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Is the Apparent Cardioprotective Effect of Recent Alcohol Consumption Due to Confounding by Prodromal Symptoms?

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Previous research has reported a protective association between alcohol drinking and acute coronary heart disease in the 24-hour period after drinking. This study investigated whether this apparent protective association resulted from confounding due to the effect of prodromal symptoms on drinking behavior. In 1992, the authors conducted a case-control study that measured recent alcohol consumption and reasons for recent abstention from alcohol among patients with acute coronary heart disease identified from a community-based disease register and a representative control sample from the same community (Auckland, New Zealand). Cases were significantly more likely than controls to report recent abstention from drinking because they felt unwell. In unadjusted analyses, a protective association was observed between recent alcohol consumption and acute coronary heart disease; however, this association was weakened considerably after adjustment for the effect of prodromal symptoms on drinking behavior. The previously reported protective association between recent alcohol consumption and acute coronary heart disease appears to be largely due to the confounding effect of prodromal symptoms on drinking. *Am J Epidemiol* 2000;151:1189–93.

alcohol drinking; case-control studies; coronary disease

Habitual alcohol consumption is associated with reduced risk of coronary heart disease (1). This apparent protective effect is not completely explained by the increased high density lipoprotein cholesterol levels in regular drinkers (2, 3), and this leads to speculation that alcohol-induced depression of platelet function and fibrinogen levels may also have an important role in alcohol-related cardioprotection (4, 5). If the protective effect of alcohol on coronary heart disease risk is mediated in part through acute effects on thrombotic factors, then recent alcohol consumption may acutely reduce coronary heart disease risk. However, alcohol also acutely impairs ventricular function (6) and increases the risk of arrhythmia (7), which could acutely increase coronary disease risk, although these effects have only been observed with heavy drinking.

Previously, we conducted a case-control study examining the relation between recent alcohol consumption and major coronary heart disease outcomes (see Jackson et al. (8)); that study suggested a protective effect of drinking in the previous 24 hours. Similar findings have since been reported in another case-control study (9). However, we were concerned that the apparent protective effect might be due to confounding if regular drinkers refrained from drinking in the 24 hours before a coronary heart disease event because of prodromal symptoms. Unfortunately, no data regarding prodromal symptoms or reasons for not drinking during this period were collected in the original study. In a new study, we repeated our original analyses but also sought additional information with which to examine the effect of prodromal symptoms on drinking behavior.

MATERIALS AND METHODS

A community-based case-control study was undertaken in a geographically defined population over a 1-year period. The study population comprised all men and women of European heritage aged 35–74 years (approximately 320,000 persons) who were living in the city of Auckland, New Zealand, and were registered on the Auckland general electoral rolls in January 1992. The population of Auckland accounts for approximately one quarter of the total New Zealand population. It is a mainly urban population. Approximately 80 percent are of European heritage, and over 95 percent of Europeans are registered on the general electoral rolls.

Controls were an age-stratified representative sample of the study population. Details on the sampling method have been published elsewhere (10). Briefly, the 1992 computerized Auckland electoral rolls were

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used as the sampling frame. Approximately 300 people from each 10-year age/sex grouping between ages 35 and 74 years were randomly selected from the rolls using a computer-generated random number table.

Cases included all hospitalized nonfatal myocardial infarction events and all hospital and community deaths from coronary heart disease occurring in the study population among persons registered on the Auckland electoral rolls during the calendar year 1992. Events were identified as part of the World Health Organization-coordinated MONICA Project, an international community-based cardiovascular disease surveillance program (11). The World Health Organization diagnostic algorithm, which uses data on symptoms, enzymes, electrocardiograms, past medical history, and postmortem findings (12), was applied to all potential cases. Over 95 percent of all nonfatal hospitalized myocardial infarction cases and fatal coronary heart disease cases in the study population were identified by this method (13).

