita* alcohol consumption nearly doubled, and mortality rates increased to a greater degree during this period.

Although our approach is not able to analytically investigate the association between trends in *per capita* alcohol consumption and liver cirrhosis mortality, we can speculate on the descriptive comparison between trends of these variables. In Southern and Western Europe, the decline in alcohol consumption began in 1973–1974, whereas the reduction in liver cirrhosis mortality occurred in 1975–1979. In Northern Europe, the increase in alcohol consumption ended in 1979, followed by a stabilization of intake. Period effects in this region increased until 1975–1979 and were steady thereafter. In Eastern Europe, *per capita* alcohol consumption increased until 1980 and decreased afterwards, whereas period effects in mortality trends increased until 1980–1984 and then a decline was observed in the next period. Our results therefore suggest that rates declined a few years after the decrease in consumption. Several authors have reported similar results. Cirrhosis mortality decreased in Europe during the First and Second World Wars, when rationing of alcohol was in force, and during the prohibition era (1919–1932) in the US,[39] whereas it returned to previous levels when rationing ceased and alcohol was made freely available.[40–43] Analogously, the decline in Canadian and Australian *per capita* alcohol consumption, registered till the middle of the 1970s, was almost contemporaneous with the decrease in cirrhosis mortality.[1,39]

It has been reported that cirrhosis death rates have declined in some countries because of better treatment of alcoholism[7,15–17] suggesting that an important determinant of the decline in liver cirrhosis mortality is the increasing proportion of people receiving treatment for alcohol misuse and the growth of self-help organizations which facilitate abstinence from alcohol. This hypothesis does not directly explain the strong relationship between *per capita* alcohol consumption and liver cirrhosis mortality. It has been reported that almost 20–30% of the European population consumes an excessive amount of alcohol and that this type of drinker probably accounts for 60–70% of the alcohol consumed.[44] This means that when the proportion of people receiving treatment for alcohol misuse in the general population increases, a reduction in average *per capita* alcohol consumption in that population should occur. If this is true, in the countries where a short-term lagged effect is observed, the reduction in liver cirrhosis mortality might not be directly due to the reduction in alcohol consumption, but to improved treatment for alcoholism; the latter directly affects the reduction of average *per capita* alcohol consumption on the one side and the decline of mortality on the other. The reported finding of a 3-month lagged effect of treatment on cirrhosis mortality[16] supports this hypothesis and suggests that treatment does not prevent cirrhosis from developing but improves the prognosis of alcoholics. It has been shown recently that higher alcohol intake is associated with higher probability of liver decompensation,[45] and several authors have also reported that the prognosis is worse for cirrhotics who continue to drink after the diagnosis.[46–49] Thus, if we assume that a pool of pre-mortality cirrhotic alcoholics exist,[16] any increase in treatment for alcoholism would be followed by an immediate reduction in mortality.

Our results showed that the decline in alcohol consumption was not homogeneous during the considered period. The highest decrease was registered in Southern Europe (25%, 1975–1989), whereas a smaller decline was observed in Western Europe (17% during the same period). On the contrary, the highest reduction in cirrhosis mortality was observed in Western Europe (18% and 11% of the period effects from 1975–1979 to 1985–1989 in males and females respectively). In Southern Europe in the same period similar effects produced a 14% and 9% decline respectively. We cannot then exclude that factors other than alcoholism treatment are involved in these phenomena.

We used age-effect analysis in an attempt to clarify the reasons for geographical variations. The effect of the age of death showed a continuously rising trend in the Eastern European population. A different pattern was observed for the Western population, in whom there was an increasing effect up to the 60–64 age group followed by a decreased or at least a stabilization in older subjects. The other regions showed intermediate patterns. It has been reported that the pattern of the mortality risk from post-hepatitic cirrhosis is characterized by a continuous exponential increase with age, whereas alcoholic cirrhosis causes the risk to peak at middle age and decrease thereafter.[50] Our results suggest that alcohol is the prime cause of cirrhosis in Western Europe, whereas in other regions, especially in Eastern Europe, the age effects are suggestive of a mixed alcoholic and viral aetiology. Therefore, besides a 'brief-term' indirect impact of *per capita* alcohol consumption on the liver cirrhosis mortality, a 'long-term' causal impact of alcohol intake could explain a portion of the variability of liver cirrhosis mortality trends, especially in Western countries. However, due to our short time series, we cannot test this hypothesis.

A birth-cohort effect was observed in the European population as a whole, showing a decreasing risk of death from cirrhosis in the most recent generations. Again, interesting geographical variations were observed: in Western and Southern Europe where the risk decreased to a greater extent than in the whole of Europe, however, the opposite was true in Eastern and Northern Europe, with a relevant increase in risk in the most recent generations. Our results therefore suggest that in Western and Southern European populations the reduction in mortality rates observed in the last decades is likely to continue in the future. Data showing a strongly increased risk of mortality for cirrhosis in the younger generations of Northern and Eastern Europe would predict, however, an increase in cirrhosis mortality in the next decades in these areas, as the generations born between 1940 and 1960 will reach the age of higher risk of death from liver cirrhosis.

This discrepancy may be due to a combination of factors changing in past years. The use of alcohol at a younger age, the risk of Hepatitis B virus infection in younger generations,[51,52] and changed dietary habits[53–57] are some of the putative factors. However, further data are needed to understand these different trends.

In conclusion, we have shown that age-period-cohort analysis is able to generate hypotheses to interpret the trends in liver cirrhosis mortality. The current application of age-period-cohort analysis on European liver cirrhosis mortality gives additional evidence about the different role of aetiological and prognostic factors in the European areas, the changing levels of exposure to the aetiological and prognostic factors in different populations, and makes it possible to hypothesize future trends in liver cirrhosis mortality. To better understand these trends, more detailed information on alcohol habits, alcoholism treatment rates, viral hepatitic infections and other factors involved in the aetiopathogenesis of the disease are required. The alarming prediction of increasing mortality from cirrhosis in some regions of Europe, should be taken as a pointer to implement preventive and educational programmes in these areas.

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