

Effect of alcohol on risk of coronary heart disease and stroke: causality, bias, or a bit of both?

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Abstract: Epidemiological studies of middle-aged populations generally find the relationship between alcohol intake and the risk of coronary heart disease (CHD) and stroke to be either U- or J-shaped. This review describes the extent that these relationships are likely to be causal, and the extent that they may be due to specific methodological weaknesses in epidemiological studies. The consistency in the vascular benefit associated with moderate drinking (compared with non-drinking) observed across different studies, together with the existence of credible biological pathways, strongly suggests that at least some of this benefit is real. However, because of biases introduced by: choice of reference categories; reverse causality bias; variations in alcohol intake over time; and confounding, some of it is likely to be an artefact. For heavy drinking, different study biases have the potential to act in opposing directions, and as such, the true effects of heavy drinking on vascular risk are uncertain. However, because of the known harmful effects of heavy drinking on non-vascular mortality, the problem is an academic one. Studies of the effects of alcohol consumption on health outcomes should recognise the methodological biases they are likely to face, and design, analyse and interpret their studies accordingly. While regular moderate alcohol consumption during middle-age probably does reduce vascular risk, care should be taken when making general recommendations about safe levels of alcohol intake. In particular, it is likely that any promotion of alcohol for health reasons would do substantially more harm than good.

Keywords: alcohol, coronary heart disease, stroke

Introduction

Case-control and cohort studies of middle-aged populations have consistently demonstrated U- (or J-) shaped relationships between alcohol consumption and the incidence of major vascular diseases (in particular coronary heart disease [CHD]) (Beaglehole and Jackson 1992; Corrao et al 2000; Reynolds et al 2003). Typically, CHD risk among middle-aged people who drink light-to-moderate amounts of alcohol (usually defined as around 20 g to 30 g of alcohol per day) is found to be between 20% and 30% lower than for those who do not drink (Corrao et al 2000). Similar findings, but perhaps weaker evidence of benefit, have been reported for stroke (Reynolds et al 2003). In contrast, the harmful effects of heavy drinking are equally well documented. People who drink excessively (usually defined as at least 40 g of alcohol per day) generally have higher rates of CHD and stroke than people who drink moderately, though often at a level only either comparable with, or slightly in excess of, the disease rates experienced by nondrinkers. While most of these studies have been of middle-aged men, several large studies have also demonstrated that these relations exist in middle-aged women (Fuchs et al 1995; Thun et al 1997).

So what could account for a U- or J-shaped relationship between alcohol consumption and the risk of CHD and stroke? Is the association between light-to-moderate drinking and lower vascular risk causal, or a consequence of unknown

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Table 1 Potential sources of bias in epidemiological studies of the relationship between alcohol consumption and the risk of vascular disease

Source of bias	Description
Confounding by type of drink or pattern of drinking	If either the type of drink consumed (eg, beer, wine, or spirits) or the pattern of drinking (eg, with/without meals, regular/episodic) have effects on risk independently of amount consumed (and if these characteristics vary with amount consumed), then these factors will confound the observed relationship between amount of alcohol consumed and risk.
Confounding by socio-economic and lifestyle characteristics	Differences in socio-economic and lifestyle characteristics between different drinking groups causes confounding of the true relationship between alcohol consumption and vascular risk. Even if attempts are made to adjust for these characteristics, some residual confounding will still generally occur.
Choice of reference group	Use of nondrinkers as the reference group with which to compare different levels of active drinking could lead to misleading results if the group includes ex-drinkers, particularly those who gave up because of ill health (see also “reverse causality bias”).
Reverse causality bias	A previous diagnosis of vascular disease might cause a change (typically a reduction) in an individual's alcohol consumption, leading to the subsequent high incidence rates among such people being incorrectly attributed to the new level of drinking.
Recall error/misclassification	Errors in the reporting of alcohol consumption can alter the magnitude and even direction of true risk-relationships with alcohol intake. For instance, cases in case-control studies might systematically under-report their previous alcohol intake.
Within-person variation	In prospective cohort studies, variations in an individual's alcohol intake over time can distort the risk-relationship between <i>average</i> alcohol intake during the study and risk, when baseline measures of alcohol intake are used in analyses.
Study design/publication bias	Case-control studies may be more susceptible to biases in exposure recall than cohort studies and also have the difficulty of finding an appropriate control group. Alcohol-disease association studies may also be more likely to be submitted for publication (and accepted) if it shows a striking result, as opposed to small studies with less striking results.

biases in observational studies? Furthermore, if moderate alcohol intake (as opposed to abstinence) does reduce vascular risk, why is heavy drinking associated with increased vascular risk? In order to address these questions, it is important to appreciate several complicating issues (summarized in Table 1). First, the amount of alcohol consumed is only one component of “alcohol exposure”. Both the type of drink consumed and the pattern of drinking may have important modifying influences on vascular risk independently of the amount. Thus, the apparent vascular benefit of light-to-moderate drinking (as well as the harm associated with heavy drinking) could be explained as much by differences in the *way that alcohol is consumed* in different drinking categories, as it is to differences in the *amount of alcohol consumed*. Second, alcohol consumption is an exposure that is difficult to measure accurately and therefore can be easily misclassified. Biases in the reporting of alcohol consumption may alter the magnitude and, if systematic, even the direction of apparent risk-relationships. This may be particularly relevant for case-control studies, in which cases are asked to recall what their drinking habits were prior to their heart attack or stroke. Perhaps more importantly, people who regularly drink light or moderate amounts of alcohol also tend to exhibit other characteristics that are particularly beneficial to health. For example, they

may be more likely to take regular physical activity. It is possible that these other characteristics are reducing vascular risk, rather than alcohol. Alcohol consumption patterns also tend to change over time, either due to the presence of disease (so called “reverse-causality”) or sometimes as a natural consequence of aging. Single assessments of alcohol consumption recorded at the beginning of a cohort study may therefore be unable to accurately reflect true “average” exposures to alcohol *during* a study. In addition, if the non-drinking category contained a significant proportion of people who had given up alcohol because of ill health, their disease risks would not be truly reflective of the true risks associated with non-drinking. Finally, there may be bias in the literature, both in the tendency for authors and journals to publish “favorable” results (publication bias), and the common tendency for authors to interpret their results only in the context of their prior beliefs. Thus, for several reasons, there is some doubt when interpreting the alcohol—vascular disease risk relationship as entirely causal. Nonetheless, alcohol is known to have some favorable biological effects that would be expected to reduce vascular risk. In particular, it increases high density lipoprotein-cholesterol (HDL-C) (Rimm et al 1999), a protective risk factor for CHD (Sacks 2002), and possibly also for (non-hemorrhagic) stroke (Lindenstrom et al 1994; Tanne et al 1997; Wannamethee et

al 2000). It also has a modest beneficial effect on thrombotic factors, particularly fibrinogen. On the other hand, it increases blood pressure, which might offset (to some degree at least) the expected benefits on blood lipids.

