Letters to the Editor

Long-term psychological stress and heart disease

From ABLA M SIBAI and HAROUTUNE K ARMENIAN

Sir—We read with interest the article of Moore et al. about the relationship between psychological stress and ischaemic heart disease (IHD) in middle-aged Caucasian men.1 Several dimensions of psychological stress, including occupational and those originating from lifestyle and life events, had little or no impact on the incidence of IHD. As their study pooled IHD into one category and was limited to men, they could not discuss the potential relationship for the different categories of heart diseases or among women.

In our previous two studies, one using the case-control2 and the other cohort approach,3 we had different results. Several measures of war-related stressful events associated significantly with heart disease morbidity and mortality, in both men and women. War-related stressors were drawn from events experienced by individuals during the war in Lebanon, similar to those originating from life events. These included acute events such as deaths, injuries and kidnappings in the family, and chronic strains such as economic pressures, frequent displacements, and crossing green lines. In both studies, long-term stress has shown more conclusive results. For example, in our case-control study, crossing the ‘green-lines’ that separated the two belligerent sides during wartime, considered an attribute of chronic stress, associated significantly with arteriographically determined coronary disease. In the more recent cohort study, while specific types of acute and chronic events associated with cardiovascular disease mortality, the largest contribution to risk of mortality in women appeared to ensue from stressors due to ‘kidnappings’ where the individual remained missing. In both studies, there was a dose-response relationship between exposure to cumulative score of war events and outcome. Moore et al correctly raise several issues and limitations in studies of psychological stress and heart disease. They also indicate that their negative findings may be explained by information bias, because of the potential of frequent change in exposure during follow-up. They suggest that, in future cohort studies, stress should be measured at regular intervals. In our cohort study,3 stressful events were assessed for the 10-year follow-up period, and were modelled in the analysis as time-dependent variables. This allowed for an examination of impact of long-term psychological stress on risk of cardiovascular disease mortality.

Although the role of psychosocial stress factors in the natural history of heart disease has been widely investigated, several issues remain not yet as clear. Studies vary in their definition of psychological stress, recall period, study population and outcome considered, allowing only very general comparisons to be made. Researchers in the field need to differentiate between the immediate impact of events and the role of accumulation of stressful experiences at different stages of the natural history of heart disease.

References


Authors’ response

From L MOORE, F MEYER and I BAIRATI

Sir—We were made aware of the interesting research conducted by Sibai et al. during our literature review. In their case-control study they investigated the relation of war stressors to coronary artery disease (CAD) as determined by coronary angiography and in their cohort study war exposures were studied with reference to CVD mortality.

We find it difficult to compare their research with ours due to the different nature of the stressors studied. Lebanon is a country that emerged in 1991 from 16 years of conflict including multiple invasions and civil disturbances. It is interesting to hypothesize that the extreme level of stress over long periods of time experienced by their study population compared to the relatively variable sources and degrees of stress experienced by the subjects of our study population could explain the difference in results. It may be that only a high level of stress experienced over a long period of time can affect cardiovascular health. Authors found CAD to be related to the number of war events and frequency of crossing green lines. It is interesting to note that the OR associated with one war-related event was below one and an increased odds ratio was only observed after two or more events. As authors have acknowledged in their article concerning the case-control study, the risk of referral bias, misclassification of exposure, over-reporting and recall bias may at least in part explain their results.

As noted by the authors, the heterogeneity of studies in this field does not allow for valid comparison. In order to correctly evaluate the differing aspects of psychological stress, a validated instrument should be used to measure exposure several times during follow-up in a large cohort. The use of regression models with time-dependent covariates could be a very useful statistical tool for analysing such data.
The Sex Ratio of Offspring of Men Exposed to Metal Fumes

From WILLIAM H JAMES

Figa-Talamanca and Petrelli report that men exposed to metal fumes have low offspring sex ratios (proportions male) at birth. They divide their workers into four graded categories of exposure (no exposure … highly exposed) and note that the two extreme offspring sex ratios are highly significantly different from one another. However one is left wondering about an overall assessment of their data in toto. For this purpose I performed a Mann-Whitney test. The resulting z-score (corrected for ties) took the value of 2.57, \( P = 0.005 \). So overall, there is a highly significant trend in these data, suggesting that paternal exposure to metal fumes is associated in a dose-related fashion with the production of excess daughters.

The authors mention two alternatives in this context, viz that

1. exposure alters men’s hormone profiles, and that—in accordance with my hypothesis—these directly affect the sex ratio at conception, and
2. exposed men somehow cause their wives to have male-biased spontaneous abortions.

In the context of my hypothesis, the authors mention that Bonde et al. reported poor semen and low fertility in welders, but no low offspring sex ratio. I should emphasize that ex hypothesi offspring sex ratio is to be regarded as a marker for unusual (pathological) hormone profiles—not as a marker for abnormal levels of individual hormones. Jacobsen et al. reported a normal sex ratio in the offspring of men ascertained at a sperm analysis clinic. So if offspring sex ratio is considered as a test, it will sometimes (as in the data of Bonde et al.) give a false negative result, but it has not (to my knowledge) been reported to give a false positive one. In other words an unusual imbalance: whereas a normal sex ratio may exist in spite of parental endocrine pathology (e.g. overall high or low hormone levels). The rationale for using offspring sex ratio as a marker for endocrine pathology is that it is useful, rapid and non-invasive; it may reflect the effects of low-level, long-term exposure; and ex hypothesi, it may be a permanent witness to hormone imbalance many years in the past. It is not a substitute for invasive testing (e.g. of sperm or endocrines) but may sometimes suggest that such procedures would be appropriate.

I should like to suggest that the authors follow up their alternatives elaborated above by considering the following questions:

1. Do the exposed men have—as I would hypothesize—low T/G ratios (where T and G are respectively a man’s standardized testosterone and gonadotrophin levels)? If these data are not immediately available, I suggest that hormone assays would now be justified (at least of the founders). An explanation of the founders’ unusual offspring sex ratio is now needed. Is it indicative of serious reproductive hazard?
2. Do the wives of exposed men (particularly founders) report a high incidence of spontaneous abortion? If so, is there a dose-related association between the incidence of abortion and level of exposure?

References

2. James WH. Evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels at the time of conception. J Theor Biol 1996;180:271–86.

Authors’ Response

From IRENE FIGA-TALAMANCA

Sir—We thank Dr. James for his useful comments and reinforcing our hypothesis about the potential role of unusual sex ratio as an indicator of environmentally induced hormone imbalance at the population level. Regarding his suggestion for further study, we answer as follows:

1. our data derive from a study of past reproductive experience and past occupational exposures. We are not in a position to reconstruct hormone profiles of these men. We are exploring the possibility of evaluating such profiles of presently exposed founders, in an attempt to provide an explanation of the unusual sex ratio observed.
2. The incidence of recognized spontaneous abortion among wives of exposed men was not higher than incidence of the non exposed (13.8% vs. 16%). This could be interpreted as evidence in favour of the hypothesis that the altered sex ratio might be the result of male hormonal interference rather than increased male-biased spontaneous abortions.