Association between maternal ritodrine hydrochloride administration during pregnancy and childhood wheezing up to three years of age: The Japan Environment and Children's Study

CONFLICT OF INTEREST

FUNDING

14 **Abstract**

15 **Background:** The effects of maternal ritodrine hydrochloride administration (MRA)

16 during pregnancy on fetuses and offspring are not entirely clear. The present study

17 aimed to evaluate the association between MRA and childhood wheezing using data

18 from a nationwide Japanese birth cohort study.

19 **Methods:** This study retrospectively analyzed data from the Japan Environment and

20 Children's Study, a nationwide birth cohort study, conducted between 2011 and 2014.

21 Data of women with singleton births after 22 weeks of gestation were analyzed. The

22 participants were divided according to MRA status. Considering childhood factors

23 affecting the incidence of wheezing, a logistic regression model was used to calculate

24 adjusted odds ratios for "wheezing ever," diagnosis of asthma in the last 12 months, and

25 "asthma ever" in women with MRA, with women who did not receive MRA as the

26 reference. Participants were stratified by term births, and adjusted odds ratios for

27 outcomes were calculated using a logistic regression model.

28 **Results:** A total of 68,123 participants were analyzed. The adjusted odds ratio for

29 wheezing ever was 1.17 (95% confidence interval, 1.12–1.22). The adjusted odds ratios

30 for the other outcomes did not significantly increase after adjusting for childhood

31 factors. The same tendency was confirmed after excluding women with preterm births.

3

32 **Conclusion:** MRA was associated with an increased incidence of childhood wheezing

33 up to three years, irrespective of term births or preterm births. It is important that

34 perinatal physicians consider both the adverse maternal side effects of MRA and its

35 potential effects on the offspring's childhood.

36

37 **KEYWORDS**

38 birth cohort study, childhood wheezing, childhood asthma, preterm birth, ritodrine

39 hydrochloride

40

INTRODUCTION

Ritodrine hydrochloride is used as a beta-sympathomimetic agent for controlling unfavorable uterine contractions. It predominantly interacts with beta-2 receptors in the uterus, resulting in the suppression of uterine contractions.[1] It has been used to treat preterm labor (PTL), achieving a lower rate of preterm births (PTB) and lower incidence of neonatal and childhood PTB-related issues, such as respiratory distress syndrome and intraventricular hemorrhage.[1-4] Most Japanese obstetricians select ritodrine hydrochloride as the first drug for tocolysis in patients with PTL,[5] as per obstetric practice guidelines in Japan.[6,7] However, maternal ritodrine hydrochloride administration (MRA) is reported to be effective within 48 hours of use and long-term MRA is reported to be harmful due to its adverse maternal side effects, such as pulmonary edema, granulocytopenia, and rhabdomyolysis.[5,8-10]

Additionally, fetal tachycardia is a side effect of MRA. However, the clinical significance of this change[11] and the other potential effects of MRA on offspring remain unclear. Although childhood asthma is also an indicated side effect of MRA,[12] the effects of childhood factors that have significant effects on the incidence of childhood asthma have not been evaluated in this relationship.[13-15] Because asthma is common during childhood, parents are concerned about the association between prenatal and

59 postnatal factors and the incidence of childhood asthma; the association between MRA

60 and childhood asthma should be clarified, accounting for childhood factors.

61   Objective diagnosis of childhood asthma is often challenging because its clinical

62 presentation is heterogeneous.[16] Therefore, the present study evaluated the association

63 between MRA and childhood wheezing and the diagnosis of childhood asthma using a

64 nationwide Japanese birth cohort dataset, accounting for childhood factors.

65

66 **METHODS**

67 **Study design**

68 The present study retrospectively analyzed data from the Japan Environment and

69 Children's Study (JECS), a nationwide, government-funded, prospective birth cohort

70 study initiated in January 2011 that investigated the effects of environmental factors on

71 children's health.[17,18] Briefly, the JECS is directly funded by Ministry of the

72 Environment, Japan and involves collaboration between the Programme Office (i.e.,

73 National Institute for Environmental Studies), Medical Support Centre (i.e., National

74 Center for Child Health and Development), and 15 Regional Centres (namely,

75 Hokkaido, Miyagi, Fukushima, Chiba, Kanagawa, Koshin, Toyama, Aichi, Kyoto,

76 Osaka, Hyogo, Tottori, Kochi, Fukuoka, and South Kyushu/Okinawa).[18] Expectant

77 mothers who resided in the study areas at the time of recruitment and were expected to

78 continually reside in Japan in the foreseeable future; had an expected delivery date from

79 August 1, 2011 until mid-2014; and were capable of participating in the study without

80 difficulty (i.e., adequate Japanese language comprehension to complete the self-

81 administered questionnaire) were considered eligible for inclusion in the JECS.

