Correspondence

EDITED BY GREG WILKINSON

Genetic epidemiology of binging and vomiting

Sir: Sullivan *et al* (1998) applied bivariate twin modelling to 1897 female twins born between 1934 and 1971, and appeared to demonstrate a strong association between binging and vomiting, with a high genetic correlation. This assumes a degree of temporal uniformity with regard to bulimia nervosa (i.e. that a subject binging or vomiting in the 1950s exemplifies the same phenotypic trait as a subject in the 1990s).

Re-interpreting original data, Russell (1995) has cogently argued that people binging and vomiting before the late 1970s may differ from those presenting with recognised bulimia nervosa in the 1980s and after. He raises the possibility that bulimia nervosa may have escalated by virtue of its clinical characterisation in 1979 ". . . in vulnerable young women who consequently acquired the illness as if by contagion" (Russell, 1995). Coupled with a low response rate (64%), this calls into question the validity of their findings and a re-analysis is suggested to account for year of birth.

Russell, G. F. M. (1995) Anorexia nervosa through time. In *Handbook of Eating Disorders – Theory, Treatment and Research* (eds G. Szmukler, C. Dare & J. Treasure), p. 15. Chichester: Wiley and Sons.

Sullivan, P. F., Bulik, C. M. & Kendler, K. S. (1998) Genetic epidemiology of binging and vomiting. *British Journal of Psychiatry*, **173**, 75–79.

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Sir: Sullivan *et al* (1998) claim that their data support a genetic contribution to binging and vomiting behaviour, but the statistical interpretation of the results is flawed and the conclusions thereby undermined. They have tested for violations of the equal environment assumption (EEA), which, if present, would invalidate the conclusions, by carrying out a logistic regression analysis of six measures of specified common environment and zygosity, with concordance for either binging or vomiting as the dependent variable. This yields 12 tests, and two of the tests for vomiting are individually significant at $P=0.02$. However, they apply a Bonferroni correction for multiple testing and claim that overall these results are not statistically significant. This is based on the argument that one of the tests would need to reach a P value of 0.004 in order to count as significant, since the probability for at least one of 12 independent tests to be significant at 0.004 by chance is $1-(1-0.004)^{12}=0.047$. The probability for at least one test to be significant at 0.02 by chance is $1-(1-0.02)^{12}=0.22$.

There are two problems with this approach. The first is that the Bonferroni correction assumes that all tests are independent and this is unlikely to be the case. Some of the measures used might plausibly be expected to be correlated, and there is very substantial overlap between binging and vomiting behaviours. If a Bonferroni correction is applied to non-independent tests such as these, then significant results can be wrongly rejected.

The second problem is that not one test is significant at $P=0.02$, but two. The probability for at least one test to be significant at $P=0.02$ is, as already stated, 0.22. To obtain the probability that more than one test will reach this level of significance we simply subtract from this figure the probability for exactly one of the 12 tests to be significant at 0.02, which is the binomial probability $(1-0.02)^{11}\times 0.02\times 12=0.19$. Carrying out this procedure gives us the result that the probability to observe two or more of the 12 tests to be significant at 0.02 by chance is only 0.023. This result is thus unlikely to occur by chance and contrary to the claims of Sullivan *et al* there is significant evidence for violation of the EEA.

Although both the significant tests relate to vomiting rather than binging, the behaviours are highly correlated. The observed violation of the EEA invalidates the conclusion that there is necessarily a genetic contribution to these behaviours.

Sullivan, P. F., Bulik, C. M. & Kendler, K. S. (1998) Genetic epidemiology of binging and vomiting. *British Journal of Psychiatry*, **173**, 75–79

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Author's reply: Morgan suggests that our findings are invalidated because we did not take age cohort effects into account. Other data certainly suggest that there are important age cohort effects on the lifetime prevalence of bulimia (Bushnell *et al*, 1990; Kendler *et al*, 1991), although detection bias may be operative (Soundy *et al*, 1995). To evaluate Morgan's concern, we stratified our sample via a median split on date of birth and then repeated the univariate twin modelling for lifetime self-reported binging and vomiting. In the older and younger strata, AE (additive genetic and individual-specific effects) models again provided the best fit to the data and the parameter estimates for a^2 ('heritability') and e^2 (environmental influences specific to an individual and thus unshared by members of a twin pair) were similar to those reported in our paper. Thus, in response to Morgan, age cohort effects do not materially alter our findings.

The more substantive issue to which Morgan alludes regards the absence of common environmental effects on the behaviours of binging and vomiting (one conceptualisation of 'contagion' would reveal itself as common environmental effects). We did not detect such effects and discuss this issue at length in our paper (Sullivan *et al*, 1998, p. 78, col. 3).

Curtis is correct in identifying the equal environment assumption (EEA) as an important assumption in twin research. He argues that our application of the Bonferroni correction was incorrect and that, contrary to our interpretation, our EEA analyses invalidate our conclusions.

We suggest that the more critical issue is the magnitude of any possible violation of the EEA rather than simply its presence or absence. This is of particular relevance in fairly sizeable samples such as ours

where small effects can none the less reach statistical significance. We note that prior research has generally supported the validity of the EEA in regard to most psychiatric disorders (Kendler & Gardener, 1998), although bulimia is a possible exception (Hettema *et al*, 1995; Kendler & Gardener, 1998). Thus, we re-analysed our data to determine whether the EEA measures of childhood treatment and similitude materially altered our results. The approach is described more fully elsewhere (Hettema *et al*, 1995); briefly, when we fit statistical models to the trait of a history of lifetime vomiting that included additive genetic, specific common environmental (childhood treatment or similitude), residual common environmental, and individual-specific environmental effects, AE models again provided the best fit to the data. Moreover, heritability estimates from the full models were similar to those reported in our manuscript.

