

Correspondence

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Short inter-pregnancy interval and schizophrenia: overestimating the risk

The short report by Gunawardana *et al*¹ succinctly argues that a short inter-pregnancy interval, a proxy for fetal undernutrition and stress, increases the offspring's risk of later schizophrenia. The authors hint at a causal relationship. This is compelling because it suggests that an affordable public health intervention via the promotion of dietary supplements in the postpartum period may later reduce schizophrenia prevalence.

Although the authors compare pre- and post-birth intervals and adjust for a number of confounders, their findings may still relate to bias and residual confounding. First, the timing of schizophrenia measurement may distort the prevalence and gender ratio of schizophrenia. This is important because a short inter-pregnancy interval is known to favour male offspring.² Looking at the cohort's median year of birth (1978) and the latest possible date of outcome measurement (2002), an individual's lifetime history of schizophrenia would be recorded at 24 years. As there is a significant gender variation in the age-specific incidence of schizophrenia,³ the median cohort age of 24 years is likely to bias the cohort towards male schizophrenia prevalence and overestimate the predictive validity of the short inter-pregnancy interval.

Second, the finding of no relationship between the post-birth inter-pregnancy interval and later schizophrenia does not discount residual confounders, including ethnicity and genetic factors, from contributing to the study's main findings. Genetic and familial factors, including ethnicity, are both associated with short inter-pregnancy intervals^{4,5} and schizophrenia.⁶ The current study did not mention adjusting for offspring ethnicity, although its design would make it possible. However, any epidemiological study would struggle to separate the prenatal effect of the inter-pregnancy interval from maternal–child genome sharing.

Epidemiological designs will only drive hypotheses so far in examining the causal relationship between prenatal micronutrient depletion and later psychopathology. That said, there would be scientific value in examining cohorts pre- and post-introduction of public health recommendations of periconceptional folic acid vitamin supplementation. In addition, further work analysing the correlates of prenatal nutrient depletion as additive risk factors could provide further evidence of a dose–response relationship. For example, are the risks of schizophrenia enhanced when there is a history of short pre-birth interval plus prior multiple births, concurrent breastfeeding or postnatal vitaminosis?

Introducing postnatal vitamin supplementation to reduce schizophrenia prevalence is an enticing idea; however, it would be important to use a variety of research designs to establish or exclude causality before implementing any change in public health policy.

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Authors' reply: We agree with Downs & Jonas that it is important to establish whether the association between inter-pregnancy interval and schizophrenia is indeed causal, and that residual confounding is a potential explanation for our findings.

Residual confounding is, of course, a potential explanation for any association in observational epidemiological studies, as we discuss in our paper.¹ However, we believe that one of the strengths of our study is that we compare the relationship between the pre-birth inter-pregnancy interval and risk of schizophrenia with that of the post-birth inter-pregnancy interval and risk of this disorder. If the association between pre-birth inter-pregnancy interval and risk of schizophrenia is due to confounding, we would expect to observe a similar relationship for the post-birth interval, but we did not find this in our study. Although it is possible that there are confounders that are associated with pre-birth, but not post-birth inter-pregnancy intervals, this seems rather unlikely for most potential confounders.

For example, Downs & Jonas suggest that one such possible confounder is ethnicity, whereby individuals born to families from specific ethnic groups may be more likely to be conceived following a shorter pre-birth inter-pregnancy interval, as well as to have an increased risk of schizophrenia. However, if this were true then we would expect to see the same (confounded) relationship between post-birth inter-pregnancy interval and risk of schizophrenia. Comparing results for pre-birth and post-birth intervals allows us to be slightly more confident (although by no means certain) that unmeasured confounders do not provide an adequate explanation for our findings, and that the increased risk of schizophrenia following a shorter pre-birth inter-pregnancy interval might be causal. What it is about a shorter pre-birth inter-pregnancy interval that leads to an increased risk of schizophrenia is, as yet, unknown,¹ although arguments that this acts as a proxy for fetal undernutrition or exposure to stress have received the greatest support in the literature to date.^{2–5}

