

Reply to Dr. Brown and Dr. Meyer

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Letter to the Editor

Reply to Dr. Brown and Dr. Meyer



With interest we read the comments by Drs. Brown and Meyer (Selten and Termorshuizen, 2017). We will not respond to all of the points they made, because the readers of Schizophrenia Research are competent enough to assess the evidence. They will certainly not need a power calculation to understand that the influenza hypothesis is not compatible with the observation that a pandemic with infection rates of 40–50% does not produce an even slightly increased risk. We gently remind Dr. Brown that he was a co-author of a paper that examined the effect of second-trimester exposure to the 1957 pandemic on the non-affective psychosis risk for Dutch citizens (Selten et al., 1999). The power of this study was large. Even if one assumes that the Relative Risk (RR) of non-affective psychosis for those exposed is only 1.3, the power to detect a significantly increased risk was 0.97 ($\alpha = 0.05$; one-tailed testing). It is self-evident that such data-sets would yield significant results for first-trimester exposure, given a high RR.

It is true, Brown et al. (2004) conducted a validity study to assess the validity of particular antibody titres to demonstrate a recent infection, but the number of cases was small ($N = 51$). The positive predictive value derived from this validity study (78%, not 100%) supports the idea that the serological studies by Brown et al. and Canetta et al. may have included some cases with non-recent infections. A neutral source states that the antibody titre should be 1:40, not 1:20 (Dowse et al., 2011).

The literature on maternal influenza and psychosis in offspring is a fine illustration of the points made by Ioannidis in his famous paper “Why most published research findings are false” (Ioannidis, 2005). The flexibility in designs, definitions, outcomes and analytical modes is almost infinite. Without any good reason the timing of exposure is claimed to be in the second trimester, the first trimester, the fourth or sixth month of gestation, or, with reference to bipolar disorder, the whole nine-month period. Such a flexibility greatly increases the risk of false-positive results.

The serological investigation (Canetta et al., 2014) that reported an association between maternal influenza and bipolar disorder with psychotic features in offspring was supported by a study that examined the prevalence of a clinical diagnosis of influenza among mothers of the

same cohort (Parboosing et al., 2013). However, we wonder whether Brown and colleagues also examined the prevalence of a clinical diagnosis of influenza among mothers of cases of schizophrenia. If they performed such a study, a publication of the pertinent results would be helpful.

Conflict of interest

The authors declare no conflict of interest.

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References

- Brown, A.S., Begg, M.D., Gravenstein, S., Schaefer, C.A., Wyatt, R.J., Bresnahan, M., et al., 2004. Serologic evidence of prenatal influenza in the etiology of influenza. *Arch. Gen. Psychiatry* 54, 322–328.
- Canetta, S.E., Bao, Y., Dawn, M., Ennis, F.A., Cruz, J., Terajima, M., et al., 2014. Serological documentation of maternal influenza exposure and bipolar disorder in adult offspring. *Am. J. Psychiatry* 171, 557–563.
- Dowse, G.K., Smith, D.W., Kelly, H., Barr, I., Laurie, K.L., Jones, A.R., et al., 2011. Incidence of pandemic (H1N1) (2009) influenza infection in children and pregnant women during the 2009 influenza season in Western Australia – a seroprevalence study. *Med. J. Aust.* 194, 68–72.
- Ioannidis, J.P., 2005. Why most published research findings are false. *PLoS Med.* 2 (8), e124 (Aug).
- Parboosing, R., Bao, Y., Shen, L., Schaefer, C.A., Brown, A.S., 2013. Gestational influenza and bipolar disorder in offspring. *JAMA Psychiat.* 70, 677–685.
- Selten, J.P., Termorshuizen, F., 2017. The serological evidence for maternal influenza as risk factor for psychosis in offspring is insufficient: critical review and meta-analysis. *Schizophr. Res.* (in press).
- Selten, J.P., Brown, A.S., Moons, K.G., Slaets, J.P., Susser, E.S., Kahn, R.S., 1999. Prenatal exposure to the 1957 influenza pandemic and non-affective psychosis in the Netherlands. *Schizophr. Res.* 38, 85–91.

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