Cross-national differences in diet, the outcome of schizophrenia and the prevalence of depression: you are (associated with) what you eat†

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Malcolm Peet (2004, this issue) presents some evidence that the international variations in the outcome of schizophrenia are associated with higher amounts of refined sugar and dairy products in the average national diet data published by the Food and Agriculture Organization of the United Nations. An association is also found between the prevalence of depression and a low dietary intake of fish and seafood. It is a simple correlational study with a multivariate statistical analysis that finds very strong associations. The regression coefficients reported suggest that these foodstuff consumption levels account for almost all the variance in the outcome of schizophrenia and the prevalence of depression. Is Peet correct in stating that previous epidemiological studies of these issues are missing crucial information, or is the reported association between diet and psychiatric disorder at a population level just a particularly dramatic example of the ecological fallacy?

CULTURAL INFLUENCES IN SCHIZOPHRENIA

The multi-centre studies of schizophrenia organised by the World Health Organization (WHO) in the latter part of the 20th century are arguably the greatest achievements in psychiatric epidemiology. The International Pilot Study of Schizophrenia (IPSS; WHO, 1973) and a ten-country study (Sartorius *et al*, 1986) convincingly demonstrated a near-uniform incidence of nuclear or Schneiderian schizophrenia in nine different countries across the globe and significant variation in the incidence of less restrictively diagnosed schizophrenia. These studies also found a very variable course and outcome that were, on average, much better in developing countries. This was related partly to social isolation and marital status and partly to the type of onset and precipitating factors but was largely unexplained (Sartorius *et al*, 1978). The Determinants of Outcome of Severe Mental Disorders (DOSMED) study further examined this issue in six of the IPSS countries and in four others (Jablensky *et al*, 1992). It confirmed the results of the IPSS and also showed that about half of patients with schizophrenia in developing countries had a very good outcome at 2 years, but it did not shed any further light on the reasons why. Various explanations have been proposed over the years, including better family support, greater preservation of social role and reduced stigmatisation in developing countries, but with no convincing or consistently-replicated evidence.

There are at least two previous ecological studies along similar lines to the study by Peet (2004, this issue). Christensen & Christensen (1988) examined the relationship between 2-year follow-up data from the WHO (1979) international follow-up study and the amount of fat in the average national diets published by the Food and Agriculture Organization (1980). Very strong correlations, similar to those reported by Peet, were found between a low percentage of total dietary fat and fat from land animals and birds (mainly saturated fats), and a good prognosis. A high percentage of dietary unsaturated fatty acids was less strongly associated. Multivariate analysis found that 97% of the variation in outcome of schizophrenia between national centres was explained by the combined variation in the percentages of fat from land animals and birds and from vegetables, fish and seafood. Gupta (1992) also found correlations between the proportion of total calorific intake from fat and outcomes in the IPSS and DOSMED, but he found similar correlations with measures of occupation, urbanicity, geography, climate and the infant mortality rate. As Gupta points out, the postulated 'explanatory' variables were themselves highly intercorrelated, making it difficult, if not impossible, to distinguish their effects.

Making such a distinction has important therapeutic implications. The obvious, if unreliable, extension of an association between dietary fat and the outcome of schizophrenia is to use low-fat diets and/or unsaturated fatty acids as treatments. We are not aware of any trials evaluating the effects of low-fat diets but there has been a lot of recent interest in the use of unsaturated fatty acids as a potential augmentation strategy in schizophrenia. Some early encouraging trials have been followed by a larger number of convincing negatives (Joy *et al*, 2003).

DIET AND DEPRESSION

Depression is associated with heart disease and the hypothesis that this is mediated by a common metabolic disturbance (e.g. fatty acid metabolism) has some support from both animal and human studies (Grippo & Johnson, 2002). A decreased consumption of omega-3 fatty acids may also be a risk factor for depression, and a positive relationship between omega-3 fatty acids and increased central serotonergic activity provides a possible biological mechanism for this finding. Observational studies have also found that the ratio of omega-3 to omega-6 fatty acids is lower in (elderly) subjects with depression than in non-depressed controls (Tiemeier *et al*, 2003), but the fact that depressive symptoms include decreased appetite is an obvious confound in these studies.

