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Review Article

Haematocrit, viscosity, erythrocyte sedimentation rate: meta-analyses of prospective studies of coronary heart disease

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Introduction

Various epidemological studies have investigated the possible associations between blood rheology (i.e. haematological characteristics that could influence blood flow) and coronary heart disease rates[1,2]. Some involved whole blood viscosity (i.e. bulk blood's intrinsic resistance to flow), but most involved its major determinants: haematocrit, plasma viscosity, and red cell aggregation (as indicated by the erythrocyte sedimentation rate) (Table 1). There is an elevated risk of occlusive vascular disease in patients with poorly controlled polycythaemia (in whom the haematocrit is markedly elevated)[3], and both prospective and retrospective epidemiological studies of the general population have reported some association between determinants of blood rheology and coronary heart disease risk.

Prospective epidemiological studies, in which coronary heart disease events are recorded for some years after 'baseline' blood collection, should be less prone to bias than retrospective epidemiological studies because they limit the influence of pre-existing disease itself on the factors being investigated. This should still be the case even in long-term prospective studies among patients with previous vascular disease since, in such studies, subsequent 'cases' are compared with 'controls' with similar disease at baseline selected from within the same study. Hence, to help determine whether there is any real association between coronary heart disease and various measures of blood rheology, we report a systematic overview (meta-analysis) of the available evidence from published prospective epidemiological studies of these factors.

Key Words: coronary heart disease, rheology, haematocrit, viscosity, meta-analysis.

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Methods

Search methods and data abstraction

Prospective studies published before mid-1998 that reported on correlations between coronary heart disease death or non-fatal myocardial infarction and haematocrit, viscosity, or erythrocyte sedimentation rate were sought by MEDLINE searches, scanning of relevant reference lists, hand searching of cardiology, epidemiology, and other relevant journals, and by correspondence with the authors of such reports. Computer searches used combinations of key words relating to these blood factors (viscosity, h(a)ematocrit, erythrocyte sedimentation rate, ESR) and to fatal coronary heart disease or myocardial infarction (e.g. coronary heart disease, isch(a)emic heart disease, myocardial infarction, atherosclerosis, vascular disease). Articles published in languages other than English were to be translated, and all relevant studies identified were included[4–30]. The following were abstracted (or, in several cases, supplied by the original investigators): geographical location of study; size and type of cohort (i.e. population based or selected on the basis of previous vascular disease); mean age and follow-up duration; assay methods; and degree of adjustment for potential confounders. Adjustment as shown in the figures is denoted[31] as + for age and sex only; ++ for these plus smoking; +++ for these plus some other standard vascular risk factors; ++++ for these plus markers of social class; and +++++ for these plus information on chronic disease at baseline.

Statistical methods

Different studies reported risk ratios on the basis of different cut-off levels (including comparisons of thirds,

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Table 1 Characteristics of haematocrit, plasma viscosity, blood viscosity, and erythrocyte sedimentation rate

Characteristic	Haematocrit	Plasma viscosity	Blood viscosity	Erythrocyte sedimentation rate
Definition	Cell volume (% of blood)	Flow resistance of plasma	Flow resistance of bulk blood	Red blood cell aggregation
Main determinants	Red blood cell count; mean red cell volume	Plasma protein concentration; plasma protein pattern	Plasma viscosity; haematocrit; red cell aggregation	Plasma protein concentration (especially fibrinogen and albumin)
Main correlates	Male sex; smoking; LDL; HDL (inverse); triglyceride; blood pressure; obesity; leucocyte count; menopause; physical inactivity	Age; fibrinogen; smoking; blood pressure; LDL; HDL (inverse); diabetes; morning and winter elevations	Male sex; smoking; blood pressure; LDL; obesity; physical inactivity	Female sex; age; fibrinogen; possibly haematocrit; possibly lipids
Baseline mean and standard deviation (SD)	44 (3)%	1·32 (0·09) mPa . s at 37 °C	3·4 (0·6) mPa . s at 37 °C	10 (8) mm . h^{-1} at ambient temperature
Approximate self-correlation (r)*	0·7	0·5	0·6	0·6
Usual values, top and bottom thirds**	46·3 vs 41·7%	1·37 vs 1·27 mPa . s	3·8 vs 3·0 mPa . s	15 vs 5 mm . h^{-1}

*Correlation coefficient (r) between two measurements of the same factors taken some years apart in the same individual.
**If a single baseline measurement is used to divide individuals into three equal-sized groups, the averages of the long-term 'usual' values in the top and bottom groups are estimated as baseline mean ± 1·09 r × SD. References for this table are available on request. LDL, HDL=low- or high-density lipoprotein cholesterol.

