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Risk of End-stage Renal Disease Associated with Alcohol Consumption

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Alcohol consumption has been linked to kidney disorders in selected patient groups, but whether it contributes to the burden of end-stage renal disease (ESRD) in the general population is unknown. The authors conducted a population-based case-control study to assess the relation between alcohol consumption and risk of ESRD. The study took place in Maryland, Virginia, West Virginia, and Washington, DC, in 1991. Participants were 716 patients who had started treatment for ESRD and 361 control subjects of similar age (20–64 years) selected by random digit dialing. The main risk factor of interest was self-reported consumption of alcoholic beverages (frequency of drinking days and number of drinks consumed per drinking day). In univariate analysis, consumption of alcohol exhibited a J-shaped association with risk of ESRD. The J shape disappeared after exclusion of persons who had ever consumed home-distilled whiskey ("moonshine") and adjustment for age, race, sex, income, history of hypertension, history of diabetes mellitus, use of acetaminophen, use of opiates, and cigarette smoking; however, the odds ratio for ESRD remained significantly increased (odds ratio = 4.0; 95% confidence interval: 1.2, 13.0) among persons who consumed an average of >2 alcoholic drinks per day. The corresponding population attributable risk was 9 percent. Thus, consumption of more than two alcoholic drinks per day, on average, was associated with an increased risk of kidney failure in the general population. A lower intake of alcohol did not appear to be harmful. Because these results are based on self-reports in a case-control study, they should be seen as preliminary. *Am J Epidemiol* 1999;150:1275–81.

alcohol drinking; ethanol; kidney failure, chronic

Prevention of end-stage renal disease (ESRD) requires knowledge of modifiable risk factors responsible for initiation and promotion of renal insufficiency (1). Modifiable risk factors for kidney failure that have been identified in population-based studies include high blood pressure (2), diabetes mellitus (3), exposure to occupational nephrotoxins (4), and chronic use of analgesics (5). However, known risk factors explain only a limited part of the overall incidence of ESRD.

Alcohol consumption is a plausible risk factor for ESRD. Historically, alcoholism or intemperance was suspected of causing kidney failure by Richard Bright (6) and William Osler (7), among others. More recently, alcohol use has been associated with immunoglobulin A nephropathy (8) and renal papillary necrosis (9). Alcohol consumption may potentiate the nephrotoxicity of lead (10) and antiinflammatory drugs (11). Patients with postinfectious glomerulonephritis who consume alcohol may be at increased risk of progression to chronic renal failure compared with their nondrinking counterparts (12). Home-distilled whiskey ("moonshine") may be particularly nephrotoxic because of its high lead content (13).

However, current evidence that alcohol consumption may cause kidney failure comes from studies conducted in selected populations or groups of patients. It is not known whether alcohol consumption is a risk factor for ESRD in the general population, nor is the contribution of alcohol-induced elevations in blood pressure to any increased risk of ESRD known. This paper reports results from a case-control study which tested the hypothesis that alcohol consumption increases risk for treated ESRD in a general population in the United States.

MATERIALS AND METHODS

The population eligible for this study consisted of 20- to 64-year-old community-dwelling residents of

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Abbreviation: ESRD, end-stage renal disease.

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the states of Maryland, Virginia, and West Virginia and the District of Columbia (Washington, DC) who had a working telephone in the home. Details on the study design have been published elsewhere (5). Cases were persons with new-onset ESRD requiring dialysis that was diagnosed between January 1991 and July 1991; they were identified through a population-based registry of persons undergoing treatment for ESRD. Of 752 eligible patients, 716 (95 percent) were interviewed. The median delay between onset of ESRD and interview was 5 months. General population controls were identified by random digit dialing. We sought to enroll half as many controls as cases, because we wanted to be able to analyze subgroups of cases defined by their underlying kidney disease. Because the incidence of ESRD increases with age, we attempted to match the age distribution of cases and controls using 5-year age intervals. Screening for eligibility was completed in 1,259 (96 percent) of 1,311 residences contacted, and the interview was completed for 361 (90 percent) of 402 eligible controls. After informed consent was obtained, a trained interviewer conducted a 20- to 30-minute telephone interview with each participant using a structured questionnaire. For ESRD cases, interview questions pertained to the period preceding the onset of kidney failure. Study procedures were approved by the institutional review boards of the Johns Hopkins University and the Health Care Financing Administration.

