Why heart disease mortality is low in France: the time lag explanation

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Summary points

Mortality from ischaemic heart disease in France is about a quarter of that in Britain, but the major risk factors are similar

Undercertification of ischaemic heart disease in France could account for about 20% of the difference

The high consumption of alcohol in France, and of red wine in particular, explains little of the difference

We propose that the difference is due to the time lag between increases in consumption of animal fat and serum cholesterol concentrations and the resulting increase in mortality from heart disease—similar to the recognised time lag between smoking and lung cancer. Consumption of animal fat and serum cholesterol concentrations increased only recently in France but did so decades ago in Britain

Evidence supports this explanation: mortality from heart disease across countries, including France, correlates strongly with levels of animal fat consumption and serum cholesterol in the past (30 years ago) but only weakly to recent levels. Based on past levels, mortality data for France are not discrepant

In France mortality from ischaemic heart disease is about a quarter of that in Britain.[1–7] The major risk factors are no more favourable in France, and this so called "French paradox" has not been satisfactorily explained. Table 1 shows the difference in mortality from heart disease between the countries, and table 2 shows the similar levels of animal fat consumption, serum total cholesterol and high density lipoprotein cholesterol concentrations, blood pressure, and (in men) smoking. The French paradox is usually attributed to the higher consumption of alcohol in France, notably of wine,[2–5] and some have suggested a specific effect of red wine. In this article we assess quantitatively the extent to which this and other possible explanations can account for the low rate of heart disease in France. We then consider a novel "time lag" hypothesis, which, we believe, is the main explanation for the paradox.

This hypothesis arises from the observation that animal fat consumption and serum cholesterol concentration have been similar in France and Britain for a relatively short time—about 15 years. For decades up to 1970, France had lower animal fat consumption (about 21% of total energy consumption *v* 31% in Britain) and serum cholesterol (5.7 *v* 6.3 mmol/l), and only between 1970 and 1980 did French values increase to those in Britain.[2 12–25] There must be a time lag between the increase in serum cholesterol concentration and the full effect of the resulting increase in coronary artery atheroma and risk of death from ischaemic heart disease. The observations that Western populations are exposed to high levels of dietary saturated fat and serum cholesterol from childhood, that atheroma progresses slowly throughout life, and that only about 1% of men die from ischaemic heart disease before the age of 50[9] suggest that decades of exposure must elapse. We propose that this is the main explanation for the low mortality from ischaemic heart disease in France. A similar time lag is recognised with smoking and lung cancer, in which it is the smoking habit of 30-40 years ago that is important in determining current risk,[26] and a long incubation period for heart disease has been previously proposed.[27]

Previous explanations of the paradox

Undercertification of ischaemic heart disease

Not all deaths caused by ischaemic heart disease in France are classified as such; French doctors tend to certify some (such as those caused by heart failure and other late complications of myocardial infarction) as poorly specified causes.[5 28] Table 1 shows that poor certification is important but can only partly explain the paradox. The excess attribution of deaths to poorly specified cardiac causes in France is equivalent to 12% of the difference in mortality from heart disease between France and Britain (45/359 in men and 15/126 in women), and to all poorly specified causes is equivalent to 19% (68/359 and 23/126).

Smoking

The prevalence of smoking in men is similar in France (32%) and Britain (29%), but in women it is lower in France (9% *v* 30%) (table 2). These patterns have persisted for over 30 years[9] and are reflected in

Table 1 Mortality (No of deaths/100 000) from ischaemic heart disease and poorly specified causes in people aged 55-64 in France and Britain in 1992[7 8]

	Men				Women			
Certified cause of death (ICD-9 code)	**France**	**Britain**	**Difference**	**Ratio**	**France**	**Britain**	**Difference**	**Ratio**
Ischaemic heart disease (410-4)	128	487	–359	1:4	27	153	–126	1:6
All poorly specified or unspecified causes:	71	3	68	24:1	25	2	23	12:1
Unspecified or unknown causes (799.9)*	24	1	23		8	0.3	8	
Poorly specified cardiac causes*:	47	2	45		17	2	15	
Ventricular or unspecified dysrhythmia (427.1, 427.4, 427.8, 427.9)	6	1			2	1		
Cardiac arrest (427.5)	9	0			3	0		
Heart failure (428)	19	1			7	1		
Unspecified heart or cardiovascular disease (429.2, 429.9, 440.9)	5	0			2	0		
Cardiogenic shock (785.5)	3	0			1	0		
Sudden death (798.1)	4	0			1	0		
Ischaemic heart disease plus poorly specified causes	199	490	–291	1:2.5	52	155	–103	1:3

*French data provided by Dr Françoise Hatton, INSERM.

mortality from lung cancer (similar in French and British men but lower in French than British women[7]). The low prevalence of smoking in French women is consistent with the fact that the ratio of mortality from ischaemic heart disease in French to British women (1:3) is lower than the equivalent ratio in men (1:2.5) (table 1). Given that the risk of ischaemic heart disease in 55-64 year old smokers is twice that of non-smokers,[29] the risk in French women $((2\times9\%)+(1\times91\%))$ divided by that in British women $((2\times30\%)+(1\times70\%))$ is 84%, and 84% of 1:3 (the ratio of mortality in French women to that in British women) is 1:2.5, the same as the ratio in men. The sex difference is explained, but not the residual mortality ratio of 1:2.5 in both sexes.

Alcohol

Figure 1 shows the relative risk of mortality from ischaemic heart disease according to alcohol consumption in the American Cancer Society's cancer prevention study I (the largest cohort study in the world, with 18 771 deaths from ischaemic heart disease),[30] cancer prevention study II (10 252 deaths from ischaemic heart disease),[31] and in the three next largest cohort studies (recording 1061 deaths,[32] 940 deaths,[33] and 611 events[34]). The studies show a consistent reduction in risk of about 20% in people who drink about one unit of alcohol a day than in people who drink none but, taken together, indicate that drinking more than about one unit a day confers little or no further protection. The data are consistent with a dose-response relation. The pattern is the same in men and women.[31 33] This non-linear dose-response relation probably reflects a summation of opposing effects of alcohol: the protective effects (mainly the increase in serum concentration of high density lipoprotein chol-

Table 2 Average values of risk factors for ischaemic heart disease in France and Britain, 1985-1990

	France	Britain
National consumption data		
No of cigarettes (per adult daily)[9]	6.4	6.5
Animal fat (% of total energy intake)[2]	25.7	27.0
Fruit and vegetables (% of total energy intake)[2]	5.0	4.3
Survey data (age 50-70 years)		
Percentage who smoked cigarettes[9-13]:		
Men	32	29
Women	9	30
Mean serum total cholesterol concentration (mmol/l)[12-19]:		
Men	6.1	6.2
Women	6.5	6.7
Mean high density lipoprotein cholesterol concentration (mmol/l)[14-19]:		
Men	1.3	1.3
Women	1.5	1.5
Mean systolic blood pressure (mm Hg)[12 13]:		
Men	150	148
Women	149	148