82   The following recruitment strategies were used: recruitment at the first prenatal

83 examination in cooperating healthcare providers and recruitment in local government

84 offices issuing pregnancy journals called Maternal and Child Health Handbooks, which

85 are provided to all expectant mothers in Japan before they receive municipal services

86 for pregnancy, delivery, and childcare. In this study, pregnant women were contacted

87 through cooperating healthcare providers and/or local government offices issuing the

88 handbooks, and those who were willing to participate were subsequently registered.

89 Women completed the self-administered questionnaires during their first and second or

90 third trimester and provided information on demographic factors, medical/obstetric

91 history, physical and mental health, lifestyle, occupation, environmental exposure at

92 home and in the workplace, housing conditions, and socioeconomic status.[18]

93

94 **Data collection**

95 The current analysis used the 2019 dataset (dataset: jecs-ta-20190930). Specifically, the

18

96 following types of data were utilized: M-T1, from a self-reported questionnaire

97 completed during the first trimester (first questionnaire), including questions about

98 maternal medical background; M-T2, from a self-reported questionnaire completed

99 during the second or third trimester (second questionnaire), including information on

100 partner lifestyle and socioeconomic status; Dr-T1 and Dr-0m, from medical record

101 transcripts that were provided by each participant's institution, including information on

102 obstetric outcomes (e.g., gestational age, birth weight) collected during the first, second,

103 and third trimesters. Medical record transcriptions were performed by physicians,

104 midwives/nurses, and/or research coordinators; C1Y, C2Y, and C3Y were obtained from

105 self-reported questionnaires collected at one, two, or three years after birth, including

106 descriptions about the infants' allergic diseases and information on childhood

107 environment, including smoking environment, milk feeding, and pet ownership.

108 Participants with singleton pregnancies after 22 weeks were included in analysis.

109 Women with missing information were excluded from analysis. There were no

110 significant differences in characteristics between those included and excluded (data not

111 shown).

112

113 **Exposure variables**

114 Data on MRA were collected from medical record transcripts. Participants who received

115 MRA intravenously or orally were defined as participants who received MRA,

116 regardless of dosage, duration, and purpose of ritodrine hydrochloride use; in the JECS,

117 there was no information regarding the dosage, duration, and purpose of ritodrine

118 hydrochloride use.

119

120 **Obstetric outcomes and confounding factors**

121 Outcomes included three variables, namely "wheezing ever," diagnosis of asthma in the

122 last 12 months, and "asthma ever." "Wheezing ever" and "asthma ever" were based on

123 the International Study of Asthma and Allergies in Childhood (ISAAC)

124 questionnaire.[12,19-21] Information regarding "wheezing ever," diagnosis of asthma in the

125 last 12 months, and "asthma ever" were obtained from the questions, "Has your child

126 ever had wheezing or whistling in the chest at any time in the past," "Does your child

127 have immune system disorder diagnosed after age 2: Asthma," and "Has your child

128 ever had asthma," respectively.

129 The following items were analyzed as potential confounding factors during

130 pregnancy: maternal age, maternal body mass index (BMI) before pregnancy, parity,

131 maternal smoking status, maternal educational status, annual household income, mode

132 of delivery, PTB before 37 weeks, low-birth-weight infants (<2500 g) (gestational age

133 and neonatal birth weight as continuous values were also used as confounding factors

134 instead of PTB and low-birth-weight infants, respectively), maternal asthma, and

135 intrauterine infection (II). The following items were analyzed as potential confounding

136 factors during childhood: smoking environment, milk feeding at one-year-old, male

137 newborn, childhood eczema, childhood rhinitis, pet ownership, and childhood

138 respiratory syncytial virus infection or lower respiratory infection (childhood viral

