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CORRESPONDENCE

Because we receive many more letters than we have room to publish we may shorten those that we do publish to allow readers as wide a selection as possible. In particular, when we receive several letters on the same topic we reserve the right to abridge individual letters. Our usual policy is to reserve our correspondence columns for letters commenting on issues discussed recently (within six weeks) in the BMJ.

Letters critical of a paper may be sent to the authors of the paper so that their reply may appear in the same issue. We may also forward letters that we decide not to publish to the authors of the paper on which they comment.

Letters should not exceed 400 words and should be typed double spaced and signed by all authors, who should include their main degree.

High density lipoprotein cholesterol is not a major risk factor for ischaemic heart disease in British men

SIR,—Dr S J Pocock and colleagues (22 February, p 515) found significantly ($p<0.001$) lower high density lipoprotein (HDL) cholesterol values in men who subsequently developed ischaemic heart disease than in those who did not. By the conventional criteria, therefore, HDL cholesterol is a risk factor for ischaemic heart disease in British men. The question of whether or not HDL cholesterol is an "independent," and therefore possibly causal, risk factor in this population has not been answered by this investigation. After multivariate analysis the negative trend between ischaemic heart disease and HDL cholesterol persisted. Although this failed to achieve statistical significance, failure to confirm an association at an arbitrary level of significance is not the same as showing the absence of that association, and for this reason I believe that the title of their paper may be misleading.

There are aspects of the laboratory procedures used in the British Regional Heart Study which may undermine the confidence of some lipidologists in its outcome with respect to HDL values. The precision of measurement of HDL cholesterol under conditions similar to those used by Dr Pocock and colleagues can be considerably lower than that of plasma total cholesterol. This was demonstrated in the Speedwell study by the inclusion of "blind duplicates" in the batches of serum sent from the place of collection to the laboratory.[1] A similar exercise in the Caerphilly and Speedwell collaborative heart disease studies[2] has produced similar results (Sweetnam PM, personal communication). Furthermore, others have found that the unmodified phosphotungstate-magnesium method used in the British study[3] is less reliable than the heparin-manganese procedure (used in most other prospective studies of HDL), owing in part to precipitation of some of the HDL by the reagents.[4,5] For this reason Kostner *et al* recommended a reduction of the reagent concentrations.[6] The change in the cholesterol assay procedure about half way through the British study will have further aggravated the problem of precision.

When discussing their results Dr Pocock and colleagues failed to mention several important studies in which HDL was found to be of predictive value for ischaemic heart disease (table). In the Lipid Research Clinics follow up study the risk ratio for ischaemic heart disease between the top and bottom quintiles of HDL was 3·0.[8] In the Procam study the bottom quintile contained 64% of ischaemic heart disease events.[11] In the Lipid Research Clinics coronary primary prevention trial the ischaemic heart disease-HDL association was seen in both the placebo and cholestyramine groups.[9] The sample sizes in all of the studies listed were much greater than those in the two essentially negative studies[12,13] included by Dr Pocock and others in their fig 2. Both of these investigations used electrophoresis to measure HDL, and the Minnesota study shared in common with the British study the use of two different cholesterol measurement methods.[12]

It is also important to clarify a number of points concerning two other studies referred to by Dr Pocock and colleagues. It is not true that the only prospective data on HDL to have been reported from Oslo were obtained using frozen sera. In a second investigation fresh sera were used (see table).[7] On this occasion the standardised regression coefficient for ischaemic heart disease on HDL cholesterol was significant at $p<0.01$ and exceeded that for total cholesterol. The large case-control difference seen in Tromsø[14] was not due to any "publication bias," as the Tromsø group had no other data on HDL and all results were included in the report. It can probably be explained by the relatively short follow up period of two years, compared with 4-25 years used in other prospective studies.

Five recent prospective studies in which HDL cholesterol was found to be a predictor of risk of ischaemic heart disease in men

Study	Year	Country	No of subjects	No of events	Follow up (years)
Oslo study[7]	1982	Norway	1135	39	5
Lipid Research Clinics follow up study[8]	1985	USA	4152	78	8·4
Lipid Research Clinics coronary primary prevention trial[9]	1985	USA	3806	478	7·4
MRFIT[10]	1985	USA	6257	420	7
Procam study[11]	1986	West Germany	1674	45	5

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1 Bainton D, Burns-Cox CJ, Elwood PC, Lewis B, Miller NE, Morgan K, Sweetnam PM. Prevalence of ischaemic heart disease and associations with serum lipoproteins in subjects aged 45 to 64 years. The Speedwell Study. *Br Heart J* 1982;**47**:483-9.
2 The Caerphilly and Speedwell Collaborative Group. Caerphilly and Speedwell Collaborative Heart Disease Studies. *J Epidemiol Community Health* 1984;**38**:259-62.
3 Whitehead TP, Bullock DG, Carter TJN, *et al*. High density lipoprotein cholesterol analysis. *News Sheet of the Association of Clinical Biochemists* 1979;**190**:7-10.
4 Warnick GR, Albers JJ. HDL cholesterol quantitation: comparison of six precipitation methods and ultracentrifugation. In: Lippel K, ed. *Report of the high density lipoprotein methodology workshop*. Bethesda: US Department of Health, Education, and Welfare, 1979:53-69. NIH Publication No 79-1661.
5 Calvert DG, Yeates RA, Mannik T. A comparison of the phosphotungstate magnesium precipitation and heparin-manganese precipitation procedures for estimating high-density lipoprotein cholesterol. *Ann Clin Biochem* 1980;**17**:105-8.
6 Kostner GM, Avogaro P, Bittolo Bon G, Cazzolato G, Quinci GB. Determination of high density lipoproteins: screening methods compared. *Clin Chem* 1979;**25**:939-42.
7 Holme I. On the separation of the intervention effects of diet and anti-smoking advice on the incidence of major coronary events in coronary high risk men. The Oslo Study. *Journal of Oslo City Hospital* 1982;**32**:31-54.
8 Jacobs DR. High density lipoprotein cholesterol and coronary