Behaviour does not fully explain the high risk of chronic liver disease in less educated men in Hungary

Beáta É. Petrovski¹, György Széles¹, Márta Melles², Vera Pataki³, László Kardos¹, Tibor Jenei¹, Róza Adány¹,⁴ Zoltán Voko¹

1 Department of Preventive Medicine, Faculty of Public Health, Medical & Health Science Centre, University of Debrecen, Kassai ut 26/b, Debrecen, Hungary, H-4012
2 National Center for Epidemiology, Gyáli ut 2-6, Budapest, Hungary, H-1097
3 GlaxoSmithKline Ltd., Csoórz u. 43, Budapest, H-1124
4 Public Health Research Group of the Hungarian Academy of Sciences, at the Medical & Health Science Centre, University of Debrecen, Debrecen, Hungary

Correspondence: Zoltán Voko, MD MSc PhD, Department of Health Policy & Health Economics, Institute of Economics, Faculty of Social Sciences, Eötvös Loránd University, H-1117 Budapest, Pázmány Péter sétány 1/a, tel: +36 1 209 0555/6865, fax: +36 1 372 2997, e-mail: voko@caesar.elte.hu

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Background: Hungary has among the highest mortality rates from chronic liver disease (CLD) and cirrhosis in Europe. Usually, conventional behavioural factors are hypothesized as the cause of the high risk of CLD. Methods: A case–control study was performed with 287 cases and 892 controls to study the relationship between socio-economic and behavioural factors and the risk of CLD. Liver disease was verified by physical examination and blood tests. Blood samples were collected for detecting hepatitis B, C and E virus infection. Information on exposure factors was recorded by the participating physicians and by self-administered questionnaire. Simple regression analysis was used to study the relationship between CLD/cirrhosis and potential risk factors as alcohol intake (amount and source), problem drinking, cigarette smoking, physical activity, viral hepatitis infections, socio-economic factors (education, financial and marital status). Multiple regression analysis was used to identify whether the effect of socio-economic factors is fully mediated by health behaviour (smoking, alcohol consumption, physical activity). Results: The univariate analysis showed that heavy alcohol consumption, problem drinking, former and heavy cigarette smoking, single, separated or divorced marital status, bad or very bad perceived financial status and lower education significantly increased the risk of CLD/cirrhosis. The effect of marital status and of education did not change after adjustment for behavioural factors, but the effect of perceived financial status disappeared. Conclusions: The effect of low socio-economic status on the risk of CLD/cirrhosis is only partially explained by conventional behavioural risk factors in Hungary.

Keywords: alcohol consumption, chronic liver disease, cirrhosis, Hungary, socio-economic status

Introduction

Chronic liver disease (CLD) and cirrhosis are among the leading causes of death in Hungary.¹ Unlike in Western societies where mortality from cirrhosis was traditionally low in the 1990s, the Central and Eastern European (CEE) countries experienced an increasing occurrence of deaths due to this disease.²,³ Mortality of CLD increased in Hungary between the 1970s and the mid-1990s, since then it decreased considerably, but even in 2005 the standardized death rate of CLD was still 4.3 higher in Hungarian men and 3.5 higher in Hungarian women than the average rate of the 15 member states of the European Union which joined before May 2004.¹,⁴

Several research groups have studied the behavioural risk factors of CLD focusing mainly on the role of alcohol consumption.⁵–⁷ One recent study has shown that alcohol accounts for a high proportion of premature mortality in CEE countries.⁸ Besides the quantity of the alcohol consumed, its quality was also put forward as a potential cause of the excess mortality.⁷,⁹ Other risk factors play a role in the aetiology of CLD independently or together with alcohol intake. Viral hepatitis alone or synergistically with alcohol may accelerate the development and progression of liver disease.¹⁰ Furthermore, cigarette smoking has also been shown to be a risk factor for CLD.¹¹ Besides behavioural factors CLD has repeatedly been reported to be associated with low socio-economic status (SES).¹²,¹³

We investigated whether behavioural risk factors including alcohol consumption, cigarette smoking, physical activity and hepatitis infection could explain the increased risk of CLD in men with low SES in Hungary.

