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Invited Letter Rejoinder

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Lahti-Pulkkinen *et al.* respond to the letter to the editor: *Maternal depression and inflammation during pregnancy* by Fujitake and Chen

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First, we thank Fujitake and Chen (2019) for their interest in our research and the letter to the editor on our recent article *Maternal Depression and Inflammation during Pregnancy* published in *Psychological Medicine*, where we showed in the Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction (PREDO) – pregnancy cohort, that diagnosis of depression before pregnancy and depressive symptoms during pregnancy was associated with higher levels of inflammatory biomarkers hsCRP and glycoprotein acetyls across pregnancy among 379 women (Lahti-Pulkkinen et al., 2019).

In their letter, Fujitake and Chen (2019) discuss thoroughly our findings and the question whether low-grade inflammation has clinical significance in pregnancy for maternal and neonatal outcomes. We agree with the authors that assessing pregnancy, neonatal and child developmental outcomes is a key venue for this field of research. Importantly, we can provide preliminary answers to the important questions Fujitake and Chen posed.

Namely, in our study sample, higher hsCRP and glycoprotein acetyl levels were not only associated with early pregnancy overweight and obesity and depression, but also with pre-eclampsia, chronic hypertension and gestational diabetes in current pregnancy. These results have been described in the Results section of the article text and in the Supplementary Table S4 of our article (Lahti-Pulkkinen et al., 2019). Furthermore, previously unpublished analyses in our study sample showed that maternal higher mean hsCRP and glycoprotein levels across pregnancy were associated also with significantly higher maximum levels of systolic [Pearson $r(355) = 0.26$, $p < 0.001$; for hsCRP and $r(327) = 0.14$, $p = 0.01$ for glycoprotein] and diastolic [$r(355) = 0.31$, $p < 0.001$ and $r(327) = 0.20$, for hsCRP and glycoprotein acetyls, respectively] blood pressure during pregnancy.

Regarding the potential confounders for our study, mentioned by Fujitake and Chen (2019), we had data on maternal weight gain in pregnancy for 307 women. In our sample, weight gain in pregnancy was correlated negatively with mean hsCRP [$r(305) = -0.21$, $p < 0.001$] and glycoprotein acetyl levels [$r(280) = -0.25$, $p < 0.001$]. However, when controlling for early pregnancy overweight/obesity, weight gain in pregnancy was no longer associated with hsCRP [partial $r(304) = -0.05$, $p = 0.40$] or glycoprotein acetyl [partial $r(279) = -0.08$, $p = 0.21$] levels in our study sample. Hence, we did not include it as a covariate in our study.

Concerning neonatal outcomes, higher mean antenatal glycoprotein acetyls were associated with shorter gestation length [$r(346) = -0.12$, $p = 0.03$] in our study sample. Associations with hsCRP levels were non-significant but in the same direction [$r(377) = -0.08$, $p = 0.14$]. Maternal inflammation levels during pregnancy were not associated with infant birth weight adjusted for sex and gestational age [$r(377) = 0.01$, $p = 0.82$ and $r(346) = 0.05$, $p = 0.33$ for hsCRP and glycoprotein acetyls, respectively].

We believe the associations of maternal inflammation during pregnancy with obstetric and neonatal outcomes we report in this letter to the editor and in our article further emphasize the clinical relevance of these inflammatory biomarkers, which were used as indicators of chronic low-grade inflammation during pregnancy. However, as pointed out by Fujitake and Chen (2019), since in our study inflammatory measurements were taken across pregnancy, for many of these associations, the direction of the associations still remains to be elucidated.

In their letter, Fujitake and Chen (2019) also mention the importance of extending the analyses to other inflammatory biomarkers in pregnant women, including interleukin-6 and prostaglandin E2 and that inflammatory biomarkers could be measured from the cervical mucus or vaginal fluid. We agree that these are important points which should definitively be addressed in further studies.

Importantly, we are continuing our work in the longitudinal PREDO cohort. In the future, we will examine the longitudinal associations of maternal inflammation during pregnancy with child physical and mental health outcomes and with child emotional and cognitive development. Recently, we completed a follow-up of the children at ages 7–11 years, and we will

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continue following them up as they age and reach adolescence. Hence, we will be able to provide additional information on child development and health outcomes, and address the important knowledge gaps and questions raised in the letter by Fujitake and Chen (2019).

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