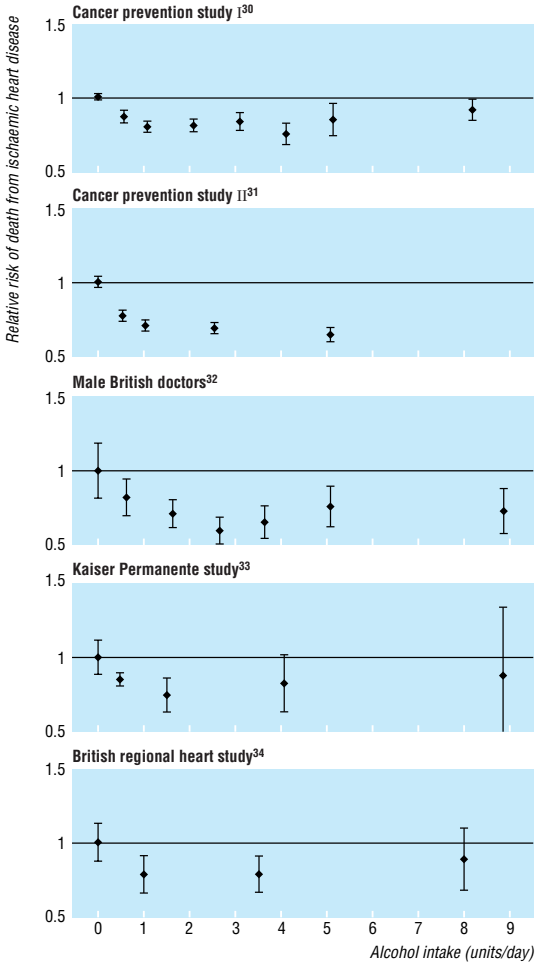

Fig 1 Relative risk (95% confidence interval) of death from ischaemic heart disease according to alcohol consumption (non-drinkers=1.0; one unit equivalent to a standard drink) in the five largest cohort studies.[30–34] (Confidence intervals of relative risk estimates calculated from those of the corresponding absolute mortalities)

esterol but also the favourable changes in haemostatic factors) are countered by the higher blood pressure, which increases risk.

If all French men and no British men drank at least one unit of alcohol a day, other factors being equal, the difference in ischaemic heart disease would be about 20%. If half of British men drank at least one unit of alcohol daily the difference would be 10%, and if three quarters of British men did so it would be 5%. The last value approximates the current prevalence,[10 12] but the difference in mortality from heart disease from differences in alcohol consumption will be even smaller than 5% because not all French men drink alcohol and because occasional alcohol consumption (<1 unit a day, more common in Britain) confers some protection. The greater alcohol consumption in France than Britain (18.4 *v* 5.7 litres of ethanol per adult in 1965, 13.1 *v* 8.5 in 1988[2]) reflects a higher average consumption per drinker rather than a higher prevalence of drinkers and so does not further reduce the incidence of ischaemic heart disease.

A specific effect of wine

There is a strong association across countries between higher consumption of wine (but not beer or spirits) and lower mortality from ischaemic heart disease.[2–5] This ecological association encouraged the view that the protective effect of alcohol was specific to wine. Wine consumption in France is high,[2] and it was natural to invoke this as an explanation for the paradox. But epidemiological evidence shows that the protective effect of wine is no greater than that of beer or spirits.[35–37] All alcoholic drinks produce the changes in serum high density lipoprotein cholesterol concentration and haemostatic factors that reduce risk,[37–42] and randomised crossover studies have shown that ethanol produces them.[41 42]

A specific protective effect of red wine has been proposed on the basis that, in relation to its alcohol content, red wine contains more phenolic compounds (with antioxidant activity) than other drinks,[43–45] although blood concentrations do not increase in proportion to dose.[43] It also increases the proportion of polyunsaturated fatty acids in platelet phospholipids.[46] But the evidence does not support an important role for either of these factors in the causation of ischaemic heart disease.[45–47] One of the five large cohort studies cited above included people who drank only red wine or only white wine, and there was no difference in their risk of heart disease.[36]

Garlic and onions

The suggestion that consumption of garlic and onions could account for the low mortality from heart disease in France is based on ecological associations,[1 48 49] and direct supportive evidence is lacking. Trials that suggested that garlic reduced serum cholesterol concentration had methodological flaws,[50] and well designed trials have shown no effect.[50 51]

The time lag hypothesis

Evidence for the hypothesis

If there is a delay between an increase in serum cholesterol concentration and the resulting increase in mortality from ischaemic heart disease, current death rates from heart disease would relate to past levels of dietary fat and serum cholesterol better than to present day levels. Figure 2 shows current (1992) mortality from heart disease in men in 20 countries plotted against their recent (1988) and their past (1965) consumption of animal fat.[2] Mortality from ischaemic heart disease was strongly associated with past animal fat consumption, accounting for 54% of the variance in mortality from heart disease between countries ($r^2=0.54$, $P<0.001$), but this was not so for recent consumption ($r^2=0.07$, $P=0.28$). The difference between past and recent consumption was highly significant ($F^1_{16}=21.8$, $P=0.003$). Entering the data on past and recent consumption together in regression analysis did not predict mortality from heart disease better than did the past data alone. With the earlier data, the position of France is less discrepant from that of other countries, and after adjustment for the French undercertification of ischaemic heart disease it fits the overall trend well.

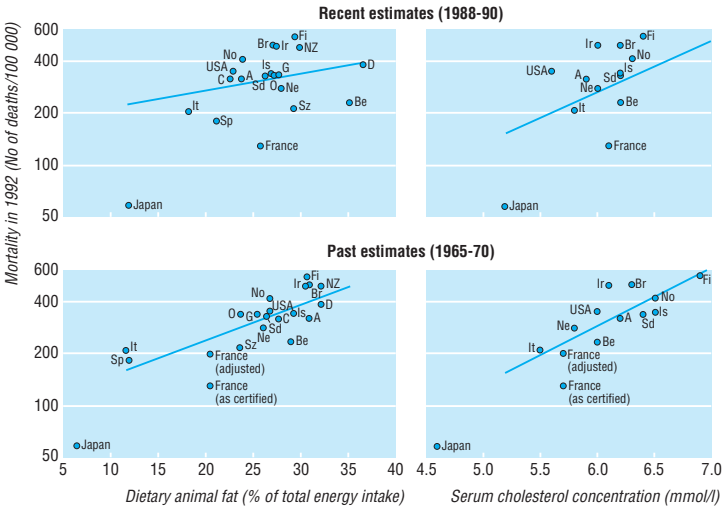

Fig 2 Mortality from ischaemic heart disease in men aged 55-64 years in 1992 related to recent and past estimates of animal fat consumption and average serum cholesterol concentrations in 20 countries. Japan was omitted as an outlier in determining the regression lines. The position of France is shown with and without allowing for undercertification of ischaemic heart disease (see table 1). Table 3 shows data used in the graphs and the code for each country

Figure 2 also shows current (1992) mortality from ischaemic heart disease in men plotted against estimates of recent (about 1990) and past (about 1970) national average serum cholesterol concentrations in 13 countries (table 3 shows the sources of the estimates). As with animal fat consumption, mortality was strongly associated with past values ($r^2=0.55$, $P=0.006$) but not with recent values ($r^2=0.08$, $P=0.36$), use of both past values and recent values did not enhance prediction of heart disease mortality compared with using past data alone, and the difference between past and recent values was highly significant ($F^1_9=15.1$, $P=0.004$). After adjustment for French undercertification of ischaemic heart disease, the position of France is not discrepant.