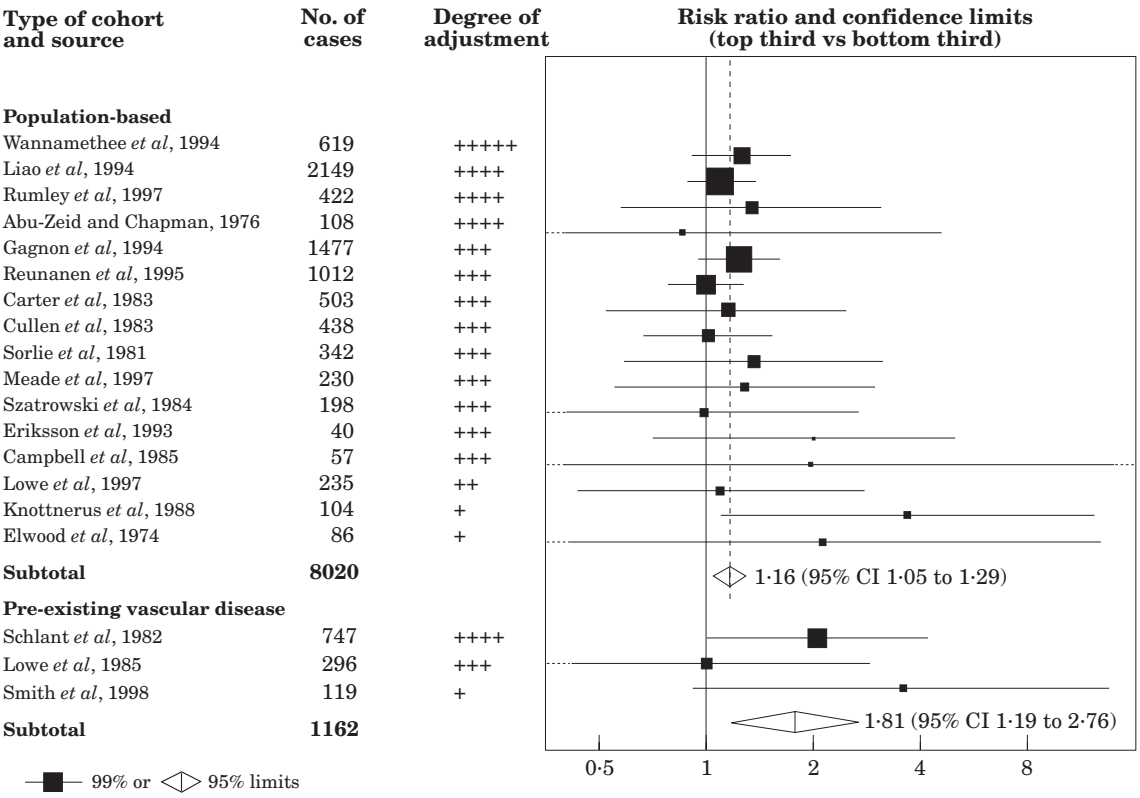

Figure 1 **Prospective studies of haematocrit and coronary heart disease.**

quarters, fifths, etc.), or as increases in risk for a given increase in the relevant factor. The risk ratios derived[31] from such publications for this review compare individuals in the top third vs those in the bottom third of baseline measurements, assuming an approximately log-linear association with disease risk over the mid-range of baseline values. Summary estimates of the risk ratios from all studies for each factor were obtained by combining the separate estimates of inverse-variance-weighted log risk ratios from each study. This was done even when different studies used different assay methods, since cases were compared directly only with controls within the same studies.

In the figures, black squares indicate risk ratios for each study, with the area of the square proportional to the number of cases. Horizontal lines indicate confidence intervals (CIs), with 99% CIs used for the individual study results to make some allowance for the increased scope for the play of chance in multiple comparisons. Diamonds are used to indicate the overall risk ratios and their 95% CIs. Heterogeneity was assessed by standard chi-squared tests. Most of the published studies related coronary heart disease risk to measurements of these factors made only at baseline, even though the levels of each factor can fluctuate markedly within individuals over time. Hence, estimates of the 'self-correlation coefficients' between measurements of the factor in blood samples collected some years apart have been used to correct for this 'regression dilution'[32,33], suggesting associations of disease risk with long-term usual levels of each factor that are substantially stronger than the corresponding associations with just a single baseline measurement of it (Table 1).

