

## SPECIAL THEME: ALCOHOL

## Alcohol and coronary heart disease\*

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The data on two questions are reviewed: does heavy alcohol intake increase the risk of coronary heart disease (CHD)? And, is moderate intake protective? Identified alcoholics and problem drinkers have an increased risk of CHD, and in Britain there is a correlation among 22 towns, between the proportion of heavy drinkers in a town and CHD mortality. Of seven longitudinal studies reviewed, one shows heavy drinkers to have an increased CHD incidence. An inverse association between alcohol consumption and CHD mortality is seen in international comparisons and in time trends in the USA. Of six case-control studies reviewed from England and the USA, all show an inverse association between CHD and alcohol consumption which persists after control for other risk factors. Longitudinal studies, in Japanese-Americans, white American men and women, British civil servants, Puerto Ricans, Yugoslavs and Australians, all show moderate drinkers to have a lower CHD risk than abstainers. Abstainers are likely to differ from moderate drinkers in a number of ways. To date it has not proved possible to show that any of these differences account for the higher CHD risk of abstainers. The apparent protective effect is not large (RR = 0.5) but the consistency of the association and the existence of plausible mechanisms increase the likelihood that the negative association is causal. However, if alcohol intake were to increase in the population the social and medical consequences would be large. An increased intake is therefore not recommended as a community measure for CHD prevention.

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Medical and political discussions of the health effects of alcohol should give prominence to the individual and social damage caused by alcohol.<sup>1</sup> In the interests of public health, it is right that any discussion should begin and end with these problems. In the middle, however, perhaps a small place may be reserved for continued exploration of why moderate drinkers appear to have a lower mortality risk, and particularly a lower incidence of coronary heart disease (CHD), than abstainers. Is the association causal? That is, do moderate amounts of alcohol exert a protective effect?

As suggested recently, non-drinkers may include a number of ex-drinkers who gave up because of ill-health.<sup>2</sup> Hence a high mortality would not be surprising. This is plausible, but other evidence suggests different reasons for the CHD advantage of moderate drinkers. I should like to consider the evidence on two questions: does heavy alcohol consumption increase the risk of CHD and does moderate consumption protect against it?

A major problem concerns the varying definitions of 'heavy' and 'moderate'. There is agreement that daily consumption of

more than 80 g of ethanol is 'heavy'.<sup>3</sup> This is the amount of alcohol contained in five pints of beer, or a bottle of table wine, or one third of a bottle of spirits (Table 1). However, others would put the dividing line between moderate and heavy at a lower level than this.<sup>4</sup> Presumably an appropriate way to define 'heavy' is the level above which alcohol-associated problems emerge; but this is a complex subject since alcohol is associated with a wide range of medical and social problems. The question considered here relates only to coronary heart disease.

It is accepted that heavy alcohol consumption can have a direct toxic effect on the myocardium,<sup>5</sup> resulting in alcoholic cardiomyopathy. This will not be considered further here.

**Table 1** Alcohol content of common beverages<sup>3</sup>

Description	Amount	Alcohol (g)	Amount containing 80 g alcohol (approx)
Draught bitter	½ pint	8.7	5 pints
Draught ale, mild	½ pint	7.4	5 pints
Port, sherry	2 oz	8.9	⅔ bottle
Table wine			
Beaujolais	4 oz	10.7	1 bottle
Sauterne	4 oz	11.5	1 bottle
Spirits (70% proof)	1 oz	8.9	⅓ bottle, 9 singles

1 oz = 28.4 ml.

100 ml alcohol = 79.4 g.

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## Does heavy alcohol consumption increase CHD risk?

Heavy alcohol consumption is related to increased total mortality, but the evidence for a relationship with cardiovascular mortality or morbidity is not consistent.

### International comparisons

As will be seen below, international comparisons show a negative association between alcohol consumption and CHD mortality. Figures for the proportion of heavy, moderate and light drinkers in different countries are not readily available.

### Regional comparisons

In the Regional Heart Study of 22 towns in Great Britain Shaper and colleagues show a positive correlation between the proportion of heavy drinkers in a town and mortality from CHD.<sup>6</sup> These data do not relate to individuals; they examine one group characteristic—heavy drinking—and relate it to another—CHD mortality.

### Studies of alcoholics or problem drinkers

Several studies on institutionalized alcoholics (e.g. by Sundby in Norway<sup>7</sup>) show them to have a high total mortality and an excess from cardiovascular disease. The generalizability of these results is uncertain as institutionalized alcoholics are likely to differ in many respects from heavy drinkers in the general population.

Two studies in industry of non-institutionalized men whose drinking interfered with their work, in the Du Pont company<sup>8</sup> and in Chicago,<sup>9</sup> showed these problem drinkers to have an increased risk of dying from cardiovascular disease. The relative risk was 2.3 for CHD in Du Pont, and 4.0 in Chicago. In Chicago, making adjustments for age, smoking and other risk factors reduced the mortality ratio a little, but it was still elevated.<sup>9</sup>

In Sweden, Wilhemsen *et al.* took registration with the Swedish Temperance Board as an indicator of heavy alcohol consumption and found an increased rate of non-fatal CHD and of sudden cardiac death, independent of blood pressure and smoking.<sup>10</sup>

### Alcohol consumption and CHD

Other studies have concentrated not on problem drinkers or alcoholics but on actual alcohol consumption; almost all have shown heavy drinkers to have either a lower or the same risk of CHD as non-drinkers. Apparently the only exceptions are one study from Chicago that showed a non-significant excess mortality<sup>11</sup> and a twin study that showed an excess of angina pectoris.<sup>12</sup>

## Does moderate alcohol protect against CHD?

### International comparisons

St Leger and colleagues<sup>13</sup> compared CHD mortality in 18 developed countries with alcohol consumption and found a significant negative correlation. The strongest association was with wine and this was independent of cigarette consumption, dietary intake and gross national product. It is unlikely that this correlation could all be due to differences in diagnosis. Such

analyses are always weakened by the absence of age-sex-social class specific consumption figures and cannot by themselves settle causal questions.

These data are consistent with a protective effect of moderate alcohol consumption—but give little clue to what 'moderate' means. From other data,<sup>14</sup> we know that in France, a country with a low rate of CHD, the mean yearly alcohol consumption of people aged 15 and over is 22.3 litres. This corresponds to the startling figure of 49 g alcohol per adult per day, or approximately six drinks per day. Presumably these figures are not adjusted for sales to visitors and they may overstate consumption. Nevertheless, a high proportion of the French population exceed any definition of moderate drinking.

### Time trends

Laporte and colleagues<sup>15</sup> studying death rates in 20 countries, two years later than St Leger, confirmed the negative association between wine and CHD mortality. They then examined time trends in the USA of CHD mortality 1950–75, and found a negative association with alcohol consumption. This negative association was strongest for beer. In an exploratory way, without prior hypothesis, they examined the relation between CHD mortality and alcohol consumption a variable number of years previously. The correlation was strongest with a lag time of five years. For total alcohol the correlation was  $-0.73$ , and for beer the correlation was  $-0.94$ . This leads to speculation that increases in alcohol consumption may have contributed to the decline in CHD in the USA, although other factors have changed at the same time.

### Case-control studies

The results of five studies comparing CHD cases with non-cases are summarized in Table 2, alcohol intake being determined before the CHD event in the study by Klatsky,<sup>19</sup> but after it in the other studies. They included studies of men and women in the USA and men in England. None suggests that heavy intake is harmful. The studies by Stason *et al.*<sup>16</sup> and Klatsky *et al.*<sup>19</sup> find a lower relative risk associated with 'heavy' intake. The others are consistent with a lower relative risk for moderate drinkers compared to non-drinkers.

### Longitudinal studies

The findings of case-control studies have been confirmed by seven longitudinal studies (Table 3). These were conducted on men and women, and in populations as culturally and ethnically different as Japanese-Americans, Yugoslavs, rural and urban Puerto-Ricans, white Americans and British civil servants. They used a variety of methods of assessing alcohol and a variety of analytical techniques. All were consistent with a higher CHD incidence in non-drinkers than in drinkers. Only the Chicago study<sup>11</sup> showed a clear-cut intake (six pints daily) above which CHD incidence may have risen. It is likely that few problem drinkers were included in these studies.

