

Alcohol Consumption and Mortality in Serbia: Twenty-year Follow-up Study

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Aim. To investigate the connection between alcohol consumption and general and specific mortality in the Serbian population.

Methods. Total of 286 healthy middle-aged participants of both genders enrolled in a prospective follow-up study in 1974. During the following 20 years, 80 deaths occurred. The data on underlying causes of death were obtained from official death certificates. Alcohol consumption was estimated from a multiple-choice questionnaire. According to the total daily alcohol intake, subjects were classified into 3 groups: none- or rare drinkers, moderate, and heavy drinkers. The relative risks (RR) adjusted for gender, smoking, body mass index, and blood pressure were calculated using non-drinkers as a reference category.

Results. Heavy drinkers exhibited significantly higher adjusted ratios for all-cause mortality (RR = 1.970, 95% confidence interval [CI] = 1.062-3.651; $p = 0.031$) and myocardial infarction (RR = 2.463, 95% CI = 1.050-5.775; $p = 0.038$), and non-significantly higher risk for death from other causes. Moderate drinkers exhibited lower adjusted risk ratios for all-cause mortality, myocardial infarction and death from other causes, but this decrease did not reach the significance level. Further, overall probability of survival at every time point was the highest among moderate drinkers and lowest among heavy drinkers.

Conclusion. Among Serbian middle-aged population moderate alcohol consumption reduced mortality from all causes, myocardial infarction and other causes of death, and increased the probability of survival in a twenty year follow-up period. Heavy drinking increased mortality rates from all causes and reduced the twenty year-survival probability in comparison with non-drinkers.

Key words: alcohol drinking; cerebrovascular accident; follow-up studies; mortality; myocardial infarction; survival

Many studies investigated the effects of alcohol consumption on mortality (1). The relation with all-cause mortality is usually reported as U- or J-shaped, with moderate consumers having the lowest risk of mortality and high consumers the highest (2-4). However, there may be problems with the selection of the non-drinkers group, since sick people may not drink because of their illness, leading to an apparent increased risk of mortality among them (5). Moderate consumption of alcohol may protect against coronary heart disease, but whether this is true for all types of alcohol or just for wine is unclear (6,7).

The aim of the study was to establish the relation between alcohol consumption and general and specific mortality during the follow-up period.

Participants and Methods

We performed a twenty-year prospective follow-up study of healthy middle-aged participants who reported their alcohol consumption, with detailed information on risk factors which might

act as confounders, including smoking, body mass index, and blood pressure.

Sample

There were 500 subjects aged 30-60 years, assessed for eligibility at the Institute for Chronic Diseases and Gerontology – Center for Hypertension, Belgrade, Serbia and Montenegro in 1974 (Fig. 1). After a detailed clinical examination, 65 subjects were excluded from the study due to the presence of chronic diseases ($n = 48$) or a refusal to participate ($n = 17$). Twenty years later (1994) the investigation was repeated in the Center for Blood Pressure Disorders, Institute for Cardiovascular Diseases of the Clinical Center of Serbia, Belgrade. During the follow-up 130 patients were lost ($n = 36$) out of 435 subjects enrolled either due to loss of contact or quitting of the study (94). After analyzing the data on 305 patients at the end of the follow-up period, we excluded 19 subjects due to insufficient information. The final analysis included 286 participants, 145 men and 141 women, who enrolled in the study in 1974. During the follow-up, 80 persons died. The information about the underlying cause of death (all causes, myocardial infarction, stroke and other causes) were obtained from official death certificates.