The purpose of this review is to consider to what degree these potential biases and potential causal mechanisms might credibly account for the shape and magnitude of the relationships between alcohol consumption and the risks of CHD and stroke. Each of the major potential sources of bias are reviewed and, where possible, the effects of taking them into account illustrated using examples from published studies. The most likely causal mechanisms and their expected effects are also reviewed using evidence from large overviews of epidemiological studies.

Alcohol and coronary heart disease

Since the early 1970s, many observational epidemiological studies have reported a cardioprotective effect of moderate amounts of alcohol. In a review of five case-control studies, seven prospective studies, two international comparisons, and one time-trend report published in 1984, it was concluded that moderate alcohol intake was associated with lower risks of CHD mortality, but that heavy drinking was associated with higher mortality compared with nondrinkers (Marmot 1984). In 2000, a meta-analysis of 28 prospective studies which investigated the relationship between alcohol and CHD risk and which, based on factors relating to study design, data collection methods and data analysis strategy, were deemed to be of a "high quality", estimated that 20 g of alcohol a day (1–2 standard drinks) was associated with a 20% (95% confidence interval [CI] 17% to 22%) reduction in the relative risk of CHD (Corrao et al 2000). This protective effect was found to persist up to a consumption as high as 72 g/day and only became significantly harmful after 89 g/day (approximately 7 standard drinks a day); see Figure 1.

Amount, type, or drinking pattern?

Total alcohol consumption, though the most widely used and probably the most informative, provides only one method of looking at an individual's overall "alcohol exposure". For many years, it has been suggested that both the type of drink consumed (eg, beer, wine, or spirits) as well as the pattern of drinking (eg, daily with meals, weekends only) may have contributing effects on CHD risk that are separate from those of the total amount of alcohol consumed. Wine, for instance, has been widely claimed to

contain substances other than ethanol that have cardioprotective effects. In fact, it has often been suggested that despite high smoking rates and typically high fat diets, the French experience low CHD rates because of their high levels of wine intake (Renaud and de Lorgeril 1992). Numerous substances in wine related to platelet aggregation, low-density lipoprotein (LDL) oxidation inhibition, vasodilating effects and effects on the endothelium have been proposed as potentially beneficial (Frankel et al 1993; Pace-Asciak et al 1995; Flesch et al 1998; Iijima et al 2002), but none have so far been confirmed to be causally important. In populations where beer, wine, and spirits are all commonly consumed, several studies have indeed found wine drinkers to be at lower CHD risk than beer or spirit drinkers (Wannamethee and Shaper 1999; Gronbaek et al 2000; Theobald et al 2000). However, when making these comparisons, it is important to take account of the very different socioeconomic characteristics these groups tend to have. In a meta-analysis of 26 observational studies, it was estimated that wine and beer reduced the risk of vascular disease by 32% and 22% respectively (Di Castelnuovo et al 2002). However, because no meaningful relationship could be found between different amounts of beer intake and vascular risk, the results were difficult to interpret. In another meta-analysis of the effects of beer, wine, and spirits on CHD risk, the authors concluded that the major portion of the benefit associated with alcohol consumption was due to ethanol itself, rather than any other components of each type of drink (Rimm et al 1996). This view is indirectly supported by the observation that in the mainly beer-drinking populations of Bavaria (Germany) and the Czech Republic, the protective effects of alcohol are similar to those observed in the mainly wine drinking Mediterranean countries (Keil et al 1997; Bobak et al 2000).

In addition to the type of alcohol consumed, the role that pattern of drinking may play in determining CHD risk has also generated much interest. In particular, drinking with meals (compared with drinking without meals) has been found to be associated with a beneficial effect on CHD risk and other outcomes (Trevisan et al 2001, 2004), possibly due to effects on blood pressure (Foppa et al 2002), thrombotic factors (Hendriks et al 1994) or lipids (Veenstra et al 1990). In contrast, irregular heavy drinking (binge drinking) has been shown to be associated with increased CHD risk for many years. Indeed, it has been debated whether binge drinking may have been responsible for the sharp rise in national cardiovascular disease rates observed in Russia during the early 1990s (following a previously

successful anti-alcohol campaign between 1984 and 1987) (Leon et al 1997; Bobak and Marmot 1999; McKee et al 2001). Several case-control and prospective studies have found that for a given level of total alcohol consumption, people who drink in binges rather than regularly tend to have higher rates of CHD (Kauhanen et al 1997b; McElduff and Dobson 1997; Rehm et al 2001; Murray et al 2002) in addition to higher rates of other forms of cardiovascular disease (including sudden cardiac death) (Wannamethee and Shaper 1992; Kauhanen et al 1997a; Wood et al 1998). In a review article published in 1999, the importance of considering drinking pattern when considering the effects of alcohol on cardiovascular disease risk was highlighted (Puddey et al 1999). The authors concluded that without proper understanding of the risks associated with different drinking patterns, public health advice regarding alcohol consumption would be limited in its scope and potentially flawed in its impact.

Choice of reference category

Most epidemiological studies of the effects of alcohol on CHD risk use nondrinkers as the reference category against which the effects of different levels of drinking are compared. However, if this group contains people who used to drink alcohol but have given up, any true benefits of alcohol consumption on risk are likely to become exaggerated. This is because ex-drinkers tend to exhibit several characteristics likely to increase their morbidity and mortality. In the British Regional Heart Study, ex-drinkers were found to have the highest prevalence of diagnosed CHD, diabetes, and bronchitis as well as the highest use of medication (Wannamethee and Shaper 1988). A high proportion smoked cigarettes, were of manual social class, were unmarried, and had measured hypertension and obesity. Similar characteristics among ex-drinkers have also been observed elsewhere (Fillmore et al 1998). While most epidemiological studies would tend to make attempts to take account of differences in the prevalence of risk factors and pre-existing disease in the different drinking groups (for instance, by excluding patients with known prior disease and making statistical adjustments for differences in the prevalence of risk factors) such corrections might only partially remove these effects. The proportion of nondrinkers comprising of ex-drinkers is also likely to vary considerably by population studied, and though for some countries this proportion may be small, for others the nondrinking category could become significantly contaminated by ex-drinkers