### Is the lower CHD risk in moderate drinkers due to factors other than alcohol?

*(a) Do non-drinkers include people who gave up drinking because they were ill?*

This could account for the higher mortality in non-drinkers, but it is unlikely to be the whole explanation. The data from

**Table 2** Case-control studies of alcohol and coronary heart disease (CHD)

Author	Study	Study population	Sex	'Moderate'	Relative risk			Controlled for risk factors
					None	Moderate	Heavy	
Stason (1976) <sup>16</sup>	Boston Collaborative Drug Surveillance	Non-fatal MI v. hospital controls	M & F	6 drinks/day	1.0	1.0	0.6 (0.3–1.1) <sup>b</sup>	Yes
Dean (1977) <sup>17</sup>	Cleveland County, England	Fatal CHD v. population controls	M	1/week to 1/month ('heavy' = most days to 2–3/week)	1.25 <sup>c</sup>	1.0	1.01	Yes
Hennekens (1978) <sup>18</sup>	Boston	Fatal cases v. neighbourhood controls	M	2 oz (59 ml) alcohol/day	1.0	0.2–0.3 <sup>a</sup>	1.0	Yes
Klatsky (1979) <sup>19</sup>	San Francisco Kaiser-Permanente	Participants in pre-paid health plan Hospitalized MI v. matched controls Sudden cardiac death v. matched controls	M & F	3–5 drinks/day	1.0	0.7	0.4 <sup>d</sup>	Yes
					1.0	0.8	0.7	
Ross (1981) <sup>20</sup>	Retirement Community, Los Angeles	Fatal CHD v. living controls (same community)	F	2 drinks/day	1.0	0.4 <sup>c</sup>		?

<sup>a</sup>  $P < 0.001$ <sup>b</sup> 95% confidence intervals.<sup>c</sup> Not significantly different.<sup>d</sup>  $P < 0.05$  (heavy drinkers v. all others). $P < 0.01$  (non-drinkers v. all others).<sup>e</sup>  $P < 0.01$ .**Table 3** Longitudinal studies of alcohol and coronary heart disease (CHD)

Author	Study	Study population	Sex	CHD	Moderate	Analysis	Controlled for risk factors
Yano (1977) <sup>21</sup>	Honolulu Heart Study	Japanese-Americans in Hawaii	M	Fatal & non-fatal	39 ml alcohol <sup>a</sup> per day	.Dose-response, inverse <sup>b</sup> .RR + 0.46 ( $\geq 40$ mls alcohol v. non-drinkers)	Yes
Dyer (1980) <sup>11</sup>	Western Electric, Chicago	Employees >2 years in company	M	CHD death	6 drinks per day	.? Inverse trend up to 5 drinks .Higher mortality in 6+ <sup>d</sup>	
García-Palmieri (1980) <sup>22</sup>	Puerto-Rico	Urban & rural population sample	M	Fatal & non-fatal	–	.Mean daily alcohol consumption	Yes
						<i>Cases</i> .Rural 1 g .Urban 11 g	
Kozarevic (1980) <sup>23</sup>	Yugoslavia CVD	Bosnia & Croatia	M	Fatal & non-fatal	Drinking daily <sup>f</sup>	.RR = 0.58–0.76 (daily drinkers v. less often) .dose-response, inverse <sup>g</sup>	Yes
Marmot (1981) <sup>24</sup>	Whitehall Study, London	Civil servants	M	Cardiovascular death	34 g alcohol per day	.Relative risk <sup>h</sup> 0 1–9 –34 >34 g/day 2.1 1.0 1.5 0.9	Yes
Gordon (1981) <sup>25</sup>	Framlingham Study	Sample of Massachusetts town	M & F	Fatal & non-fatal	–	.Mean daily alcohol <i>Cases</i> 12 g <i>Others</i> 25 g	Yes
Cullen (1982) <sup>26</sup>	Busselton, Western Australia	Population of small town	M & F	CHD death	Drinker v. non-drinker	Mortality in 13 years (%)	Yes
						<i>Non-smokers</i> Smokers	

<sup>a</sup> No clear dividing line: in highest category ( $\geq 40$  ml alcohol), risk was lower than in previous category.<sup>b</sup>  $P < 0.001$  for linear negative trend.<sup>c</sup> No clear dividing line: in highest category ( $\geq 6$  drinks), risk was lower than in previous category.<sup>d</sup> Not significant.<sup>e</sup>  $P < 0.05$ .<sup>f</sup> They did not have more detailed information on alcohol dosage.<sup>g</sup>  $P < 0.01$  for negative trend.<sup>h</sup> Total mortality was also higher in non-drinkers than moderate drinkers. Only U-shaped curve of mortality was tested for significance ( $P = 0.065$ ).

the recent Swedish study, by themselves, are not convincing.<sup>2</sup> Petersson and colleagues did not report any data on past drinking habits. Their speculation that the high mortality in abstainers occurs to ex-drinkers is based on a total of seven deaths in the abstainers, of which four had been diagnosed at the time the alcohol questionnaire was administered and two (lung embolism and hepatitis) *may* have been alcohol related. Whether these men had been drinkers in the past is not known.

Yano *et al.*, in the study of Japanese-Americans,<sup>21</sup> did find that ex-drinkers had a higher mortality than life-time abstainers, but life-time abstainers had a higher mortality than current drinkers.

As a different approach to this question, in the Whitehall Study,<sup>27</sup> we analysed separately the 10-year all-cause mortality of men who were 'unhealthy' at entry into the study (history of diabetes, symptoms of cardiovascular or chronic respiratory disease, or taking any medication), and compared them with the supposedly healthy remainder. In both the 'healthy' and the 'unhealthy' groups mortality was higher in non-drinkers.

**(b) Could inaccuracies in alcohol history lead to the observed results?**

Alcohol histories are notoriously inaccurate, although when they have been compared with biochemical measures of the effects of alcohol the correlation has been found to be high enough for some purposes. Simple inaccuracies would blur true associations and therefore could not account for the observed results; neither could underreporting by heavy drinkers unless they declared themselves to be total abstainers. Two of the studies, in Hawaii<sup>21</sup> and San Francisco,<sup>19</sup> found an inverse dose-response relationship (higher alcohol-lower CHD). It seems unlikely that denial of drinking could *per se* account for this association.

**(c) Non-drinkers may differ in other ways that put them at higher risk.**

Most of the studies reviewed above controlled for major known coronary risk factors, particularly smoking, and the negative association between CHD and alcohol was independent of these. It remains a possibility that non-drinkers may differ from moderate drinkers in other ways that put them at high risk, e.g., personality type, or diet. One recent study found drinkers in the 'upper moderate' range (25–49 g alcohol) but not 'lower moderate' range (1–24 g alcohol) to differ in nutrient intake from non-drinkers. But differences in fat intake were small and inconsistent for men and women.<sup>28</sup>

To account for the above findings one would have to postulate that this factor X was more common in abstainers and non-abstainers in Yugoslavs, in Puerto Ricans, in Japanese-Americans, and in the other populations studies, and in men and women. This factor X would have to be more common in countries with lower than countries with higher alcohol consumption, and would have to have changed in frequency in the USA in the opposite way to alcohol consumption, increasing in the late 1940s and 1950s and declining again in the 1960s and 1970s.

There may indeed be a complex of factors that could explain away the above findings. A simpler explanation is that moderate drinking is protective.

## How might alcohol protect against CHD?

### Type of alcohol

If one type of alcohol beverage were more strongly 'protective' against CHD, this would make it more likely that it was not alcohol *per se*. The findings on this point do not, at the moment, implicate one type of drink over another. St Leger *et al.*<sup>13</sup> found the inverse association between countries to be strongest with wine, but Laporte *et al.* found the inverse association with time trends in the USA to be strongest with beer.<sup>15</sup> In three studies<sup>18,21,23</sup> different types of alcoholic drinks were all shown to be more or less equally associated with lower CHD risk. The other studies did not distinguish type of alcoholic drink. Nevertheless, it remains a possibility that components of alcoholic drink other than ethanol are responsible for a 'protective' effect.

### Possible mechanisms

#### Atheroma

There is not general agreement, but there have been reports of less atheroma in alcoholics at autopsy.<sup>15</sup> In general these were studies of heavy, not moderate drinkers.

One study of patients undergoing coronary angiography<sup>29</sup> found significantly lower occlusive scores in moderate than in non-drinkers. Such studies are difficult to interpret because of the biased selection of patients.

#### Lipids

Several studies have shown HDL cholesterol levels to be higher in moderate drinkers<sup>15,30</sup> and high levels of HDL cholesterol are associated with lower CHD risk. However, the fraction associated with lower CHD risk is HDL<sub>2</sub>, whereas alcohol may increase the HDL<sub>3</sub> fraction, although this has not been definitely established.

#### Thrombosis

Alcohol in large amounts can produce thrombocytopenia and decreased platelet aggregation. Meade has reported that drinkers have lower fibrinogen levels and higher fibrinolytic activity than non-drinkers.<sup>31</sup> These effects could protect against CHD.

## Is the negative association causal?

There is some evidence of an increased risk of CHD in heavy drinkers. This is not a crucial public health question, however, as there is sufficient evidence of the hazards of heavy drinking to make it undesirable, regardless of a possible relation with CHD.

The evidence that moderate alcohol consumption may be protective may be assessed in relation to the formal criteria for a causal association.

### Strength

The relative risk for moderated alcohol consumption is of the order of 0.5. It is quite conceivable that some third factor(s) may account for an observed association of this order of strength.