Alcohol use was ascertained by asking questions adapted from the National Health Interview Survey (14). One question addressed the participant's usual frequency of drinking any type of alcoholic beverage, in days per week, month, or year. Participants who were not total abstainers were asked to specify the average number of alcoholic drinks they consumed on the days when they drank alcohol. Similar questions were asked about consumption of "moonshine." No distinction was made between types of alcoholic beverages. No question was asked about duration of alcohol consumption. Alcohol consumption was expressed in number of drinks per day, week, or month, and data were grouped into mutually exclusive categories (see tables 1 and 2). In addition, we examined four patterns of drinking based on frequency of drinking days (≤3 vs. >3 days per week) and number of drinks consumed on a day when any drinking occurred (<5 vs. ≥5 drinks per day), to identify a possible risk associated with binge drinking. Each drink represents approximately 12 g of ethanol.

The interview also assessed potentially confounding factors: hypertension duration (none and ≤5, >5–≤15, >15–≤25, and >25 years) and severity (as reflected by hospitalization due to hypertension), diabetes type and duration (none and ≤5, >5–≤15, >15–≤25, and >25 years), use of acetaminophen (<2 pills per week, <2 pills per day, and ≥2 pills per day), cigarette smoking (0, ≤10, and >10 pack-years), use of heroin or other opiates (ever vs. never), total annual household income (<$10,000, $10,000–$19,999, $20,000–$39,999, and ≥$40,000), and years of education completed.

Cases and controls were compared by cross-tabulation. Odds ratios for ESRD were computed by logistic regression (15). Population attributable risks were estimated by $1 - \Sigma p_i/OR_i$, where p_i represents the proportion of cases at a given level of exposure and OR_i represents the corresponding fully adjusted odds ratio estimate (16).

RESULTS

Forty-two percent of the 716 cases and 65 percent of the 361 controls were women; 54 percent of the cases were Black, but only 14 percent of the controls were Black. The age distributions of cases and controls were identical (mean = 47 years, standard deviation 12 years), reflecting frequency-matching on age.

Abstinence was as common in cases as it was in controls (34.4 percent and 34.3 percent, respectively; $p = 0.97$), but compared with controls, cases had more drinking days per year (74 days vs. 57 days; $p = 0.015$), consumed more alcohol on the days on which they drank (2.4 drinks vs. 1.4 drinks; $p < 0.001$), and consumed more alcoholic drinks per year (416 drinks vs. 152 drinks; $p < 0.001$). The univariate association between alcohol consumption and ESRD was J-shaped, with a nadir below one drink per week and significant increases in risk above two drinks per day (table 1). A categorization which took into account temporal patterns and intensity of drinking on any day when alcohol was consumed yielded similar results: Persons who consumed fewer than five drinks per day on days when they drank alcohol were at slightly lower risk of ESRD than abstainers, while those who consumed five or more drinks on a drinking day were at higher risk.

Drinking "moonshine" was strongly associated with ESRD, but few persons reported any consumption of moonshine in their lifetime.

Adjusted analyses

After exclusion of the 68 persons (53 cases, 15 controls) who reported having ever consumed moonshine, the odds of ESRD across four levels of alcohol consumption retained a J-shaped pattern (table 2, first group of odds ratios). Adjustment for age, sex, and race weakened all odds ratios for ESRD (table 2, second group); in particular, the odds ratio associated with binge drinking regressed to 1. Contrary to our expectations, further

TABLE 1. Alcohol consumption among patients with end-stage renal disease and population controls in Maryland, Virginia, West Virginia, and Washington, DC, 1991

