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RESEARCH LETTER

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Prenatal antibiotic use, caesarean delivery and offspring's food protein-induced enterocolitis syndrome: A National Birth Cohort (JECS)

To the Editor,

Food protein-induced enterocolitis syndrome (FPIES) is a non-immunoglobulin E (IgE) mediated gastrointestinal food hypersensitivity that manifests as vomiting, diarrhoea, leading to dehydration, hypovolemic shock and lethargy in the acute setting, or continuous diarrhoea and/or intermittent vomiting, leading to weight loss, failure to thrive in the chronic phase.[1] FPIES prevalence may have increased,[2] but risk factors for FPIES during the perinatal period have not been well documented yet. Katz et al.[3] found infant FPIES caused by cow's milk was more common with caesarean than vaginal delivery. They did not examine other triggers except cow's milk. Furthermore, other factors have not been reported. FPIES is a gastrointestinal disorder, so the disease is focused on the gastrointestinal organ. We hypothesized that gut modulating factors such as maternal lactic acid bacteria intake, yogurt intake, antibiotic use and caesarean delivery during the prenatal period might affect the consequent onset of infant FPIES after birth.

This general birth cohort was a national, multicentre, prospective study: the Japan Environment and Children's Study (JECS)[4] funded by the Ministry of the Environment, Japan. We enrolled a general population of 103,060 pregnancies and 51,239 pregnancies with participating fathers from January 2011 to March 2014. Eligibility criteria were as follows: (1) currently pregnant; (2) living in the Study Area for the foreseeable future; (3) expected delivery between 1 August 2011 and mid-2014; and (4) ability to understand the Japanese language. In total, 104,062 records/foetal records were enrolled in the JECS. Caregivers answered questionnaires regarding their child and family during pregnancy and children aged 1, 6 and 18 months. We extracted medical chart information related to the prenatal period. For maternal medication use during the prenatal period, we had an interview face to face during the pregnancy. The study Programme Office performed the data management. The present study used the fixed data set "jecs-ta-201901930," released in October 2019, including medical record transcriptions data, laboratory data and questionnaire data. The registry of the JECS is the University Hospital Medical Information Network (UMIN000030786). The JECS was conducted based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. The JECS protocol was released and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological studies and the Ethics Committees of all participating institutions (no. 100910001). We obtained written informed consent from all participants.

We assessed the cumulative prevalence of infant's FPIES episode, acute FPIES, and FPIES caregiver's report at 18 months answered by caregiver's questionnaires[5] as the outcome variables for this study. We evaluated maternal lactic acid bacteria intake, yogurt intake, antibiotic use, caesarean delivery during the prenatal period as the exposure variables. We used the validated Japanese version Food Frequency Questionnaire (FFQ)[6] during the second/third trimester (MT2) for maternal lactic acid bacteria intake and yogurt intake. For *Lactobacillus* intake during pregnancy and yogurt intake during pregnancy, the quartile points of each variable for frequency of intake were calculated for the entire population analysed, and the new variables were used, with 0 for intake categories below the first quartile (25%ile) point and 1 for intake categories above the first quartile point. Prenatal antibiotic use was identified from the maternal interview during pregnancy and medical record transcriptions. The medical record transcriptions defined delivery mode. Confounding factors were maternal allergic history, highest education, maternal age, sibling, study place, sex, child's atopic dermatitis (AD) diagnosis until 6 months of age, and birth weight via the questionnaire during pregnancy and medical record transcriptions.

The analysis populations were the children of singleton and full-term (37 weeks gestation or later and first baby in the JECS registered) births who participated in the JECS until the age of 1.5 years. To examine the associations of gut modulation factors with infant's FPIES outcomes, we applied logistic regression models for FPIES episode, acute FPIES episode and FPIES caregiver's report as the reference group. We estimated the unadjusted (univariable model) or adjusted (multivariable model) odds ratios (odds ratio: OR adjusted odd ratio: aOR, respectively) and their associated 95% confidence intervals (CI). We estimated aORs using multivariable logistic regression models to adjust all confounders. We also implemented the multiple imputations by a chained equation algorithm with 20 iterations (R package MICE, version 3.14.0.) to account for missing confounders and present the results using multiple imputation data. We attributed a *p*-value for the estimates in the tables for reference. This study was exploratory, and it aimed to assess the magnitude of the association between gut modulating factors and infant's FPIES. We focused on the magnitude of the odds ratio estimate

See Appendix for the members of the JECS.

