it might be worthwhile to investigate these issues in larger populations. The present study forms the basis to encourage and initiate such studies.

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Blood viscosity and the risk of death from coronary heart disease

See page 515 for the article to which this Editorial refers

In this issue Danesh et al. pooled data from prospective studies (meta-analysis) to determine if there is an association between haematocrit, viscosity and erythrocyte sedimentation rate and the incidence of coronary heart disease events. They combined results from 18 studies on haematocrit and found that patients in the top third (usual values >46%) had a 30% increase in coronary heart disease events compared to those in the lower third (<42%). Pooled data from a smaller number of studies also demonstrated an increased incidence of coronary heart disease in patients with elevated plasma viscosity, total blood viscosity and elevated erythrocyte sedimentation rate. The reason for reporting these analyses together is that both haematocrit and erythrocyte sedimentation rate are related to blood viscosity.

Ideally, meta-analyses analyse combine data from randomized, controlled trials. Even then, critics emphasize the intrinsic weaknesses of such an approach, primarily because pooled results incorporate biases from each of the individual studies. New sources of bias are introduced from selection of the studies and from the inevitable heterogeneity among them. In fact meta-analyses fail to predict the results of large, randomized, controlled trials (the gold standard for evaluations of efficacy of clinical interventions). 35% of the time. Errors are more likely when meta-analyses are used to analyse observational studies because comparison groups have not undergone randomization and the degree and direction of biases within each study might not have been identified and are apt to lead to a false-positive association. This is especially true for studies where the strength of association is less than 2; one of the most important criteria for causality.

Results from the three largest studies on haematocrit were heterogeneous. The Framingham study compared the highest fifth to the middle third of haematocrit values for the risk of dying from cardiovascular disease or coronary heart disease over a 34-year follow-up period. They found that
middle-aged females had a threefold increase of coronary heart disease deaths, and an increase in all-cause mortality. The same comparison in men did not show an increase in deaths from coronary heart disease although morbidity from cardiovascular disease was increased. The NHANES I study found a small but statistically significant increased risk in men of having myocardial infarction or coronary heart disease on either the death certificate or hospital record, but no increased risk in females[5]. In a Finnish study, there was no increased risk for death from coronary heart disease in either men or women[6].

Nevertheless, the results reported by Danesh et al. are interesting for several reasons. First, it is possible that the association between haematocrit and the incidence of coronary heart disease was underestimated. There is considerable intra-individual variation in haematocrit over time, partly due to seasonal differences[7]. Secondly, the association of blood viscosity with coronary heart disease is biologically plausible and blood viscosity is modifiable.

Blood viscosity is determined by the red cell concentration, the physical characteristics of the red cells (deformability, aggregability, and size), the plasma proteins, platelet count and leukocyte number and characteristics[8]. The primary cause of increased viscosity is the interaction between erythrocytes that occurs in the presence of fibrinogen and other plasma factors. Many factors are associated with increased haematocrit values and blood viscosity; Smoking increases both haematocrit and blood viscosity; others include acute psychological stress[9], obesity, hypertension, and a chronic mild state of dehydration[10].

Interventions to lower the haematocrit might include increased fluid intake, and phlebotomies. Chronic dehydration can lead to a decreased plasma volume, increased haematocrit values, and increased blood viscosity. It has been shown in a small group of subjects living in a hot dry environment that forced fluid intake can initially correct a decreased plasma volume and that the effect continues even after forced fluid intake has been stopped[10]. Besides long-term benefits, adequate hydration improves exercise tolerance and well-being in dehydrated subjects. It is not clear however, if mild chronic dehydration is prevalent and if forced hydration is either beneficial or practical. There are no studies on frequent phlebotomies, but there is evidence that blood donation in males decreases the incidence of cardiovascular disease, possibly due to a decrease in iron stores[11].

Chronic phlebotomy would have an added public health benefit of increasing the blood supply for transfusions, but acceptability of such therapy would need to be tested. Cautious use of phlebotomy is needed because iron deficiency leads to increased blood viscosity.

In summary, there is only weak evidence for a causal association between haematocrit/blood viscosity and coronary heart disease. Yet, Danesh et al. have done us a service in demonstrating the suggestive moderate association. Perhaps their efforts will lead to interventional studies that include frequent phlebotomies and/or controlled increased fluid intake.

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