HHS Public Access

Author manuscript

Ann Epidemiol. Author manuscript; available in PMC 2015 May 27.

Published in final edited form as:

Ann Epidemiol. 2007 May ; 17(5 0): S8–S12. doi:10.1016/j.annepidem.2007.01.003.

Alcohol Intake and Non-Coronary Cardiovascular Diseases

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Abstract

Moderate drinking has complex associations with cardiovascular diseases other than coronary heart disease. Recent cohort studies examining the relationship between alcohol use and ischemic stroke have shown a modest association, with risk ratios approximating 0.8, and the lowest risk among those who drink less than daily. In contrast, alcohol use is generally associated with a roughly dose-dependent risk for hemorrhagic stroke throughout the full range of intake.

Several prospective studies of alcohol intake and congestive heart failure have found lower risk with moderate drinking. This risk is also dose-dependent through the moderate range, but its underlying mechanism remains uncertain. Accounting for the lower risk of myocardial infarction associated with moderate intake does not eliminate the observed association. Cohort studies have found no association of chronic alcohol intake with risk of atrial fibrillation below levels of at least three standard drinks per day. Finally, two prospective studies have found lower risks of claudication or clinically more severe peripheral arterial disease among moderate drinkers, an association also supported by cross-sectional studies of alcohol intake and ankle-brachial index.

Keywords

Alcohol drinking; stroke; heart failure; peripheral arterial disease; atrial fibrillation

Although the relationship of alcohol consumption and coronary heart disease (CHD) has been extensively addressed in dozens of studies (1–3), alcohol consumption has also been associated with other cardiovascular diseases, including ischemic and hemorrhagic stroke, congestive heart failure (CHF), atrial fibrillation (AF), and peripheral arterial disease (PAD) (4–7). These associations include both positive and inverse associations, even at moderate levels of consumption, although the strength of evidence surrounding these relationships is not yet as strong as for CHD. Complicating this issue further, these cardiovascular diseases are quite heterogeneous, both across diseases and even within a single disease. In this review, I will examine and summarize some of the evidence linking alcohol to these conditions and identify new areas for future research.

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Stroke

The clinical syndrome of stroke is a quintessential example of the heterogeneity among cardiovascular diseases. It comprises two main types of cardiovascular disease – ischemic and hemorrhagic – and several subtypes of each (e.g., atherothrombotic, lacunar, embolic, subarachnoid hemorrhage, intracerebral hemorrhage). Alcohol appears to have decidedly different associations with these various types.

Ischemic stroke, the most common type in the United States and Europe, is the result of vascular occlusion of an intracerebral artery, either through local thrombosis or distal embolism. It is noteworthy that two of the strongest chronic risk factors for ischemic stroke are hypertension and atrial fibrillation (8), both of which have been attributed to heavy drinking (see below). Thus, even though ischemic stroke shares an atherosclerotic and thrombotic etiology with CHD, the particular factors that most strongly predict ischemic risk appear to be in the subset of cardiovascular risk factors that are exacerbated by heavy alcohol use. As a consequence, it may not be surprising that the apparent inverse association of moderate alcohol intake with ischemic stroke risk occurs at a lower dose of alcohol consumption and with a lower magnitude of risk reduction than does the corresponding association with CHD risk (9, 10). It is also not surprising that heavy drinking is consistently associated with higher stroke risk.

For many years, observational (and largely case-control) studies of the relationship between alcohol consumption and risk for ischemic stroke have suggested a relatively strong inverse relationship (4, 11). For example, in the Nurses' Health Study cohort, Stampfer and colleagues documented 66 incident ischemic strokes and found relative risks of 0.3 (95% confidence interval [CI], 0.1–0.7) for intake of 5–14 grams of alcohol per day, and 0.5 (95% CI, 0.2–1.1) for intake levels of 15 or more grams per day (12). However, more recent studies have called the magnitude of lower risk into question. In a meta-analysis restricted to 19 cohort studies, Reynolds and colleagues found that light drinking (<12 grams per day) was associated with a relative risk of 0.82 (95% CI, 0.73–0.92), but that consumption of 12–60 grams per day was not associated with risk (4). In a representative study, Klatsky and colleagues reported a U-shaped association between alcohol intake and hospitalization for ischemic stroke among members of a single insurance plan. Relative risks were 0.8 (95% CI, 0.7–1.0) among those who consumed between one drink a month and one drink a day, and 1.0 (95% CI, 0.8–1.2) among those who consumed three or more drinks per day (10). For comparison, these authors found a direct inverse association between alcohol use and risk of CHD hospitalization, with relative risks of 0.6 among women and 0.7 among men who consumed 3 or more drinks per day (9). In an analysis of the Cardiovascular Health Study, a lower risk of ischemic stroke was confined to consumers of 1–6 drinks per week (hazard ratio 0.75; 95% CI, 0.53–1.06), although even this level of intake did not significantly increase the risk among carriers of the APOE4 allele (13). In the same population (14), the corresponding magnitude of lower risk for CHD was lower and occurred at an intake of 14 or more drinks per week.