Outcome Measures

Anthropometric parameters and arterial pressure were measured at the outpatient clinic, usually in the early morning. Body

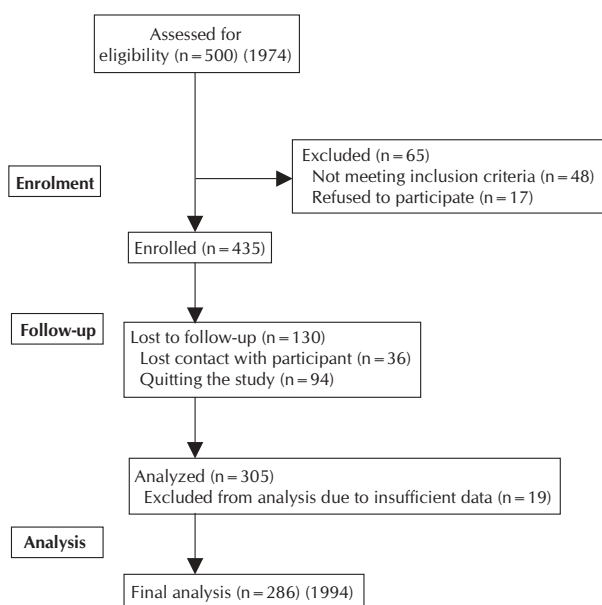


Figure 1. Scheme of the study.

weight was measured in underwear and body height without shoes, and from these the body mass index was calculated (weight [kg]/height² [m²]). Blood pressure (mmHg) was measured at the end of the physician’s examination, with the participant lying down, and the average of 3 consecutive measurements was recorded

All participants filled in a self-administered questionnaire concerning general characteristics: age, marital status, education, personal and family history of cardiovascular diseases, and various health related issues, including drinking and smoking habits.

Considering smoking habits, the subjects reported if they had never smoked or were former or current smokers; the latter two groups were united for the further analysis due to low number of former smokers.

Participants were asked in the multiple-choice format to describe their intake of alcoholic drinks, separately for each beverage type (beer, wine, and spirits). The choices were hardly ever/never, monthly, weekly, or daily. One standard drink is generally considered to be 1 bottled beer (350 ml), 1 glass of wine (150 ml), or 1 measure (40 ml) of distilled spirits. Each of these drinks contains roughly the same amount of absolute alcohol – 10 to 12 grams (8). According to the guidelines from the National Institute on Alcohol Abuse and Alcoholism, Bethesda, USA, moderate drinking is defined as no more than 1 drink a day for women (not pregnant), and no more than 2 drinks a day for men (8). The subjects were then classified into 3 groups according to the total daily intake of alcohol: rarely or never (less than 1 beverage a day), moderate drinking (1-2 beverages a day), and heavy drinking (more than 2 drinks a day). The comparison of distribution according to drinking habits among the participants who survived showed that 84% of them stayed in the same category of alcohol consumption at the end of the study. That is why we hypothesized that changes in drinking habits did not affect the reliability of statistical reasoning for the whole sample.

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Statistical Analysis

Descriptive statistics were presented as mean values ± standard deviation (SD) for numeric variables, or as percents (relative numbers) for categorical variables.

Differences in the age at the beginning of the study, body mass index, and systolic and diastolic blood pressure between groups were compared with parametric one-way analysis of variance (ANOVA) and least significant differences (LSD) *post hoc* test for multiple comparisons, because these data had normal distribution.

Differences between categorical data were tested by chi-square test. Because we performed 15 consecutive statistical analyses with chi-square test, we chose a level of significance of 0.003 – α -adjustment according to modified Bonferroni procedure for multiple comparisons.

Cox’s regression analysis was performed in order to calculate adjusted relative risks for consumption and mortality from all causes and from specific causes (myocardial infarction, stroke, and other causes), using the nondrinkers as a reference category. Relative risk was adjusted for gender, smoking habits, body mass index, and blood pressure groups (according to the 7th Report of the Joint National Committee on detection, evaluation, and treatment of high blood pressure, ref. 9). Also, Kaplan-Meier method was used for survival analysis.

Statistical analyses were performed using Statistica (Version 6; StatSoft, Inc., Tulsa, OK, USA).

With α error of 0.05 and β error of 0.20 (power 80%) and this sample size, statistically significant difference in proportions that could be identified equaled 0.2.