The regression line of past serum cholesterol concentration on ischaemic heart disease (fig 2) indicates that a decrease in serum cholesterol of 0.6 mmol/l is associated with a 37% lower mortality from ischaemic heart disease (95% confidence interval 18% to 52%),

Table 3 Mortality (No of deaths/100 000) from ischaemic heart disease in men aged 55-64 in 20 countries, with past and recent values of animal fat consumption, serum cholesterol concentration, and alcohol consumption

Country	Mortality from ischaemic heart disease 1992[7]	Animal fat consumption (% of total energy intake)†		Mean serum cholesterol concentration (mmol/l) in men aged 50-70*		Alcohol consumption, 1988 (litres ethanol/person)[2]
		1965	1988	1970	1990	
Japan[22 52-54]	58	6.6	11.9	4.6	5.2	6.0
France[13-17 20 21]	128	20.5	25.7	5.7	6.1	13.1
Spain (Sp)	179	12.0	21.1			12.2
Italy (It)[17 22 55 56]	204	11.7	18.2	5.5	5.8	10.2
Switzerland (Sz)	211	23.6	29.1			11.1
Belgium (Be)[17 22]	228‡	28.9	35.0	6.0	6.2	9.5
Netherlands (Ne)[17 22 57]	275	26.0	27.8	5.8	6.0	8.1
Canada (C)	311	27.6	22.5			9.1
Australia (A)[22 58]	311	30.8	23.7	6.2	5.9	9.2
West Germany (G)	322	25.4	27.5			10.7
Austria (O)	328	23.7	27.1			11.3
Sweden (Sd)[22 59 60]	329	26.5	26.2	6.4	6.2	5.6
Iceland (Is)[22]	333	29.3	26.8	6.5	6.2	3.5
United States (USA)[22]	345	26.7	22.8	5.9	5.6	7.2
Denmark (D)	377	32.0	36.4			9.5
Norway (No)[17 22 61 62]	405	26.7	23.8	6.5	6.3	4.4
New Zealand (NZ)	476	32.1	29.7			9.6
Ireland (Ir)[22 63]	482	30.4	27.3	6.1	5.9	7.1
Britain (Br)[12 18 19 22]	489	30.8	27.0	6.3	6.2	8.5
Finland (Fi)[22 64-66]	547	30.5	29.2	6.9	6.3	6.9

*Reference numbers after countries refer to sources of estimates of serum cholesterol concentration.
†Derived from data from food balance sheets of United Nations Food and Agricultural Organisation.[2] Although data were available, Israel was not included as data on fat consumption in 1965 may not apply to present population because of more recent immigration. ‡1989 mortality.

virtually identical to the estimate from the seven countries study.[67] Serum cholesterol concentration in 1970 was 0.6 mmol/l lower in France than in Britain (5.7 *v* 6.3 mmol/l, table 3), and this explains most of its lower mortality from heart disease. It may seem surprising that the associations of heart disease with recent animal fat and cholesterol were so weak: they became significant when Japan (an outlier) was included in the analysis, but the relation with past values remained substantially stronger (for animal fat, $F^1_{17}=22.7$, $P<0.001$; for serum cholesterol, $F^1_{10}=18.9$, $P=0.001$). The associations were unaffected by including data on tobacco consumption[9] and fruit and vegetable consumption[2] as potential confounders.

Dietary confounding and the failure of the wine hypothesis

Wine consumption is associated with lower mortality from ischaemic heart disease across countries, as discussed above. Including wine with recent animal fat consumption in a multivariate analysis resulted in more of the variance in heart disease being explained, and this observation was interpreted as indicating a protective effect of wine.[3 4] But in a multivariate analysis in which past animal fat consumption is used instead of recent consumption, wine consumption (past or recent) is no longer associated with mortality from heart disease and does not add to the variance explained. The association between wine and low ischaemic heart disease arose because wine consumption is associated across countries with the change in animal fat consumption from 1965 to 1988 ($r^2=0.46$, $P=0.001$). Countries with high wine consumption are those in which saturated fat consumption used to be low but increased in recent years (France, Italy, Spain, and Switzerland, for example). The low mortality from ischaemic heart disease reflects the earlier low levels of saturated fat consumption, for which wine is simply an indirect marker—a confounding factor.

Duration of the time lag

The data in figure 2 indicate that the time lag between an increase in fat consumption and its maximal effect on heart disease risk is at least 25 years. It could be longer, but the analysis cannot be repeated with data from before 1965-70 as these are scanty and may be unreliable. The time lag could be as long as 35 years because this was the interval between the peak in the production of food of animal origin in Britain (which increased by two thirds between 1880 and 1936 but did not materially increase thereafter[24 25]) and the peak in mortality from ischaemic heart disease (which attained a plateau in 1971).

This slow increase in mortality from ischaemic heart disease after an increase in serum cholesterol concentration contrasts with the much more rapid decrease in mortality from ischaemic heart disease after a reduction in serum cholesterol. The randomised controlled trials of reducing serum cholesterol concentration show that the maximal reduction in mortality from heart disease is largely attained after about two years.[67] Slow inception and rapid reversal are not inconsistent, and one should not be used to suggest that the other is incorrect. The relative risk of smoking related diseases also increases slowly after starting smoking but falls soon after stopping smoking.[26]

Possible contrary observations

Data on mortality from heart disease in France now cover a period of about 15 years since the increase in animal fat consumption. Some increase in heart disease in France relative to Britain might now be expected, but none is seen.[7] No inference can be drawn, however, because, since 1980, mortality from heart disease has decreased by about half in all economically developed countries,[7] largely due to the introduction of effective preventive treatments, and this effect is likely to dominate the effect of trends in risk factors. The treatments seem to have been used more extensively in France than in Britain: in 1993, 34% of survivors of infarcts in France took cholesterol lowering drugs compared with 4% of survivors in Britain, 63% took aspirin compared with 38%, 20% took anticoagulants compared with 5%, and 48% took β blockers compared with 20%.[12 68] Also, a study suggests that serum cholesterol concentrations in France, having peaked in about 1980, may have subsequently decreased (by 0.4 mmol/l).[69] The persistently low mortality from heart disease in France is therefore not surprising and does not refute the time lag hypothesis. Indeed, France is not unique in this; in Japan fat consumption and serum cholesterol concentration increased over the same period (fig 2), but heart disease has not.

The time lag hypothesis may help to explain the difference in heart disease between Britain and France but not the north-south difference across Britain, since dietary patterns in one part of the country relative to another have not materially changed over the past 40 years.[22 25] This difference is likely to be due to the persistent differences between north and south in smoking and diet.[70] In France the data are insufficient to

determine whether the time lag hypothesis may partly explain its regional variations in heart disease. Britain is colder than France (by 2°C on average), but even if temperature were a causal factor it could explain little of the difference in heart disease either across each country or between the countries. The 20% excess winter mortality from heart disease in Britain (largely explained by higher concentration of clotting factors attributable to winter respiratory infections[71]) relates to an average temperature difference of 6°C,[70] so the 2°C temperature difference would account for a difference in heart disease of only about 7%. This, and the small effect of its below average alcohol consumption, may help to explain why Britain has slightly higher than expected heart disease mortality in figure 2.

Public health implications

The time lag hypothesis, we believe, explains an interesting epidemiological paradox. But it is important to recognise that mortality from all causes in French men is similar to that in British men, despite their lower mortality from ischaemic heart disease (see table 4). The excess mortality from alcohol related causes is so large that it abolishes the survival advantage from the low mortality from heart disease, highlighting the public health problem from alcohol in French men. French women, in contrast, have done well: their mortality from all causes is a third lower than that in British women (table 4), a consequence of their moderate alcohol consumption, their diet, and their relatively low rate of smoking. Our paper has highlighted two important public health problems, the high mortality from heart disease in Britain and the high mortality from alcohol related causes in French men. Both are preventable.