(particular for older study populations). The overall bias this could introduce has been suggested by some to be small (Maclure 1993), nonetheless it is clearly desirable for epidemiological studies of the effects of alcohol on health to be able to separate ex-drinkers from lifelong abstainers so as to examine these potential effects. In an updated 23-year report from the British Doctor's Study, for instance, ex-drinkers were separated from never drinkers. The study found that 2–3 units (16–24 g) of alcohol a day was associated with a reduction in CHD death of 28% (95% CI 12% to 42%) (Doll et al 2005). However, it has been argued by some that lifelong abstainers should not provide the reference category for estimation of the health effects of alcohol consumption either (Wannamethee and Shaper 1997; Fillmore et al 1998). In countries where alcohol consumption is socially normal, lifelong abstainers often form a small and self-selected group and have been suggested to possess characteristics that could increase their risk of mortality, particularly from non-cardiovascular causes. Given the concerns regarding the suitability of nondrinkers (with or without first separating out ex-drinkers) to act as a valid reference group, a "low" active drinking exposure group (for instance people who drink only on special occasions) may provide a larger more reliable reference category on which to base risk comparisons. To illustrate the impact such a change in reference category could have, Figure 1 shows the relationship between alcohol intake and CHD risk estimated by a meta-analysis of 28 cohort studies (Corrao et al 2004), and shows that if people who drink 1 g of alcohol a day are used as the reference category instead of nondrinkers, both the estimated benefits of moderate alcohol intake on CHD risk and the level at which alcohol causes notable harm are substantially reduced. While several studies now routinely use low active drinking groups as the reference category, many still use nondrinkers (often without first removing ex-drinkers) as their comparison group.

Reverse causality bias

Part of the concern over the use of nondrinkers as the reference category for alcohol-CHD association studies lies in the possibility that some people may give up alcohol because of ill health prior to enrolment into a study. If this ill health is CHD, reverse causality bias occurs, ie, pre-existing CHD causes a change in alcohol intake (rather than vice-versa), with the consequent risk that the high CHD incidence observed in this group is incorrectly attributed to their new level of drinking. Several studies have shown that

after exclusion of people with prior CHD, the apparent benefits of light-to-moderate drinking (compared with nondrinking) are reduced (Shaper 1990; Lazarus et al 1991; Farchi et al 1992). However, in a deductive meta-analysis published in 1993 (Maclure 1993), this “sick quitter” hypothesis was refuted on the basis of contrary evidence from several very large cohort studies, including the Nurse’s Health Study (Stampfer et al 1988), the American Cancer Society (Boffetta and Garfinkel 1990), the Health Professionals Follow-up Study (Rimm et al 1991) and the Kaiser Permanente Study (Klatsky et al 1990), all of which found the association between alcohol and CHD to be essentially unaffected by exclusion of ex-drinkers and people with chronic illness (though in the latter study it was noted that differences in total mortality between nondrinkers and drinkers may well be exaggerated by the presence of people with prior chronic illnesses in the nondrinking group; [Klatsky et al 1990]).

Within-person variation in alcohol consumption

Almost all prospective studies of alcohol–CHD relationships use single baseline assessments of alcohol intake (usually ascertained by interview or questionnaire) in analyses. However, characterization of an individual’s “exposure to alcohol” (irrespective of how this is actually defined) based on a single assessment may not accurately reflect that person’s true long-term “usual” or “average” alcohol exposure throughout the duration of the study. Recall bias in alcohol intake, short-term deviations from a person’s “normal” drinking habit at baseline, and long-term true changes in an individual’s drinking habit (referred to as “within-person variation in alcohol exposure”) can lead to misclassification of individuals, which in turn can distort the true nature of the risk-relationship between “usual” alcohol exposure and CHD risk. Moreover, without knowing the nature of the misclassification (ie, whether it is random or systematic), one cannot predict whether the apparent “baseline” risk-relationship underestimates, overestimates, or even reverses the direction of the “true” risk-relationship. Nonetheless, many studies have reported associations between CHD risk and single measures of alcohol intake ascertained five, ten, or even twenty years earlier, with little, if any, discussion of the potential effect that within-person variation in alcohol exposure might have. However, by asking people about their alcohol intake at one or more follow-up assessments during a study, the nature and magnitude of this variation may be estimated and its effects

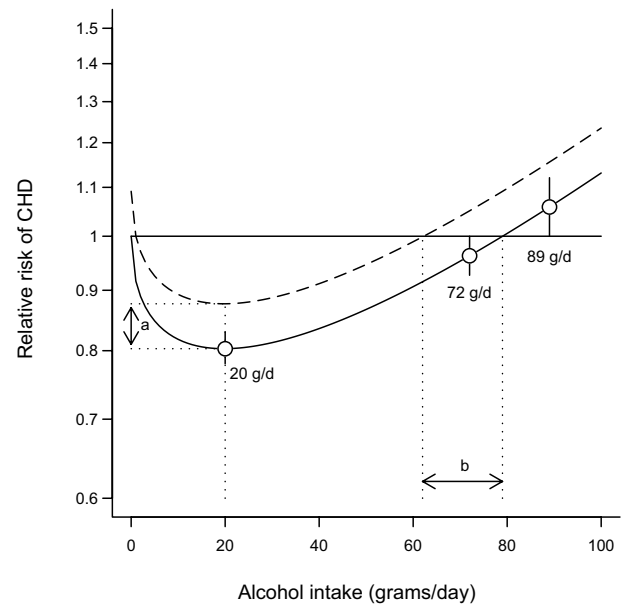


Figure 1 Impact of choice of reference category on the relationship between alcohol intake and the risk of coronary heart disease. The solid line shows data from 28 cohort studies (adapted and reproduced with permission from Figure 2 of Corrao et al. 2004. A meta-analysis of alcohol consumption and the risk of 15 diseases. *Prev Med*, 38: 613-19) and shows the estimated risk-relationship when nondrinkers are used as the reference category. The dashed line shows the same curve with light drinkers (1 g/day) as the reference category. The distances a and b represent the extent that use of nondrinkers as the reference category might lead to overestimation of the benefits of moderate alcohol consumption and overestimation of the level at which alcohol consumption may become cardiotoxic.