Results

The majority of participants reported no or rare consumption of alcoholic beverages, whereas moderate and heavy alcohol consumption were reported by a quarter of the respondents each (Table 1). The gender distribution of the participants was similar: 145 (50.7%) men and 141 (49.3%) women. However, men predominated in the group with heavy alcohol consumption and women were the majority in the other two groups ($p < 0.001$). No statistically significant differences were observed considering the average age of the participants at the beginning of the study ($p = 0.083$).

There was significant correlation between alcohol consumption and smoking habits of the study

Table 1. Characteristics of study participants according to alcohol consumption at the beginning of the study 1974.

Characteristic	Alcohol consumption			Total	p
	rarely or never	moderate (1-2 drinks/day)	heavy (≥3 drinks/day)		
No. (%) of participants	140 (49.0)	71(24.8)	75 (26.2)	286 (100.0)	
Age at the beginning of the study	43.8 ± 6.7	43.4 ± 7.9	44.9 ± 6.6	43.6 ± 7.1	0.083*
Percent of men	28.3 [‡]	24.8 [§]	46.9	50.7	<0.001 [†]
Prevalence of smokers (%):					
current	32.86 [‡]	28.17	33.33	31.82	<0.001 [†]
former	1.43	1.41	2.67	1.75	
Body mass index (kg/m ²)	26.5 ± 3.4	27.2 ± 3.4	27.6 ± 3.3	27.0 ± 3.3	0.056*
Systolic blood pressure (mmHg)	135.3 ± 19.9	128.3 ± 15.9	137.4 ± 18.7	134.1 ± 18.9	0.008*
Diastolic blood pressure (mmHg)	87.5 ± 11.2	83.8 ± 11.2	89.2 ± 12.3	87.0 ± 11.5	0.012*

*ANOVA.

[†]Chi square test.

[‡] $p < 0.002$ vs moderate, and $p < 0.001$ vs heavy; chi-square test.

[§] $p < 0.001$ vs heavy; chi square test.

^{||} $p < 0.023$ vs moderate; LSD *post hoc* test.

^{††} $p = 0.004$ vs heavy; LSD *post hoc* test.

Table 2. Distribution of death events (No., %) in the 1974-1994 period according to alcohol consumption in 1974

Cause of death	Alcohol consumption			Total (n = 286)	p*
	rarely or never (n = 140)	moderate (n = 71)	heavy (n = 75)		
All causes	36 (25.7) [†]	10 (14.1) [‡]	34 (45.3)	80 (28.0)	<0.001
Myocardial infarction	15 (10.7) [‡]	5 (7.0) [‡]	22 (29.3)	42 (14.7)	<0.001
Stroke	5 (3.6)	2 (2.8)	0 (0.0)	7 (2.4)	0.372
Other causes	16 (11.4)	3 (4.2) [§]	12 (16.0)	31 (10.8)	0.016

*Chi square test.

[†]p = 0.003 vs heavy; chi square test.[‡]p < 0.001 vs heavy; chi square test.[§]p = 0.019 vs heavy; chi square test.**Table 3.** Mortality rate (per 1,000 person/years) for death from all causes, myocardial infarction, stroke and death from other causes in relation to alcohol consumption

Cause of death	Alcohol consumption		
	rarely or never	moderate	heavy
All causes	13.94	7.40	27.07
Myocardial infarction	5.81	3.70	17.52
Stroke	1.94	1.48	0.0
Other causes	6.20	2.22	9.55

Table 4. Relative risks (95% confidence intervals, CI) adjusted for gender, smoking, body mass index, and blood pressure of total mortality, myocardial infarction, stroke and death from other causes in relation to alcohol consumption

Cause of death	Relative risk (95%CI) [†]		
	rarely or never*	moderate	heavy
All causes	1	0.533 (0.258-1.102)	1.970 [‡] (1.062-3.651)
Myocardial infarction	1	0.515 (0.180-1.473)	2.463 [‡] (1.050-5.775)
Stroke	1	1.138 (0.207-6.268)	— [§]
Other causes	1	0.418 (0.118-1.481)	2.488 (0.863-7.177)

*Reference value.