### Dose-response

An inverse dose-response relationship has not been found consistently, possibly due to inaccuracies in determining alcohol consumption. Whatever the reason, this is a weakness in the current evidence.

### Temporal sequence

A number of studies have established that non-drinking preceded the onset of CHD.

### Consistency

One of the strongest arguments in favour of causality is that the inverse association with alcohol has been found in several different populations, in case-control and longitudinal studies, in international comparisons and in analyses of mortality time trends. Each of these types of study has its own weaknesses. Consistent findings from such varied sources make it more likely that moderate alcohol consumption is protective.

### Independence

Where studied, the association between non-drinking and CHD has been found to be independent of other major cardiac risk factors.

### Plausibility

The effect of alcohol on HDL cholesterol offers a plausible mechanism (or did so, until recent doubts arose on the relevance of the HDL fraction influenced by alcohol), as does the effect on haemostasis.

### Specificity

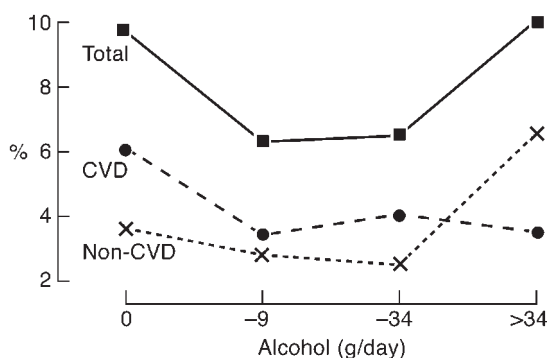
There is some evidence that deaths from other causes may be commoner in non-drinkers, but not to the same extent as cardiovascular disease,<sup>24</sup> and this has been found less consistently.

In summary, the evidence is far from complete; but it does point towards a protective effect of moderate alcohol consumption. If there is a level of alcohol which is no longer 'safe' for CHD, it is probably in excess of six drinks per day (approx 50 g alcohol). If the apparent protective effect is due to confounding variables, they have yet to be identified.

## What recommendations should be made?

If, as an interim judgement, we assume that the protective effect of moderate alcohol consumption is likely to be causal, two further aspects must be considered in making recommendations: what is the upper limit of 'moderate' and what are the likely effects of recommending moderate alcohol intake?

The figure from the Whitehall study shows a U-shaped relationship of mortality to alcohol; we took 34 g alcohol per day (about four drinks) as the start of our 'heavy' category of consumption. It is difficult to know at precisely what level of alcohol consumption the non-CVD mortality starts to increase, but data from other studies show blood pressure to be higher with four drinks (or even less) per day.



**Figure 1** 10-year mortality (age adjusted %) all causes, cardiovascular (CVD) and non-cardiovascular (non-CVD) causes according to daily alcohol consumption<sup>24</sup>

The Royal College of Psychiatrists has recommended<sup>32</sup> a maximum limit of twice this amount (about eight drinks per day), but this seems to be too high. There is an association between the mean level of alcohol consumption of a community and the proportion of problem drinkers,<sup>14</sup> and anything that encourages an increase in average consumption is likely to lead to disastrous consequences in a minority, as well as to more widespread social costs and an increase in road accidents. These considerations, linked with the fact that the role of moderate intake in protecting against CHD is not certain, lead the author to agree with the conclusion of the recent WHO Expert Committee on the Prevention of CHD: 'Increased alcohol intake is not recommended as a preventive measure in CHD, either in populations or in individuals.'

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## Commentary: Reflections on alcohol and coronary heart disease

Michael G Marmot

Real authors, as opposed to those of us who write scientific prose, are mixed on the question of re-reading. Some claim not to be able to bear reading their previous writing. Others depend on it. One author finds re-reading what she has just written an essential part of the creative process. Robert Browning when asked to re-read and then interpret one of his poems replied something like: when I wrote that only God and Robert Browning knew what it meant; now only God knows.

I find it odd to re-read, odder still to write a commentary on a paper that I had written more than 16 years ago.<sup>1</sup> The infelicities of style set my teeth on edge. The difficulty I had of knowing the difference between a drink and a unit and of calculating precisely how many grams of alcohol are in a bottle of wine are just plain embarrassing. (While re-reading, I went back to other things I had written on alcohol and found another arithmetical error that was worse—reference withheld.) Wordsworth wrote of his youth ‘I cannot paint what then I was’.<sup>2</sup>(p.105) Regrettably, I can.

Of perhaps more interest than a mixture of personal hubris and self-indulgence—they are closely connected—is what has and has not changed on the question of alcohol and the heart. I want to use this to reflect on several issues, some of which were touched on in that 1984 review and some not. (In writing this I do not have the benefit of knowing what other commentators have to say on that article.)

### Criticism and the growth of knowledge

This was the title of an important collection of writings on the philosophy of science edited by Imre Lakatos and which could be seen as Thomas Kuhn’s summary of his reactions to Karl Popper and Kuhn’s critics reactions to him.<sup>3</sup> The different philosophers of science differ on their views on how science does or should proceed. Criticism emerges as a strong part of it. I wrote that 1984 review in response to criticism.

I had published a report from the Whitehall study in 1981 (with Martin Shipley who is my close colleague after more than 20 years of publishing together, and Geoffrey Rose) entitled ‘Alcohol and mortality: a U-shaped curve’.<sup>4</sup> The stimulus for this was twofold. Klatsky, at Kaiser Permanente in California

had published papers showing that moderate alcohol was protective against coronary heart disease (CHD).<sup>5</sup> Nancy Day and Robin Room, who were at Berkeley when I was there in the early 1970s, had published analyses showing that non-drinkers had higher mortality than drinkers. They raised the question of separating the drink from the drinker.<sup>6</sup> Pearl, as far as I was aware, was the first to draw attention to the U shape of the relation of alcohol consumption to mortality. The copy of his 1926 book in the library of the London School of Hygiene is inscribed 'To Major Greenwood, a noble drinking pal'.<sup>7</sup> Re-reading Pearl before I wrote this, I now cannot find a reference to the U-shaped curve and wonder where I did find the term if not from him. He studied a sample of working men, resident in Baltimore Maryland, and showed that 'moderate drinking of alcoholic beverages did not shorten life. On the contrary moderate steady drinkers exhibited somewhat lower rates of mortality and greater expectation of life than did abstainers.' His study confirmed that heavy drinkers 'exhibited considerably increased rates of mortality,' as compared with abstainers or moderate drinkers.

Among the responses to my 1981 article were three types of criticism: alcohol consumption was determined with imprecision; non-drinkers included people who had given up drinking because they were ill or who had not taken up drinking for the same reason; non-drinkers differed from drinkers in other ways that put the non-drinkers at risk of CHD. These were later summarized by Shaper.<sup>8-12</sup> The 1984 review was a response to those criticisms. The criticisms were all credible and *a priori* were possible reasons why the apparent protective effect of alcohol on CHD might not be causal. I set out in that 1984 paper why I judged the criticisms, although important, to be misplaced. Misplaced in the sense that they did not, in my view, provide the reasons why moderate drinkers had lower CHD rates than non-drinkers. I returned to the issue in 1991,<sup>13</sup> 1995<sup>14</sup> and 1998.<sup>15</sup> My view of the causal nature of the association was strengthened by findings subsequent to 1984. Differences between non-drinkers and drinkers, other than alcohol, do not appear to account for the lower CHD rate in moderate drinkers. A recent systematic review of 42 studies confirmed the protective effect of regular moderate alcohol consumption on CHD.<sup>16</sup> A recent Study from Scotland, not in that systematic review, found 'no robust relation between consumption of alcohol and mortality from coronary heart disease.'<sup>17</sup> They did find that men who consumed 8-14 units a week had a relative CHD mortality rate of 0.79 (0.61 to 1.01) compared to non-drinkers after adjustment for own and father's social class, other socioeconomic characteristics and markers of baseline illness.

In this age of systematic reviews and meta-analyses, the methods used in my 1984 paper look a little quaint. I would argue that such quaint methods have advantages. Two characteristics of the studies made them unlikely candidates for meta-analyses, heterogeneity of methods and heterogeneity of populations studied. It was precisely this heterogeneity that weighed in favour of causation. If a range of different methods led to the same conclusion, it made artefact a less likely reason for the association. This is close to Bradford Hill's consistency. I argued that if non-drinkers have higher CHD rates in populations as diverse as Yugoslavs, Puerto Ricans, white male residents of Framingham, women in a retirement community in Los Angeles,

white male civil servants in London, Japanese physicians, Japanese Americans in Hawaii then confounding was less plausible. Because statistical control for measured confounders had not explained away the association, the confounding argument had to revolve around logic rather than statistical analyses of confounders that had not been measured.