Dulli has emphasized how the heterogeneity of ischemic stroke may influence its association with alcohol intake (15). To address this, we examined ischemic stroke risk in the Health

Professionals Follow-up Study (16). Concordant with previous work, lower risk was restricted to consumers of an average of 0.1–9.9 grams of ethanol per day, and particularly those whose consumption was spread out over 3–4 days per week (hazard ratio 0.56; 95% CI, 0.31–1.02). However, stroke subtype appeared to modify risk substantially. Compared with abstention, the hazard ratios associated with intake of 0.1–9.9 grams per day were 0.76 (0.50–1.15) for confirmed thrombotic stroke, but 2.20 (95% CI, 0.84–5.76) for confirmed embolic stroke. Larger studies with effective classification of ischemic stroke subtypes are needed to confirm these findings.

It should be repeated that little controversy exists regarding the relationship of heavier drinking with a higher risk of ischemic stroke (4, 16). Moreover, even single episodes of intake of 3 or more drinks or drinking to intoxication may acutely and transiently increase the risk of ischemic stroke for the ensuing 24 hours (17–21).

Hemorrhagic stroke is a common stroke type in Asia, where most studies addressing it have been performed, and includes both subarachnoid and intracerebral subtypes. In a meta-analysis of cohort studies of subarachnoid hemorrhage, Feigin found increased risk restricted to heavier intake (>150 grams per week), with a summary relative risk of 2.1 (95% CI, 1.5–2.8) (22). In a comparable meta-analysis of case-control studies of intracerebral hemorrhage, Ariesen found summary odds ratios of 2.05 (95% CI, 1.35–3.11) for intake ≤56 grams per day, and 4.11 (95% CI, 2.54–6.65) for intake >56 grams per day (23), although a large cohort study published subsequently found an increase in risk to be confined to consumers of 6 or more drinks per day (24). These results are largely consistent with Renaud's hypothesis that the effects of moderate drinking are mediated, at least in part, through activity of platelets and prothrombotic factors (25). If this hypothesis is correct, one would anticipate that moderate drinking would decrease the risk of thrombotic events, such as myocardial infarction and ischemic stroke, but increase the risk of bleeding in the brain and possibly other sites (26), exactly as has been observed.

Congestive heart failure

For decades (27), clinical investigators interested in the cardiac effects of ethanol focused their efforts on alcoholic cardiomyopathy, a dilated cardiomyopathy attributed primarily to cardiotoxic effects of ethanol and secondarily also associated with malnutrition (28). Interestingly, although it has long been recognized that only substantial ethanol intake leads to cardiomyopathy (although less so in women) (29), only recently have studies demonstrated that in subjects with cardiomyopathy, controlled drinking could be as effective as abstinence in stabilizing or restoring myocardial function (30).

More recent interest in CHF has been spurred by three observations. First, with the aging of Western populations, CHF has rapidly become a serious public health concern. In 2003 alone, over one million Americans were hospitalized with a primary diagnosis of CHF (31). Second, a substantial portion of the burden of CHF in the U.S. and Europe is the consequence of CHD and ischemic cardiomyopathy. If moderate alcohol use is associated with a lower risk of CHD, one might anticipate that it would be associated with a lower risk of CHF also. Third, physiological experiments have suggested that alcohol consumption

may induce effective atrial natriuretic peptide (ANP)-mediated diuresis (32, 33) and lower pulmonary artery pressure (34), both of which would be expected to reduce the incidence of CHF; the association of alcohol intake with ANP has now been confirmed in a large observational study (35).

The observed association of alcohol use with risk for CHF has justified this interest but has also added new complexity. In at least four large prospective studies (7, 36–38), investigators have found that moderate drinking is associated with a roughly 50% lower risk of congestive heart failure, although the level of intake linked to lowest risk varies somewhat. Interestingly, in all four studies, accounting for incident coronary disease did not eliminate the relationship, so that even where previous myocardial infarction was not involved, risk appeared to be to some degree inversely related to moderate drinking. Some (39), but not all (40, 41), studies of alcohol intake among patients with established left ventricular dysfunction have also suggested a benefit from light or moderate drinking; one study has suggested an association with lower mortality in men but higher mortality in women (42).