Methods

A case–control study was conducted involving 287 cases and 892 controls. Participants were recruited from the source population of the General Practitioners’ Morbidity Sentinel Station Program (GPMSSP) in four counties (Hajdú-Bihar, Gyor-Moson-Sopron, Szabolcs-Szatmár-Bereg, Zala). Details of the GPMSSP have already been published.¹⁴ Briefly, in the sentinel station programme general practitioners report the occurrence of non-communicable diseases with major public health importance in a quality-managed system. Besides
continuous monitoring, the programme provides a research framework for epidemiological and health services research.

The four counties involved in the study represent well-recognized differences in health as well as economic development in Hungary. The source population of the study consisted of men who were 45–64 years old on 31 December 2004 and were registered at one of the participating 55 district general practitioners’ (GP) practices as of 1 May 2005. Written informed consent was obtained from all participants. The study was approved by the local ethical committee of the University of Debrecen.

Potential cases were patients who had been reported to have CLD or liver cirrhosis in the regular monitoring programme. In the framework of this study, these people were examined by their family physicians and blood samples were taken for laboratory tests. Only those people were included as case in the study who fulfilled the following diagnostic criteria: had at least two symptoms of spider nevus, ascites, palmar or plantar erythema, jaundice, enlarged, firm liver with rounded or nodular edge and had at least one positive laboratory test result of increased level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl-transpeptidase (γGT), alkaline phosphatase, bilirubin or decreased serum albumin. Controls were randomly selected from the source population. Case verification was performed among controls as well. Those who met the case criteria (100 people) were included in the study both as case and as control.

Blood samples were tested for the presence of antibodies to hepatitis C and E antigen (anti-HCV and anti-HEV), hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B core antigen (anti-HBc) (ELISA method, Biomerieux, France and DiaPro, Italy). A person was considered hepatitis B virus infected if the HBsAg or the anti-HBc was found positive. Similarly, people positive for anti-HCV and anti-HEV were considered hepatitis C and E virus infected, respectively.

Participants were asked to fill in a self-administered questionnaire about their SES including marital status, education and financial status, on health behaviours including physical activity, alcohol consumption (both the amount and the source of alcohol) and smoking. Marital status was categorized as married or lives with a partner; single, separated or divorced; and widowed. Financial status was categorized based upon the subjects’ own assessment into very good or good; satisfactory; and bad or very bad. Educational level was categorized as elementary school or less; high school without certificate of final examination; high school with certificate of final examination; and college or university degree. According to the frequency and quantity of alcohol consumed, alcohol consumption was classified into four categories. Those participants were considered heavy drinkers who had consumed >14 U of alcohol in the week before being asked or their daily alcohol consumption exceeded 5 U on any day of the week (1 U equals 15 g of alcohol); moderate drinkers were those who had consumed alcohol in the week before being asked, but did not qualify as heavy drinkers; occasional drinkers had not consumed alcohol in the week before being asked but before that period had consumed an alcoholic drink; men who never consumed alcoholic beverages were considered abstinent. The CAGE (Cut-Annroyed-Guilty-Eye) questionnaire on problem drinking was also part of the self-administered questionnaire. The CAGE questionnaire consists of four questions. A person who answered at least two questions positively was identified as a problem drinker. Non-problem drinkers were those who gave less than two positive answers. Besides the quantity and the form of alcohol consumed, questions were asked about the source of wine and spirit consumed. The source was categorized as controlled or uncontrolled (black market, house- or self-made). Smoking was categorized as never smoker, former smoker, occasional smoker (smokes but not every day), daily smoker (everyday but <20 cigarettes per day) and heavy smoker (at least 20 cigarettes per day). Based upon the type and frequency of the activity, physical activity was classified as sufficient physical activity (at least 150 min week−1 spent on walking/moderate/intensive activity in the previous 7 days), insufficient physical activity (less than sufficient but more than inactive) and inactive (no time spent on walking/moderate/intensive activity in the past 7 days).

The chi-square ($\chi^2$) test was used to test differences of the distributions of categorical variables. To study the relationship between the CLD/cirrhosis and the potential risk factors, we first fitted simple logistic regression models with each risk factor. We are reporting crude odds ratios (ORs) and their 95% confidence intervals (CIs) from these models. Next, to study whether the effect of socio-economic factors is fully mediated by health behaviour, we fitted a multiple regression model with the socio-economic factors (education, financial status, marital status), behavioural factors (smoking, alcohol consumption, physical activity) and age as explanatory variables. We did not adjust for the source of wine and the source of spirit consumed because none of these were associated with education, financial status or marital status, and we had a lot of missing values on these two variables. The multiple logistic regression model was fitted on the data of 638 controls and 181 cases who did not have missing values on any variable.