Variable	Cases (n = 716)		Controls (n = 361)		Odds ratio	95% confidence interval
	No.	%	No.	%		
Alcohol consumption						
Abstainer	246	34.4	124	34.3	1.0*	
≤1 drink/month	109	15.2	70	19.4	0.8	0.5, 1.1
>1 drink/month and ≤1 drink/week	55	7.7	46	12.7	0.6	0.4, 0.9
>1 drink/week and ≤1 drink/day	133	18.6	82	22.7	0.8	0.6, 1.2
>1 drink/day and ≤2 drinks/day	64	8.9	22	6.1	1.5	0.9, 2.5
>2 drinks/day and ≤4 drinks/day	41	5.7	7	1.9	3.0	1.3, 6.8
>4 drinks/day	61	8.5	5	1.4	6.1	2.4, 15.7
No answer	7	1.0	5	1.4		
Drinking pattern						
Abstainer	246	34.4	124	34.3	1.0*	
≤3 days/week and <5 drinks/day	312	43.6	184	51.0	0.8	0.6, 1.1
>3 days/week and <5 drinks/day	48	6.7	33	9.1	0.7	0.4, 1.2
≤3 days/week and ≥5 drinks/day	45	6.3	11	3.0	2.1	1.0, 4.1
>3 days/week and ≥5 drinks/day	58	8.1	4	1.1	7.3	2.6, 20.6
No answer	7	1.0	5	1.4		
Consumption of home-distilled whiskey ("moonshine")						
Never	662	92.5	345	95.6	1.0*	
Ever	53	7.4	15	4.2	1.8	1.0, 3.3
No answer	1	0.1	1	0.3		

* Referent.

adjustment for hypertension duration and severity strengthened the association between alcohol consumption and ESRD, but the "protective" effect of moderate alcohol consumption became nonsignificant (table 2, third group). Thus, the excess risk of ESRD among persons who were consuming more than two

TABLE 2. Odds ratios for the association between end-stage renal disease and alcohol consumption among persons who never drank "moonshine," Maryland, Virginia, West Virginia, and Washington, DC, 1991

	Unadjusted odds ratio (n = 999)		Adjustment factors: Adjusted for age,* sex, and race† (n = 997)		Adjusted for age, sex, race, and hypertension‡ (n = 997)		Adjusted for age, sex, race, hypertension, and income§ (n = 925)		Adjusted for age, sex, race, hypertension, income, diabetes,¶ acetaminophen use,# smoking,** and opiate use†† (n = 912)	
	OR‡‡	95% CI‡‡	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Alcohol consumption										
≤1 drink/day	0.7	0.6, 1.0	0.7	0.5, 1.0	0.9	0.6, 1.4	1.2	0.8, 1.8	1.1	0.7, 1.9
1–2 drinks/day	1.3	0.7, 2.3	0.8	0.4, 1.5	1.1	0.5, 2.7	1.4	0.6, 3.5	1.6	0.6, 4.3
>2 drinks/day	4.1	2.1, 8.2	2.0	0.9, 4.1	2.7	1.1, 6.7	3.6	1.3, 10.1	4.0	1.2, 13.0
Drinking pattern										
≤3 days/week and <5 drinks/day	0.8	0.6, 1.1	0.8	0.5, 1.0	1.0	0.7, 1.7	1.2	0.8, 1.9	1.2	0.7, 2.0
>3 days/week and <5 drinks/day	0.7	0.4, 1.1	0.4	0.2, 0.8	0.7	0.3, 1.5	1.0	0.4, 2.4	1.3	0.5, 3.6
≤3 days/week and ≥5 drinks/day	1.5	0.8, 2.6	1.0	0.5, 1.9	1.5	0.6, 3.4	2.0	0.5, 5.3	1.5	0.6, 4.6
>3 days/week and ≥5 drinks/day	6.7	2.4, 18.9	3.0	1.0, 8.8	3.0	0.9, 10.6	3.0	0.8, 10.7	4.0	0.9, 17.1

* Ages 20–64 years, in 5-year categories.
† White, Black, and Other.
‡ Duration of hypertension (none, ≤5 years, >5–≤15 years, >15–≤25 years, and >25 years) and hospitalization for hypertension.
§ Annual household income (<$10,000, $10,000–$19,999, $20,000–$39,999, and ≥$40,000).
¶ Type of diabetes (type 1 vs. type 2) and duration of diabetes (none, ≤5 years, >5–≤15 years, >15–≤25 years, and >25 years).
# Average consumption during lifetime (<2 pills/week, <2 pills per day, and ≥2 pills/day).
** Pack-years of cigarette smoking (nonsmoker, ≤10 pack-years, and >10 pack-years).
†† Ever use of heroin or other opiates (vs. never use).
‡‡ OR, odds ratio; CI, confidence interval.

drinks per day could not be attributed to hypertension secondary to alcohol use on the basis of the available data. In fact, both cases and controls who had had hypertension for a long time drank less than those who had normal blood pressure or hypertension of more recent onset (data not shown).

