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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-pregancy 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.

1 Gunawardana L, Davey Smith G, Zammit S, Whitley E, Gunnell D, Lewis S, et al. Pre-conception inter-pregnancy interval and risk of schizophrenia. *Br J Psychiatry* 2011; **199**: 338–9.

2 Greenberg RA, White C. The sexes of consecutive sibs in human sibships. *Hum Biol* 1967; **39**: 374–404.

3 Thorup A, Waltoft BL, Pedersen CB, Mortensen PB, Nordentoft M. Young males have a higher risk of developing schizophrenia: a Danish register study. *Psychol Med* 2007; **37**: 479–84.

4 Rodgers JL, Kohler HP, Christensen K. Genetic variance in human fertility: biology, psychology, or both? In *The Biodemography of Human Reproduction and Fertility* (eds JL Rodgers, HP Kohler): 229–50. Springer, 2003.

5 Rawlings JS, Rawlings VB, Read JA. Prevalence of low birth weight and preterm delivery in relation to the interval between pregnancies among white and black women. *N Engl J Med* 1995; **332**: 69–74.

6 Fearon P, Kirkbride JB, Morgan C, Dazzan P, Morgan K, Lloyd T, et al. Incidence of schizophrenia and other psychoses in ethnic minority groups: results from the MRC AESOP Study. *Psychol Med* 2006. **36**(11): 1541–50.

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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