Finally, we studied whether the remaining effect of socio-economic factors could be explained by hepatitis B or E virus infection.

We used the statistical software package Stata (Intercooled Stata 8.0, Stata Corporation, College Station, TX, USA) for the analysis.

## Results

We selected 692 persons as potential cases, who were reported to have CLD/cirrhosis in the regular monitoring programme. Of them, 407 agreed to participate, but only 187 fulfilled the diagnostic criteria. From the source population 1181 persons were randomly selected as potential controls. Of them 892 persons agreed to participate in the study. Hundred selected controls fulfilled the diagnostic criteria for being a case; therefore they were included as cases and controls as well according to the planned case-reference study design.

Heavy alcohol consumption was associated with >2-fold increased risk, and former/heavy smokers had significantly increased risk of CLD/cirrhosis. Problem drinking increased the risk of CLD/cirrhosis four times in the univariate analysis (table 1). Half of the participants, both cases and controls, obtained their wine from uncontrolled sources, and one-fifth of the cases and one-quarter of the controls got their spirit consumed from uncontrolled sources (table 1). Single, separated or divorced marital status statistically significantly increased the risk of CLD/cirrhosis compared with being married or living with a partner. Participants with higher education (high school with certificate, college or university degree) had CLD/cirrhosis risks reduced by 40 and 70% compared with participants with only elementary education. Persons who thought that their financial status was bad or very bad had an 80% increased risk of the disease compared with persons with good or very good perceived financial status (table 1).

Table 2 shows that the effect of marital status and the effect of education basically did not change after adjustment for behavioural factors, whereas the effect of perceived financial status disappeared.
The prevalence of HBV infection was 9.8% and the prevalence of HEV infection was 8.2% among cases. The corresponding figures among controls were 9.7 and 9.7%, respectively. Only five persons had HCV infection. Neither hepatitis B (OR 1.0, 95% CI 0.67–1.7) nor hepatitis E (OR 0.89, 95% CI 0.55–1.5) infection was associated with the risk of CLD/cirrhosis. Since hepatitis E infection was not associated either with CLD or with marital status, or with education, it could not explain the remaining effects of the socio-economic factors. On the other hand HBV infection was statistically significantly associated with education. The prevalence of the infection was 13.4% among persons with only elementary education and 7.5% among those who had college or university degree. Nevertheless, adding hepatitis B to the multivariate model did not change the effect estimates of education and marital status.

The association between socio-economic factors, health behaviour and the risk of CLD/cirrhosis after adjustment for health behaviour factors are presented in Table 2.

**Table 2** The association between socio-economic status and the risk of CLD/cirrhosis after adjustment for health behaviour factors

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marital status</td>
<td></td>
</tr>
<tr>
<td>Married or lives with a partner</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Single, separated or divorced</td>
<td>1.9 (1.2–3.1)</td>
</tr>
<tr>
<td>Widowed</td>
<td>1.6 (0.67–3.7)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Elementary school or less</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>High school without certificate</td>
<td>0.94 (0.61–1.5)</td>
</tr>
<tr>
<td>High school with certificate</td>
<td>0.64 (0.37–1.1)</td>
</tr>
<tr>
<td>College or university degree</td>
<td>0.35 (0.16–0.77)</td>
</tr>
<tr>
<td>Perceived financial status</td>
<td></td>
</tr>
<tr>
<td>Good/very good</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Satisfactory</td>
<td>0.94 (0.53–1.7)</td>
</tr>
<tr>
<td>Bad/very bad</td>
<td>0.98 (0.50–1.9)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.

**Discussion**

We found that Hungarian men aged 45–64 years had an increased risk of developing CLD/cirrhosis if they were heavy or problem drinkers, former or heavy smokers, single, separated or divorced or had bad or very bad perceived financial status. Higher education was associated with a decreased risk.