Downs & Jonas also argue that short inter-pregnancy intervals favour male offspring and that, given the gender variation in age-specific incidence of schizophrenia, this could lead to an

overestimation of the effect of a shorter inter-pregnancy interval. However, if male gender was indeed on the causal pathway between inter-pregnancy interval and schizophrenia, this would not, of itself, lead to a biased estimate of association between inter-pregnancy interval and schizophrenia. Furthermore, if male gender was indeed on the causal pathway, then adjusting for gender should lead to an attenuation of the association between inter-pregnancy interval and schizophrenia; however, adjusting for gender made no difference to our results,¹ indicating that gender is unlikely to be an adequate explanation as a mechanism for the association with shorter inter-pregnancy interval.

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Care clusters and mental health Payment by Results

In their piece on mental health Payment by Results,¹ Macdonald & Elphick note ‘a lack of reassurance that costs per case within a cluster will be similar enough to support a viable tariff calculation’. This may underestimate the difficulties with the proposed new payment mechanism, which may have effects wider than disruption of nascent routine outcome measurement systems.

The UK has come relatively late to the process of payment reform for mental health services, but despite this it has followed an approach unlike that in other countries. The fundamental principle behind the care cluster approach seems to be the presumption that individuals with similar needs for care, as notionally defined by clusters of scores on the Health of the Nation Outcome Scales (HoNOS), will receive similar care and therefore incur similar costs. Importantly, costs themselves did not enter into the original process of defining care clusters.²

The approach pioneered by Fetter at Yale³ in developing the original Medicare prospective payment system in the 1980s was to combine consultation with clinicians and statistical analysis of clinical, administrative and cost data using variance reduction so that case-mix groupings are both expected to produce similar ‘clinical responses’ and also do in fact demonstrate acceptable homogeneity of costs. This approach was also followed by Australia and New Zealand,^{4,5} when they attempted to develop payment systems based on HoNOS. Achieving homogeneous costs within groups is crucial because it minimises the random risk to providers (the risk that appropriately incurred costs and therefore revenue differ randomly from those reimbursed). A typical cut-off for acceptable cost homogeneity is for each case-mix group to have a coefficient of variation of one or less (mean divided by standard deviation). It is also essential to make sure that factors relevant in resource use which may be more or less prevalent among different providers are also represented; otherwise there

may be an element of systematic risk, with certain providers being systematically underpaid and others systematically overpaid. Even when this more standard approach is followed, it may not be successful, especially in mental health, where cost variation is high. Infamously, the original Medicare prospective payment system was never implemented in specialist mental health units in the face of evidence that resource homogeneity was too low and that the system would systematically disadvantage those units, and has now been abandoned in favour of an across the board per diem payment system for psychiatric in-patients.⁶ Neither the Australian nor New Zealand systems were ever implemented.

In the light of the foregoing comments, it is perhaps not surprising that the Department of Health’s own pilot studies from 2006 demonstrate both that resource homogeneity of care clusters is unacceptably low, with only 1 of 13 clusters having a coefficient of variation of less than one, and also that far better homogeneity could have been achieved, especially for in-patients, had the standard variance-reduction approach been followed.⁷ At present, it seems to me that the lowest risk approach to reforming payment for mental health services is to adopt a basic system of activity-based funding, and use the data collected in this way, along with clinical and administrative data, as part of a slow and careful process of reform. Certainly, payment for mental health services in the UK is ripe for reform, as variations in resource use between providers are far wider than could be accounted for by any difference in case-mix.⁸ But this may not be the best way of approaching it.

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The key to doing routine mental health outcomes well¹ is to make them relevant, meaningful and available to practitioners, service users and managers. The Health of the Nation Outcome Scales (HoNOS) is now a front-runner for a general outcome measure since it is required for Payment by Results, a new contracting system for mental healthcare in the UK. Only one HoNOS rating is currently required in order to allocate patients to Payment by Results care clusters, so managers have little incentive to take the extra step and mandate more than one HoNOS rating to assess the effectiveness of interventions. The simplest way to introduce outcome measurement with HoNOS would be to mandate at least two ratings, one at the outset of an intervention and one