Women's health and diet

SIR — On behalf of the investigators responsible for mounting the NIH Women's Health Initiative (WHI), we wish to comment on the article (*Nature* **366**, 11; 1993) summarizing the recent assessment of WHI by a committee appointed by the Institute of Medicine.

The committee focused primarily on the clinical trial, one of three components of WHI, which is already under way at 16 US clinical centres.

The clinical trial is designed to measure the effects of hormone replacement therapy, dietary modification and calcium and vitamin-D supplementation on the overall health of postmenopausal women. All three treatments are already widely used, and each is presumed to have major public health implications. We believe that it is essential to obtain reliable and up-to-date information on the benefits and risks of these interventions in the middle and later decades of women's lives.

Although the committee was critical of some aspects of the clinical trial, it recommended that each component of it should continue, and confirmed that the budget was not excessive — hardly a "thorough condemnation of a study designed by fellow professionals".

The article implies that WHI is a "hastily put together programme", ignoring our work in successful preliminary studies among large numbers of postmenopausal women over the past decade. In particular, these studies have led to the development of a practical, successful programme for adopting a low-fat eating pattern.

On the dietary modification part of the clinical trial, the committee reported that its members support hypotheses relating a low fat-eating pattern to a reduced risk of coronary heart disease and of colorectal cancer, but regard the data supporting a reduced risk of breast cancer as weak. In our view, except for the link between dietary factors and blood cholesterol, evidence relating dietary fat to coronary heart disease is virtually identical to that for breast cancer. Specifically, analyses of variations in international disease rates, of national time trends in disease rates and of the experience of migrant populations support the existence of relationships for both coronary heart disease and breast cancer, whereas case control and cohort studies yield inconsistent results for both. Furthermore, fundamental problems in assessing the diets of individuals make it unlikely that additional case-control and cohort studies alone can reliably answer whether or not a dietary change can reduce the risk of breast cancer.

The article correctly reports the committee's concern about aspects of the WHI statistical design, citing specifically an assumption of a linear halving of breast cancer risk over five years among women who adhere to the dietary change programme as compared to women who make no dietary change. In fact, this is one place where the committee misunderstood our 147-page protocol. The actual design assumption assumed risk to be halved over a ten- rather than a five-year period. Careful allowances for lack of adherence to dietary goals, secular trends in control group dietary habits and deaths from competing risks then lead to a projected 14 per cent lower breast cancer risk for dietary intervention group as compared to control group women.

Brief responses to the other design issues are as follows. We believe it is important to establish whether or not a combination of calcium and vitamin D can prevent hip and other fractures, and less immediate to know the relative contributions of each to any preventive success; we believe that it is important to have some study of the effects, for example, in respect to quality of life and safety, of undertaking both hormone replacement therapy and a low-fat eating pattern, but that a statistically powerful test for "interaction between the two regimens" is less important. As the treatments to be assessed are already being widely adopted, we believe that testing in the general population, rather than just in women thought to be at high risk for selected diseases, is needed, and clinical-trial sample sizes have been chosen accordingly.

The consent forms being used in the WHI have undergone a considerable process of standardization, review and approval, including review and approval by our external Data and Safety Monitoring Board and by the Investigational Review Boards of each of our institutions. But we welcome the committee's encouragement to strive for the highest standard for communicating possible risks and benefits. To this end we are systematically examining all our consent procedures with a view to adding more quantitative information while avoiding information overload on participants.

Finally, as you report, the committee was concerned that the current budget allocations may be insufficient for this ambitious programme. However, we believe that the average 9-year follow-up period in the WHI clinical trial with lower costs in later years, and the design efficiencies resulting from cost-assessment components of the extensive feasibility and pilot studies, will allow the WHI clinical trial to continue in a cost-efficient manner. In fact, our own cost projections indicate that the project can be completed within the planned budget.

In summary, we appreciate the committee's thoughtful recommendations, including that of a formal clinical trial assessment at an earlier date than had been intended, which we do not regard as 'condemnation' but as encouragement to conduct the strongest, most efficient study possible.

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SIR — In her article on the NIH women's study, Barbara J. Culliton mentions osteoporosis and the complications of calcium intake. Studies of the influence of vitamin D on the occurrence and severity of osteoporosis in white women should be possible by comparing groups of postmenopausal white women living in a temperate climate with a lack of winter sunlight and those living in a sunny tropical climate.

On a small scale (60 participants), we made such study two years ago in the Netherlands and in Curaçao in the Netherlands Antilles (*Am. J. clin. Nutrit.* **58**, 106; 1993). The calcium intake in the Curaçao women was only moderately lower than in the Dutch group, so that the vitamin-D synthesis in the skin of both groups is most probably the chief influence on bone density. We estimate the cost of the published part of our investigation at less than £35,000.

The small size of the white population of Curaçao makes an investigation on a larger scale desirable. The participation of a few hundred white women living in a temperate and in a tropical climate might clarify the phenomenon of periodic (winter) vitamin-D deficiency in postmenopausal women.

If organized, such an investigation need take at most two years. The cost might be higher than in thrifty Holland, but should be less than £300,000.

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