Results

Haematocrit

Nineteen prospective studies of haematocrit and coronary heart disease were identified (including three in patients with myocardial infarction[21,22] or peripheral vascular disease[23]), involving a total of 9182 cases with a weighted mean age at baseline of 55 years and a weighted mean follow-up of 16 years (Fig. 1)[4–23]. The studies were conducted in Australia[17,18], Finland[9], Hawaii[10], Japan[13], the Netherlands[19], Norway[14], Puerto Rico[11], the United Kingdom[4,6,12,15,16,20,22,23], and the U.S.A.[5,7,8,21]. All used standard assay methods (such as microhaematocrit measurements[34] or blood cell counters) and adjusted for at least age and sex, and most adjusted for smoking and lipids. There was no significant heterogeneity between the 19 study results ($\chi^2_{18}=18{\cdot}2$; $P>0{\cdot}1$), although there was some indication of a more extreme risk ratio in the studies of people with pre-existing vascular disease ($\chi^2_1=4{\cdot}3$; $P=0{\cdot}04$).

In principle, some heterogeneity could be caused by the preferential publication of small studies with striking findings (i.e. publication bias[35]), but in practice little

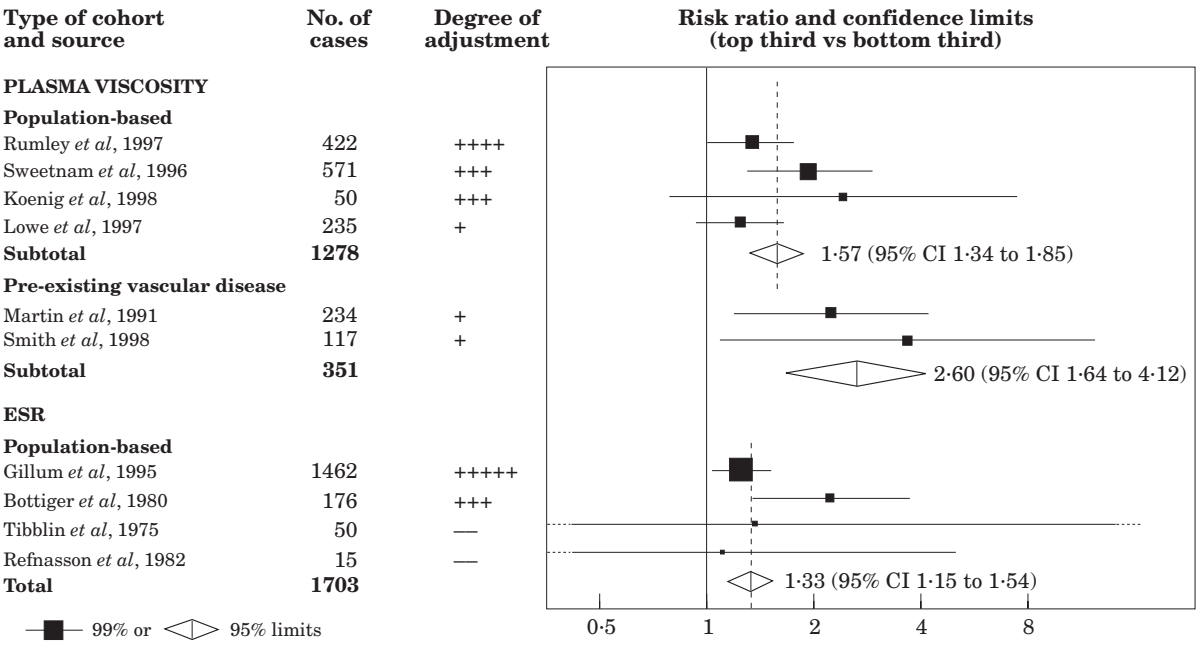

Figure 2 **Prospective studies of coronary heart disease and viscosity or erythrocyte sedimentation rate.**

difference is made either to the overall result or to the evidence of heterogeneity by restricting attention to just the seven studies of the general population that involved more than 400 cases. The results from these larger studies had all been adjusted for at least smoking and other standard risk factors (Fig. 1). Together they involved 6620 cases, or about four-fifths of the total, and there was no strong evidence of heterogeneity among them (χ^2_6=4·4; P>0·1). Overall, in these seven studies comparison of the top third vs the bottom third of baseline haematocrit yielded a risk ratio of 1·13 (95% CI 1·02–1·25; 2P<0·05), which is similar to the overall risk ratio in all 16 population-based studies of 1·16 (95% CI 1·05–1·29: Fig. 1). The estimated usual mean haematocrit values in the top and bottom thirds were 46·3% and 41·7%, respectively, after correction for regression dilution (Table 1). Subdivision of the published results on coronary heart disease and haematocrit (and the other haematological factors described in this review) by possibly relevant characteristics, such as study location, sex, and fatal non-fatal coronary heart disease, is not possible because the data are too sparse, or reported in insufficient detail, or both.