[†]Cox's regression analysis.[‡]p < 0.05.[§]Statistical analysis was not conducted due to lack of death cases.

group. Less than a third of all smokers (including ex-smokers) belonged to moderate drinkers, with the tendency of increase among abstainers and heavy drinkers ($p < 0.001$). Statistically, most smokers belonged to the group of heavy drinkers, less to rare or never drinkers, and the least percent to moderate drinkers. The same pattern was observed for blood pressure values: systolic pressure levels were the lowest among moderate drinkers and increased in abstainers and heavy drinkers; the differences between moderate and non- or rare drinkers were highly statistically significant ($p = 0.011$) as well as differences between moderate and heavy drinkers ($p = 0.004$). Diastolic pressure levels were also lower among moderate drinkers compared to the other two groups ($p = 0.012$). Moderate drinkers had significantly lower diastolic blood pressure compared to non- or rare drinkers ($p = 0.023$), or heavy drinkers ($p = 0.004$). The three groups had similar values of body mass index at the beginning of the study ($p = 0.056$).

A total of 80 deaths were registered during the twenty-year follow up; 42 of these were attributable to myocardial infarction, 7 to stroke, and 31 to other causes of death (Table 2). The average age at the time of death was 60.9 ± 6.8 years and similar in all 3 groups of alcohol consumption. Considering death from all causes, myocardial infarction and other causes, the lowest fraction of participants who died

were moderate drinkers, with important increase among abstainers and heavy-drinking participants – the differences reaching high statistical significance for general mortality and myocardial mortality ($p < 0.001$) and mortality from other causes ($p = 0.016$). Similarly, the lowest number of participants who died from stroke included moderate drinkers, whereas all others were abstainers, showing no statistical difference between the groups ($p = 0.372$).

Between-group comparisons revealed highly significant differences between moderate and heavy drinkers considering death from all causes, myocardial infarction and death from other causes. The frequency of death from all causes and myocardial infarction was significantly higher among heavy drinkers compared to rare or non-drinkers.

Moderate drinkers exhibited the lowest crude mortality rates for death from all causes, myocardial infarction, stroke and death from other causes (Table 3). Heavy drinkers exhibited the highest crude mortality rates for all-cause mortality, myocardial infarction and death from other causes. Abstainers or those who rarely drank had the highest mortality rate for stroke compared to moderate alcohol consumption category.

Moderate drinkers exhibited two times lower adjusted ratios for total mortality, myocardial infarction, and death from other causes (Table 4). The risk for stroke was nearly the same as for non-drinkers, which can be explained by a small number of deaths from this specific cause. Heavy drinkers exhibited significantly higher adjusted ratios compared to non-drinkers for all causes of mortality except stroke. The adjusted ratios reached statistical significance for death from all causes ($p = 0.031$) and myocardial infarction ($p = 0.038$). Compared with abstainers, the average risk of all cause of death among heavy pattern drinkers was increased up to three times; risk from myocardial infarction death was increased up to five times, whereas risk of death from other causes was increased up to six times, when adjusted for gender, smoking, body mass index, and blood pressure.

Kaplan-Meier model was used for the estimation of the overall survival rates among the 3 groups of alcohol consumption (Fig. 2). The overall probability of survival at any time point was the highest among moderate drinkers, the lowest among heavy drinkers, and the survival rate for non- or rare drinkers was somewhere in the middle between the other two groups ($p < 0.001$). Between-group comparisons revealed that the survival rate was significantly higher among rare or never drinkers compared to heavy

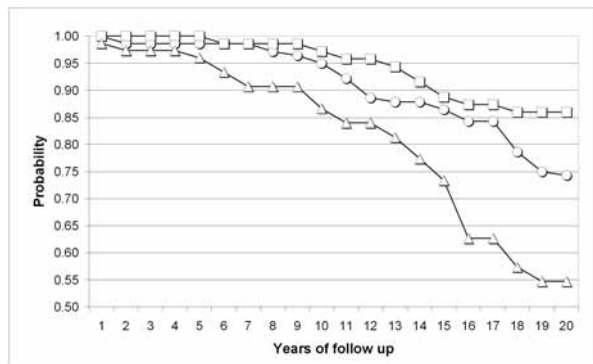


Figure 2. Estimation of general survival according to alcohol consumption. Kaplan-Meier Test statistics for equality of survival distributions for alcohol consumption. Circles – rarely or never drinking; squares – moderate drinking; triangles – heavy drinking. Log rank = 19.84, $p < 0.001$; rarely vs moderate: $p = 0.064$; rarely vs heavy: $p = 0.001$; moderate vs heavy: $p = 0.001$.

drinkers ($p < 0.001$), as well as among moderate drinkers compared to heavy drinkers ($p < 0.001$).