Another possible explanation for the "protective" effect of moderate alcohol consumption was a higher socioeconomic status among moderate drinkers. Adjustment for both hypertension history and household income eliminated the reduced risk of ESRD in persons who consumed up to two alcoholic drinks per day, but it strengthened the increased risk of ESRD among persons who consumed more than two drinks per day (table 2, fourth group). Results were similar after adjustment for education instead of income (data not shown). Further adjustment for type and duration of diabetes, use of opiates, use of acetaminophen, and smoking history yielded relative odds estimates in excess of 3 for the highest levels of alcohol consumption (table 2, last group). Odds ratios for drinking more than two drinks per day were higher when moonshine drinkers were included in the analysis and data were merely adjusted for moonshine consumption (results not shown).

Subgroup analyses

Odds ratios for the association between alcohol consumption and ESRD were stronger in men than in women and stronger in Blacks than in Whites (table 3). However, the 95 percent confidence intervals were wide because of the small sample size in each subgroup, and interaction terms for sex × alcohol consumption and race × alcohol consumption that were tested in a logistic regression analysis were not significant ($p = 0.52$ and $p = 0.43$, respectively). Associations between alcohol consumption and odds of ESRD were also estimated for subtypes of ESRD (table 4). The relation was strongest for ESRD of unknown cause and was absent for ESRD attributed to diabetes; however, the confidence intervals were extremely wide.

Population attributable risks

Reductions in the overall incidence of treated ESRD that could be expected if drinking of >2 alcoholic beverages per day were eliminated, based on adjusted relative risk estimates, amounted to 9.4 percent in the general population, 17.4 percent in men, 1.4 percent in women, 13.4 percent in Blacks, and 6.9 percent in Whites.

DISCUSSION

To our knowledge, this study was the first to examine the relation between alcohol consumption and treated ESRD in the general population. Consumption of more than two alcoholic beverages per day was associated with an approximately fourfold increase in the risk of ESRD. This finding confirms the clinical acumen of well known physicians from the past (6, 7) and suggests that evidence of alcohol-related nephrotoxicity gathered in clinical studies of selected patient groups (8–12) may be generalized to the broader population. The relation between alcohol consumption and ESRD remained strong even after adjustment for potential confounders, which strengthens the evidence in favor of a causal relation. Population attributable risk estimates suggest that the association may be of considerable public health importance: Assuming causality, avoidance of drinking >2 drinks per day on average could reduce the incidence of treated ESRD by approximately 9 percent in the general population. Our observation that alcohol consumption was most strongly related to ESRD of unknown origin stresses

TABLE 3. Adjusted* odds ratios for the association between end-stage renal disease and alcohol consumption among subgroups of persons who never drank "moonshine," Maryland, Virginia, West Virginia, and Washington, DC, 1991

Level of alcohol consumption	Sex				Race†			
	Men (*n* = 432)		Women (*n* = 480)		Whites (*n* = 536)		Blacks (*n* = 355)	
	OR‡	95% CI‡	OR	95% CI	OR	95% CI	OR	95% CI
≤1 drink/day	1.5	0.6, 3.7	1.0	0.5, 1.9	1.3	0.7, 2.5	0.7	0.3, 2.0
1–2 drinks/day	2.3	0.6, 8.2	1.2	0.1, 15.7	1.5	0.4, 4.8	2.3	0.2, 28.5
>2 drinks/day	6.6	1.6, 26.8	2.1	0.1, 103.7	3.5	0.9, 13.9	9.8	0.8, 128.5

* Adjusted for age (ages 20–64 years, in 5-year categories), sex (except when stratified by sex), race (White, Black, and Other, except when stratified by race), duration of hypertension (none and ≤5, >5–≤15, >15–≤25, and >25 years), hospitalization for hypertension, annual household income (<$10,000, $10,000–$19,999, $20,000–$39,999, and ≥$40,000), type (type 1 vs. type 2) and duration (none and ≤5, >5–≤15, >15–≤25, and >25 years) of diabetes mellitus, acetaminophen use (<2 pills/week, <2 pills/day, and ≥2 pills/day), cigarette smoking (nonsmoker, ≤10 pack-years, and >10 pack-years), and use of heroin or other opiates (ever vs. never).