Those of us engaged in this debate in the 1980s and 1990s, behaved with the passion of those who have had new insight into a problem. It is salutary to re-read Pearl. Compare his description of confounding with that in a modern epidemiological paper. 'It has been suggested by many persons, at different times, that the similarity in the mortality rates of abstainers and moderate drinkers, or the possible slight superiority of the moderates as compared with the abstainers, is mainly due to factors not connected directly with alcohol at all. This argument, in one form, runs as follows: The abstainer is really a poor risk, and knows it, or believes that he knows it. He therefore abstains from alcohol, thinking that it will do harm to his already poor health. On the contrary the moderate drinker is an average, healthy sort of person who is in fact a good insurance risk. It is then concluded that if the persons in the moderate group had been abstainers instead of moderate drinkers, they would have shown a greatly superior duration of life, on the average, to the real abstainers. The reason they have in fact only about the same, or a little higher expectation of life, is because their real vital superiority to the abstainer group has been curtailed by the harmful biological effects of their moderate drinking.'<sup>7(p.170)</sup>

Pearl asks himself what he would do to control confounding if he were conducting an animal experiment on alcohol. His answer is to compare sibs in a litter randomly assigned to drinking and non-drinking. His best approximation is to find, in his sample, 94 male abstainers who had 113 moderate drinking brothers. He shows that the abstainers have higher mortality than the moderate drinkers.

Pearl also quotes Stevenson's discussion of differences in 'temperament' between the typical teetotaler, and drinker. Stevenson's summary is that 'on the one hand, then, we have the combination of drink and the devil, and on the other hand of teetotalism and the crank.'<sup>7(p.171)</sup> While not subscribing to the terminology, we did examine an aspect of this question in the Whitehall II study. We showed that the lower plasma fibrinogen level in drinkers compared to abstainers could not be explained by a number of different psychosocial factors.<sup>18</sup>

## Beverage type

There was a great deal of interest then, as now, in whether wine may be more protective than other beverages. All round the world small groups of healthy readers religiously consume their red wine because of its presumed antioxidant properties. I concluded in 1984 that the findings do not 'at the moment, implicate one type of drink over another' (this was one of the sentences where I do not now disagree with the thought so much as the way it was expressed). There are at least three reasons why wine could appear to be more protective: it may contain substances other than alcohol, biophenols for example; wine drinkers may be different from other beverage consumers e.g. higher socioeconomic position;<sup>13</sup> the pattern of drinking wine may differ from the pattern of drinking other beverages.

The lack of consideration of patterns of drinking was a major omission from the literature and my 1984 review. Two recent pieces of evidence, one from Keil and one from my own group, confirm my view that it is the alcohol in wine that is protective rather than other substances, although pattern of drinking may be important. In Bavaria and the Czech Republic the predominantly beer-drinking population drink beer somewhat like people in Mediterranean countries drink wine: with meals as a daily occurrence. In both these populations non-drinkers have higher CHD rates than regular beer drinkers.<sup>19,20</sup>

This demonstration that beer may be as protective as wine if drunk in the same way, is an interesting example of how epidemiological studies can throw light on the mechanism question. It is not the case that epidemiology is limited to demonstrating associations but can say little on why they come about. The presumed extra protection afforded by wine led to a search for the protective properties of wine other than alcohol. If it is true that beer drunk in the same way as wine has the same protective effect it should divert attention towards alcohol and the patterns of consumption.

## Patterns of drinking

Most of the literature on alcohol and heart disease in 1984, and since, contained little on patterns of drinking. At the time, there was speculation that the high mean alcohol consumption of France, Italy and Spain might, while protecting from CHD, lead to chronic liver disease and certain cancers of the upper aerodigestive tract. By contrast, the lower mean, but more episodic consumption, of Scotland or Finland would convey little protection from heart disease but could lead to cerebrovascular disease, and problems associated with drunkenness.

The findings on beer from Bavaria and the Czech Republic tend to rule out a special role for wine. They do not rule out the possibility that the pattern of drinking may be important. Pharmacologically, binge drinking has to be different from moderate daily drinking. Drinking with meals could change the effect of other dietary nutrients.<sup>21</sup>

A particular issue has arisen in relation to the mortality crisis in the former Soviet Union. There is speculation that recent rapid trends in mortality are related to binge drinking.<sup>22</sup> The two biggest contributors to the East-West gap in mortality in Europe are external causes of death and cardiovascular disease (CVD), mainly CHD. There is little question that binge drinking could increase deaths from accidents and violence. There is, however, a question as to whether the Russian pattern of binge drinking could increase CHD.

I had never described the relation of alcohol to CHD as U shaped. The 'U' applied to total mortality. In my 1984 review, I pointed out that the data on heavy drinking and cardiovascular disease were inconsistent. Some studies of problem drinkers had shown them to be at higher risk of CHD, but studies of alcohol consumption had consistently failed to find an association between heavy drinking and CHD. The apparent discrepancy may be because epidemiological studies are likely to underrepresent people whose drinking has led to severe social problems. This raises the question of whether it is something else about the problem drinkers that puts them at higher risk of CHD.

A recent systematic review<sup>16</sup> found 37 prospective studies of alcohol and CVD that met its inclusion criteria. The review

confirmed the protective effect of moderate regular alcohol consumption but found only seven studies that examined drinking patterns or heavy drinking. These studies did, in general, find that heavy drinkers—binges, hangovers, intoxication, alcohol treatment, problems with work—had increased risk of cardiac death compared to non-drinkers. It is important scientifically to understand if heavy drinking does have different biological effects from moderate drinking and hence a different relation to cardiac death. Problem drinkers have, in addition, other features that may put them at high risk.

There is also evidence that heavy drinking may increase risk of ischaemic, if not haemorrhagic stroke.<sup>14</sup>

## Interaction or effect modification

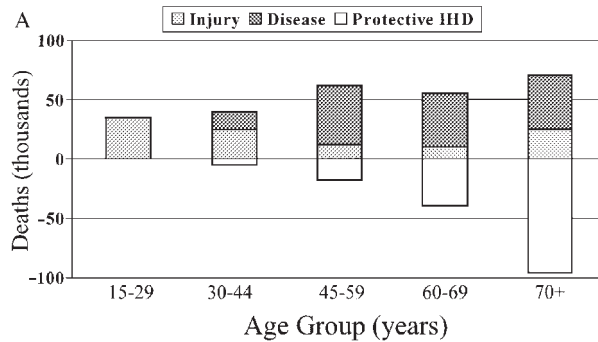
In my 1984 review I was so concerned with the question of confounding, that I did not pause to wonder if there might be effect modification. In other words, the evidence suggested that moderate drinkers were at lower risk of CHD because of their drinking, not for some other reason. It did not occur to me to ask, nor did the literature really permit the question, whether the apparent protective effect of alcohol might differ in subgroups of the population. This has still not been the subject of much study. The Nurses Health Study found beneficial effects of alcohol on CHD. These were not seen in the population in the lowest quartile of folate intake.<sup>23</sup> Folate is of interest, of course, because increased intake of folic acid is associated with lower levels of plasma homocysteine and a presumed consequent reduction in CHD incidence.

These data are therefore consistent with an interaction of alcohol and nutrition. It raises the possibility that in the former Soviet Union, not only may binge drinking be a particular problem but alcohol may not have a protective effect on CHD because of patterns of nutrition that result, among other things, in low folate intake.

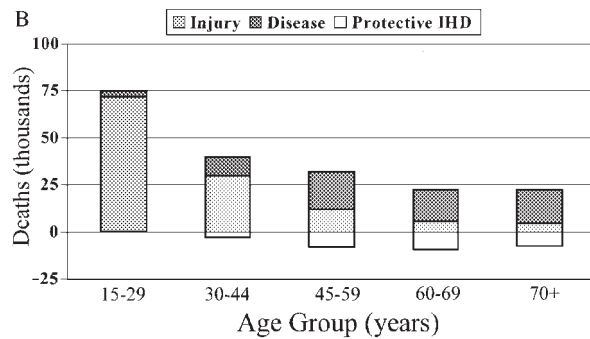
The question of interaction is especially relevant when attention broadens beyond CHD to embrace all causes of morbidity and mortality. One obvious factor to be taken into account is age. At younger ages when CHD is uncommon, there will be little protective effect on all-cause mortality. This is clearly seen in a review of three studies of adolescents and five studies of adults with a starting age in their 20s.<sup>24–26</sup> These studies confirmed the adverse effect on all-cause mortality of heavy drinking and found no consistent protective effect of moderate drinking. They did not report cause of death, but these findings are to be expected if CHD was an infrequent cause of death in these relatively young populations.

