Epidemiologists continue to conduct prospective studies of the association between alcohol consumption and mortality; both all-cause mortality and one of its biggest drivers, deaths from coronary disease. Our fascination centres on the health-enhancing effects of light to moderate frequent drinking. This is the halcyon zone where alcohol is anxiolytic and relaxing, improves our meal, enhances our social life, and prevents our coronary disease without appearing to inflict much damage. Some have suggested we are fooling ourselves. Couldn’t these J-shaped curves result from biases common to all of the studies?

While there is an impressive consistency about the shape of the relationships between alcohol and mortality in many studies, with closer scrutiny there is an interesting heterogeneity in the levels and patterns of drinking that are associated with risk and benefit. Several methodological issues affect prospective non-randomized studies of alcohol consumption and mortality that contribute to this variation, and threaten the validity of these studies.

The first is that alcohol consumption is very strongly socially determined and so it is likely that there is substantial residual confounding of its association with mortality by factors other than those measured and adjusted for. That is to say, moderate frequent drinkers have other reasons to die less often than non-drinkers, and heavy drinking is a marker of a short life as well as a cause.

Second, drinking pattern is important for at least the two biggest determinants of alcohol-related mortality, coronary disease and injury (Rehm et al., 2003). However measurement of drinking pattern has been inconsistent between studies and incomplete within them. Thus the influence of the frequency of drinking on mortality risk reduction in light-to-moderate drinkers has not been clearly separated from the effects of volume, and has sometimes been reported to be different in women and in men, even though the putative mechanisms of effect are the same.

The third area of concern is the measurement of volume of alcohol consumption itself. The potential misclassification of alcohol exposure has several components, some of which are present in most studies. Self-reported consumption may be inaccurate; it is commonly under-reported but varies with the type of questions used and about the time period asked (Lemmens et al., 1992; Stockwell et al., 2004). Exposure is sometimes measured only at the baseline of a study with long-term follow-up of outcomes, even though changes in consumption levels are fairly common, and vary with age [references in Fillmore et al. (2006)]. In particular, undocumented movement in or out of the non-drinker reference categories may be a source of error.

The categorization of non-drinkers has been evolving. Used as a reference group, the zero-level alcohol consumers are the key to the J-shaped curve. They are at higher risk than the light-to-moderate drinkers and at lower risk than the heavy drinkers. Who are they? They have variously included all current non-drinkers (lifetime abstainers and ex-drinkers), or non-drinkers along with occasional drinkers (e.g. once a month or less), or more recently, the definition has been restricted to lifetime abstainers.

Challenges to the epidemiological evidence about the protective effect of alcohol started early. In 1988 Shaper, Wannamethee and Walker (Shaper et al., 1988) put forward the ‘sick quitter’ hypothesis, whereby ex-drinkers who had quit due to poor health contaminated the non-drinker group and increased their average risk, resulting in the impression of a protective effect of light drinking.

Much more recently in a commentary in the Lancet (Jackson et al., 2005), Jackson proposed ‘uncontrollable confounding’ as an explanation for some or all the protective association of low levels of alcohol consumption and coronary heart disease (CHD) mortality. Alcohol and mortality studies have often reported residual confounding as inevitable (but not a plausible explanation of the findings), or have ‘dealt’ with confounding by adjusting for a few key variables. Studies with better control for confounders tend to report smaller effect sizes (Corrao et al., 2000) and this could be logically extended. The cautionary tale of hormone replacement therapy and its putative protective effect on CHD was used by Jackson to illustrate the possibility that an effect may not be revealed to be artefactual without a randomized controlled trial. This article also reflected the view that misclassification of non-drinkers was no longer an issue since new studies using lifetime abstainers as a reference group still showed a lowering of risk in the light to moderate drinkers (See e.g. Fagrell et al., 1999; Tolvanen et al., 2005; Mukamal et al., 2006).

Fillmore and colleagues (Fillmore et al., 2006) took on the issue of misclassification of non-drinkers again, and explored the effects on the J-shaped curve of including ex-drinkers and/or occasional drinkers in the abstainer category in past studies. This paper demonstrated the plausibility that at least some of the observed protective effect of alcohol was due to methods of non-drinker classification. One of the criticisms of these meta-analyses has been the use of broad exposure categories for alcohol consumption that could obscure or reduce effects at low levels of drinking. The widespread use of categorization of average alcohol consumption, which is an intrinsically

INVITED COMMENTARY
THE LIFE AND TIMES OF THE J-SHAPED CURVE
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continuous variable, is another potential source of error in alcohol studies that is coming under scrutiny.

Two papers in this issue of *Alcohol and Alcoholism* contribute to the ongoing debates. Baglietto and colleagues from the Melbourne Collaborative Cohort Study (Baglietto et al., 2006) report on the association between average alcohol consumption and all cause mortality with an average follow-up of >10 years, and describe J-shaped curves for men and women. Lifetime abstainers, separated from ex-drinkers, were used as the reference group, but drinking was assessed only at baseline. Fractional polynomials (Royston et al., 1999) were used in some analyses to avoid arbitrary categorization of the alcohol consumption variables. However, the 1958 British Birth Cohort Study (Caldwell et al., 2006), calls the homogeneity of the reference group in such studies into question once more. This time it is not the definition of the reference group, as lifetime abstainers, that is at issue but the veracity of the self-reported lifetime abstinence. If the experience of this cohort is generalizable to other major prospective studies this will revive concern about the misclassification of non-drinkers and the influence this might have on risk estimates.

In the case of hormone replacement therapy (HRT) it was randomized controlled trials that answered the question about cardiac protection and revealed uncontrolled confounding in the previous studies, but it seems that large randomized trials of alcohol consumption, even at light to moderate consumption levels, are unlikely. Interesting new studies lend support to the existence of both protective effects and substantial confounding. For example, the nested case-control study of alcohol and risk of myocardial infarction reported by Mukamal et al. (2005) measured biological markers of the main putative mechanisms of effect (HDL cholesterol, fibrinogen, haemoglobin A1c), and showed that the protective effect was diminished by 75% in women and completely in men when the markers were controlled in the analysis. On the other hand, Lin et al. (2005) found a protective effect of moderate alcohol consumption for all cause mortality in Japanese populations, where haemorrhagic stroke and cancer, not coronary disease, are the dominant causes of death and one might expect alcohol consumption to have a negative impact.

It may be that everyone is right to some extent; that misclassification and confounding account for some, but not all, of the protective effect associated with moderate drinking. It certainly seems that the life of the J-shaped curve will be long, whether or not it ultimately survives.

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