explored. Several studies have either directly or indirectly assessed the effects of within-person variation in alcohol exposure in this way. In the British Doctors’ Study, it was concluded that because a reasonable degree of consistency between alcohol intake at the beginning and end of the study was observed, their results would have been quite robust to the effects of within-person variation (Doll et al 1994). Of the studies that have attempted to directly take account of within-person variation in alcohol exposure, most have used just two assessments of alcohol intake, and findings have been inconsistent (Fillmore et al 2003; Wellmann et al 2004). For example, in the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA)-Augsburg cohort, it was found that the estimated benefits of light alcohol consumption increased after taking the second measure of alcohol consumption into account (Wellmann et al 2004), while in the First National Health and Nutrition Examination Survey, no elevated mortality was observed when consistent never drinkers were compared with light drinkers (Fillmore et al 2003). In the Health Professionals Follow-up Study, assessment of alcohol intake every 4 years allowed examination of the effects of changes in alcohol consumption on the 12-year risk of

myocardial infarction (MI). In this large American study, the beneficial effects of alcohol consumption on the risk of MI estimated using baseline measurements were found to be similar to estimates derived from analyses that fitted alcohol consumption as a “time-dependent” covariate (Mukamal et al 2003). However, three other large American studies have demonstrated that baseline measures of drinking groups may be particularly unreliable for younger samples, longer follow-up, and heavier drinkers (Kerr et al 2002). Recently, an analysis of the British Regional Heart Study demonstrated that by taking into account information on alcohol intake obtained after 5, 13, 17, and 20 years of follow-up (in addition to the information obtained at baseline), individuals could be categorized into exposure groups that were much better at predicting 20-year CHD risk than groups defined only from baseline information (Emberson et al 2005). When compared with occasional drinking (defined as 1–2 times a month or on special occasions), the relative risk of CHD associated with heavy drinking increased from 1.08 (95% CI 0.86 to 1.35) to 1.44 (95% CI 1.21 to 1.72) when repeat information on alcohol intake was taken into account. This suggests that studies that relate CHD rates to single assessments of alcohol intake recorded many years earlier may systematically underestimate true risks associated with heavy drinking.

Confounding

We now come to a common problem that arises when interpreting any epidemiological study – the possibility for associations to be distorted because of confounding. Specifically, characteristics that are related both to alcohol consumption and to CHD risk have the potential to modify both the shape and magnitude of the true alcohol–CHD relationship. For instance, it is well recognized that regular light drinkers tend to exhibit a range of socioeconomic, behavioral, and physical characteristics which are advantageous to health. This was confirmed in a recent telephone survey of 200 000 adults in the US, in which 27 out of 30 cardiovascular risk factors were found to be significantly more prevalent among nondrinkers than light-to-moderate drinkers (Naimi et al 2005). Observational studies attempt to take this into account by adjusting for these characteristics in statistical analyses. In the INTERHEART study of about 15 000 cases of MI and 15 000 controls from 52 countries, regular alcohol use (defined as 3 or more times per week) was associated with a 21% (95% CI 14% to 27%) reduction in MI risk after adjustment for age, sex and smoking, but only a 9%

reduction after further adjustment for other coronary risk factors, though it should be recognised that this included factors likely to mediate the alcohol–MI relationship, eg, blood lipids (Yusuf et al 2004). Simple adjustment for measured levels of confounders may not remove all of the effects of confounding however. This is because confounders are typically measured only crudely, eg, cigarette smoking exposure may be recorded as current, ex, or never rather than in a more detailed manner that included type of cigarette smoked and pack-years smoked. Thus, even after “adjustment” for these characteristics, some of the remaining coronary benefit associated with light-to-moderate drinking in epidemiological studies may still be due to confounding (referred to as “residual confounding”). Nonetheless, it has been argued that the degree of consistency in the alcohol–CHD relationship that is observed across diverse populations reduces the likelihood that the benefits of light-to-moderate amounts of alcohol can be due entirely to confounding, leaving causality as the only remaining plausible explanation (Marmot 1984; Maclure 1993). Residual confounding among heavy drinkers also has the potential to explain some (perhaps all) of the coronary hazard associated with heavy drinking (since heavy drinkers tend to possess several harmful characteristics). The potential for this “bi-directional” confounding to occur (ie, confounding as a possible explanation both for the protective effect of alcohol among light drinkers *and* the harmful effect of alcohol among heavy drinkers), has led some to suggest that the coronary-protective effects of alcohol might actually only become apparent at moderate-to-heavy levels of drinking, and not light levels of drinking at all (Jackson et al 2005). Of course, any possible benefits on coronary risk from moderate-to-heavy levels of drinking would be greatly outweighed by increases in non-vascular risks (Corrao et al 2004).

Study design and biases in the literature

Studies of the effect of alcohol on CHD risk tend to be either prospective cohort studies or case-control studies (though occasionally nested case-control designs are also used). Cohort studies have the intrinsic advantage over case-control studies that they should be less prone to reverse causality bias, since assessments of alcohol exposure are typically made before the onset of CHD. Case-control studies (though usually much more efficient than cohort studies in terms of time, money and effort) have the additional problems of finding an appropriately matched control group and ensuring that no recall biases in alcohol consumption are introduced

(Schulz and Grimes 2002). In particular, any differential biases in the recall of alcohol consumption between cases and controls could be especially problematic, having important implications for the estimation of risk-associations. In a meta-analysis of studies of the relationship between alcohol and CHD published between 1966 and 1998, significant differences were observed between the findings of cohort and case-control studies. Cohort studies typically observed lower protective effects of moderate alcohol consumption (Corrao et al 2000). Another obstacle facing researchers who wish to provide an overview of the effects of alcohol on CHD risk is that there may be substantial publication bias in the literature. This became evident in the meta-analysis carried out by Corrao et al (2000). Small studies reporting adverse effects of moderate drinking were found to be less likely to be published than small studies reporting beneficial (or no) effects of moderate alcohol consumption on CHD risk (Corrao et al 2000). Finally, there may also be an intrinsic bias in the literature caused by the tendency of some authors to present and interpret their results in a way that best confirms their prior beliefs, though the effect of this potential source of bias is of course much more difficult to quantify.

Alcohol intake and stroke

Alcohol was first recognized as a possible risk factor for stroke in 1725. More recently, many epidemiological studies have studied the association between alcohol and stroke, generally finding, as for CHD, that light to moderate drinkers have a lower risk than abstainers, and heavy drinkers have increased risks. In a meta-analysis of 35 observational studies published between 1966 and 2002, which combined the results from 16 case-control and 19 prospective studies, drinking up to 12 g of alcohol a day was associated with a 17% (95% CI 9% to 35%) reduction in the risk of total stroke (compared with nondrinking), while drinking more than 60 g of alcohol a day was associated with a 64% (95% CI 39% to 93%) increase in the risk of stroke (Reynolds et al 2003).