In parts of the world where ischaemic heart disease (IHD) is relatively uncommon, there will similarly be less protective effect. This is shown by the calculations Murray and Lopez performed for their Global Burden of Disease study. Figure 1 from that study illustrates the effect of alcohol use on deaths caused and averted by alcohol use in men in two regions of the world: established market economies and sub-Saharan Africa. In the latter, at every age, the number of deaths attributed to alcohol use, from injury and alcohol associated diseases, outweighed the protective effects on IHD. In the established market economies, only at age 70 and above do the number of deaths prevented exceed the numbers caused.<sup>27</sup> For premenopausal women, among whom IHD is uncommon, alcohol has little protective effect.<sup>14</sup>





**Figure 1a** Deaths attributable/averted by alcohol use in established market economies<sup>27</sup> (Males 1990)



**Figure 1b** Deaths attributable/averted by alcohol use in sub-Saharan Africa<sup>27</sup> (Males 1990)

Another modifier of the harmful effect of alcohol may be socioeconomic position. Given how consumed I have become with the question of social inequalities in health, I am surprised at how little mention I made of this issue in 1984. By 1991, I had come to speculate on whether the apparent greater protection from wine could arise from the fact that moderate drinkers of wine tend to be of higher social class than moderate drinkers of other beverages.<sup>13</sup> In light of the data from the Czech Republic and Bavaria on the protective effect of beer drinking, the question should be whether moderate daily drinkers are of different socioeconomic position compared to non-drinkers. In the first Whitehall study we controlled for employment grade in examining the effect of alcohol on mortality, as did the British Regional Heart Study.<sup>8,28</sup>

The other intriguing phenomenon to do with social pattern is that, in Britain, neither mean alcohol consumption, nor prevalence of heavy drinking show much of a social gradient. By contrast, as Table 1 shows, there is a social gradient in mortality from many alcohol associated causes.<sup>29</sup> This suggests either that the pattern of drinking differs according to social position, or that other factors associated with position in society interact with alcohol to increase the risk of problems associated with drinking. A third possibility is that, although alcohol consumption differs little by social class in social surveys, people with alcohol associated problems are downwardly mobile. If such people are underrepresented in social surveys, this could account for increased mortality at the bottom end of the social

**Table 1** Standardized mortality ratios by social class. England and Wales, 1991–1993<sup>29</sup>

Social class	Men aged 20–64 years			
	Alcohol dependence	Chronic liver disease and cirrhosis	Accidents	Car crashes
I	73	67	54	66
II	58	75	57	65
III <sub>NM</sub>	89	115	74	86
III <sub>M</sub>	95	97	107	113
IV	110	119	106	101
V	253	242	226	185

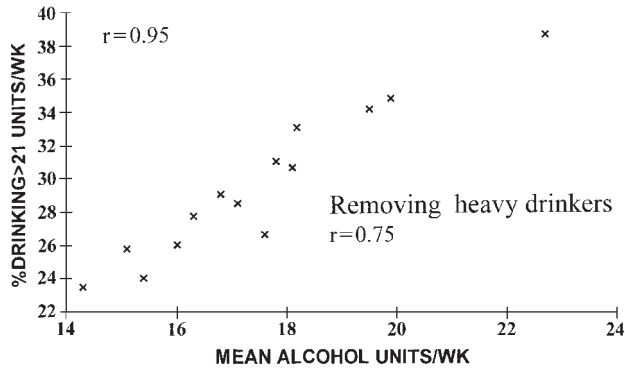
distribution despite the lack of a social gradient in alcohol consumption.

## Policy implications

1984 was a happy period of my life in so far as I sat on no committees. The advantage of such a situation is clear. If there be any disadvantage, it may be that there is less possibility for the research to influence policy. At least, that is my current rationalization. I may not have been involved in policy discussions in 1984 but I was concerned in principle. I situated my review of alcohol and the heart within the context of the harmful effects of alcohol and I ended without a recommendation.

When subsequently asked to chair a Working Group representing the British Royal Colleges of Physicians, Psychiatrists and General Practitioners, I took this perspective with me.<sup>14</sup> We concluded that moderate alcohol consumption was protective from IHD. We were concerned, however, with the other effects of alcohol. Above 21 units a week for men, and 14 for women, the frequency of psychosocial problems increases with amount drunk. Similarly, mortality rates increase with amount drunk. We reviewed 15 studies on alcohol and all-cause mortality in men, and four in women. The largest of the studies, the American Cancer Society Prospective Study of more than a quarter of a million men showed all-cause mortality to increase steadily from one drink a day.<sup>30</sup> We concluded therefore that the advice of a sensible limit of 21 units a week for men and 14 for women should stand. Subsequent to our report, a second American Cancer Society Study of relatively affluent, well-educated volunteers showed a similar pattern of alcohol and all-cause mortality: mortality increased from one drink a day, although non-drinkers who smoked were the highest risk group.<sup>31</sup>

One argument for not recommending an increase in the sensible limit guideline was the risk curve relating individual consumption to morbidity and mortality. The second argument was the population theory of alcohol consumption.<sup>32</sup> The argument was that anything that increased the mean consumption of alcohol would be likely to increase the prevalence of heavy drinking. I was somewhat dismayed when a British Government committee ignored our advice and recommended a relaxation of the sensible limit guideline.<sup>33</sup> Given the heterogeneity among the 15 studies we reviewed on alcohol and mortality, I was surprised that the Government committee felt able to choose a cutpoint that was slightly different from the one we had endorsed.



**Figure 2** Mean consumption predicts heavy drinking from the Health Survey for England in 14 regions<sup>34</sup>

The second plank of their argument was that the single population theory might not apply in Britain. Challenged by this, we examined data from the Health Survey for England and showed that across 14 regions there was a clear association between mean consumption and the prevalence of heavy drinking (Figure 2).<sup>34</sup>

For those who would rather not muddy their hands with policy implications of their work, they have Pearl for consolation. Having concluded that alcohol abuse has disastrous consequences, he says that science can contribute little to the question of what to do about it '... man is not a wholly rational animal in respect of his behaviour. In fact he only acts rationally, if by natural endowment capable of doing so, when the consequences of failing so to act are immediately and sufficiently painful. Otherwise his emotions and tastes get full play.'<sup>7</sup>(pp.228–29)

## Afterthoughts

I am still unclear as to whether the benefits of re-reading outweigh the hazards. I am not even sure whether agreeing or disagreeing with what one wrote 16 years ago is the preferable option. If one disagrees, at least one could argue that time and experience have brought a change of view. If one agrees, is it that the younger man got it right, or that there has been little personal intellectual development over the intervening period?

With such uncertainty in mind, I do find myself in broad agreement with what I wrote then. Those scientific views have very much informed my participation in policy discussions. The major scientific areas that need attention relate to patterns of drinking, particularly binge drinking, and interaction with other determinants of morbidity and mortality. If attention is paid to these, we may then be in a better position to gauge the extent to which alcohol consumption may be responsible for trends in morbidity and mortality over time, across social groups and internationally.

## Acknowledgements

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## Commentary: Alcohol, coronary heart disease and public health: which evidence-based policy?

Pascal Bovet and Fred Paccaud

In a comprehensive review of the evidence available in 1984, Marmot concluded that moderate alcohol intake was associated with decreased coronary heart disease (CHD) mortality while heavy drinking resulted in higher mortality compared to non-drinkers.<sup>1</sup> The consistency of the findings across ecological, case-control and prospective studies and the availability of convincing data on plausible mechanisms suggested a cardio-protective effect of moderate alcohol consumption. However, Marmot warned that increased intake was not recommended in view of the social and medical consequences of an increase of alcohol consumption in the population. Epidemiological data published since this review support the original conclusions by Marmot and have provided further information to fine tune our understanding of the relation of alcohol to CHD and their relevance to policy.

Large prospective cohort studies have provided further solid data since 1984. Cohorts among middle-aged or elderly people included, for example, 51 529 American male health professionals with information on alcohol consumption studied for 12 years,<sup>2</sup> 87 526 American female nurses followed for 4 years,<sup>3</sup> 276 802 men enrolled by the American Cancer Society followed for 12 years,<sup>4</sup> 490 000 American men and women from the American Cancer Study II followed for 9 years,<sup>5</sup> 123 840 American adults from a prepaid health plan followed

for 8 years,<sup>6</sup> 12 321 British male doctors followed for 13 years,<sup>7</sup> 36 250 middle-aged French men followed 12–18 years<sup>8</sup> or 13 285 Danish men and women followed for an average of 13.5 years.<sup>9</sup> These and most other studies and reviews<sup>10–14</sup> have consistently found that consumption of 1–6 drinks a day was associated with a 20–50% lower risk of CHD. (One 120–150 ml glass of wine, one 280–360 ml bottle/can of light beer or one 20–30 ml measure of spirit each typically correspond to one 'unit' or 'drink' and contain 10–17 ml alcohol or 8–15 g of alcohol). Moderate alcohol intake has also been associated with a 20–30% reduced risk of stroke and other cardiovascular diseases<sup>5,7</sup> and a 20% reduced risk of sudden death.<sup>15</sup> Consistency of results among various populations and analytical control for several potential confounders in many of these studies makes it very unlikely that the apparent inverse relation between alcohol intake and CHD results from selection biases or confounding factors. In particular, results were generally not substantially altered in analyses excluding people with illnesses or abnormal risk factor levels at baseline. This argues against the view that higher mortality in non-drinkers relates to the inclusion of sick people (including former drinkers) into the categories of non-drinkers.<sup>16</sup> Although ethical and feasibility issues preclude the conduct of clinical trials of alcohol consumption, current epidemiological evidence supports, virtually irrefutably, that light-to-moderate drinking substantially reduces the risk of CHD.

