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Following the publication of our article, we were contacted by SAS with suggestions for reducing the time needed to obtain Markov-Chain Monte-Carlo (MCMC) posterior samples in PROC GENMOD. Our paper was originally written using SAS 9.2. With SAS version 9.3 or higher, it is possible to specify the algorithm for sampling the posterior distribution. The default in 9.2 and 9.3 is ARMS, but faster sampling algorithms now available are the Gamerman method (SAMPLING=GAMERMAN), which is the default in 9.4, and the independent-Metropolis method (SAMPLING=IM).

Thus a faster run may be obtained by modifying the BAYES statement in our appendix as follows:

bayes nmc=100000 coeffprior=normal(input=prior3) stats(percent=2.5 50 97.5) seed=1234 diagnostic=all plots=all sampling=IM

Using SAS 9.3 on a computer with 6 Gb RAM, a 2.7 GHz processor and a 64-bit operating system running Windows 7, this modified code greatly reduced the MCMC run time in our example, from nearly 5 h to about 3.5 min.

The run time can be further reduced by using only the default diagnostics. The default set of diagnostics is DIAGNOSTICS=(AUTOCORR ESS GEWEKE). By specifying DIAGNOSTICS=ALL in the BAYES statement, GENMOD computes the Gelman-Rubin diagnostic, with three chains whose samples are not used in the posterior inference. When the model was run using the default settings, the run time reduced further to 1 min 50 s. However, we recommend that final runs for publication statistics include the Gelman-Rubin diagnostic by specifying DIAGNOSTICS=ALL, to reduce the risk of undiagnosed convergence failure.

Finally, we have noted a discrepancy between the sample syntax provided in the appendix of our paper and the supplementary files. In the appendix, the model specified DIAGNOSTICS=ALL whereas, in the actual .sas file, the syntax read DIAGNOSTICS=(AUTOCORR ESS). The run time of ‘more than 1 h’ reported on p. 312 of our article was obtained when only the AUTOCORR and ESS options were specified.

Paracetamol, oxidative stress, vitamin D and autism spectrum disorders

From John J Cannell

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Brandlstuen *et al.* recently documented the detrimental role that gestational paracetamol exposure has on childhood neurodevelopment, putatively due to oxidative stress.1 Although the authors did not use the words ‘autism spectrum disorder’ (ASD), clearly some of the adverse neurodevelopmental effects they demonstrated are consistent with ASD.

This is not the first time that paracetamol has been implicated in ASD. In an ecological analysis, Bauer and Kriebel found a strong correlation between use of paracetamol and prevalence of ASD.2 If paracetamol causes ASD, and if oxidative stress is the mechanism, then the antioxidant capability of the mother and child would be key to explaining why some exposed children develop ASD and some do not.

Activities of superoxide dismutase, glutathione reductase and glutathione peroxidase are all strongly associated with serum vitamin D levels.3 Asemi *et al.* found, in a randomized controlled trial of 48 pregnant women, that vitamin D supplementation increased total plasma antioxidant capacity (P-interaction = 0.002), and total glutathione concentrations (P-interaction = 0.02) compared with controls.4 Another randomized controlled trial of vitamin D3 found that
it increased human antioxidant capabilities. Thus, the fetuses of vitamin D-deficient mothers would be less able to bear the oxidative stress caused by gestational paracetamol exposure.

A recent review concluded that vitamin D deficiency may be a major risk factor for ASD, in part due to lack of the antioxidative properties of vitamin D. Three recent studies, using community controls, have found that vitamin D levels are significantly lower in children with ASD. Two of the studies (Mostafa et al. and Gong et al.) also found that ASD severity, as rated on standard ASD rating scales, is inversely correlated with vitamin D levels. Mostafa et al. found an R value of -.86 for the association of serum vitamin D with ASD severity on rating scales.

This model (oxidative stress triggering ASD in vitamin D-deficient pregnant women and young children) is one of the theories of ASD with significant support. Other insults that increase oxidative stress are implicated in ASD, such as infections, toxins, fever and inflammation. It may be that paracetamol exposure is one of several oxidative stressors that trigger ASD development in vitamin D-deficient pregnant women and young children.

Potential conflict of interest: J.J.C. is executive director of the non-profit Vitamin D Council and receives remuneration from Purity Products.

References

Authors’ Response: More research on paracetamol is required

From Ragnhild Eek Brandlistuen, Eivind Ystrom, Irena Nulman, Gideon Koren and Hedvig Nordeng

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In his letter to the editor, John Cannell of the Vitamin D Council proposes ideas on how paracetamol might be linked to autism spectrum disorder (ASD) in women with vitamin D deficiency. These are interesting thoughts that deserve attention. In the letter, Cannell proposes that the adverse neurodevelopmental symptoms observed in our study are consistent with ASD. However we would like to argue that the symptoms described in our paper could be equally relevant to other neurodevelopmental disorders such as attention deficit hyperactivity disorder or language disorders. It is correct that communication problems are a central feature of ASD, but not all children with communication problems have ASD. In fact most children with communication, behavioural or motor problems do not have ASD. Moreover a central feature of ASD is social problems. We did not find any association between paracetamol and sociability in our study. Studies involving clinical diagnoses are necessary to confirm or refute a possible connection between prenatal paracetamol exposure and ASD or other neurodevelopmental disorders. Such a future study would be possible to perform by linking the Norwegian Mother and Child Cohort study to an existing national patient registry by a personal identification number.

In our study we reported symptoms not previously reported in association with paracetamol exposure during pregnancy. It is...