During 1992, nonfatal-case patients were interviewed by one of three nurse interviewers using a standard questionnaire, usually while the cases were in the hospital following their myocardial infarction. Next of kin of fatal-case patients were interviewed by the same interviewers, using the same questionnaire, approximately 6–8 weeks after the case's death. Control subjects were identified at the beginning of 1992 and invited to visit one of two central study centers, where a standard questionnaire (the same as that used for the cases) was administered by one of five interviewers, three of whom also interviewed cases. To enable the same staff members to interview both cases and controls, controls were interviewed approximately 1 year after the cases, between January 1993 and March 1994. This delay is unlikely to have caused any bias, since the cardiovascular risk profile of the study population during the control interview period would have been very similar to the profile during the previous year (i.e., the case ascertainment period). It was not possible to blind the interviewers to the case or control status of participants.

All participant exposure data were collected using a standard interviewer-administered questionnaire. Regular alcohol consumption was assessed using the "typical occasions" method (14). Respondents were asked how often they usually drank alcohol and what they typically drank on these occasions. The questions were based on usual consumption over the 3 months prior to the case event or control interview. Only participants who drank regularly at least once per month were included in the present study. To examine the effects of recent consumption, we collected data on the cases' alcohol consumption during the 24-hour period before the acute coronary heart disease event. For both fatal and nonfatal events, the drinking period examined was the 24 hours before the onset of major symptoms. For controls, alcohol consumption in a randomly selected 24-hour period during the week before interview was assessed. Participants who did not drink during the specified 24-hour period were asked whether they had not drunk because they had felt unwell. Pretesting of the questionnaires showed that cases (and their relatives) readily recalled alcohol consumption in the 24 hours before the event, even when questioned 4–8 weeks later. In contrast, controls had difficulty remembering alcohol consumption more than about 7 days previously. A history of coronary heart disease was defined as a positive result on the Rose angina questionnaire (15), previous hospitalization for coronary heart disease, or current use of anti-angina medication.

Odds ratios were calculated as estimates of incidence rate ratios (or relative risks) and are presented as relative risks. All variables were defined categorically except for age. Unconditional multiple logistic regression was used to calculate adjusted relative risks with 95 percent confidence intervals, using SAS software (SAS Institute, Cary, North Carolina). Potential confounders evaluated were the same as those examined in the original study (8); they included age, cigarette smoking (current, former, never), habitual alcohol consumption (moderate and heavy drinking: at least once per day; light drinking: at least once per week; occasional drinking: at least once per month), and previous coronary heart disease (yes, no).

RESULTS

Response rates among controls were approximately 78 percent for men and 74 percent for women. Response rates among cases were 88 percent for men and 93 percent for women. Participants who reported drinking less than once per month, on average, were excluded from all subsequent analyses. Tables 1 and 2 show demographic and other characteristics of male and female cases and controls, stratified by their drinking status during the 24-hour period under investigation. There were no consistent differences in usual drinking patterns, smoking, or coronary heart disease history between those who drank during the specified 24-hour period and those who did not drink during that period, although there was a trend towards greater habitual alcohol consumption among cases reporting recent drinking, particularly men. Case-control differences for the standard coronary heart disease risk factors pointed in the expected directions. Cases were far more likely than controls to have refrained from drinking during the specified 24-hour period because they felt unwell.

TABLE 1. Characteristics of male controls and cases in a study of coronary heart disease events, by whether or not they drank alcohol during a specified 24-hour period, Auckland, New Zealand, 1992–1993

	Controls				Nonfatal cases				Fatal cases			
	Did drink† (*n* = 439)		Did not drink (*n* = 324)		Did drink (*n* = 154)		Did not drink (*n* = 159)		Did drink (*n* = 80)		Did not drink (*n* = 50)	
	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%
Age (years)	55.8		53.2**		58.8		59.8		62.1		64.0	
Regular alcohol consumption (g/day)	30.5		28.9		34.4		27.7*		43.5		23.3*	
Specific alcohol consumption‡ (g/day)	33.3		0.0		34.5		0.0		36.1		0.0	
Current smoker		14.8		14.5		35.7		38.4		31.3		22.0
Previous coronary heart disease		7.5		6.8		36.4		42.1		42.5		70.0**
No drinking because unwell		0.0		1.2		0.0		14.3		0.0		24.0

* $p < 0.05$; ** $p < 0.01$.