Plasma viscosity and blood viscosity

Six prospective studies of plasma viscosity and coronary heart disease were identified (including two in patients with myocardial infarction[26] or peripheral vascular disease[23]), involving a total of 1629 cases with a weighted mean age at baseline of 58 years and a weighted mean follow-up of 6 years (Fig. 2)[6,16,23–26]. The studies were conducted in Germany[25] and the United Kingdom[6,16,23,24,26]. All but one[26] used capillary viscometers (which are more accurate than rotational viscometers[2]) and all adjusted for at least age and sex. There was no significant evidence of heterogeneity among the published studies (χ^2_5=4·5; P>0·1). Overall, in the four studies of the general population, comparison of individuals with plasma viscosity values in the top third with those in the bottom third at baseline yielded a risk ratio of 1·57 (95% CI 1·34–1·85; 2P<0·0001, Fig. 2). After correction for regression dilution, the estimated mean usual plasma viscosity values in these two groups were 1·37 and 1·27 mPa . s, respectively (Table 1). Additionally, blood viscosity measurements[15,16] or calculations[6] were made by viscometry in two of these studies, involving a total of 657 cases with a weighted mean age of 57 years and a weighted mean follow-up of 5 years. There was no evidence of heterogeneity between these two published studies (χ^2_1=0·1; P>0·1), and a combined analysis for blood viscosity of individuals in the top third with those in the bottom third at baseline yielded a risk ratio of 1·24 (95% CI 0·74–2·10; P>0·1). After adjustment, the estimated mean usual blood viscosity values in these two groups were 3·8 and 3·0 mPa . s (Table 1).

Erythrocyte sedimentation rate

Four population-based prospective studies of erythrocyte sedimentation rate and coronary heart disease were identified, involving a total of 1703 cases with a weighted mean age at baseline of 61 years and a weighted mean follow-up of 14 years (Fig. 2)[27–30]. The studies were conducted in Sweden[28–30] and the U.S.A.[27]. All used standard assays (Westergren or Wintrobe methods[2]), but only two[27,28] reported any adjustment for age, sex,

smoking or standard risk factors. There was no evidence of heterogeneity among the four published studies (χ^2_3=7·3; P>0·05). Overall, comparison of individuals with erythrocyte sedimentation rate values in the top third with those in the bottom third at baseline yielded a risk ratio of 1·33 (95% CI 1·15–1·54; 2P<0·0001). After correction for regression dilution, the estimated mean usual erythrocyte sedimentation rate values in these 2 groups were about 15 and 5 mm . h^{-1} (Table 1).

Discussion

Despite the statistically significant association between haematocrit and coronary heart disease in the general population, the risk ratio is only slightly elevated above 1·0 and its relevance remains uncertain. Haematocrit levels are correlated with a number of standard vascular risk factors (Table 1) and adjustment for the measured values of these factors in some studies reduces the strength of the associations between haematocrit and coronary heart disease. Hence, adjustment for the long-term usual values of those factors (and other possible confounders) should reduce the risk ratio still further towards 1·0. It is also possible that the available evidence on haematocrit and coronary heart disease has been exaggerated somewhat by publication bias[35]. Assays for haematocrit are widely available, so other relevant studies of haematocrit and incident coronary heart disease may well exist (e.g., in trials of vascular disease prevention) that have not yet been reported. Indeed, separate results for coronary heart disease were not reported in a few long-term prospective studies of haematocrit and all-cause mortality[36,37], but any bias owing to the absence of these published studies is not likely to be substantial since they include less than 5% of the deaths in the available studies.

Similar considerations apply to the prospective studies of coronary heart disease and viscosity, even fewer of which are published, with five of the six publications being reported only since 1996 (Fig. 2). So, further measurement of these rheological factors (and of various possible confounders or mediators) in some large studies might substantially change the present overall results and their interpretation. With regard to erythrocyte sedimentation rate, few studies are available and only two reported adjustment for standard risk factors, while none reported adjustment for fibrinogen.

Hence, as yet, the relevance of these rheological factors to the risk of coronary heart disease remains uncertain. More detailed combined analyses, perhaps based on individual participant data from each of the prospective studies, might help to characterize the shapes of any dose–response relationships, reduce any bias related to the selection of particular cut-off levels, allow more complete adjustment for other risk factors, and assess associations in particular subgroups.

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