The effects of moderate alcohol consumption on all-cause mortality depends on a person's underlying (or absolute) risk

of disease that can be improved or worsened by alcohol.<sup>17</sup> Moderate alcohol intake reduces the relative risk of CHD and ischaemic stroke but alcohol consumption has a linear relationship with mortality from hepatic cirrhosis, injury from external causes, haemorrhagic stroke,<sup>3,6,18</sup> upper digestive tract cancers and probably breast cancer<sup>19</sup> and large-bowel cancer.<sup>20</sup> Hence, the reduction in all-cause mortality among middle-aged and elderly people associated with light to moderate alcohol intake (15–50 g, typically 1–3 drinks) is related to the distribution of deaths from cardiovascular disease and from conditions potentially worsened by alcohol. For example, among the 226 871 men aged 56 years on average and free of cancer and cirrhosis at baseline (among whom one drink per day was associated with a 20% reduction in all-cause mortality), 47% of the 25 424 deaths occurring during 9-year follow-up were due to cardiovascular conditions while only 10% were due to conditions potentially worsened by alcohol.<sup>5</sup> In a recent cohort of 1536 Italian middle-aged men followed for 30 years, age-adjusted life expectancy was 2 years longer for men drinking 49–84 g alcohol per day (typically 3–6 drinks) than for men drinking 0–12 g per day (a similar 2-year longer life expectancy was found for non-smokers compared to smokers).<sup>21</sup>

In contrast to the situation in the middle-aged, moderate drinking is generally associated with increased all-cause mortality in young adults as mortality in this age group results mainly from violent deaths (accidents, suicide, homicide) which are all worsened by alcohol. For example, moderate drinking was associated with a 30–50% increase in all-cause mortality in a cohort study of 49 618 young Swedish military conscripts in which there were only 38 fatalities from myocardial infarction among a total of 1473 deaths over a 25-year follow-up.<sup>22</sup> This and other studies<sup>17</sup> suggest that benefits of moderate alcohol intake may outweigh harm among men in their 40s and women in their 50s.

Irrespective of age, more benefit (in terms of absolute risk) will result from moderate alcohol intake in people with multiple cardiovascular risk factors. Conversely, more harm will result from moderate alcohol consumption in populations with high rates of deaths from external causes or alcohol-related diseases. Also worthy of consideration is the fact that populations with low CHD mortality (which relates inversely with alcohol intake) tend to have high death rates from haemorrhagic stroke (which relates directly with alcohol intake). Hence, it is no surprise that alcohol consumption results in a heavier burden of disease in developing countries (low CHD mortality, high mortality from haemorrhagic stroke and injury, demographically young populations) than in western countries (where opposite characteristics are found).<sup>23</sup>

A causal interpretation of the inverse relation between moderate alcohol consumption and CHD is supported by consistent evidence linking alcohol intake with several factors associated with CHD, particularly high density lipoprotein (HDL) cholesterol and apolipoprotein AI. A recent meta-analysis of 42 experimental studies demonstrates that moderate alcohol drinking substantially reduces HDL cholesterol, apo A lipoprotein, lipoprotein(a), fibrinogen, plasminogen and tissue type plasminogen activator antigen.<sup>24</sup> On the basis of published studies (considering that no single study has simultaneously calculated the risk of CHD associated with all biological factors), the authors calculated that an intake of 30 g alcohol a day

would cause a 25% reduction in risk of CHD. However, it has been suggested that alcohol preferentially increases a type of HDL particles (LpAI:AI) that are less clearly associated with cardioprotection.<sup>25,26</sup> This issue is not yet fully clarified and needs further research. Cardioprotection from moderate alcohol consumption has also been challenged on the grounds that alcohol intake increases blood pressure. However, while heavy alcohol intake (e.g. >4 drinks/day) is known to induce hypertension,<sup>27,28</sup> the response is less clear at levels of light-to-moderate intake.

An inverse relationship between alcohol intake and CHD has been described in populations with widely different traditional consumption patterns of alcoholic beverages, suggesting a common effect of ethanol. However, several studies have suggested a larger effect of grape or rice wine over other beverages,<sup>8,9,29</sup> although a reduced risk of CHD has also been demonstrated for beer<sup>30,31</sup> or spirit.<sup>2</sup> The issue is complicated because, in several countries, wine drinkers tend to be better educated, earn more, have a healthier diet, and get more medical care; thus, they tend to have different risks of diseases and different drinking patterns compared to other drinkers. Wine, unlike most other alcoholic beverages, contains phenolic substances that are known to inhibit oxidation of low-density lipoprotein,<sup>32</sup> affect platelet functions<sup>33</sup> and inhibit stages of carcinogenesis.<sup>34</sup> The different effects of alcoholic beverages could also relate to nitrosamine, a potentially carcinogenic substance, which is found in beer and spirits but insignificantly in wine.<sup>35</sup> A recent large Danish cohort study found that upper digestive tract cancers were strongly associated with beer and even more so with spirits while no consistent relation was found for wine intake.<sup>36</sup> Violent deaths were found to be less frequent in wine drinkers than in beer drinkers.<sup>37</sup> Further research should clarify the role of substances other than ethanol in different beverage types and characteristics of drinkers of specific beverages. Such factors could explain part of the variation in mortality from alcohol-related diseases between populations.

Drinking pattern has specific health consequences irrespective of total alcohol intake. A Finnish population-based prospective study showed, for example, that beer bingeing was associated with increased all-cause mortality, deaths from external causes, and fatal myocardial infarctions regardless of the total average consumption of beer, wine and spirits.<sup>38</sup> Binge drinking may also partly explain the lack of reduced CHD mortality in a cohort of Scottish middle-aged men<sup>39</sup> and may be a key factor in the current rise in mortality in Eastern European countries.<sup>40</sup> In contrast to binge drinking, regular alcohol consumption with meals might result, for example, in slowed alcohol absorption, lower blood alcohol, less alcohol-related damage and more sustained stimulation of high-density lipoproteins. The relationship between alcohol intake and CHD and all-cause mortality is therefore likely to differ among populations where binge drinking and spirit consumption are common as compared to populations where regular moderate drinking of wine is predominant.

Societies largely rely on historical, cultural and religious attitudes for their stances toward alcohol consumption. There are 'temperance' cultures (e.g. UK, Scandinavia) and 'non-temperance' cultures (e.g. France, Italy, Belgium). Alcohol consumption per capita is twice as high in the latter but Alcoholics Anonymous groups are four times higher in the former.<sup>41</sup> An average of 21 drinks per week may appear as quite ordinary

drinking in the latter but define a 'problem drinker' in the former. Religious beliefs may acquiesce with moderate drinking (Saint Paul advised to 'use a little wine for thy stomach's sake') while others (typically Protestant and Islamic religions) favour abstinence. More subtle influences are also likely. Authors of publications demonstrating substantial benefits from moderate alcohol intake have often refrained, unusually, from generalizing their findings, while moderate alcohol consumption was an explicit criterion for a healthy lifestyle in a recent large American primary prevention study using diet and lifestyle.<sup>42</sup> It is therefore important to acknowledge that interpretation of data and subsequent recommendations related to alcohol consumption can be influenced to various extents by societal and cultural preferences.

However, from an epidemiological point of view, the evidence currently available is large enough to guide recommendations on alcohol consumption. A net health benefit can be expected in people aged at least 40 and drinking no more than 2–3 drinks a day. How long moderate alcohol consumption must continue for these benefits to occur is however unknown. Benefits are accrued in people who are at high risk of CHD; conversely, the health risk of individuals at low risk of CHD is potentially worsened by alcohol intake. In that sense, the available evidence does not point to a universal threshold for a safe (less so preventive) alcohol intake that would apply to all adults, as is often suggested. In addition, old prescriptions still hold: one should abstain from drinking in case of pregnancy, personal or family history of alcoholism, when taking a medication that interacts with alcohol or when planning to drive or engage in other activities that require one to be alert. Therefore no simple recommendations can be advised for alcohol consumption. Because the risk reduction in CHD mortality associated with moderate alcohol intake can be as large as that associated with cardioprotective drugs (e.g. aspirin, beta-blockers or cholesterol-lowering drugs), individual advice for moderate consumption of alcohol, and preferably wine, should be considered for patients at high risk of CHD and without contraindications. This includes in particular patients who have had myocardial infarction.<sup>43</sup> An approach based on absolute risk has similarly influenced the rationale of recent guidelines for the clinical management of raised blood pressure, dyslipidaemia and, generally, CHD.<sup>44,45</sup>

Possible strategies in this field include the provision of clear information on the benefits and harms of alcohol consumption, which should be an integral part of health education programmes for health professionals, the general public and children. At the same time, innovative approaches to strengthen social norms protecting against alcohol problems should be developed. Knowledge-based orientation to prevention may be of particular importance in young adults to clarify the ambivalence found in many societies about alcohol and drinking, e.g. institutional perspectives encouraging abstinence in teenagers but experimentation in young adults.<sup>46</sup> These strategies would be better than the current propagation of mixed messages or simplistic views, including the misleading claim that 'a small amount of alcohol is safe' (achieved through skilful marketing by the industry), and the numerous and many-sided information channels currently available.