† Excludes 26 persons who were neither White nor Black.

‡ OR, odds ratio; CI, confidence interval.

TABLE 4. Adjusted* odds ratios for associations between four subtypes of end-stage renal disease (ESRD) and alcohol consumption among persons who never drank "moonshine," Maryland, Virginia, West Virginia, and Washington, DC, 1991

Level of alcohol consumption	Hypertensive ESRD		Diabetic ESRD		Other specified cause of ESRD		Cause of ESRD unknown	
	OR†	95% CI†	OR	95% CI	OR	95% CI	OR	95% CI
≤1 drink/day	1.5	0.6, 3.7	0.8	0.1, 4.5	0.9	0.5, 1.8	2.2	0.7, 6.2
1–2 drinks/day	4.9	0.7, 35.1	1.4	0.0, 2,193	1.2	0.3, 4.0	2.3	0.3, 19.0
>2 drinks/day	6.1	0.7, 51.9	0.8	0.0, 20.3	4.0	1.0, 16.3	12.6	1.7, 95.9

* Adjusted for age (ages 20–64 years, in 5-year categories), sex, race (White, Black, and Other), duration of hypertension (none and ≤5, >5–≤15, >15–≤25, and >25 years), hospitalization for hypertension, annual household income (<$10,000, $10,000–$19,999, $20,000–$39,999, and ≥$40,000), type (type 1 vs. type 2) and duration (none and ≤5, >5–≤15, >15–≤25, and >25 years) of diabetes mellitus, acetaminophen use (<2 pills/week, <2 pills/day, and ≥2 pills/day), cigarette smoking (nonsmoker, ≤10 pack-years, and >10 pack-years), and use of heroin or other opiates (ever vs. never).

† OR, odds ratio; CI, confidence interval.

that alcohol-related kidney damage is clinically unrecognized. Consumption of moonshine was also related to ESRD but was too uncommon in our population to represent a substantial contribution to the overall incidence of ESRD.

A protective effect of moderate alcohol consumption?

In univariate analysis, alcohol consumption exhibited a J-shaped association with the risk of treated ESRD: Drinking ≤2 drinks per day on average appeared to be protective, while heavier drinking (>2 drinks per day) was associated with an increased risk. This seemingly "protective" effect of moderate alcohol consumption may be due to causation, reverse causation, confounding, or bias.

A protective vascular effect of moderate alcohol consumption may be mediated by increased high density lipoprotein cholesterol levels (17, 18), decreased platelet adhesiveness (19), inhibition of coagulation (20), or enhanced fibrinolysis (21). In a population-based autopsy study, hyalinization of renal arterioles was inversely correlated with alcohol consumption (22). In addition, a J-shaped association has been observed between alcohol consumption and blood pressure in selected studies (23, 24), although whether this reflects causality or results from biased self-reports is debatable (25). In either case, since high blood pressure contributes to the development and progression of renal disease (2, 26), lower blood pressure in those who report moderate drinking may explain their reduced risk of renal failure. In the present study, persons who had been hypertensive for a long time reported drinking less, and the flattening of the J-shaped distribution after adjustment for hypertension duration and severity suggests that these variables contributed, at least in part, to the apparently protective effect of moderate alcohol consumption.

Intentional reduction of alcohol consumption following a diagnosis of hypertension (which affects virtually all cases and can precede the onset of ESRD by many years) may have contributed to the apparently preventive effect of moderate drinking. This hypothesis would require that moderate drinkers, but not heavier drinkers, reduce their alcohol intake as a measure of blood pressure control. Such a mechanism would correspond to reverse causation, whereby incipient disease modifies exposure to the risk factor. Because we have not collected data on alcohol consumption over time, we cannot rule out or confirm this hypothesis.