Atrial fibrillation

Atrial fibrillation (AF) is the most common chronic cardiac arrhythmia and is closely linked with hypertension and CHF. Clinicians have long recognized the temporal association of episodic heavy alcohol use with onset of AF, dubbed the “holiday heart” syndrome (43, 44). However, the association of regular alcohol intake with risk for AF has only recently begun to receive attention. Given the association of heavy drinking with risk for AF, one might hypothesize that even moderate drinking would be associated with higher risk, although animal models have suggested the opposite (45, 46). In human populations, some studies have shown positive relationships in men but not women (47), while some have even shown inverse relationships (48). However, most studies have suggested a threshold effect (6, 44, 49–51). In these studies, there has generally been no discernible difference in risk between abstainers and moderate drinkers, but a higher risk for the heaviest drinkers. While the absolute threshold of risk is uncertain, the largest study to date suggests that AF risk does not increase below a chronic level of intake of at least 28 and probably 35 drinks per week (51).

An interesting area for future investigation is the effect of alcohol consumption on individuals with chronic AF, most of who are likely to be prescribed warfarin or similar anticoagulants. Although guidelines have often explicitly recommended that individuals taking warfarin abstain from drinking entirely (52), the limited available data suggest that the risk for excessive anticoagulation is not higher in moderate drinkers than it is in abstainers, although it may be elevated in binge drinkers (53, 54).

Peripheral arterial disease

The final manifestation of cardiovascular disease to be discussed here is peripheral arterial disease (PAD), most commonly localized to the lower extremities; for practical purposes, we also consider abdominal aortic aneurysm (AAA) here. Although PAD has generally received the least attention from researchers among the major atherosclerotic vascular

diseases, it is nonetheless widely prevalent and a major cause of disability, primarily related to walking.

The body of evidence linking moderate drinking to PAD is modest. The Strong Heart Study and Rotterdam Study both found inverse cross-sectional associations of moderate drinking with PAD (defined as a low ankle-brachial index) that tended to be strongest in women (55, 56), although other cross-sectional studies have not consistently confirmed this finding (57, 58). Surprisingly, a subsequent analysis of the progression of the ankle-brachial index in one of these latter studies has suggested an inverse relationship between alcohol use and a 5-year change in the ankle-brachial index (59). To our knowledge, two prospective cohort studies have assessed the risk of PAD in the general population. In an analysis of symptomatic claudication from the Framingham Heart Study (5), Djoussé and colleagues found hazard ratios of 0.67 (95% CI, 0.42–0.99) associated with intake of 13–24 grams per day for men and 0.44 (95% CI, 0.23–0.80) associated with intake levels of 7–12 grams per day for women. In the Physicians' Health Study (60), Camargo and colleagues found a hazard ratio of 0.74 (95% CI, 0.57–0.97) associated with an intake of 7 or more drinks per week, although the composite outcome included only 66 cases of lower-extremity arterial disease that required revascularization. In contrast, Ciccarone and colleagues found no association of alcohol intake with risk of PAD among diabetic adults (61).

There has been relatively little investigation into the relationship of moderate alcohol consumption with risk of AAA. In an analysis of male smokers, Tornwall and colleagues found a U-shaped relationship, with relative risks for AAA of 0.74 (95% CI, 0.49–1.13) among consumers of up to 15 grams of ethanol per day and 0.60 (95% CI, 0.36–1.02) among consumers of 16–30 grams of ethanol per day (62).

Conclusions

In summary, the relationship between moderate alcohol consumption and non-coronary cardiovascular diseases is complex, in part reflecting their heterogeneity. The relationship between alcohol use and the different subtypes of stroke have received the most attention, but even these relationships are not without controversy. To date, evidence generally suggests a J-shaped relationship between alcohol use and ischemic stroke, with lower risk limited to consumers of approximately 1 drink every other day and clearly higher risk among consumers of 3 or more drinks per day. The risk of hemorrhagic stroke appears to rise in a graded fashion with higher alcohol intake. The risks of PAD and CHF both seem to be lower with moderate intake in a range of up to 1–2 drinks per day, but larger prospective studies are needed to define these associations more precisely. Finally, AF seems to be unrelated to alcohol use throughout the moderate range of consumption.

Acknowledgments

My research to date has been funded entirely by the National Institutes of Health and the American Heart Association.

Abbreviations

AAA	abdominal aortic aneurysm
AF	atrial fibrillation
ANP	atrial natriuretic peptide
CHD	coronary heard disease
CHF	congestive heart failure
PAD	peripheral arterial disease

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