† Participants who did drink alcohol during the 24-hour period under investigation (for controls, a randomly selected period in the week before interview; for cases, the 24 hours before their coronary heart disease event).

‡ Alcohol consumption during the 24-hour period under investigation.

Table 3 shows the adjusted relative risks for nonfatal myocardial infarction and coronary disease death associated with recent alcohol consumption from the original case-control study (8) and the current study. For the current study, relative risks using the original study criteria are presented first, and results obtained after exclusion of participants who had refrained from drinking because they felt unwell are presented second. When we used the original study criteria, relative risks from both the original study and the current study showed a protective association between recent alcohol consumption and coronary heart disease, although the estimates were less precise in the current study, particularly for coronary disease death. The effect estimates for myocardial infarction among both men and women in the current study were similar to the estimates from the original study and showed statistically significant protective associations. These protective associations for myocardial infarction were attenuated after exclusion of participants who reported refraining from drinking because they felt unwell. Changes in the effect estimates for coronary disease death in both men and women were difficult to interpret because of poor precision.

Table 4 shows the results of a logistic regression analysis including both men and women, fatal and

TABLE 2. Characteristics of female controls and cases in a study of coronary heart disease events, by whether or not they drank alcohol during a specified 24-hour period, Auckland, New Zealand, 1992–1993

	Controls				Nonfatal cases				Fatal cases			
	Did drink† (*n* = 278)		Did not drink (*n* = 289)		Did drink (*n* = 19)		Did not drink (*n* = 31)		Did drink (*n* = 17)		Did not drink (*n* = 13)	
	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%	Mean	%
Age (years)	55.4		52.0***		63.1		63.0		65.8		60.2	
Regular alcohol consumption (g/day)	19.5		19.7		17.1		15.7		31.3		14.6	
Specific alcohol consumption‡ (g/day)	20.8		0.0		15.8		0.0		28.8		0.0	
Current smoker		11.5		12.5		42.1		25.8		47.1		38.5
Previous coronary heart disease		7.2		4.8		57.9		54.8		52.9		38.5
No drinking because unwell		0.0		2.1		0.0		19.4		0.0		0.0

*** $p < 0.001$.

† Participants who did drink alcohol during the 24-hour period under investigation (for controls, a randomly selected period in the week before interview; for cases, the 24 hours before their coronary heart disease event).

‡ Alcohol consumption during the 24-hour period under investigation.

TABLE 3. Adjusted* relative risks of myocardial infarction and coronary disease death associated with recent alcohol consumption among regular drinkers, Auckland, New Zealand, 1992–1993

	Drinking in past 24 hours	Men				Women			
		Myocardial infarction		Coronary death		Myocardial infarction		Coronary death	
		RR†	95% CI†	RR	95% CI	RR	95% CI	RR	95% CI
Original study by Jackson et al. (8)	No	1.0		1.0		1.0		1.0	
	Yes	0.75	0.62, 0.90	0.64	0.50, 0.82	0.61	0.40, 0.92	0.45	0.19, 1.10
Current study (using the same criteria as the original study)	Yes	0.70	0.49, 1.00	0.89	0.53, 1.51	0.38	0.17, 0.89	0.94	0.36, 2.49
Current study (excluding 24-hour nondrinkers who felt unwell)	Yes	0.89	0.62, 1.28	0.79	0.48, 1.31	0.73	0.31, 1.13	0.74	0.29, 1.91

* Adjusted for age, regular drinking pattern, smoking, and previous coronary heart disease.
† RR, relative risk; CI, confidence interval.

