

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

SM, HT, AO, HK, and SI identified the significance, and wrote and edited the manuscript.

ORCID

Shigeki Matsubara  <http://orcid.org/0000-0003-4378-221X>

Shigeki Matsubara¹ 
Hironori Takahashi¹
Akihide Ohkuchi¹
Hideki Kumagai²
Shizukiyo Ishikawa³

¹Department of Obstetrics and Gynecology, Jichi Medical University, Shimotsuke, Japan

²Department of Pediatrics, Jichi Medical University, Shimotsuke, Japan

³Medical Education Center, Jichi Medical University, Shimotsuke, Japan
Email: matsushi@jichi.ac.jp

REFERENCES

1. Ogawa K, Tanaka S, Limin Y, et al. Beta-2 receptor agonist exposure in the uterus associated with subsequent risk of childhood asthma. *Pediatr Allergy Immunol.* 2017;28:746-753.
2. Rusconi F, Gagliardi L. Pregnancy complications and wheezing and asthma in childhood. *Am J Respir Crit Care Med.* 2017. <https://doi.org/10.1164/rccm.201704-0744pp>. [Epub ahead of print]
3. Neilson JP, West HM, Dowswell T. Betamimetics for inhibiting preterm labour. *Cochrane Database Syst Rev.* 2014;(2):CD004352.
4. Helmo FR, Alves EAR, Moreira RAA, et al. Intrauterine infection, immune system and premature birth. *J Matern Fetal Neonatal Med.* 2017. <https://doi.org/10.1080/14767058.2017.1311318>. [Epub ahead of print]
5. Challis JR, Hooper S. Birth: outcome of a positive cascade. *Baillieres Clin Endocrinol Metab.* 1989;3:781-793.
6. Elliott WJ, Powell LH. Diagonal earlobe creases and prognosis in patients with suspected coronary artery disease. *Am J Med.* 1996;100:205-211.
7. McNamara HC, Crowther CA, Brown J. Different treatment regimens of magnesium sulphate for tocolysis in women in preterm labour. *Cochrane Database Syst Rev.* 2015;(12):CD011200.
8. European Medicines Agency. Restrictions on use of short-acting beta-agonists in obstetric indications – CMDh endorses PRAC recommendations. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Short-acting_beta-agonists/human_referral_prac_000013.jsp&mid=WC0b01ac05805c516f (announced at 25 of November 2013). Accessed December 16, 2017.

DOI: 10.1111/pai.12873

Reply to Matsubara et al

To the Editor,

This letter is in response to the letter to the editor by Matsubara et al,¹ arguing whether beta-2 receptor agonist (B2RA) is a real culprit. Matsubara et al¹ brought up that the association between intrauterine exposure to B2RA and the later occurrence of childhood asthma at 2 years of age, which was suggested by our recent article, may be confounded by underlying inflammatory/pro-inflammatory intrauterine condition or pre-existing stress with fetus being “destined” to be born preterm.

Matsubara et al argued that underlying inflammatory/pro-inflammatory intrauterine condition may be a culprit of asthma. We basically agree with the concept and the possibility of their speculation. They stated that patients with preterm labor are more likely to show intrauterine infection than their counterparts and preterm delivery is a strong risk factor for childhood asthma. Such inflammatory condition seems to be reflected in gestational age at birth, as inflammatory intrauterine condition is one of the primary causes of preterm birth.^{3,4} This means gestational age should be treated as a proxy variable of underlying inflammatory/pro-inflammatory intrauterine condition among baby when we analyze a multivariate model to explore the risk of asthma onset. We suppose not only gestational age but also cesarean delivery and prenatal antibiotic exposure are variables that might reflect underlying inflammatory/pro-inflammatory

intrauterine condition. When we report an epidemiological paper, we must convert any concept such as inflammation into variables to be analyzed statistically. Therefore, we carried out multiple logistic regression analysis by including gestational age, cesarean delivery, and prenatal antibiotic exposure as variables of the confounding factors in this multivariate model. If they insist on another model different from that we presented, they should show a different variable except gestational age, cesarean delivery, and prenatal antibiotic exposure to represent the underlying inflammatory/pro-inflammatory intrauterine condition. If they think the underlying inflammatory/pro-inflammatory intrauterine condition among baby should be added as a different factor in addition to the variables we used, the added new variable must be verified not causing the multicollinearity with the variables we used.