To what extent might these associations be causally attributed to alcohol consumption? Many of the issues already discussed regarding the potential sources of bias in alcohol-CHD risk relationships apply equally for alcohol-stroke risk relationships. Thus, the apparent benefit of light-to-moderate drinking on total stroke risk observed in most populations could be due to residual confounding, contamination of the non-drinking group by ex-drinkers, or failure to take account of within-person variation in alcohol intake. In the British Regional Heart Study, for

instance, taking within-person variation into account removed the apparent excess stroke risk experienced by nondrinkers (compared with occasional drinkers), and increased the relative risk of stroke for heavy drinkers relative to occasional drinkers from 1.54 (95% CI 1.06 to 2.22) to 2.33 (95% CI 1.46 to 3.71) (Emberson et al 2005). In another study of ~20 000 middle-aged Japanese men followed for 11 years (the Japan Public Health Center [JPHC] Study Cohort I [Iso et al 2004]), occasional and light drinkers (defined as <21 g/day) had the highest proportion of nonsmokers, the highest proportion of people who exercised at least once a week and the highest frequency of fruit intake, whereas people who drank at least 64 g of ethanol a day had the lowest proportions of each of these characteristics. Using occasional drinkers as the reference category, and taking differences in these confounders into account (as well as differences in BMI, education level, and history of diabetes) the risk of any stroke was found to increase linearly with alcohol intake to a relative risk of 1.55 (95% CI 1.11 to 2.15) amongst the heavy drinkers. These results were comparatively unaffected by "updating" alcohol intake using repeated information collected in 90% of people still alive after 5 years of follow-up.

Stroke sub-type and alcohol

In the JPHC study, stroke risk increased linearly with alcohol intake, apparently contradicting the U-shaped relationship observed in most cohort studies. However, if ischemic and hemorrhagic strokes are considered separately, the reason for this apparent discrepancy becomes evident. In most Western countries, approximately 70% to 80% of strokes occurring in middle-age are ischemic. Thus, the relationship between alcohol and total stroke in these populations generally reflects that observed with ischemic stroke. In the Physicians' Health Study, for instance, light and moderate drinking (1 drink/week and 2-4 drinks/week respectively) were found to be associated with reduced risks of ischemic stroke (relative risk [RR]=0.73 [0.52-1.00] and 0.74 [0.56-0.98] respectively), after adjustment for other stroke risk factors and compared with individuals who drank <1 drink/week, that were similar to those observed for all stroke (Berger et al 1999). However, for hemorrhagic stroke, no significant association (in either direction) with alcohol intake was observed. Similarly, in the Nurses' Health Study of ~87 000 female nurses, a decreased risk of ischemic stroke among those drinking moderate amounts of alcohol (1.5 g to 14.9 g per day) was observed (Stampfer et al 1988), but hemorrhagic stroke tended to be more common among this

group than among the nondrinkers. In the JPHC study however, only around half of the strokes were ischemic. Separating strokes according to etiology, light-drinkers (<21 g per day) were found to have a reduced rate of ischemic stroke (RR=0.61 [0.39–0.97]) consistent with that observed in the American studies, while hemorrhagic stroke displayed a strong log-linear relationship with alcohol intake (RR=2.51 [1.43–4.41] for men who drank >64 g a day compared with occasional drinkers) (Iso et al 2004). Thus, the overall relationship between alcohol intake and stroke in the JPHC study was much more influenced by hemorrhagic stroke than is the case in most other studied populations. In a 2003 meta-analysis of alcohol and stroke (Reynolds et al 2003), 15 studies contained information on ischemic stroke and 12 contained information on hemorrhagic stroke. In these studies, people who drank less than 12 g of alcohol a day (equivalent to less than 1 drink per day) had the lowest risk of ischemic stroke (RR=0.80, 95% CI 0.75 to 0.91, compared with nondrinkers), while those who drank greater than or equal to 60 g a day had a RR of 1.69 (1.34–2.15). For hemorrhagic stroke however, a linear dose-response association was observed among people who drank any alcohol, with individuals who drank at least 60 g/day having a RR of 2.18 (95% CI 1.48 to 3.20) compared with nondrinkers. Subsequently, in another meta-analysis of observational studies looking at several different causes of mortality including ischemic and hemorrhagic stroke, a non-statistically significant protective effect for ischemic stroke for alcohol intake of 25 g/day was observed when compared with nondrinkers. For hemorrhagic stroke, alcohol consumption of 25 g/day, 50 g/day, and 100 g/day was associated with RRs of 1.19 (0.97–1.49), 1.82 (1.46–2.28), and 4.70 (3.35–6.59) respectively, when compared with nondrinking. Again, the consistency in risk-relationships observed across different study designs in different populations strongly indicates that these alcohol-stroke relationships are, to some degree at least, causal. The question is, how?

Biological mechanisms

While there is an abundance of evidence to suggest that light-to-moderate alcohol intake protects against CHD as well as ischemic (but not hemorrhagic) stroke, evidence concerning the mechanisms by which these benefits are achieved has historically been more limited. General opinion now however agrees that alcohol consumption is likely to influence the risk of vascular disease primarily through beneficial effects on lipids and fibrinolytic activity (Rimm

et al 1999), the effects of which are probably offset to some degree by adverse effects on blood pressure (Marmot et al 1994).