Discussion

In this 20-year follow-up study, we found evidence of potentially important protective as well as hazardous effects of different drinking patterns on health. First, it showed that a half of the studied population, consisting mainly of women, abstained from alcohol or rarely consumes alcohol beverages. Most of the male participants, on the other hand, consumed alcohol drinks every day in different amounts. At the initial phase of the investigation, all groups were overweight (10). Previous studies have showed that being overweight might be an independent risk factor for hypertension and heart failure (11,12). The average values of both systolic and diastolic pressure were indicative of prehypertension, according to the 7th Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (9). The correlation between smoking and alcohol consumption was expected (13), but smoking habits probably did not change the specific relation between alcohol and coronary disease mortality (14).

Other studies have also pointed out the existence of U- or J-shaped relationship between alcohol consumption and total mortality rate (2-4,15-20), death from cardiovascular diseases (2,14,21-23), stroke (2,24), and death from other causes (4).

Possible biological mechanisms include an increase in high density lipoprotein cholesterol, a decrease in platelet coagulability, and a decrease in plasma fibrinogen associated with alcohol intake (25-27).

Several limitations of this study should be considered. In particular, the small number of participants and their relatively young age at the beginning of the study could have masked some of the possible long-term health hazards of alcohol consumption, especially in older men and women. In addition, we were unable to exclude former drinkers from the non-drinking category. This could have resulted in an

increased mortality rate in the nondrinkers group; however, we were able to eliminate participants with prevalent cardiovascular disease.

The validity of self reported alcohol consumption as a measure of consumption during the follow up period can also be questioned. The main problems include underreporting of alcohol consumption probably because people tend to forget light drinking occasions. Although our measure of an average drinking pattern was the usual quantity of consumed alcohol at a time over the past 12 months, which is likely to give a good estimate on the long term drinking pattern, it is possible that some subjects later changed their drinking pattern. Such changes are likely to dilute the observed association compared with the actual one. The problem of standard drink dose and the definition of "moderate drinking" should be standardized in order to avoid misunderstandings and allow precise comparisons between various populations.

The control for confounding factors included adjustments for smoking, body mass index, and blood pressure, but they did not influence the risk estimates. The limitation of this study was that we did not control for diabetes mellitus as a confounding factor for mortality. We also excluded cases with previous cardiovascular diseases reported at the baseline examination, because they might have changed their drinking patterns after the onset of the disease. Drinking patterns can be influenced by and correlated to many other factors: general health status, dietary habits, physical activity level, and general tendency to healthy or unhealthy behavior, but we were not able to control all these possible confounders at this moment.

Public health implications of alcohol consumption are of great importance. According to the World Health Organization reports Serbia and Montenegro is ranked in the lower 50th percentile among European countries in transition with regard to alcohol consumption *per capita* (average = 7.3 liters *per capita per year*). The average consumption did not significantly change in the last decade of the 20th century. This is very close to the situation in the surrounding countries, such as Romania, Bulgaria, and Bosnia and Herzegovina, with the exception of Croatia, Slovenia, and Hungary where alcohol consumption is much higher (1,28).

The results of this twenty-year follow-up study confirm the U- or J-shaped relation between alcohol consumption and mortality from all causes, myocardial infarction and other causes and support recommendations for moderate alcohol consumption (one to two drinks a day) in general population. Heavy drinking significantly increased the risk for all-causes mortality and the mortality from myocardial infarction compared to non-drinking and moderate drinking.

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