Our results regarding the behavioural factors are in line with previous findings. It has been shown that not only the amount of the alcohol consumed should be considered in the development of liver disease, but also the quality of the alcohol.9 However, our proxy measure of the quality of alcohol consumed—the source of obtaining it—was not related to the risk of CLD/cirrhosis in our study. The relationship between former smoking, regular smoking and the risk of liver disease has been shown previously.11 Cigarette smoking itself has been suggested to play a crucial role in the late stage of liver disease development and CLD patients may benefit from earlier smoking cessation.10

The association between HBV and liver disease development is well established.21,22 It is widely accepted that viral hepatitis and alcohol, independently or combined, can have a liver damaging effect.15 Furthermore, HEV infection can cause acute exacerbations in both recognized and unrecognized asymptomatic HBV-related CLD.23 Almost every 10th person was HBV or HEV infected in our study population; however, we did not find a significant association between hepatitis infection and CLD/cirrhosis.

A limitation of this study is the use of prevalent cases of CLD/cirrhosis, thus cases with rapid progression were less likely to be included in it. This may result in an underestimation of the effect of risk factors that are also related to the poor prognosis of the disease. Therefore this bias may explain why we did not find an association between hepatitis B infection, source of alcohol consumed and the risk of CLD/cirrhosis. Since the disease status and the potential risk factors were assessed at the same time, it is possible that in some instances the presence of a risk factor was the consequence of CLD/cirrhosis. Taking into account the nature of the studied risk factors, this may bias the association of marital status, financial status and CLD/cirrhosis. Since we did not have 100% response rate either among the cases or among the controls, selection bias could occur in our study. The distribution of the social and behaviour factors among the participants probably did not entirely represent the distributions.

**Table 1** The relationship between socio-economic factors, health behaviour and the risk of CLD/cirrhosis

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Cases (N = 287)</th>
<th>Controls (N = 892)</th>
<th>Crude OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinent</td>
<td>55.0 (0.3)</td>
<td>53.8 (0.2)</td>
<td>1.5 (1.2–1.9)*</td>
</tr>
<tr>
<td>Occasional drinker</td>
<td>34 (13.5)</td>
<td>152 (18.3)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Moderate drinker</td>
<td>12 (4.8)</td>
<td>84 (10.1)</td>
<td>0.64 (0.31–1.3)</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>39 (15.5)</td>
<td>184 (22.2)</td>
<td>0.95 (0.57–1.6)</td>
</tr>
<tr>
<td>Problem drinking</td>
<td>167 (66.3)</td>
<td>410 (49.4)</td>
<td>1.8 (1.2–2.8)</td>
</tr>
<tr>
<td>Non-problem drinker</td>
<td>82 (34.2)</td>
<td>499 (68.6)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Problem drinker</td>
<td>158 (65.8)</td>
<td>228 (31.4)</td>
<td>4.2 (3.1–5.7)</td>
</tr>
<tr>
<td>Source of wine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>112 (50.2)</td>
<td>331 (31.0)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>111 (49.8)</td>
<td>318 (49.0)</td>
<td>1.0 (0.76–1.4)</td>
</tr>
<tr>
<td>Source of spirit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>135 (79.9)</td>
<td>417 (74.6)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>34 (20.1)</td>
<td>142 (25.4)</td>
<td>0.74 (0.49–1.1)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>62 (22.0)</td>
<td>288 (32.8)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>100 (35.5)</td>
<td>270 (30.8)</td>
<td>1.7 (1.2–2.5)</td>
</tr>
<tr>
<td>Occasional smoker</td>
<td>10 (3.5)</td>
<td>28 (3.2)</td>
<td>1.7 (0.77–3.6)</td>
</tr>
<tr>
<td>Daily smoker</td>
<td>33 (11.7)</td>
<td>95 (10.8)</td>
<td>1.6 (1.0–2.6)</td>
</tr>
<tr>
<td>Heavy smoker</td>
<td>77 (27.3)</td>
<td>197 (22.4)</td>
<td>1.8 (1.2–2.7)</td>
</tr>
<tr>
<td>Physical Activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>7 (3.4)</td>
<td>10 (1.5)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Insufficient</td>
<td>15 (7.4)</td>
<td>45 (6.6)</td>
<td>0.48 (0.15–1.5)</td>
</tr>
<tr>
<td>Sufficient</td>
<td>182 (89.2)</td>
<td>628 (91.9)</td>
<td>0.41 (0.16–1.1)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married or lives with a partner</td>
<td>216 (75.5)</td>
<td>747 (84.3)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Single, separated or divorced</td>
<td>58 (20.3)</td>
<td>116 (13.1)</td>
<td>1.7 (1.2–2.5)</td>
</tr>
<tr>
<td>Widowed</td>
<td>12 (4.2)</td>
<td>23 (2.6)</td>
<td>1.8 (0.88–3.7)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary school or less</td>
<td>86 (30.2)</td>
<td>205 (23.3)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>High school without certificate</td>
<td>139 (48.8)</td>
<td>387 (43.9)</td>
<td>0.86 (0.62–1.2)</td>
</tr>
<tr>
<td>High school with certificate</td>
<td>46 (16.1)</td>
<td>183 (20.8)</td>
<td>0.60 (0.40–0.90)</td>
</tr>
<tr>
<td>College or university degree</td>
<td>14 (4.9)</td>
<td>106 (12.0)</td>
<td>0.30 (0.17–0.58)</td>
</tr>
<tr>
<td>Perceived financial status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good/very good</td>
<td>28 (9.8)</td>
<td>122 (13.8)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Satisfactory</td>
<td>194 (67.6)</td>
<td>606 (68.5)</td>
<td>1.4 (0.90–2.2)</td>
</tr>
<tr>
<td>Bad/very bad</td>
<td>65 (22.6)</td>
<td>157 (17.7)</td>
<td>1.8 (1.1–3.0)</td>
</tr>
</tbody>
</table>