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Table 4 Mortality (No of deaths/100 000) from alcohol related and other causes in people aged 55-64 in France and Britain, 1992[7 8]

	Men			Women		
Cause of death (ICD-9 code)	France†	Britain	Ratio	France†	Britain	Ratio
Alcohol related causes:	348	105	3:1	82	40	2:1
Alcohol related cancers[71]:						
Mouth and pharynx (140-149)	56	11		5	4	
Oesophagus (150)	44	28		4	9	
Liver (155.0)	26	5		3	1	
Larynx (161)	31	6		1	1	
Alcoholic dependence and alcoholic psychoses (291, 301)†	20	1		4	0	
Cirrhosis of liver (571)	72	19		27	11	
Motor vehicle accidents (E810-9)	17	9		8	4	
Non-transport accidents (E880-E929)	43	12		13	5	
Suicide (E950-9)	39	14		17	5	
Ischaemic heart disease and poorly specified causes (from table 1)	199	490	1:2.5	52	155	1:3
Lung cancer (162)	184	161	1:1	18	74	1:4
All other causes	631	618	1:1	365	543	1:1.5
All causes	1362	1374	1:1	517	812	1:1.5

†French data provided by Dr Françoise Hatton, INSERM.

1 Tunstall-Pedoe H. Autres pays, autres moeurs: theories on why the French have less heart disease than the British. *BMJ* 1988;297:1559-60.
2 Criqui MH, Ringel BL. Does diet or alcohol explain the French paradox? *Lancet* 1994;344:1719-23.
3 Renaud S, De Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet* 1992;339:1523-6.
4 Hegsted DM, Ausman LM. Diet, alcohol and coronary heart disease in men. *J Nutr* 1988;118:1184-9.
5 St Leger AS, Cochrane AL, Moore F. Factors associated with cardiac mortality in developed countries with particular reference to the consumption of wine. *Lancet* 1979;i:1017-20.
6 Artaud-Wild SM, Connor SL, Sexton G, Conner WE. Differences in coronary mortality can be explained by differences in cholesterol and saturated fat intakes in 40 countries but not in France and Finland. *Circulation* 1993;88:2771-9.
7 World Health Organisation. *World health statistics annuals, 1985-95*. Geneva: WHO, 1986-96.
8 Office of Population Censuses and Surveys. *1992 mortality statistics: cause*. London, HMSO 1993.
9 Nicolaides-Bouman A, Wald N, Forey B, Lee P. *International smoking statistics*. London, Oxford: Wolfson Institute of Preventive Medicine, Oxford University Press, 1993.
10 Office of Population Censuses and Surveys. *Social survey division. Living in Britain: results from the 1994 general household survey*. London: HMSO, 1996.
11 Wald N, Nicolaides-Bouman A. *UK smoking statistics*. London, Oxford: Wolfson Institute of Preventive Medicine, Oxford University Press, 1991.
12 Office of Population Censuses and Surveys Social Survey Division. *Health survey for England 1991-3*. London: HMSO, 1993-5.
13 World Health Organisation. *The WHO MONICA project: a worldwide monitoring system for cardiovascular diseases. World health statistics annual 1989*. Geneva: WHO, 1990.
14 Schlienger JL, Simon C, Aby MA, Arveiler D, Schaffer P. Bilan lipidique dans une population adulte representative d'une region Francaise (Bas-Rhin). *Pathol Biol* 1991;39:195-9.
15 Laurier D, Chau NP, Segond P, PCV-Metra Group. Cholesterol and other cardiovascular risk factors in a working population in Ile-de-France (France): first results of the PCV-Metra study. *Eur J Epidemiol* 1992;8:693-701.
16 Bonithon-Kopp C, Levenson J, Scarabin P, Guillanneuf M, Kirzin J, Malmejac A, et al. Longitudinal associations between plasma viscosity and cardiovascular risk factors in a middle-aged French population. *Atherosclerosis* 1993;104:173-82.
17 SENECA investigators. Nutritional status: serum lipids. *Eur J Clin Nutr* 1991;45(suppl 3):53-61.
18 Office of Population Censuses and Surveys Social Survey Division. *The dietary and nutritional survey of British adults*. London: HMSO, 1990.
19 Mann JI, Lewis B, Shepherd J, Winder AF, Fenster S, Rose L, et al. Blood lipid concentrations and other cardiovascular risk factors: distribution, prevalence, and detection in Britain. *BMJ* 1988;296:1702-6.
20 Cambien F, Ducimetiere P, Richard J. Total serum cholesterol and cancer mortality in a middle-aged male population. *Am J Epidemiol* 1980;112:388-94.
21 Malaspina JP, Bussière H, Le Calve G. The total cholesterol/HDL cholesterol ratio: a suitable atherogenesis index. *Atherosclerosis* 1981;40:373-5.
22 Law MR, Wald NJ. An ecological study of serum cholesterol and ischaemic heart disease between 1950 and 1990. *Eur J Clin Nutr* 1994;48:305-25.
23 Jolliffe N, Archer M. Statistical associations between international coronary heart disease death rates and certain environmental factors. *J Chronic Dis* 1959;9:636-52.
24 Hollingsworth D. The application of the newer knowledge of nutrition. In: Drummond JC, Wilbraham A. *The Englishman's food*. London: Jonathan Cape, 1957. (Reissued by Pimlico, 1991.)
25 Ministry of Agriculture Fisheries and Food. *Household food consumption and expenditure, 1954, 1960, 1970 and 1980*. London: HMSO 1956, 1962, 1973, and 1982.
26 Doll R, Peto R. The causes of cancer: appendix E. *J Natl Cancer Inst* 1981;66:1292-305.
27 Rose G. Incubation period of coronary heart disease. *BMJ* 1982;284:1600-1.
28 McMichael J. French wine and death certificates. *Lancet* 1979;i:1186-7.
29 Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. *BMJ* 1976;ii:1525-36.
30 Boffetta P, Garfinkel L. Alcohol drinking and mortality among men enrolled in an American Cancer Society prospective study. *Epidemiology* 1990;1:342-8.
31 Thun MJ, Peto R, Lopez AD, Monaco JH, Henley J, Heath CW, et al. Alcohol consumption and mortality among middle-aged and elderly US adults. *N Engl J Med* 1997;24:1705-14.
32 Doll R, Peto R, Hall E, Wheatley K, Gray R. Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. *BMJ* 1994;309:911-8.
33 Klatsky AL, Armstrong MA, Friedman GD. Alcohol and mortality. *Ann Intern Med* 1992;117:646-54.
34 Shaper AG, Wannamethee G, Walker M. Alcohol and coronary heart disease: a perspective from the British regional heart study. *Int J Epidemiol* 1994;23:482-94.
35 Rimm EB, Klatsky A, Grobbee D, Stampfer MJ. Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits? *BMJ* 1996;312:731-6.
36 Klatsky AL, Armstrong MA, Friedman GD. Red wine, white wine, liquor, beer, and risk for coronary artery disease hospitalization. *Am J Cardiol* 1997;80:416-20.
37 Marques-Vidal P, Ducimetière P, Evans A, Cambou J, Arveiler D. Alcohol consumption and myocardial infarction: a case-control study in France and Northern Ireland. *Am J Epidemiol* 1996;143:1089-93.