Effect of alcohol on lipids and hemostatic factors

It is often stated that between 40% and 60% of the beneficial effect of light-to-moderate alcohol consumption on the risk of CHD is mediated through increases in HDL-C alone (Langer et al 1992; Suh et al 1992; Gaziano et al 1993; Marques-Vidal et al 1996), with further benefits achieved through improvements in fibrinogen level and other clotting factors (Rimm et al 1999). In a case-control study of 340 patients with MI, for instance, the log relative risk of MI associated with drinking more than 3 drinks a day compared with drinking less than 1 drink a month was attenuated by 60% after adjustment solely for the levels of the HDL₂ and HDL₃ subfractions (Gaziano et al 1993). In the Nurses' Health Study and the Health Professionals Follow-up Study, nested case-control studies of alcohol and MI risk showed that at least 75% (higher in men) of the benefit associated with frequent drinking (defined as at least 3 to 4 days per week) and MI risk could be explained by advantageous levels of HDL-C, fibrinogen and hemoglobin A_{1c} among the frequent drinkers (Mukamal et al 2005). Large population-based studies have confirmed alcohol consumption to be related to beneficial levels of HDL-C and fibrinogen (Wannamethee et al 2003; Schroder et al 2005), while genetic association studies of the alcohol dehydrogenase type 3 (ADH3) polymorphism further support a causal effect of alcohol on CHD risk that is mediated by HDL-C (Hines et al 2001; Davey Smith and Ebrahim 2003). In a meta-analysis of experimental studies investigating the effects of alcohol consumption on blood lipids and haemostatic factors in people with no prior history of chronic disease and no history of alcohol dependence, 30 g of ethanol per day was estimated to increase HDL-C by 3.99 mg/dL, increase apolipoprotein A₁ by 8.82 mg/dL and decrease fibrinogen by 7.5 mg/dL, but also to increase triglycerides of 5.69 mg/dL. The authors predicted that through its effects on these four biological markers, 30 g of ethanol a day would be expected (from epidemiological studies) to reduce the risk of CHD by 25% (Rimm et al 1999). The effect of moderate alcohol consumption on HDL-C would also be expected to lead to a reduction in ischemic, but not hemorrhagic, stroke. However, the anticoagulant

effects of alcohol, though beneficial for ischemic stroke, may play an important role in increasing the risk of hemorrhagic stroke.

Effect of alcohol on blood pressure

Though alcohol has some favorable effects on blood lipids and hemostatic factors, it also increases blood pressure, one of the most important determinants of cardiovascular disease risk (PSC 2002). In 1994, the International Study of Electrolyte Excretion and Blood Pressure (INTERSALT), a study designed to investigate the relations between salt and blood pressure in 50 centres worldwide, presented data on alcohol and blood pressure (Marmot et al 1994). As well as ascertaining whether the total amount of alcohol consumed was related to blood pressure, the study investigated whether different patterns of alcohol consumption might have differential influences on blood pressure level. Results showed that heavy alcohol intake (≥ 300 ml/week [34 g/day]) was related to both higher systolic blood pressure (SBP) and higher diastolic blood pressure (DBP) levels: in men, mean blood pressure (SBP/DBP) was 2.7/1.6 mm Hg higher among heavy drinkers than among nondrinkers; this figure was 3.9/3.1 mm Hg in women. Furthermore, differences in blood pressure between drinkers and nondrinkers were found to be greater among "episodic drinkers" (people with the highest daily variation in alcohol consumption) than among people who drank a regular amount of alcohol each day. Similar adverse effects of binge drinking on blood pressure level (independent of amount of alcohol consumed) have also been observed elsewhere (Stranges et al 2004). In a recent meta-analysis of epidemiological studies which looked at the association of alcohol consumption with the risk of 15 diseases, alcohol at doses of 25 g/day, 50 g/day, and 100 g/day were associated with relative risks of hypertension of 1.43 (95% CI 1.33–1.53), 2.04 (1.77–2.35) and 4.15 (3.13–5.52) respectively (when compared with individuals who did not drink alcohol) (Corrao et al 2004). In another meta-analysis of randomized controlled trials of alcohol reduction, reducing alcohol intake by an average of 67% (from 3–6 drinks per day to 1–2 drinks per day) reduced SBP by 3.3 mm Hg and DBP by 2.0 mm Hg (Xin et al 2001). Though relatively small, long-term differences in blood pressure of this magnitude can have important effects on the risk of CHD and, particularly, stroke. Using estimates of the relations between usual blood pressure and the risk of CHD and stroke mortality from the Prospective Studies Collaboration of one million

individuals from 61 prospective studies, it can be calculated that during middle-age (40–59 years) a difference in SBP of 3.3 mm Hg is associated with an approximate 12% higher risk of fatal CHD and 19% higher risk of fatal stroke (similar for both ischemic and hemorrhagic), while a 2.0 mm Hg higher DBP level is associated with a 16% higher risk of fatal CHD and 23% higher risk of fatal stroke (PSC 2002).

Summary

The consistency of the relationship between light-to-moderate alcohol intake and reduced risks of CHD, together with the existence of plausible biological mechanisms, strongly suggests that moderate alcohol consumption does reduce CHD risk. However, the true magnitude of benefit at any given level may be lower than suggested by most observational studies (mainly because of the difficulties in removing confounding from comparisons as well as the problems caused by the use of nondrinkers as the reference group). Drinking pattern (specifically, drinking with meals) may also have as much influence on reducing CHD risk as overall alcohol amount, though there is little reliable evidence to indicate that any particular type of drink is more or less beneficial than any other. Heavy drinking is associated with increased CHD risk, but the degree that this may be causal is uncertain because while previous studies may have systematically underestimated the risks by not taking within-person variation into account, the observed hazards could also be due to residual confounding. For stroke, the observed relationship between alcohol consumption and risk in a given population depends on the proportion of strokes that are hemorrhagic. Light-to-moderate alcohol intake is associated with a lower risk of ischemic stroke which is likely to be, in part, causal. Hemorrhagic stroke, on the other hand, displays a log-linear relationship with alcohol intake.

In conclusion, drinking 20 g to 30 g of alcohol a day probably reduces major vascular risk in middle-aged people by up to one fifth. However, given that alcohol intake displays clear positive relationships with total mortality in younger people (as well as positive relationships with nonvascular causes of death in middle-aged people), considerable caution in making any general statements about safe levels of alcohol consumption is needed. In particular, any policy that resulted in an overall increase in population average alcohol consumption would be likely to do substantially more harm than good.

