Screening brief

Screening for ischaemic heart disease by serum homocysteine measurement

The disorder

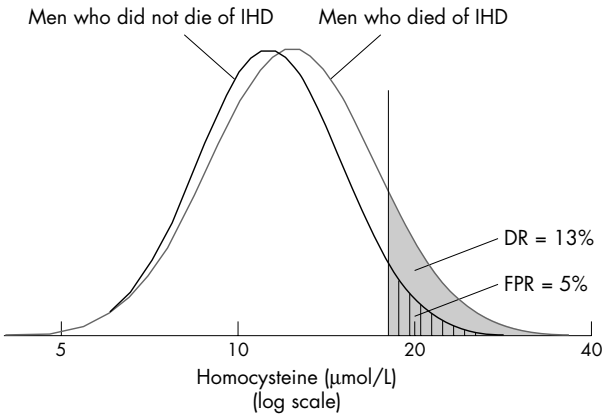
- Ischaemic heart disease (IHD) is the leading cause (responsible for at least 20%) of deaths in most Western countries.

Homocysteine, IHD, and folic acid

- Homocysteine is an aminoacid, a metabolite of methionine. It may promote endothelial injury and thrombosis mechanisms implicated in the pathogenesis of atherosclerosis
- Retrospective studies and most prospective studies show a dose-response relationship between increasing serum homocysteine concentration and IHD risk[1 2]; the average serum homocysteine concentration for a Western population aged 40–65 is about 12 µmol/l.[1–3] A 5 µmol/l increase in serum homocysteine increases the risk of a coronary event by about a third.[2]Across the range of homocysteine values in Western populations the association is continuous—the lower the homocysteine the lower the risk of IHD
- Folic acid reduces serum homocysteine; the maximum serum homocysteine reduction is about 3 µmol/l (25%) and is achieved by about 0.8mg folic acid/day.[3] From the above association this would be expected to reduce IHD risk by about 15%[3 4]
- Folic acid produces some reduction in homocysteine from all starting levels in Western populations.

Homocysteine as a screening test for IHD

- The figure shows the distribution of homocysteine levels in men who subsequently died of IHD and men who did not, based on data from a large cohort study. Wide separation between the homocysteine distributions of men who did and did not die of heart disease would indicate a good screening test; substantial overlap (as here) indicates a poor screening test[5]; results from other cohort studies are similar.[2 6] Using a cut-off of 18 µmol/l the false positive rate is 5% (an accepted standard) and the detection rate is 13%. Whatever homocysteine cut-off is chosen, the proportion of those who died of the disease is little greater than the proportion of those who did not.



Overall assessment

- Serum homocysteine is a poor screening test for IHD; screening based on homocysteine measurement is not justified
- This does not mean that population-wide homocysteine reduction is not useful.

1 Boushey CJ, Beresford SAA, Omenn GS, *et al*. A quantitive assessment of plasma homocysteine as a risk factor for vascular disease. *JAMA* 1995;**274**:1049–57.
2 Danesh J, Lewington S. Plasma homocysteine and coronary heart disease:systematic review of published epidemiological studies. *J Cardiovasc Risk*;1998;**5**:229–32.
3 Homocysteine Lowering Trialists' Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomized trials. *BMJ* 1998;**16**:894–8.
4 Wald DS, Bishop L, Wald NJ, *et al*. Randomized trial of folic acid supplementation and serum homocysteine levels. *Arch Int Med* 2001;**161**:695–700.
5 Wald NJ, Watt HC, Law MR, *et al*. Homocysteine and Ischaemic Heart Disease. Results of a Prospective Study With Implications Regarding Prevention. *Arch Intern Med* 1998;**158**:862–7.
6 Whincup PH, Refsum H, Perry IJ, *et al*. Serum total homocysteine and coronary heart disease: prospective study in middle aged men. *Heart* 1999;**82**:448–54.
7 Wald NJ, Hackshaw AK, Frost CD. When can a risk factor be used as a worthwhile screening test? *BMJ* 1999;**319**:1562–5.