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LETTER

Epigenetics or ephemeral genetics?

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The paper by Kaati *et al*[1] claiming to show that a surfeit of food during a paternal grandfather's slow growth period could lead to an increased risk of death from diabetes continues to attract interest in this journal.[2] I believe, however, that the analysis of the data reported is inappropriate or at the very least inadequately described as regards a number of aspects and that, pending valid analysis or clarification, these epigenetic claims should be treated with caution.

The first point is that it seems highly probable that some of the 239 probands analysed had two or more grandparents in common, that is to say that some probands were siblings or first cousins of each other. The fact that sampling was performed by birth year 1890, 1905 or 1920 may reduce the number of consanguinities, in particular siblings, and of course the 50% sample will contribute further to this, but some discussion of this point is owed to the reader. If it is the case that some probands *are* cousins, then the observations cannot be treated as independent, but must be seen as repeated measures on the grandparent in question. In fact, a satisfactory model may require several stages of hierarchy. It is well known that treating correlated observations as independent leads to 'spurious precision' with artificially low standard errors and *P*-values and confidence intervals that are too narrow. A highly relevant analogous field to epigenetics is that of teratology. Here it is well understood that when toxicological experiments are carried out on pregnant rats, the resulting pups must be treated as repeated measures on the dams[3] and mixed models are needed.[4] Failure to analyse data in this way is to regard two cousins, both of whom died of diabetes and whose common paternal grandfather had a surfeit of food in his slow growth period as providing the same evidence as two unrelated probands dying of diabetes, each of whose *two* paternal grandparents had a surfeit of food in their slow growth period.

The second point is that where so many possible hypotheses are being investigated, it is inappropriate to concentrate only on those which after the fact turn out to have 'significant' results attached to them. If this is to be done, then some sort of adjustment for multiplicity ought to be applied, most simply, but not necessarily most appropriately, using a Bonferroni correction. If such adjustments are not performed, then the totality of the evidence has to be accepted and the fact that many specific individual null hypotheses investigated were not rejected calls for caution as regards accepting any *particular* variant of the epigenetic hypothesis. (see Senn, 1997, Chapter 10 for a discussion of these issues[5]).

Finally, in the multiple regression model used by Kaati *et al*[1] age at death has been included as a predictor variable. This is a conceptual error that tends in the opposite direction to the first two. Age at death is (at least partially) an outcome of the disease process. Diabetics may be expected to die younger than those who are healthy. Thus, age at death cannot naively be used as a predictor variable.

In short, while Kaati *et al*[1] have collected some interesting data, researchers should be extremely cautious, pending further clarification, in accepting their conclusion that 'these epidemiological findings draw attention to the transgenerational effects down the male line of nutrition-related circumstances during a period of childhood' (p. 688).

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Reply to Senn

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Stephen Senn's first point is a valid one and we are grateful for the opportunity to clarify the situation. The 2002