We never deny underlying inflammatory/pro-inflammatory intrauterine condition may be one of the culprits to cause offspring's asthma; however, only such an abstract concept cannot be analyzed without calculable variables. Hence, we analyzed our data using multivariate analysis including the variables that represent the concept of underlying inflammatory/pro-inflammatory intrauterine condition. As a result of multivariate analysis, we have found B2RA was one of the significant risk factors to cause childhood asthma.

Another factor they proposed to add as a risk factor for childhood asthma is babies' tendency/constitution to be "born preterm" although they understand such tendency has not yet been determined and its adjustment is difficult. Nevertheless, they claimed this should be stated as an inevitable limitation of this retrospective study. As a solution, they suggested comparison between B2RA and magnesium may be meaningful. First, we must clarify their misrecognition of the study design. This study is not a retrospective study, but a typical prospective study such as birth cohort study which can show chronological-causal relationship. Second, if babies' tendency/constitution to be "born preterm" is a true risk factor and B2RA is a confounding factor, magnesium must have been also detected as a risk factor for childhood asthma as with B2RA. However, there has been neither paper nor conference proceeding which showed magnesium might be a risk factor for asthma. Third, our original study question, "whether B2RA exposure in utero is a risk of subsequent asthma," was arisen based upon robust evidence for significant effect of chronic single long-acting B2RA use on further severe exacerbation in both childhood asthma and adulthood asthma.^{5,6} Thus, the results delivered from this study suggest the causal relationship rather than confounding effect.

Both Matsubara et al and we agree with the following remark "Long term administration of B2RA as a tocolytic agent should not be recommended"; however, they did not agree with stating B2RA as a risk factor for childhood asthma and proposed maternal and fetal/neonatal inflammatory/pro-inflammatory conditions and/or a tendency to be born preterm as true risk factors. As described above, we have already incorporated maternal and fetal/neonatal inflammatory/pro-inflammatory conditions as variables of risk factors for asthma confounded to the variable of B2RA. Furthermore, magnesium has not been reported as a risk factor for asthma. There is no logical or rational ground to deny our results by their argument.

ORCID

Kohei Ogawa  <http://orcid.org/0000-0003-0997-2845>

Limin Yang  <http://orcid.org/0000-0002-3936-6371>

Naoko Arata  <http://orcid.org/0000-0003-2667-7653>

Kiwako Yamamoto-Hanada  <http://orcid.org/0000-0003-1288-9620>

Yukihiro Ohya  <http://orcid.org/0000-0002-1560-3942>

Kohei Ogawa^{1,2} 

Satomi Tanaka¹

Limin Yang³ 

Naoko Arata¹ 

Haruhiko Sago^{1,2}

Kiwako Yamamoto-Hanada³ 

Masami Narita³

Yukihiro Ohya³ 

¹Center of Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, Tokyo, Japan

²Collaborative Departments of Advanced Pediatric Medicine, Graduate School of Medicine, Tohoku University, Sendai, Japan

³Division of Allergy, Department of Medical Subspecialties, National Center for Child Health and Development, Tokyo, Japan

REFERENCES

1. Matsubara S, Takahashi H, Ohkuchi A, et al. Association between intrauterine beta-2-receptor-agonist (ritodrine) exposure and childhood asthma: is ritodrine a real culprit? *Pediatr Allergy Immunol*. 2018; <https://doi.org/10.1111/pai.12864>
2. Ogawa K, Tanaka S, Limin Y, et al. Beta-2 receptor agonist exposure in the uterus associated with subsequent risk of childhood asthma. *Pediatr Allergy Immunol* 2017;28:746-753.
3. Goncalves LF, Chaiworapongsa T, Romero R. Intrauterine infection and prematurity. *Ment Retard Dev Disabil Res Rev*. 2002;8:3-13.
4. Yoon BH, Romero R, Moon JB, et al. Clinical significance of intra-amniotic inflammation in patients with preterm labor and intact membranes. *Am J Obstet Gynecol*. 2001;185:1130-1136.
5. McMahon AW, Levenson MS, McEvoy BW, Mosholder AD, Murphy D. Age and risks of FDA-approved long-acting beta(2)-adrenergic receptor agonists. *Pediatrics*. 2011;128:e1147-e1154.
6. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*. 2006;129:15-26.