TABLE 4. Adjusted* relative risks of myocardial infarction and coronary disease death among regular drinkers, Auckland, New Zealand, 1992–1993

	Relative risk	95% confidence interval
Alcohol drinking during the past 24 hours	1.07	0.78, 1.48
Prodromal symptoms†	9.21	3.90, 21.77
Previous coronary heart disease	9.19	6.72, 12.58
Gender‡	4.11	3.01, 5.61
Age (per year)	1.05	1.04, 1.06
Regular moderate–heavy drinking§	0.65	0.41, 1.02
Regular light drinking§	0.78	0.53, 1.14
Current smoking¶	5.12	3.64, 7.20
Former smoking¶	1.20	0.88, 1.63

* Adjusted for all other variables in the table.
† Symptoms that caused the participant to refrain from drinking because he or she felt unwell.
‡ Reference category: female.
§ Moderate–heavy drinking, at least once per day; light drinking, less than once per day and at least once per week. The reference category was occasional drinking (less than once per week and at least once per month).
¶ Reference category: never smoking.

nonfatal cases, and persons who refrained from drinking. Overall, there was no effect of recent drinking on coronary heart disease risk (relative risk = 1.07; 95 percent confidence interval: 0.78, 1.48). However, participants who had refrained from drinking because they felt unwell had a substantial increase in risk (relative risk = 9.21; 95 percent confidence interval: 3.90, 21.77). As expected, a history of previous coronary heart disease, cigarette smoking, and male gender were associated with increased coronary heart disease risk. When the analyses were repeated after exclusion of participants who did not drink because they felt unwell (results not shown), the effect estimates were suggestive of a small possible protective association between recent drinking and coronary heart disease (relative risk = 0.83; 95 percent confidence interval: 0.61, 1.13). Other coronary heart disease risk factors, including body mass index, physical activity, diabetes, and hypertension, were excluded from the regression equations because preliminary analyses indicated that they were not confounders.

DISCUSSION

This new case-control study suggests that the previously reported acute cardioprotective effect of recent alcohol consumption (8, 9) was partly a result of confounding due to the effect of prodromal symptoms on drinking behavior. When the new data were analyzed without adjustment for the effect of prodromal symptoms, there appeared to be a strong protective effect for nonfatal myocardial infarction, as previously reported. However, when we excluded individuals who had not drunk during the 24-hour period investigated because they had felt unwell, the cardioprotective association was attenuated. The ninefold increase in coronary heart disease risk among people who did not drink because they felt unwell indicates the prognostic significance of prodromal symptoms. This observed prodromal effect may be an overestimate, because cases are more likely to recall feeling unwell than controls; however, the magnitude of the effect was so great that it is likely to be real, albeit smaller. Given this strong predictive effect, prodromal symptoms should be taken into account in studies examining the effect of transient exposures on coronary heart disease risk.

In contrast to the findings for nonfatal myocardial infarction, an attenuation of risk was not observed for fatal coronary heart disease after exclusion of the unwell nondrinkers. While it is possible that the relation of prodromal symptoms with fatal coronary heart

disease differs from the relation with nonfatal myocardial infarction, it is more likely to be due to the prodromal symptom data being less reliable for persons who died, since this information was reported by next of kin.

The results of this study suggest that any acute cardioprotection due to recent alcohol consumption is likely to be small, and the possibility that high density lipoprotein cholesterol is the major beneficial mechanism is enhanced by the data presented here. Due to limitations in statistical power, a small short term protective effect of recent alcohol consumption cannot be ruled out. Nevertheless, if alcohol-induced thrombotic effects are cardioprotective, they probably act largely over a period of longer than 24 hours. This is consistent with the findings of many epidemiologic studies which show that there is a significant cardioprotective effect of drinking several times per week (1).

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