Data in the columns of cases and controls are counts (%) for categorical or means (SD) for continuous variables. a: Corresponding to 10 years difference in age. OR, odds ratio; CI, confidence interval.
in the source population. Nevertheless, we did not want to estimate the occurrence of these factors in the population but studied the strength of association between them. If the associations between these factors and the non-response were similar among cases and controls, then this selection bias could hardly bias the association measures.

Marital status and education were strongly related to the risk of CLD/cirrhosis even after adjustment for the studied behavioural factors. This means that there must be other important behavioural or environmental factors, which are related to low socio-economic and are important risk factors of CLD/cirrhosis. Diet, obesity and diabetes are known to be associated with the risk of CLD/cirrhosis.24,25 In our study, we had no information about these risk factors prior to the occurrence of CLD/cirrhosis.

Interestingly, the effect of bad perceived financial status was entirely explained by the behavioural factors. In the Hungarian National Health Interview Survey 2003, the association between financial status and smoking was much stronger and unambiguous as compared with the association between smoking and education.26 Financial status was categorized in five categories in that survey by the combination of the household income and property. The odds of heavy drinking were approximately half in every category of the financial status compared with the poorest. Heavy drinking was not related to education. Physical activity was strongly related to financial status but not to education. In a recently published paper, the association between health and subjective and objective measures of the SES among Hungarian adolescents was reported. The authors concluded that 'SES self-assessment proved to be a significant predictor of adolescents’ psychosocial health and health behaviours; ... parents’ employment status and schooling had a limited influence on their children’s health outcomes'.27 One explanation for these and our findings can be that perceived financial status is a subjective and education, parents’ employment status and schooling are objective measures of the SES. Wilkinson put forward the theory that it is not the absolute levels of SES that are important for health but rather inequality resulting from relative standing.28 Our findings might be an empirical evidence supporting this theory. Our results on the other hand also support the view that explaining the high risk of CLD in men with low SES only by behavioural factors is probably an oversimplification.

Although reducing smoking and heavy alcohol consumption should be among the top priorities of any public health programmes in Hungary, better understanding of the risk factors of CLD/cirrhosis that are related to low SES would give new clues to find other means to reduce the high level of premature mortality due to this disease.

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Conflicts of interest: None declared.

Key points

- Behavioural risk factors do not fully explain the increased risk of CLD/cirrhosis in men with low SES in Hungary.
- Better understanding of the risk factors of CLD/cirrhosis that are related to low SES would give new clues for reducing the high level of premature mortality due to this disease in Hungary.
- Reducing smoking and heavy alcohol consumption should remain being among the top priorities of any public health programmes in Hungary.

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