38 Gaziano JM, Buring JE, Breslow JL, Goldhaber SZ, Rossner B, VanDenburgh M, et al. Moderate alcohol intake, increased levels of high-density lipoprotein and its subfractions, and decreased risk of myocardial infarction. *N Engl J Med* 1993;329:1829-34.
39 Suh I, Shaten J, Cutler A, Kuller L. Alcohol use and mortality from coronary heart disease: the role of high-density lipoprotein cholesterol. *Ann Intern Med* 1992;116:881-7.
40 Hendriks HFJ, Veenstra J, Velthuis-te Wierik EJM, Schaafsma G, Kluft C. Effect of moderate dose of alcohol with evening meal on fibrinolytic factors. *BMJ* 1994;308:1003-6.
41 Forman MR, Beecher GR, Lanza E, Reichman ME, Graubard BI, Campbell WS, et al. Effect of alcohol consumption on plasma carotenoid concentrations in premenopausal women: a controlled dietary study. *Am J Clin Nutr* 1995;62:131-5.
42 Pellegrini N, Pareti FI, Stabile F, Brusamolino A, Simonetti P. Effects of moderate consumption of red wine on platelet aggregation and haemostatic variables in healthy volunteers. *Eur J Clin Nutr* 1996;50:209-13.
43 Duthie GG, Pedersen MW, Gardner PT, Morrice PC, Jenkinson AM, McPhail DB, et al. The effect of whisky and wine consumption on total phenol content and antioxidant capacity of plasma from healthy volunteers. *Eur J Clin Nutr* 1998;52:733-6.
44 Frankel EN, Kanner J, German JB, Parks E, Kinsella JE. Inhibition of oxidation of human low-density lipoprotein by phenolic substances in red wine. *Lancet* 1993;341:454-7.
45 Hertog MGL, Hollman PCH. Potential health effects of the dietary flavonol quercetin. *Eur J Clin Nutr* 1996;50:63-71.
46 Pellegrini N, Simonetti P, Brusamolino A, Bottasso B, Pareti FI. Composition of platelet phospholipids after moderate consumption of red wine in healthy volunteers. *Eur J Clin Nutr* 1996;50:535-41.
47 Muldoon MF, Kritchevsky SB. Flavonoids and heart disease. *BMJ* 1996;312:458-9.
48 Keys A. Wine, garlic, and CHD in seven countries. *Lancet* 1980;i:145-6.
49 Buck C, Donner AP, Simpson H. Garlic, oil and ischaemic heart disease. *Int J Epidemiol* 1982;11:294-5.
50 Neil HAW, Silagy CA, Lancaster T, Hodgeman J, Vos K, Moore JW, et al. Garlic powder in the treatment of moderate hyperlipidaemia: a controlled trial and meta-analysis. *J R Coll Physicians Lond* 1996;30:329-33.
51 Simons LA, Balasubramaniam S, von Konigsmark M, Parfitt A, Simons J, Peters W. On the effect of garlic on plasma lipids and lipoproteins in mild hypercholesterolaemia. *Atherosclerosis* 1995;113:219-25.
52 Okayama A, Ueshima H, Marmot MG, Elliott P, Yamakawa M, Kita Y. Different trends in serum cholesterol levels among rural and urban populations aged 40-59 in Japan from 1960-1990. *J Clin Epidemiol* 1995;48:329-37.
53 Kuzuya F, Shimokata H. Longitudinal changes in plasma cholesterol and triglyceride levels in Japanese male workers, 1977-1992. *Ann N Y Acad Sci* 1995;748:510-3.
54 Research Committee on Serum Lipid Level Survey 1990 in Japan. Current state of and recent trends in serum lipid levels in the general Japanese population. *J Atherosclerosis Thromb* 1996;2:122-33.
55 Pujia A, Gnasso A, Cortese C, Angotti E, Colonna A, Mattioli PL. Early extracoronary atherosclerosis and coronary heart disease risk factors in a sample of civil servants in southern Italy. *Atherosclerosis* 1993;102:1-7.
56 Vaccarino V, Borgatta A, Gallus G, Sirtori CR. Prevalence of coronary heart disease risk factors in northern-Italian male and female employees. *Eur Heart J* 1995;16:761-9.
57 Verschuren WMM, Boerma GJM, Kromhout D. Total and HDL-cholesterol in the Netherlands: 1987-1992. *Int J Epidemiol* 1994;23:948-56.
58 Bennett SA, Magnus P. Trends in cardiovascular risk factors in Australia. *Med J Aust* 1994;161:519-27.
59 Arnetz BB, Kallner A. Epidemiological assessment of hyperlipidaemia management in primary health care. *Eur J Public Health* 1994;4:38-45.
60 Lindeberg S, Nilsson-Ehle P, Terént A, Vessby B, Scherstén B. Cardiovascular risk factors in a Melanesian population apparently free from stroke and ischaemic heart disease: the Kitava study. *J Intern Med* 1994;236:331-40.
61 Fonnebo V. Coronary risk factors in Norwegian seventh-day adventists: a study of 247 seventh-day adventists and matched controls. *Am J Epidemiol* 1992;135:504-8.
62 Jacobsen BK, Stensvold I, Fylkesnes K, Kristiansen IS, Thelle DS. The Norland health study. *Scand J Soc Med* 1992;20:184-7.
63 Shelley E, Daly L, Collins C, Christie M, Conroy R, Gibney M, et al. Cardiovascular risk factor changes in the Kilkenny health project. *Eur Heart J* 1995;16:752-60.
64 Strandberg TE, Salomaa VV, Vanhanen HT, Naukkarinen VA, Sarna SJ, Miettinen TA. Mortality in participants and non-participants of a multifactorial prevention study of cardiovascular diseases: a 28 year follow up of the Helsinki businessmen study. *Br Heart J* 1995;74:449-54.
65 Vartiainen E, Puska P, Jousilahti P, Korhonen HJ, Tuomilehto J, Nissinen A. Twenty-year trends in coronary risk factors in North Karelia and in other areas of Finland. *Int J Epidemiol* 1994;23:495-504.
66 Pekkanen J, Uutela A, Valkonen T, Vartiainen E, Tuomilehto J, Puska P. Coronary risk factor levels: differences between educational groups in 1972-87 in eastern Finland. *J Epidemiol Community Health* 1995;49:144-9.
67 Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease. *BMJ* 1994;308:367-72.
68 De Lorgeril M, Salen P, Caillat-Vallet E, Hanauer M-T, Barthelemy JC, Mamelle N. Control of bias in dietary trial to prevent coronary recurrences: the Lyon diet heart study. *Eur J Clin Nutr* 1997;51:116-22.
69 SENECA Investigators. Longitudinal changes in serum lipids of elderly Europeans. *Eur J Clin Nutr* 1996;50:S25-31.
70 Law MR, Morris JK. Why is mortality higher in poorer areas and in more northern areas of England and Wales? *J Epidemiol Community Health* 1998;52:344-52.
71 Woodhouse PR, Khaw KT, Plummer M, Foley A, Meade TW. Seasonal variations of plasma fibrinogen and factor VII activity in the elderly: winter infections and death from cardiovascular disease. *Lancet* 1994;343:435-9.
72 Blot WJ. Alcohol and cancer. *Cancer Res* 1992;52(suppl):2119-23S.