Hence, rather than considering the EEA as an 'all-or-nothing' rule as Curtis implies, our analyses indicate that even if the EEA were violated with respect to vomiting, its impact was evidently small and insufficient to alter either our results or our conclusions.

Bushnell, J. A., Wells, J. E., Hornblow, A. R., *et al* (1990) Prevalence of three bulimia syndromes in the general population. *Psychological Medicine*, **20**, 671–680.

Hettema, J. M., Neale, M. C. & Kendler, K. S. (1995) Physical similarity and the equal-environment assumption in twin studies of psychiatric disorders. *Behavior Genetics*, **25**, 327–335.

Kendler, K. S., MacLean, C., Neale, M., *et al* (1991) The genetic epidemiology of bulimia nervosa. *American Journal of Psychiatry*, **148**, 1627–1637.

__ & Gardener, C. O. (1998) Twin studies of adult psychiatric and substance dependence disorders: are they biased by differences in the environmental experiences of mono- and dizygotic twins in childhood and adolescence? *Psychological Medicine*, **28**, 625–633.

Soundy, T. J., Lucas, A. R., Suman, V. J., *et al* (1995) Bulimia nervosa in Rochester, Minnesota from 1980 to 1990. *Psychological Medicine*, **25**, 1065–1071.

Sullivan, P. F., Bulik, C. M. & Kendler, K. S. (1998) Genetic epidemiology of binging and vomiting. *British Journal of Psychiatry*, **173**, 75–79.

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Reserpine exhumed

Sir: The editorial on reserpine by Healy & Savage (1998) was provocative and interesting but appeared to be needlessly offensive in one minor respect. When questioning the ability of physicians to correctly diagnose depression, the authors note that the opinions of physician authors from Geelong and Otago need to be interpreted with caution. Why are the physicians from these two large regional towns in Australia and New Zealand singled out in this way when the physician authors of other similar reports are not? Are Healy and Savage implying that physicians in regional antipodean towns in the mid-1950s were in some way less competent than those in Britain and North America? If so, I doubt whether they can adduce any evidence that this was the case. I think the authors should withdraw these comments or inform us of the reason why these two towns were singled out for mention in their article.

Healy, D. & Savage, M. (1998) Reserpine exhumed. *British Journal of Psychiatry*, **172**, 376–378.

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Author's reply: The particular mention of authors from Geelong and Otago (Healy & Savage, 1998) stemmed from the fact that these were the authors of the two articles that immediately preceded the randomised trial of reserpine in depressive disorders conducted by Davies & Shepherd (1955). On two facing pages of this article you can see an article by Wallace from Geelong and the first page of the Shepherd trial. For anyone sensitive to defining moments in history this conjunction has considerable resonance. The authors of these pieces, therefore, were clearly the ones to focus on in order to bring out this aspect of the story. We took considerable care, however, to research the background of Dr Wallace, in particular, and to know a good deal about this career. In brief, he was a physician who appears to have been well esteemed by his colleagues but he was not one who appears to have had a particular interest in mainstream adult psychiatry at the time he wrote his report and did not develop one subsequently. In contrast, some of the other physicians referred to noted not only reserpine's capacity to cause distress but also its potential usefulness for the treatment of depression.

Healy, D. & Savage, M. (1998) Reserpine exhumed. *British Journal of Psychiatry*, **172**, 376–378.

Davies, D. L. & Shepherd, M. (1955) Reserpine in the treatment of anxious and depressed patients. *Lancet*, *ii*, 117–121.

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Clozapine-induced extrinsic allergic alveolitis

Sir: The following case highlights potentially life-threatening cardio-respiratory complications of clozapine. A 45-year-old male with schizophrenia, with a medical background of heavy smoking and asymptomatic right ventricular hypertrophy, had an uneventful commencement of clozapine. Fifteen days into treatment, on 200 mg twice daily, he presented with lethargy and pyrexia. Additional findings included: a leucocytosis with eosinophilia, elevated erythrocyte sedimentation rate (90) and irregular tachycardia/creatine kinase (124). Clinical examination was essentially unremarkable: clear chest, no increase in venous pressure, normal range blood pressure, no pericardial rub, no chest discomfort. However, malodorous smell and incontinence of urine were noted.

Despite a five-day course of antibiotics treatment for a presumed urinary tract infection, the pyrexia persisted, and additional symptoms appeared; non-productive cough and external dyspnoea.

The chest X-ray after commencement of clozapine revealed striking changes from the pre-clozapine X-ray, widespread abnormal markings in both lungs, which were reticular and linear were shown. There were also extensive septal lines in the periphery of the lung and a fairly dense perihilar haze. The appearances were suggestive of an acute inflammatory process. A computerised tomography scan showed small bilateral pleural effusions with widespread non-specific interstitial shadowing, having the appearance of a drug-induced reaction. Clinically, an elevated venous pressure and a gallop rhythm were noted. There was no demonstrated 'wheeze' or 'stridor'. Despite the advanced radiological and examination findings, the patient appeared surprisingly well. A diagnosis of extrinsic allergic alveolitis was made and the clozapine was discontinued.