A plausible confounding variable which may explain the protective effect of moderate drinking is socioeconomic status. Wealthier and more educated persons are more often moderate drinkers than persons in lower socioeconomic strata, and they are at lower risk of ESRD (27, 28). Possible reasons for the latter finding include better access to health care and lower exposure to infectious agents and environmental nephrotoxins—i.e., mechanisms other than moderate consumption of alcohol. The disappearance of the protective effect of moderate drinking after adjustment for income indicates that confounding by socioeconomic status played a role in this study.

Selection bias could have occurred if alcohol consumption affected participation in the study differently in cases and controls. This is unlikely to have happened, because participation rates were high. Information bias may have occurred if, for instance, underreporting of alcohol intake by heavy drinkers had been more frequent among controls than among ESRD patients. Evidence based on liver function tests in abstainers suggests that such underreporting may occur (25). However, we have no reason to believe that this phenomenon should have differed by disease status; if it had, greater underreporting of a socially reprehensible behavior by patients with ESRD would seem more plausible than the opposite. Lacking independent information on alcohol consumption, we cannot ascertain whether recall bias occurred in our study.

It is therefore uncertain whether the seemingly protective effect of moderate alcohol consumption on ESRD risk is entirely due to confounding and/or bias or is partially real. Further research may clarify this problem by measuring all suspected intermediate and confounding variables.

Alcohol consumption as a risk factor for ESRD

Contrary to the putative protective effect of moderate drinking, the harmful effect of drinking an average of >2 alcoholic beverages per day withstood any amount of adjustment. The estimated relative risk was fourfold, similar to or stronger than the relative risk of overall mortality in drinkers (29, 30). Several possible pathogenic pathways may relate alcohol consumption to chronic kidney failure. Alcohol consumption may increase the risk of kidney failure by initiating and/or promoting atherogenic risk factors, such as high blood pressure (31, 32), hyperuricemia (33), insulin resistance (34), and diabetes (35). The finding in our study that adjustment for hypertension and diabetes strengthened rather than weakened odds ratios for ESRD associated with alcohol consumption may reflect a secondary reduction of alcohol intake by many patients who have received a diagnosis of hypertension or diabetes. Both hypertension (2) and diabetes (36) have been shown to increase the risk of ESRD in prospective studies.

Furthermore, alcohol consumption may favor the occurrence of small vessel disease, similar to that which causes an increased risk of hemorrhagic stroke in drinkers (37–39); but whether this type of vascular disease affects the kidney is currently unclear. Finally, alcohol (or unknown components or contaminants of alcoholic beverages) may exercise a direct toxic effect on the kidney, particularly in the presence of other nephrotoxic exposures (9–12). Nonetheless, while hypotheses abound, the pathogenicity of alcohol-related kidney damage remains obscure.

The relative risk of ESRD in persons who drank more than two alcoholic beverages per day was probably underestimated in our study, because variability in reported alcohol consumption weakens the estimated association between alcohol intake and ESRD (regression dilution bias (40)). In addition, the case participants may have reduced their consumption of alcohol during the years preceding the onset of ESRD, leading to an underestimate of their average lifetime exposure.

Our study had several limitations. As in all studies that rely on participants' reports, recall bias may have produced a spurious association. We believe that recall bias is an unlikely explanation for an odds ratio of 4, especially since alcohol consumption was only one of several risk factors explored in the interview. However, only prospective studies can settle this question. Hence, our observation of an increased risk of ESRD in people who consume more than two drinks per day should be deemed tentative until it is confirmed or rejected by prospective studies. Furthermore, our study could not assess risk associated with lifetime alcohol consumption or with specific types of alcoholic beverages (beer, wine, liquor, etc.). Incomplete adjustment may have contributed to the residual odds ratios associated with alcohol consumption; in particular, we did not have data on the quality of blood pressure control among people with hypertension. Finally, the sample size was reasonable for estimation of overall risk only; it was insufficient for subgroup analyses and for exploration of effect modification.

With these limitations in mind, the results of our study raise an important public health issue. If they are confirmed by prospective studies, our results suggest that prevention of drinking an average of >2 alcoholic drinks per day (or three British units (41)) should be adopted as part of a global strategy to reduce the incidence of ESRD. This is consistent with other public health recommendations for moderation in alcohol intake (41–44).

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