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Commentary: Alcohol and other dietary factors may be important

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Law and Wald predict that it is only a matter of time before the "French paradox" resolves itself as the similar pattern of risks factors (animal fat consumption, serum cholesterol concentrations, and blood pressure) between France and Britain will become translated into similar death rates from coronary disease. Although alcohol consumption remains higher in France than in Britain, the authors reject this as a possible explanation because they consider that alcohol intake greater than one unit a day confers no greater benefit. The evidence for this assumption is tenuous; many studies find a continuous graded association between increasing intake and lower levels of coronary mortality.[1 2] Moreover, the French tradition of drinking alcohol with meals may be more beneficial than other patterns of intake.[3] Hence, Law and Wald may be too quick to dismiss the role of alcohol as a partial explanation.

They make an important point in distinguishing the relatively rapid decrease in risk of heart disease after reduction in cholesterol concentrations from the slow increase in risk associated with increased concentrations. It is disappointing, however, that their entire explanation rests on a small number of well established coronary risk factors. Although the importance of these risk factors is not disputed, it is clear that differences in their distribution can explain only part of the variability in the occurrence of coronary heart disease. Obviously, other factors must play a role.

The main value in identifying ecological contrasts in disease rates, such as the French paradox, is to stimulate new hypotheses. The time lag hypothesis is one such idea, but the similarity of levels of traditional risk factors over a fairly long period strongly suggests that other behavioural differences may be at work. We would like to know more about differences between France and Britain in intake of folate,[4–6] cereal fibre,[7 8] nuts,[9 10] α linolenic acid,[11] and the glycaemic load of the diet.[12 13] Differences in these dietary variables have little impact on total or high density lipoprotein cholesterol concentrations, but in US populations each has been associated with marked differences in levels of coronary heart disease across the range of normal levels of intake. Data from the World Health Organisation and the Food and Agricultural Organisation, derived from estimates of food disappearance, suggest that per capita intake of nuts and fibre has been two to three times higher in France than the United Kingdom since 1965.

The Lyon heart study provides an important case in point. In this clinical trial patients who had survived a myocardial infarction were randomly assigned to their normal diet or a Mediterranean style diet. The experimental diet was rich in fruits, vegetables, monounsaturated fat, and α linolenic acid.[14] Alcohol intake was similar in the two groups. The experimental diet was not designed to lower blood lipids, and indeed the concentrations of total, low density lipoprotein, and high density lipoprotein cholesterol in the two groups were similar throughout the two years on the diet. Blood pressures were also similar. Despite the similarities in the traditional risk factors, the experimental group experienced a 73% decrease in subsequent myocardial infarction or mortality from coronary heart disease, and overall mortality was reduced by 70% (95% confidence interval 18% to 89%).

Differences in intake of types of fat that have a benefit disproportionate to their impact on serum cholesterol concentrations may also contribute to the French paradox. For example, intake of oils rich in polyunsaturated fat has been nearly twice as high in France as in the United Kingdom over the past 30 years.

Coronary heart disease is complex and multifactorial, which is a good thing. It means that many avenues for intervention can be applied. Changes in concentrations of total and low density lipoprotein cholesterol and blood pressure have doubtless had an enormous beneficial impact in reducing the risk of this disease. However, many other paths to prevention remain relatively unexplored. Law and Wald might be correct that the French paradox will in time dissolve, but we think it more likely that the difference in coronary mortality rests on behavioural (especially dietary) differences that have not received adequate attention.

1 Klatsky AL, Armstrong MA, Friedman GD. Risk of cardiovascular mortality in alcohol drinkers, ex-drinkers, and nondrinkers. *Am J Cardiol* 1990;66:1237-42.
2 Rimm EB, Giovannucci EL, Willett WC, Colditz GA, Ascherio A, Rosner B, et al. A prospective study of alcohol consumption and the risk of coronary disease in men. *Lancet* 1991;338:464-8.
3 Hendriks HF, Veenstra J, Velthuis-te Wierik EJM, Schafsma G, Kluft C. Effect of moderate dose of alcohol with evening meal on fibrinolytic factors. *BMJ* 1994;308:1003-6.
4 Rimm EB, Willett WC, Hu FB, Sampson L, Colditz GA, Manson JE, et al. Folate and vitamin B_6 from diet and supplements in relation to risk of coronary heart disease among women. *JAMA* 1998;279:359-64.
5 Morrison HI, Schaubel D, Desmeules M, Wigle DT. Serum folate and risk of fatal coronary heart disease. *JAMA* 1996;275:1893-6.
6 Parodi PW. The French paradox unmasked: the role of folate. *Med Hypotheses* 1997;49:313-8.
7 Pietinen P, Rimm EB, Korhonen P, Hartman AM, Willett WC, Albanes D, et al. Intake of dietary fiber and risk of coronary heart disease in a cohort of Finnish men: the alpha-tocopherol, beta-carotene cancer prevention study. *Circulation* 1996;94:2720-7.
8 Rimm EB, Ascherio A, Giovannucci E, Spiegelman D, Stampfer MJ, Willett WC. Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. *JAMA* 1996;275:447-51.
9 Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, et al. Frequent nut consumption and risk of coronary heart disease in women: prospective cohort study. *BMJ* 1998;317:1341-5.
10 Fraser GE, Sabate J, Beeson WL, Strahan TM. A possible protective effect of nut consumption on risk of coronary heart disease. The adventist health study. *Arch Intern Med* 1992;152:1416-24.
11 Hu FB, Stampfer MJ, Manson JE, Rimm E, Wolk A, Colditz GA, et al. Prospective study of dietary intake of alpha-linolenic acid and risk of coronary heart disease among women. *Am J Clin Nutr* (in press).
12 Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *JAMA* 1997;277:472-7.
13 Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, et al. A prospective study of dietary glycemic load and risk of myocardial infarction in women. *FASEB J* 1998;12:A260.
14 De Lorgeril M, Renaud S, Mamelle N, Salen P, Martin JL, Monjaud I, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;343:1454-9.

Commentary: Intrauterine nutrition may be important

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Szent-Gyorgi wrote that "for every complex problem, there is a simple, easy to understand, incorrect answer." Hitherto, only simple explanations—such as the protective effects of red wine, garlic, or onions—have been brought forward to explain why French people have such low rates of coronary heart disease despite their "unhealthy" lifestyles. Not surprisingly, these simple ideas have not stood the test of time. Law and Wald have carried out a more subtle analysis. They conclude that, for the population of France, retribution has merely been postponed, and an epidemic of coronary heart disease is now approaching. Their hypothesis rests on the assumption that trends in the disease follow closely on trends in animal fat consumption and serum cholesterol concentrations, an assumption that can readily be challenged. Findings in the monitoring trends and determinants in cardiovascular disease (MONICA) study, for example, show that recent trends in coronary heart disease are only weakly related to trends in serum cholesterol.

An alternative explanation of the French paradox derives from recent research which suggests that coronary heart disease originates in utero, through adaptations that the fetus makes to undernutrition.[1 2] According to this hypothesis, coronary heart disease "represents a stage of improving nutrition between chronic maternal malnutrition and nutrition at a plane that allows the mother to nourish her fetus adequately throughout gestation." Because fetal nutrition depends on the mother's body composition and size as well as her diet in pregnancy, optimal maternal nutrition depends on the nutrition of girls through childhood and adolescence as well as the nutrition of adult women.

Two hundred years ago the populations of Britain and France were chronically malnourished. It has been estimated that towards the end of the 18th century a person's average energy intake in England was similar to that in India today, while that in France was lower, similar to that in Rwanda today.[3] What Fogel has called "the escape from hunger" got under way in the 19th century, but, despite increasing food supplies in both countries, women, babies, and children remained poorly nourished. At the start of the 20th century, the poor physique of would-be army recruits enlisting to fight in the Boer war drew attention to the plight of Britain's youth. A committee set up in 1903 drew a shocking picture of our children—malnourished, deprived, and poorly housed.[4] In the years up to the first world war, the report of this committee fuelled a series of public health programmes for infants and children, which included feeding of schoolchildren, promotion of breast feeding, and care of pregnant women.[5] As this infant and child welfare movement developed in Britain, it had a useful role model—France.

