Profiles of risk factors in users and non-users of oestrogen in two studies

	Current user*	Past user	Never used
Nurses' health study[4]			
Current smoker (%)	11·2	14·7	14·5
% With hypertension	23·2	25·0	21·8
% With diabetes	2·7	3·8	3·5
% With high serum cholesterol	9·9	11·2	7·6
% With parental myocardial infarction before age 60	10·6	10·0	9·3
% Taking vigorous physical activity ≥ once per week	48·2	43·1	42·4
% With body mass index ≥ 29 kg/m²	9·8	13·3	15·0
Lipid Research Clinics programme[5]*			
< High school education	16		25
% Smokers	33		31
% Taking regular exercise	12		10
% Drinking alcohol	82		79
Mean body mass index (kg/m²)	24·7		25·7
Mean age (years)	53·8		52·6
Mean systolic blood pressure (mm Hg)	129·0		127·7
Mean diastolic blood pressure (mm Hg)	79·9		79·5
Mean cholesterol	234·8		235·2

*In Lipid Research Clinics programme data for current and past users were combined.

would be greater than those in the relatively homogeneous populations from which much of our understanding of the epidemiology of hormones and heart disease derives. The table shows the distribution of risk factors for two large epidemiological studies that have provided data on oestrogen replacement therapy and heart disease; the differences in the profiles of risk factors are fairly modest. Moreover, adjustment for these differences has not materially altered the estimates of relative risk. Hence selection of healthier women for hormone treatment is unlikely to explain a major portion of the reduction in coronary heart disease.

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Benefits women with established cardiovascular disease

EDITOR,—Ward F M Posthuma and colleagues postulate that the reported benefits of hormone replacement therapy in reducing the risk of cardiovascular disease in postmenopausal women may be due to unintended selection of relatively healthy women.[1] The implication of this is that, had sufficient women with cardiovascular disease been present at the start of the epidemiological studies, a result with a lower significance would have been obtained. It is relatively simple to analyse this hypothesis by using data that were only partially considered in their review.[2]

Sullivan *et al* presented findings from a cohort of 1822 women with cardiovascular disease documented angiographically.[2] Over 10 years the relative risk of death from cardiovascular disease fell by 89% among women using oestrogen compared with non-users. This implies that there is a greater benefit for postmenopausal women with established cardiovascular disease than for healthy women. It should also be remembered that premenopausal women with oestrogen deficiency resulting from a surgical or premature menopause have a risk of cardiovascular disease roughly three times that of women with normal oestrogen concentrations.

A second fundamental flaw in Posthuma and colleagues' paper is that the authors chose total cancer as being a disease that is "unlikely to be influenced by oestrogen." This assumption may be unsound. Fotsis *et al* showed that 2-methoxyoestradiol, an endogenous oestrogen metabolite, is a potent inhibitor of the proliferation and migration of endothelial cells and an inhibitor of angiogenesis both in vitro and in vivo.[3] Angiogenesis is essential for successful tumour growth, and the antiangiogenic properties of interferon alfa have been shown to be promising in the treatment of haemangiomas.[4] Such findings in no way confirm a protective effect against cancer in oestrogen users after the menopause but may go some way to explaining the absence of the much predicted increase in breast cancer in such women. More fundamentally, it shows that one must be careful about making assertions about the impossibility of an observed effect.

Although the degree of protection that oestrogen replacement therapy offers against cardiovascular disease may be subject to selection bias favouring healthy subjects, whether this results in an overestimate or an underestimate of the true benefit cannot be stated with certainty. It remains to be elucidated whether oestrogen replacement therapy may also reduce the risk of all cancers in postmenopausal women through an effect on angiogenesis.

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1 Posthuma WFM, Westendorp RGJ, Vandenbroucke JP. Cardioprotective effect of hormone replacement therapy in postmenopausal women: is the evidence biased? *BMJ* 1994;**308**:1268-9. (14 May.)
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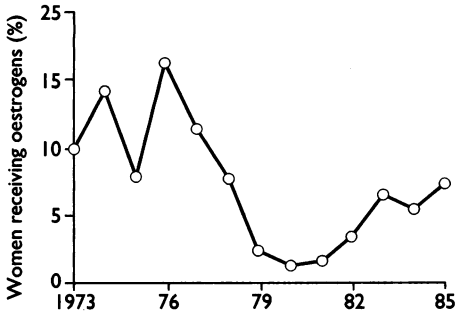
Authors' reply

EDITOR,—For reasons other than David Spiers suggests, the paper by Sullivan *et al* clarifies the subject. The figure, based on their data, shows the percentage of women using oestrogens at the time of cardiac catheterisation for each year of the study. The downward trend in the late 1970s indicates that the prescription of oestrogens was omitted in patients with signs and symptoms of coronary artery disease. The authors ascribed this reluctance to prescribe oestrogens to the increased frequency of myocardial infarction observed in men receiving oestrogens for secondary prevention. Most probably, oestrogen replacement therapy was stopped in patients who developed coronary artery disease and continued only in those with a favourable course. This differential prescription may explain why the effect of use of oestrogen was not significant when the data were analysed by treatment received at the time of



Percentage of women receiving oestrogen replacement therapy at time of diagnostic coronary angiography (data from Sullivan et al's study[1])

angiography. It also explains the lower mortality in women who subsequently used oestrogens.[1]

Even more fundamental than making assertions about the (im)possibility of an effect is weighing arguments for a plausible biological explanation.[2] Here we have to consider the possible beneficial effect of 2-methoxyoestradiol as an antiangiogenic compound not only for haemangiomas but, as stated in the original paper, also for rheumatoid arthritis, psoriasis, and diabetic retinopathy. As 2-methoxyoestradiol is an endogenous oestrogen metabolite the concentrations are probably higher in women. 2-Methoxyoestradiol is unlikely to have an important action because in most of these diseases neither sex predominates, whereas rheumatoid arthritis is almost exclusively a disease of women. On the other hand, recent Swedish evidence has led to the conclusion that the high oestrogen concentrations associated with pregnancy have a long term protective effect against breast cancer by inducing differentiation of normal mammary stem cells but increase the risk by stimulating the growth of cells that have undergone the early stages of malignant transformation.[3]

Now we know that the observational studies on cardiovascular diseases have been subject to selection of healthy subjects we should realise that their results are difficult to interpret.[4,5] They give us clues for further development of scientific ideas on the relation between sex hormones and cardiovascular disease. An inference about preventive measures is a step too far.

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Supervision registers for mentally ill people

EDITOR,—Glynn Harrison and Peter Bartlett set out several anxieties concerning the implementation of supervision registers for mentally ill people.[1] In particular, they question the clarity of the Department of Health's guidance about which patients should be included on the registers.