There is some experimental evidence linking fatty acid intake or supplementation to the outcome of depression. A short randomised placebo-controlled study of 30 out-patients with bipolar disorder found that omega-3 fatty acid supplementation had positive effects on depressive symptoms and relapse (Stoll *et al*, 1999). These results are supported by two further short-term studies, one randomised (Su *et al*, 2003) and one apparently non-randomised (Nemets *et al*, 2003). All three trials examined the efficacy of omega-3 fatty acids in addition to usual medication. However, a randomised trial of advice to increase dietary fish intake in 452 men with angina found no effect of fish on mood and, after controlling for baseline mood, found some evidence of deterioration in those given advice to eat more fish. In a further study of healthy volunteers (Wells *et al*, 1998), subjects on a low-fat diet showed a deterioration in mood (in the domain 'anger–hostility') compared with control

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subjects, although the relationship to plasma fatty acids was unclear.

In summary, there is some evidence that omega-3 fatty acids may be associated with depressive symptoms, but the direction of causality has not yet been firmly established. Three trials have shown evidence of efficacy but there is a general lack of appropriately designed randomised controlled trials to examine whether an increased intake of dietary omega-3 fatty acids is effective in the treatment of depression.

CRITICAL APPRAISAL

Peet (2004, this issue) reports an ecological study of dietary factors associated with the outcome of schizophrenia and the prevalence of depression. For schizophrenia, 2-year outcome data were used from two prospective studies (IPSS, DOSMED) covering eight and ten countries, respectively. For depression, data were taken from two separate studies covering eight separate countries, but the Japanese data did not use structured instruments for diagnosis or randomised population sampling methods. Japan also has a very high consumption of fish and a low prevalence of depression (Hibbeln, 1998), which may have disproportionately affected the results. Data on diet were taken from an international database reflecting domestic food production, plus imports minus exports, taking into account food lost through processing. Pearson correlations and stepwise regression coefficients were calculated by taking into account the consumption of other foodstuffs.

Peet's study has other important limitations. Domestic food consumption may not reflect individual intake because it is difficult to take account of food wastage, which may differ in developed *v.* developing countries. As an ecological study, the data are aggregated for a whole country and may not reflect individual consumption. The relationships found may therefore represent a form of ecological fallacy in which the relationship between diet and mental disorder at an aggregate level may not reflect differences at an individual level. There have been several other ecological relationships that have, in time, proved to be spurious. The relationship between increasing numbers of psychiatrists and increasing suicide rates is one.

The food consumption data are likely to be confounded by individual social and economic effects and by other factors (e.g. gross domestic product) that act at a population level and may be associated with living conditions, health care and other important determinants of psychiatric morbidity. The regression analysis takes no account of these important potential confounds. There is no evidence of a dose–response relationship within individuals or population strata from each country and no evidence that dietary habits precede the onset of psychiatric symptoms. Thus, the relationship between outcome and prevalence with diet is strong, at least in terms of P value and R^2, but there is no assurance that the relationship is genuine and not attributable to bias or confounding.

ECOLOGICALLY FALLACIOUS?

Peet's study meets only the strong association criterion for assessing causation (Hill, 1965). Whether or not the results are biologically plausible is a value judgement. Dietary explanations for just about everything are the spirit of the age and popular in lay circles, at least in developed countries; whereas those, like us, who believe in evidence-based everything prefer their data served up from rigorous prospective cohort studies and randomised controlled trials. Arguably, however, dietary factors deserve just as much study as the other ill-defined influences on international differences in psychiatric epidemiology for which they may be a proxy. Ultimately, if Peet's study serves to rekindle interest in the cultural influences on major psychiatric disorders, it will have been a valuable contribution.

DECLARATION OF INTEREST

None.

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