The demoralising defeat in the Franco-Prussian war (1871) together with concerns about the small number of children in the country, through a combination of low birth rate and high infant mortality, led to fears that the French army would soon be inadequate and that France would cease to be a military power. Over the next 30 years various measures were introduced to protect the nutrition and health of the country's children. School meals were established: by 1904, when the *Lancet* sent a representative to Paris to report on this, a meal (soup, meat, and vegetables) was being provided to every schoolchild. In both Paris and the provinces there were infant welfare centres promoting breast feeding and, when this failed, providing sterilised cows' milk from milk depots. Communes were taking responsibility for the welfare of pregnant women. In the wake of the interdepartmental committee report, medical officers of health in Britain looked to "the French system" as they devised their own welfare programmes for infants and children.

Did better nourishment of girls, better nutrition in pregnancy, and better infant feeding protect the generations of French people born from the turn of the century onwards from coronary heart disease? Have the French population successfully "escaped from hunger" without an epidemic of coronary heart disease by focusing improved nutrition on mothers, babies, and young children? If so, this is an important message for countries like India, where coronary heart disease is now epidemic and is rapidly becoming the commonest cause of death.

1 Barker DJP. Fetal origins of coronary heart disease. *BMJ* 1995;311:171-4.
2 Barker DJP. *Mothers, babies and health in later life.* Edinburgh: Churchill Livingstone, 1998.
3 Fogel RW. Second thoughts on the European escape from hunger. Famines, chronic malnutrition, and mortality. In: Osmani SR, ed: *Nutrition and poverty.* Oxford: Clarendon Press, 1991.
4 Acheson ED. Tenth Boyd Orr memorial lecture. Food policy, nutrition and government. *Proc Nutr Soc* 1986;45:131-8.
5 Dwork D. *War is good for babies and other young children.* London: Tavistock Publications, 1987.

Commentary: Heterogeneity of populations should be taken into account

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Law and Wald suggest that the "French paradox" can be explained by their time lag hypothesis—that decades of exposure to high dietary saturated fat and serum cholesterol concentrations must elapse before risk of mortality from ischaemic heart disease starts to rise. The observations that have given rise to the notion of a French paradox and inspired Law and Wald's hypothesis are all based on national averages: national mortalities from heart disease and average prevalences of risk factors. The figures are stratified by sex, but there is no allowance for the regional and socioeconomic variations that characterise the occurrence of heart disease and its risk factors.[1 2] There are several reasons why this is problematic.

Firstly, the heterogeneity of populations may make it difficult to obtain valid estimates of national averages of risk factor levels. Law and Wald have drawn on a wide variety of sources, particularly for serum cholesterol concentrations. Among their sources, they have included regional studies (such as French studies from Ile-de-France and Alsace) and studies among specific socioeconomic groups (such as studies on civil servants and employees in Italy). They do not explain how they derived their national averages, but it is likely that these (weighted?) averages have non-negligible margins of uncertainty.

Secondly, regional and socioeconomic variations will affect behavioural patterns generally and may therefore lead to a clustering of risk factors in certain subgroups of the population. If these risk factors potentiate each other's effect on ischaemic heart disease a simple comparison of national averages may be misleading. Smoking enhances the effect of hypercholesterolaemia on ischaemic heart disease,[3] and a country in which smoking and hypercholesterolaemia cluster in the same subgroups of the population will therefore have a higher national mortality from heart disease than a country in which smoking and hypercholesterolaemia are concentrated in different subgroups even if their national averages for these risk factors are the same. A similar reasoning may be applied to risk factors that diminish each other's effect, perhaps alcohol consumption and intake of animal fat.[3] We know relatively little about the clustering of risk factors, but evidence from survey data suggests that socioeconomic variation in smoking and dietary factors is more consistent in the north of Europe than in the south, including France.[4] A clustering of smoking and hypercholesterolaemia in the lower socioeconomic groups is therefore more likely to be found in northern Europe than in the south, and it seems at least theoretically possible that the French paradox is partly explained by this phenomenon.

This brings us to another example of the heterogeneity of populations that may help to explain the French paradox. In a comparative study of socioeconomic inequalities in mortality from ischaemic heart disease in 12 industrialised countries we found that there was a strong correlation between the extent of inequalities in mortality from heart disease (measured as the relative risk of dying among men in manual occupations compared with men in non-manual occupations) and the share of ischaemic heart disease in the total number of deaths among middle aged men. Southern Europe, including France, is generally characterised by both small socioeconomic differences in ischaemic heart disease and low national death rates from ischaemic heart disease. For example, while the relative risk of manual workers was 1.50 (95% confidence interval 1.32 to 1.71) in England and Wales, it was 0.96 (0.92 to 1.00) in France.[5]

It is tempting to see a causal connection between the two: couldn't it be partly because of the small socioeconomic differences that the national death rate from ischaemic heart disease in France is so low? Given the fact that the manual classes make up about half of the male, middle aged population, the socioeconomic gradient in Britain would produce a 25% higher national mortality from ischaemic heart disease even if the death rates in the non-manual classes were the same (in fact, they are substantially lower in France). In view of the 250% excess mortality from ischaemic heart disease in Britain compared with France it is clear that the proportion "explained" by the socioeconomic gradient in Britain is modest. On the other hand, the figures do show that looking at subnational patterns of mortality from ischaemic heart disease and risk factors is worth while, and we suggest that further attempts to explain the French paradox take advantage of the heterogeneity of national populations in order to identify the specific constellations of factors that explain a country's high or low national mortality from ischaemic heart disease.

1 World Health Organisation. *Atlas of mortality in Europe; subnational patterns, 1980/81 and 1990/91. WHO Regional Publications, European Series, No. 75.* Copenhagen: WHO, 1997.
2 Kaplan G, Keil J. Socioeconomic factors and cardiovascular disease: a review of the literature. *Circulation* 1993;88:1973-97.
3 Mancia G. Etiology and background of smoking-induced cardiovascular risk. *Am Heart J* 1988;115:240-2.
4 Cavelaars AEJM, Kunst AE, Mackenbach JP. Socioeconomic differences in risk factors for morbidity and mortality in the European Community: an international comparison. *J Health Psychol* 1997;2:353-72.
5 Kunst AE, Groenhof F, Andersen O, Borgan JK, Costa G, Desplanques G, et al. Occupational class and ischemic heart disease mortality in the United States and 11 European countries. *Am J Public Health* 1999;89: 47-53.

Authors' response

In any comparison between populations of disease rates and exposures to causes of disease, duration of exposure must be taken into account. We believe that the commentators, Stampfer and Rimm apart, have not sufficiently considered the importance of duration. None would dispute, for example, that decades of cigarette smoking are necessary for chronic bronchitis and emphysema to progress to a severity that could cause death or for the incidence of lung cancer to become appreciable.[1] Hence mortality from these diseases is higher in Britain than in Greece or Spain even though Greece and Spain now have the higher cigarette consumption; the mortality differences reflect their past low levels of smoking.[2 3] Our "time lag" explanation must apply equally to heart disease as to other chronic diseases; what is surprising is that this has been overlooked until now. We do not attribute the entire French paradox to the time lag as the commentators suggest; we emphasise inaccurate death certification and, in women, low rates of smoking. Other factors may also contribute, but we consider the time lag to be quantitatively the most important explanation.