References

- Beaglehole R, Jackson R. 1992. Alcohol, cardiovascular disease and all causes of death: a review of the epidemiological evidence. *Drug Alcohol Rev*, 11:175-89.
- Berger K, Ajani UA, Kase CS, et al. 1999. Light-to-moderate alcohol consumption and risk of stroke among U.S. male physicians. *N Engl J Med*, 341:1557-64.
- Bobak M, Marmot M. 1999. Alcohol and mortality in Russia: is it different than elsewhere? *Ann Epidemiol*, 9:335-8.
- Bobak M, Skodova Z, Marmot M. 2000. Effect of beer drinking on risk of myocardial infarction: population based case-control study. *BMJ*, 320:1378-9.
- Boffetta P, Garfinkel L. 1990. Alcohol drinking and mortality among men enrolled in an American Cancer Society prospective study. *Epidemiology*, 1:342-8.
- Corrao G, Bagnardi V, Zamboni A, et al. 2004. A meta-analysis of alcohol consumption and the risk of 15 diseases. *Prev Med*, 38:613-19.
- Corrao G, Rubbiati L, Bagnardi V, et al. 2000. Alcohol and coronary heart disease: a meta-analysis. *Addiction*, 95:1505-23.
- Davey Smith G, Ebrahim S. 2003. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*, 32:1-22.
- Di Castelnuovo A, Rotondo S, Iacoviello L, et al. 2002. Meta-analysis of wine and beer consumption in relation to vascular risk. *Circulation*, 105:2836-44.
- Doll R, Peto R, Boreham J, et al. 2005. Mortality in relation to alcohol consumption: a prospective study among male British doctors. *Int J Epidemiol*, 34:199-204.
- Doll R, Peto R, Hall E, et al. 1994. Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. *BMJ*, 309:911-18.
- Emberson JR, Shaper AG, Wannamethee SG, et al. 2005. Alcohol intake in middle age and risk of cardiovascular disease and mortality: accounting for intake variation over time. *Am J Epidemiol*, 161:856-63.
- Farchi G, Fidanza F, Mariotti S, et al. 1992. Alcohol and mortality in the Italian rural cohorts of the Seven Countries Study. *Int J Epidemiol*, 21:74-81.
- Fillmore KM, Golding JM, Graves KL, et al. 1998. Alcohol consumption and mortality. I. Characteristics of drinking groups. *Addiction*, 93:183-203.
- Fillmore KM, Kerr WC, Bostrom A. 2003. Changes in drinking status, serious illness and mortality. *J Stud Alcohol*, 64:278-85.
- Flesch M, Schwarz A, Bohm M. 1998. Effects of red and white wine on endothelium-dependent vasorelaxation of rat aorta and human coronary arteries. *Am J Physiol*, 275:H1183-90.
- Foppa M, Fuchs FD, Preissler L, et al. 2002. Red wine with the noon meal lowers post-meal blood pressure: a randomized trial in centrally obese, hypertensive patients. *J Stud Alcohol*, 63:247-51.
- Frankel EN, Kanner J, German JB, et al. 1993. Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. *Lancet*, 341:454-7.
- Fuchs CS, Stampfer MJ, Colditz GA, et al. 1995. Alcohol consumption and mortality among women. *N Engl J Med*, 332:1245-50.
- Gaziano JM, Buring JE, Breslow JL, et al. 1993. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *N Engl J Med*, 329:1829-34.
- Gronbaek M, Becker U, Johansen D, et al. 2000. Type of alcohol consumed and mortality from all causes, coronary heart disease, and cancer. *Ann Int Med*, 133:411-19.
- Hendriks HF, Veenstra J, Velthuis-te Wierik EJ, et al. 1994. Effect of moderate dose of alcohol with evening meal on fibrinolytic factors. *BMJ*, 308:1003-6.
- Hines LM, Stampfer MJ, Ma J, et al. 2001. Genetic variation in alcohol dehydrogenase and the beneficial effect of moderate alcohol consumption on myocardial infarction. *N Engl J Med*, 344:549-55.
- Iijima K, Yoshizumi M, Ouchi Y. 2002. Effect of red wine polyphenols on vascular smooth muscle cell function—molecular mechanism of the 'French paradox'. *Mech Ageing Dev*, 123:1033-9.
- Iso H, Baba S, Mannami T, et al. 2004. Alcohol consumption and risk of stroke among middle-aged men: the JPHC Study Cohort I. *Stroke*, 35:1124-9.
- Jackson R, Broad J, Connor J, et al. 2005. Alcohol and ischaemic heart disease: probably no free lunch. *Lancet*, 366:1911-12.
- Kauhanen J, Kaplan GA, Goldberg DD, et al. 1997a. Frequent hangovers and cardiovascular mortality in middle-aged men. *Epidemiology*, 8:310-14.
- Kauhanen J, Kaplan GA, Goldberg DE, et al. 1997b. Beer bingeing and mortality: results from the Kuopio ischaemic heart disease risk factor study, a prospective population based study. *BMJ*, 315:846-51.
- Keil U, Chambless LE, Doring A, et al. 1997. The relation of alcohol intake to coronary heart disease and all-cause mortality in a beer-drinking population. *Epidemiology*, 8:150-6.
- Kerr WC, Fillmore KM, Bostrom A. 2002. Stability of alcohol consumption over time: evidence from three longitudinal surveys from the United States. *J Stud Alcohol*, 63:325-33.
- Klatsky AL, Armstrong MA, Friedman GD. 1990. Risk of cardiovascular mortality in alcohol drinkers, ex-drinkers and non-drinkers. *Am J Cardiol*, 66:1237-42.
- Langer RD, Criqui MH, Reed DM. 1992. Lipoproteins and blood pressure as biological pathways for effect of moderate alcohol consumption on coronary heart disease. *Circulation*, 85:910-15.
- Lazarus NB, Kaplan GA, Cohen RD, et al. 1991. Change in alcohol consumption and risk of death from all causes and from ischaemic heart disease. *BMJ*, 303:553-6.
- Leon DA, Chenet L, Shkolnikov VM, et al. 1997. Huge variation in Russian mortality rates 1984-94: artefact, alcohol, or what? *Lancet*, 350:383-8.
- Lindenstrom E, Boysen G, Nyboe J. 1994. Influence of total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease: the Copenhagen City Heart Study. *BMJ*, 309:11-15.
- Maclure M. 1993. Demonstration of deductive meta-analysis: ethanol intake and risk of myocardial infarction. *Epidemiol Rev*, 15:328-51.
- Marmot MG. 1984. Alcohol and coronary heart disease. *Int J Epidemiol*, 13:160-7.
- Marmot MG, Elliott P, Shipley MJ, et al. 1994. Alcohol and blood pressure: the INTERSALT study. *BMJ*, 308:1263-7.
- Marques-Vidal P, Ducimetiere P, Evans A, et al. 1996. Alcohol consumption and myocardial infarction: a case-control study in France and Northern Ireland. *Am J Epidemiol*, 143:1089-93.
- McElduff P, Dobson AJ. 1997. How much alcohol and how often? Population based case-control study of alcohol consumption and risk of a major coronary event. *BMJ*, 314:1159-64.
- McKee M, Shkolnikov V, Leon DA. 2001. Alcohol is implicated in the fluctuations in cardiovascular disease in Russia since the 1980s. *Ann Epidemiol*, 11:1-6.
- Mukamal KJ, Conigrave KM, Mittleman MA, et al. 2003. Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. *N Engl J Med*, 348:109-18.
- Mukamal KJ, Jensen MK, Gronbaek M, et al. 2005. Drinking frequency, mediating biomarkers, and risk of myocardial infarction in women and men. *Circulation*, 112:1406-13.
- Murray RP, Connett JE, Tyas SL, et al. 2002. Alcohol volume, drinking pattern, and cardiovascular disease morbidity and mortality: is there a U-shaped function? *Am J Epidemiol*, 155:242-8.
- Naimi TS, Brown DW, Brewer RD, et al. 2005. Cardiovascular risk factors and confounders among nondrinking and moderate-drinking U.S. adults. *Am J Prev Med*, 28:369-73.
- Pace-Asciak CR, Hahn S, Diamandis EP, et al. 1995. The red wine phenolics trans-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: implications for protection against coronary heart disease. *Clin Chim Acta*, 235:207-19.