Any strategy in this field should be carefully monitored and evaluated. Although promotion of regular drinking of small amounts of alcohol restricted to specific population segments

seems attractive, it is hardly feasible. Noticeably, no trial has yet assessed whether increased problem drinking would outweigh the benefit of reduced CHD mortality if regular drinking of small amounts of alcohol were to be advocated for specific population subgroups. Specifically, longitudinal studies should gather more information on who would start drinking, who would maintain light-to-moderate drinking and who would progress to heavier or hazardous drinking.

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# Commentary: Alcohol and coronary heart disease—laying the foundation for future work

E Rimm

In the epidemiology of modifiable risk factors for chronic disease, evidence is first gathered from relatively simple cross-cultural studies and then from more rigorous and time-consuming studies of observational and experimental design. With a sufficient body of evidence, a general consensus about the strength of the association can be established and reviews, book chapters and meta-analyses soon follow. For the association between alcohol and coronary heart disease (CHD), the evidence as far back as the late 1970s suggested an inverse association between moderate alcohol consumption and lower risk of CHD. Professor Marmot provided the first real comprehensive review<sup>1</sup> to cover the range of health risks associated with light, moderate and heavy alcohol consumption. In just seven pages the review covered the most controversial areas and highlighted the strengths and weaknesses of the available evidence. Maybe as important, it created a framework or foundation from which all future work in this area could be based. For over a decade after its publication, research articles in the field cited Marmot's review even though excellent updated reviews were published.<sup>2,3</sup> Marmot's review was quite insightful and has survived the test of time.

Many of the scientific issues he discussed are still not resolved in the literature, although public health guidelines for moderate alcohol consumption have come a long way in the last decade. Recent guidelines for the moderate consumption of alcohol in the United Kingdom and the United States most certainly were based on Marmot's early insights.<sup>4,5</sup> Below I summarize several of the key areas he highlighted and the advances we have made since 1984.

## Does heavy alcohol consumption increase CHD risk?

Evidence at the time of the review as well as newer evidence have shown that heavy drinkers have equal or lower risk of CHD than abstainers. Any discussion of the effects of heavy alcohol consumption is merely academic because benefits from heavy consumption are far outweighed by increased risks from other causes of mortality.<sup>6</sup>

## Does moderate alcohol consumption protect against CHD?

Even in 1984 there was substantial literature to suggest that moderate alcohol consumption lowered risk of CHD. Professor Marmot wrestled with the issue of 'sick quitters', an idea later carefully examined in detail.<sup>7</sup> In most prospective studies, non-drinkers include a percentage of individuals who were sick and

subsequently stopped drinking alcohol; however, this potential bias still cannot explain the strong inverse association between moderate alcohol consumption and CHD.<sup>8,9</sup>

Inaccuracy in reporting of alcohol consumption has and always will be a problem with observational studies. However, if the goal is to assess moderate alcohol consumption, then many of our current assessment tools are adequate and can differentiate moderate drinkers at lowest risk of CHD from those who abstain. A recent review in this area concluded that methods that inquire about both the frequency and amount consumed for beer, wine, and liquor separately yield the most realistic levels of intake.<sup>10</sup> Marmot also postulated that non-drinkers may differ in other ways that put them at higher risk. As with the explanation for the sick quitters, this surely is the case, as many studies have now shown that non-drinkers and moderate drinkers differ in many important lifestyle characteristics (e.g. physical activity, diet and smoking). Over the last 17 years, better methods for assessing these characteristics have become available. With time, we have gained better insight into the independent inverse association for moderate alcohol consumption and as a consequence gained a keener insight into other factors which co-vary with alcohol, namely, the more deadly effects of cigarette smoking. Unable to document adequately an alternative explanation for the apparent inverse association for moderate alcohol consumption and CHD, Marmot simply concludes that moderate drinking is protective (i.e. causal). Although the definition of 'moderate' was yet not well defined and not universally accepted, the overall conclusion of this statement, though basic in nature, is now accepted by almost all scientists familiar with this field.

## How might alcohol protect against CHD?

Professor Marmot used the published associations between moderate alcohol consumption and a better lipid and haemostatic profile as support for a negative causal association between moderate alcohol consumption and CHD. We have learned much since this time and now know alcohol from any source can have a significant benefit on many biological parameters.<sup>11</sup> Evidence for beneficial effects of ethanol may go beyond just effects on high density lipoprotein cholesterol and fibrinogen levels since these factors may only explain 50–80% of the risk-lowering effect. Other factors such as insulin sensitivity, platelet aggregation, endothelial function and inflammation also may be beneficially affected by moderate alcohol consumption.

## What recommendations should be made?

Marmot ends his review on a conservative note citing a WHO expert committee on the prevention of CHD: 'Increased alcohol intake is not recommended as a preventive measure in CHD,

either in populations or in individuals.' More recent national and international guidelines have refined this statement and generally conclude that, on an individual basis, if you do drink alcoholic beverages, then do so in moderation. Moderation is generally described as less than 30 g of alcohol a day (in the US, this equals two drinks, and in the UK, this equals three units). Although the evidence is much more substantial now than it was 17 years ago, we still have much to learn in this important area of research. Whether drinking patterns, dietary constituents or genetic predisposition to ethanol metabolism modify the basic underlying association which Marmot described is still yet to be thoroughly explained.

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# Commentary: Could abstinence from alcohol be hazardous to your health?

AL Klatsky

'Those who cannot remember the past are condemned to repeat it.'

George Santayana 1905

William Heberden's classic description of angina pectoris in 1786<sup>1</sup> included: 'Wine and spirituous liquors ... afford considerable relief'. This observation, plus the cutaneous facial vasodilatation often induced by alcohol, led to the presumption by some observers that alcohol was a coronary vasodilator.<sup>2,3</sup> However, exercise ECG test data<sup>4,5</sup> suggested only subjective symptomatic benefit and indicated no acute increase in myocardial oxygenation from alcohol. Thus, angina relief may be due to an anaesthetic effect of alcohol. Physiological studies do not convincingly establish a major immediate effect of alcohol upon coronary blood flow.<sup>6,7</sup> In any case, angina is subjective, difficult to measure, and has been relatively little used as an endpoint in epidemiological studies of alcohol and coronary heart disease (CHD).

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In the first half of the 20th century there were reports of an apparent inverse relationship between heavy alcohol consumption and atherosclerotic disease.<sup>8–11</sup> Some speculated that premature deaths in alcoholics precluded development of CHD,<sup>12,13</sup> but vascular benefit in cirrhotics from higher blood oestrogens or an effect on lipoprotein lipase was also suggested. In 1961 Stare<sup>14</sup> wrote 'Whatever the mechanism—cirrhosis is accompanied by a sparing of the vascular intima, especially of the coronary circulation'.

Preceding other reports of the J-shaped alcohol-mortality curve by half a century, Pearl described this relationship in a Baltimore, Maryland study of tuberculosis patients and controls.<sup>15</sup> 'Heavy/steady' drinkers had the highest mortality; 'abstainers' were next; and 'moderate' drinkers had the lowest mortality. Pearl did not know that the favourable mortality of moderate drinkers was due to lower CHD risk and the study coincided with the US Prohibition era. He made the cautious interpretation that moderate drinking was 'not harmful'. We scientists may not care to admit it, but cultural context often influences what research gets done and how it is interpreted. This is especially the case if, as with alcohol effects, the area



of interest arouses strong feelings. Perhaps Pearl's major contribution was to realise the fallacy in comparing health risks of all drinkers to abstainers. Such comparison masks differences between the risks of heavy and light/moderate drinkers.

In the 1970s epidemiological studies began to appear which consistently show an inverse relationship between light-moderate alcohol drinking and either fatal or non-fatal CHD. With respect to moderate drinking and CHD, Dr Marmot's 1984 article,<sup>16</sup> cites five case-control and seven longitudinal studies, plus two international comparisons and one time-trend report. A literature search through 1998 done for a meta-analysis<sup>17</sup> uncovered no fewer than 196 articles on the subject.