Barker states that our time lag explanation can be challenged because the MONICA study shows little relation between trends in serum cholesterol concentration and trends in heart disease. But his observation that, over the 15 years of MONICA, the incidence of heart disease was no greater on average in populations where serum cholesterol had increased than in populations where it had not shows that 15 years is a short period in relation to atherogenesis. This supports rather than refutes the time lag explanation.

Barker attributes the low mortality from heart disease in France to school meals and other initiatives that improved childhood nutrition around 1900. Similar improvements took place in Britain soon afterwards, with nationwide provision of school meals by 1907 and redistribution of income to the poor in the "people's budget" of 1909. The resulting improvement in child health in Britain was shown by mortality from measles, which fell over the following decade by two thirds from its Victorian level of one death per 1000 children.[4] Barker speculates that this temporary nutritional difference increased lifelong risk of heart disease in British people born in 1900-9 and that British girls born in this period grew up to be undernourished mothers, predisposing their children to heart disease. Even if this were true it would not explain the French paradox. Heart disease continues to be more common among British people born in every subsequent decade up to the 1960s and beyond.[2] High death rates cannot be attributable to a temporary difference in exposure 50 years before people were born. Moreover, Barker's explanation is specific to France, but France is not the only country with low mortality from heart disease in relation to its present intake of dietary fat. Heart disease is lower than expected in Spain, Italy, Belgium, and especially Japan (see fig 2 of our article) and also in Soweto.[5] Common to these diverse populations is a relatively recent increase in dietary fat intake and serum cholesterol concentration.

Mackenbach and Kunst claim that our measures of exposure in some countries were from unrepresentative samples, undermining our results. We disagree. In our analysis of animal fat consumption (20 countries) we used national data, all from the same source,[6] and this yielded a similar result as the cholesterol analysis (13 countries). Errors would be random in direction, so masking the association not strengthening it, and would be greater in the past (when there were less data and quality may have been poorer). Yet mortality from heart disease was more strongly related to past than recent data. Smoking would not confound the association as Mackenbach and Kunst suggest because it is not strongly associated with serum cholesterol either within or between countries.

Mackenbach and Kunst have shown a tendency for mortality from heart disease to be lower in countries where there is little difference between manual and non-manual workers within the country in their risk of heart disease.[7] This is not of itself an explanation of the French paradox. The association arises because low mortality ratios between manual and non-manual workers are correlated across countries ($r = 0.73$) with the past low levels of animal fat consumption that accounted for the variation in heart disease in our analysis. The association

between low risk of heart disease and high wine consumption had the same explanation. In the traditionally agricultural countries of southern Europe dietary fat has been low until relatively recently (which can explain the low mortality from heart disease); in addition, wine consumption is high and risk factors for heart disease vary little with occupation, so these are associated with low rates of heart disease.

Stampfer and Rimm claim an important role for alcohol, but we think it is minor. The protective effect of alcohol does not significantly increase beyond 1-2 units a day (see fig 1 in our article), so the higher average consumption per drinker in France confers no additional benefit. The data from the five largest cohort studies, recording in total 28 800 heart disease events (6500 in people who consumed ≥2 units of alcohol a day) establish this conclusively. Of the two studies cited by Stampfer and Rimm in support of a continuous association, one confirms the plateau (risk relative to lifelong abstainers was 0.7 in drinkers of 1-2 units per day and 0.8 in drinkers of ≥6 units a day[8]) while the other recorded only 37 heart disease events in heavier alcohol drinkers.[9] Such small studies are uninformative: the confidence intervals are so wide as to be consistent with either a continuous association or a plateau.[9]

Stampfer and Rimm also cite the dietary interventions in the Lyon trial (more fruit and vegetables, less meat, substitution of unsaturated oils for butter and cream[10]). They suggest that such dietary factors could help explain the French paradox, but our analysis of animal fat consumption between countries (adjusted for consumption of fruit and vegetables) took these into account. They speculate on other dietary factors not tested in the trial (cereal fibre, nuts, the glycaemic load of the diet), which are difficult to assess individually because of dietary confounding. These hypotheses, like Barker's, assume that the paradox is unique to France. It is not: heart disease is low in relation to current risk factors in populations as diverse as Belgium, Japan, and Soweto, which share with France a recent increase in animal fat consumption but differ with respect to the other dietary factors.

After allowance for undercertification (and, in women, smoking), heart disease is 2.5 times more common in Britain than France. We believe that the time lag explanation is the major reason and that the alternative explanations offered in the commentaries are quantitatively unimportant.

1 Doll R, Peto R. The causes of cancer: appendix E. *J Natl Cancer Inst* 1981;66:1292-305.
2 World Health Organisation. *World health statistics annuals, 1995-6.* Geneva: WHO, 1996-7.
3 Nicolaides-Bouman A, Wald N, Forey B, Lee P. *International smoking statistics.* London, Oxford: Wolfson Institute of Preventive Medicine, Oxford University Press, 1993.
4 McKeown T. *The role of medicine: dream, mirage or nemesis?* Princeton: Princeton University Press, 1979.
5 Walker ARP. Cholesterol: how low is low enough? *BMJ* 1999;318:538-9.
6 Criqui MH, Ringel BL. Does diet or alcohol explain the French paradox? *Lancet* 1994;344:1719-23.
7 Kunst AE, Groenhof F, Andersen O, Borgan J, Costa G, Desplanques G, et al. Occupational class and ischaemic heart disease mortality in the United States and 11 European countries. *Am J Public Health* 1999;89:47-53.
8 Klatsky AL, Armstrong MA, Friedman GD. Risk of cardiovascular mortality in alcohol drinkers, ex-drinkers and nondrinkers. *Am J Cardiol* 1990;66:1237-42.
9 Rimm EB, Giovannucci EL, Willett WC, Colditz GA, Ascherio A, Rosner B, et al. Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet* 1991;338:464-8.
10 De Lorgeril M, Renaud S, Mamelle N, Salen P, Martin J, Monjaud I, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;343:1454-9.

Not playing with a full DEC: why development and evaluation committee methods for appraising new drugs may be inadequate

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The consultation document *A First Class Service: Quality in the New NHS*[1] heralded the introduction of the National Institute for Clinical Excellence (NICE). A key task of the institute is to provide rapid appraisal of new drugs in the period before licensing. New products may be accepted or refused NHS reimbursement, or they may be allocated "continuing research status."

The review process described in *A First Class Service* and developed in a subsequent discussion paper[2] mirrors that used for regionally funded development and evaluation committee (DEC) reports. Development and evaluation committee reports are produced by an independent arbitration committee comprising senior clinicians and others, who review the quality of available evidence, give explicit consideration to cost utility estimates, and make recommendations about interventions. Reports are published by NHS Research and Development (www.epi.bris.ac.uk/rd). Are the methods used by the development and evaluation committee up to the task?

Summary points

The National Institute for Clinical Excellence will appraise 30-50 drugs and technologies each year to inform decisions on whether these should be accepted or refused NHS reimbursement

The appraisal process will mirror that of regional development and evaluation committees, but this may lead to poor decision making since the methods used are inappropriate

The cost utility method of ranking treatments is based on strong assumptions and selective use of available evidence

New drugs should be appraised in terms of physical outcomes that mean something to doctors and patients