- [PSC] Prospective Studies Collaboration. 2002. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*, 360:1903-13.
- Puddey IB, Rakic V, Dimmitt SB, et al. 1999. Influence of pattern of drinking on cardiovascular disease and cardiovascular risk factors—a review. *Addiction*, 94:649-63.
- Rehm J, Greenfield TK, Rogers JD. 2001. Average volume of alcohol consumption, patterns of drinking, and all-cause mortality: results from the US National Alcohol Survey. *Am J Epidemiol*, 153:64-71.
- Renaud S, de Lorgeril M. 1992. Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet*, 339:1523-6.
- Reynolds K, Lewis B, Nolen JD, et al. 2003. Alcohol consumption and risk of stroke: a meta-analysis. *JAMA*, 289:579-88.
- Rimm EB, Giovannucci EL, Willett WC, et al. 1991. Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet*, 338:464-8.
- Rimm EB, Klatsky A, Grobbee D, et al. 1996. Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits. *BMJ*, 312:731-6.
- Rimm EB, Williams P, Fosher K, et al. 1999. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ*, 319:1523-8.
- Sacks FM. 2002. The role of high-density lipoprotein (HDL) cholesterol in the prevention and treatment of coronary heart disease: expert group recommendations. *Am J Cardiol*, 90:139-43.
- Schroder H, Ferrandez O, Jimenez Conde J, et al. 2005. Cardiovascular risk profile and type of alcohol beverage consumption: a population-based study. *Ann Nutr Metab*, 49:100-6.
- Schulz KF, Grimes DA. 2002. Case-control studies: research in reverse. *Lancet*, 359:431-4.
- Shaper AG. 1990. Alcohol and mortality: a review of prospective studies. *Br J Addict*, 85:837-47; discussion 849-61.
- Stampfer MJ, Colditz GA, Willett WC, et al. 1988. A prospective study of moderate alcohol consumption and the risk of coronary disease and stroke in women. *N Engl J Med*, 319:267-73.
- Stranges S, Wu T, Dorn JM, et al. 2004. Relationship of alcohol drinking pattern to risk of hypertension: a population-based study. *Hypertension*, 44:813-19.
- Suh I, Shaten BJ, Cutler JA, et al. 1992. Alcohol use and mortality from coronary heart disease: the role of high-density lipoprotein cholesterol. The Multiple Risk Factor Intervention Trial Research Group. *Ann Int Med*, 116:881-7.
- Tanne D, Yaari S, Goldbourt U. 1997. High-density lipoprotein cholesterol and risk of ischemic stroke mortality. A 21-year follow-up of 8586 men from the Israeli Ischemic Heart Disease Study. *Stroke*, 28:83-7.
- Theobald H, Bygren LO, Carstensen J, et al. 2000. A moderate intake of wine is associated with reduced total mortality and reduced mortality from cardiovascular disease. *J Stud Alcohol*, 61:652-6.
- Thun MJ, Peto R, Lopez AD, et al. 1997. Alcohol consumption and mortality among middle-aged and elderly U.S. adults. *N Engl J Med*, 337:1705-14.
- Trevisan M, Dorn J, Falkner K, et al. 2004. Drinking pattern and risk of non-fatal myocardial infarction: a population-based case-control study. *Addiction*, 99:313-22.
- Trevisan M, Schisterman E, Mennotti A, et al. 2001. Drinking pattern and mortality: the Italian risk factor and life expectancy pooling project. *Ann Epidemiol*, 11:312-19.
- Veenstra J, Ockhuizen T, van de Pol H, et al. 1990. Effects of a moderate dose of alcohol on blood lipids and lipoproteins postprandially and in the fasting state. *Alcohol Alcohol*, 25:371-7.
- Wannamethee G, Shaper AG. 1988. Men who do not drink: a report from the British Regional Heart Study. *Int J Epidemiol*, 17:307-16.
- Wannamethee G, Shaper AG. 1992. Alcohol and sudden cardiac death. *Br Heart J*, 68:443-8.
- Wannamethee SG, Lowe GD, Shaper G, et al. 2003. The effects of different alcoholic drinks on lipids, insulin and haemostatic and inflammatory markers in older men. *Thromb Haemost*, 90:1080-7.
- Wannamethee SG, Shaper AG. 1997. Lifelong teetotallers, ex-drinkers and drinkers: mortality and the incidence of major coronary heart disease events in middle-aged British men. *Int J Epidemiol*, 26:523-31.
- Wannamethee SG, Shaper AG. 1999. Type of alcoholic drink and risk of major coronary heart disease events and all-cause mortality. *Am J Public Health*, 89:685-90.
- Wannamethee SG, Shaper AG, Ebrahim S. 2000. HDL-Cholesterol, total cholesterol, and the risk of stroke in middle-aged British men. *Stroke*, 31:1882-8.
- Wellmann J, Heidrich J, Berger K, et al. 2004. Changes in alcohol intake and risk of coronary heart disease and all-cause mortality in the MONICA/KORA-Augsburg cohort 1987-97. *Eur J Cardiovasc Prev Rehabil*, 11:48-55.
- Wood D, De Backer G, Faergeman O, et al. 1998. Prevention of coronary heart disease in clinical practice: recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. *Atherosclerosis*, 140:199-270.
- Xin X, He J, Frontini MG, et al. 2001. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension*, 38:1112-17.
- Yusuf PS, Hawken S, Ounpuu S, et al. 2004. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*, 364:937-52.