Dr Marmot prefaces his discussion by mention of two difficulties. First, he discusses the 'major problem' of varying definitions of 'heavy' and 'moderate' drinking, with the suggestion that the boundary should be the imprecise level 'above which alcohol-associated problems emerge'. In 2001 we still have a variety of definitions, although there is some consensus that 3+ drinks/day (36+ g of alcohol) may exceed the safe limit for men and less consensus that 2+ drinks/day (24+ g of alcohol) may exceed the safe limit for women. Second, he points out that the myocardial toxicity of chronic heavy drinking has nothing to do with the alcohol-CHD relationship. This disparity, plus other cardiovascular conditions related to heavy drinking (hypertension, arrhythmias, haemorrhagic stroke) still confounds reports using 'cardiovascular' and 'coronary' disease synonymously.

From here on, I shall adopt Dr Marmot's query-response format:

### Does heavy alcohol consumption increase CHD risk?

The 1984 conclusion that the evidence is 'not consistent' remains accurate. Studies of alcoholics and problem drinkers show high CHD risk. Some population studies suggest the same situation, while other population studies of the entire usual drinking range show heavy drinkers at the same or lower CHD risk as non-drinkers. Studies of CHD *mortality* generally show a U-shaped or J-shaped alcohol-CHD relationship, with heavy drinkers at the same or higher risk than abstainers. Many studies of *non-fatal CHD* show an L-shaped graph, with heavy drinkers and light drinkers both at lower risk than abstainers.<sup>7</sup> Non-fatal myocardial infarction (MI) may be a more reliable end-point than reported CHD deaths among heavy drinkers because death data may be confounded by erroneous diagnoses of cardiomyopathy or other conditions. Yet there is plausibility in higher risk of CHD among some heavy drinkers, because of alcohol's probable roles in hypertension, hypertriglyceridaemia, and genesis of arrhythmias. These consequences can interact with unfavourable effects of binge-drinking patterns in many heavy drinkers.

The relationship of heavy drinking to CHD was one of the foci of a recent meta-analysis<sup>17</sup> which indicated that CHD risk was increased in heavier drinkers. Of 196 articles screened, 51 (43 cohort studies and 8 case-control studies) met inclusion criteria. Most used CHD mortality or combined mortality/morbidity as end-points. The threshold for increased risk occurred at 89 g (approximately 7 standard drinks) per day. This is well above all usual definitions of moderate drinking and higher than

Dr Marmot's estimate of 50 g of alcohol as the level of drinking no longer 'safe' for CHD.

Another recent meta-analysis<sup>18</sup> led to the conclusion that five or more drinks per day 'are not associated with a reduced risk of death and CHD'. That effort involved 8 cohort studies for assessment of CHD death and 12 cohort plus 2 case-control studies for assessment of non-fatal MI.

### Does moderate alcohol consumption protect against CHD?

A consistent inverse empiric relationship in the studies reviewed in 1984 is robustly bolstered by a near-unanimous finding of lower CHD risk in the much larger number of studies now reported. Reviews<sup>6,7,18-21</sup> provide details, so there is no need for further elaboration here. Corrao *et al.*'s meta-analysis yielded an estimated risk reduction of 20% at 0-20 g ( $\leq 2$  standard drinks) per day and some reduction of risk up to 72 g/day, or 6 standard drinks.<sup>17</sup>

### Is the lower CHD risk due to factors other than alcohol?

As discussed in 1984, when reporting their alcohol intake some people 'underestimate', a polite euphemism for 'lie'. While often mentioned as casting doubt upon the existence of the inverse alcohol-CHD relationship, it is difficult to plausibly explain how this phenomenon might spuriously produce the apparent protective effect of light drinking against CHD.

Controversy about protection persists in 2001 on the basis that correlates of abstinence and lighter drinking could explain the higher risk of abstainers. The so-called 'sick-quitter' hypothesis has been much debated. Forcefully advanced in 1988,<sup>22</sup> this hypothesis suggested that the movement of people at high CHD risk, largely ex-drinkers, into the abstainer group could explain the U-shaped curve. A number of subsequent prospective population studies<sup>6,7,18-21</sup> separated lifelong abstainers from ex-drinkers and/or carefully controlled for baseline CHD risk; these showed lower CHD risk in light drinkers than in abstainers. Several studies were controlled for dietary habits and physical exercise. Various reports involve both sexes, multiple ethnic groups, populations with low and high CHD risk or small and large proportions of abstainers, people with and without diabetes, people without evident CHD and those with MI, smokers, ex-smokers and never smokers, and drinkers of wine, beer, or spirits. So it is worth repeating that 'There may indeed be a complex of factors that could explain away the above findings. A simpler explanation is that moderate drinking is protective'.<sup>16</sup>

Proof of total independence from indirect explanations is best achieved by prospective controlled experiments. Observational data cannot control for all possible confounders. Since satisfactory experiments of alcohol drinking and CHD development may never be done, the prospective population studies are likely to be the best data we will ever have.

### How might alcohol protect against CHD?

With no explanation evident, the first Kaiser Permanente report in 1974<sup>23</sup> offered protection as only one of several possible explanations for the lower CHD risk of drinkers. By 1984, data

about plausible protective mechanisms had surfaced, including higher high density lipoprotein (HDL) cholesterol levels in drinkers and anti-thrombotic effects of alcohol.

The link via HDL (both HDL<sub>2</sub> and HDL<sub>3</sub>) is now much more solidly established<sup>6,7,18–21</sup> and higher HDL seems to account for about 50% of the observed lower CHD risk in alcohol drinkers. Evidence for possible anti-thrombotic actions of alcohol has also grown, perhaps most convincingly with respect to lowered blood fibrinogen levels. An anti-thrombotic action of alcohol could partially account for the lower CHD risk at very light drinking levels (e.g. several drinks per week) seen in several of the epidemiological studies, but this protective mechanism is less established than the HDL cholesterol pathway. Evidence about other mechanisms, including decreased insulin resistance and myocardial 'preconditioning' in drinkers remains preliminary. Consideration of possible benefit from anti-anxiety or stress-reducing effects of alcohol has frequently been raised, but there are no convincing data to support this hypothesis.

The lack of evidence that one particular beverage type is more protective than others was considered a point favouring a role for alcohol itself in 1984. This issue has become more complicated over the ensuing 20 years. One major hypothesis is that non-alcoholic ingredients in red wine offer additional CHD protection to that of beer or spirits. Support for this hypothesis was found in ecologic studies as early as 1979.<sup>24</sup> Reports of non-alcohol antioxidant phenolic compounds or anti-thrombotic substances in wine, especially red wine,<sup>6,7,18–21</sup> provide plausible biological explanations for extra CHD protection. However, prospective population studies show no consensus about the wine/liquor/beer issue.<sup>18,25,26</sup> There is evidence of benefit from each beverage type. Most of the data about protective mechanisms deal with alcohol itself. Patterns of drinking and disparities in the traits of people who prefer wine, beer, or spirits are potential confounders, especially in the ecologic international comparison studies. This wine/liquor/beer question remains unresolved at this time. This is not an 'either/or' issue. Since it is likely that alcohol is protective, the true issue is probably the existence and magnitude of *extra* protection by specific beverages.

### Is the negative association causal?

To my knowledge, Marmot's article was the first to apply epidemiological criteria of causality to the moderate drinking-CHD association. Using *strength, dose-response, temporal sequence, consistency, independence, plausibility, and specificity*, his conclusion was a qualified 'yes'. In 2001 the data about *consistency, independence, plausibility* are more solid. Possibly fuelled by disappointing results in recent reports about CHD protection by oestrogenic hormones and vitamin E, the demand for a controlled experiment as proof for any causal association has also gained strength.<sup>27</sup> It seems probable that debate about causality will long continue, but practical decisions about advice must often be made without certainty of knowledge.

### What recommendations should be made?

Here, cultural context clearly influences attitudes. The need for great care is universally recognised. It is essential to avoid

any inducement or even rationalization of heavy drinking. Much media dissemination about the possible CHD benefits of moderate alcohol drinking and of red wine, in particular, has occurred. This has resulted in increased red wine sales in the U.S., but it is not clear what, if any effect has occurred upon individual drinking habits. The general public is becoming increasingly sophisticated about health matters. Partially because of media presentation of conflicting reports, the public is also increasingly sceptical.

Risk of progression to problem drinking is the major health risk of moderate drinking. Other possible, but unproven, risks of moderate drinking include fetal alcohol syndrome, haemorrhagic stroke, large bowel cancer, and female breast cancer. The most troublesome data are those about moderate drinking and possible increased risk of breast cancer,<sup>27</sup> especially since women <50 years of age are generally at very low CHD risk.

One widely used definition of a 'safe limit' is no more than two drinks per day for men or one per day for women, amounts associated with evidence of lower risk of CHD. Both the number and the size of drinks compromising the safe limit should always be specified. One thread which has emerged with increasing consistency in the medical literature is the need to individualize advice. Age, sex, family and personal history of drinking, and specific medical history all must be known to make a judgement about the individual risk benefit equation.<sup>27–30</sup> It is easier and more satisfactory for a knowledgeable health practitioner to advise his or her patient than to formulate rules for all. In the end, the responsibility to give wise and honest counsel falls upon the shoulders of the professional.

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