139 infections). These confounding factors were selected based on clinical importance.[13-15,22-

140 25]

141   Maternal participants were divided into three age groups: <20, 20–34, and ≥35

142 years.[26,27] Maternal BMI before pregnancy was categorized as <18.5, 18.5–24.9, and

143 ≥25.0 kg/m^2.[28] Parity was categorized as nulliparous and multiparous. Maternal

144 participants provided information about their smoking status by choosing one of the

145 following: "Currently smoking," "Never," "Previously did, but quit before realizing

146 current pregnancy," and "Previously did, but quit after realizing current pregnancy." The

147 smoking category included those who chose "Currently smoking," whereas the non-

148 smoking category consisted of the remainder. Based on the number of years of

149 education, maternal educational status was categorized into junior high school, <10

150   years; high school, 10–12 years; technical/vocational college or university, 13–16 years;

151   and graduate school, ≥17 years. Annual household income was categorized into

152   <2,000,000, 2,000,000–5,999,999, 6,000,000–9,999,999, and ≥10,000,000 JPY. Mode

153   of delivery was divided into vaginal deliveries and cesarean section based on medical

154   record transcripts. PTB was defined as childbirth before 37 weeks and low-birth-weight

155   was weight <2500 g at childbirth. Maternal asthma was diagnosed from the information

156   collected in the first trimester questionnaire. Paternal asthma was not considered owing

157   to a large amount of missing data. II data was derived from medical record transcripts.

158   II was clinically diagnosed by physicians at each institution. There were no unified

159   criteria for II in the JECS; however, most Japanese obstetricians refer to the criteria

160   recommended in the guidelines for obstetrical practice in Japan (i.e., maternal fever and

161   one of the following: maternal tachycardia beyond 100 beats/min, uterine tenderness,

162   abnormal discharge, or elevated maternal white blood cell counts beyond 15,000/μL).[29]

163   Histological findings of chorioamnionitis were not required for the diagnosis of II in the

164   JECS. Smoking environment around the children, milk feeding, male newborn,

165   childhood eczema, childhood rhinitis, pet ownership, and childhood viral infections

166   were defined according to the questionnaire; data on milk feeding were collected

167   through the questionnaire administered at one year after childbirth; data on childhood

168 viral infections were collected through the questionnaire administered at two years after

169 childbirth; and other data were collected using the questionnaire administered at three

170 years after childbirth.

171

172 **Statistical analysis**

173 Participants' characteristics were summarized based on MRA status. The chi-square test

174 was used to compare the characteristics (expressed as categorical variables) between the

175 groups. A multiple logistic regression model was used to calculate the crude odds ratios

176 (ORs), adjusted ORs (aORs), and 95% confidence intervals (CIs) for wheezing ever,

177 diagnosis of asthma in the last 12 months, and asthma ever in women with MRA with

178 women who did not receive MRA as the reference. In Model 1, ORs were adjusted for

179 potential confounding factors during pregnancy. In Model 2, ORs were adjusted for

180 potential confounding factors during childhood, except for childhood viral infection, in

181 addition to those during pregnancy. In Model 3, ORs were adjusted for potential

182 confounding factors during childhood in addition to those during pregnancy.

183 Additionally, participants, excluding those with PTB, were analyzed using a multiple

184 logistic regression model with women who did not receive MRA as the reference and

185 with adjustment for confounding factors in Models 1, 2, and 3; here, PTB was removed

186   from the confounding factors.

187   Statistical analysis was performed using SPSS version 26 (IBM Corp., Armonk,

188   NY, USA). *P* < 0.05 was considered statistically significant.

189

190   **RESULTS**

191   There were 104,062 fetal records of women who delivered from 2011 to 2014, and

192   68,123 participants met the study inclusion criteria (Figure 1); 18,141 (26.6%)

193   participants received MRA (MRA group), whereas the remaining 49,982 (73.4%)

194   participants comprised the reference group. After excluding 2,989 participants with

195   PTB, 16,560 (25.4%) participants received MRA, and the remaining 48,574 (74.6%)

196   participants comprised the reference group.

197   Table 1 summarizes the demographic and clinical characteristics of participants

198   based on MRA status. The difference of confounding factors between the groups was

199   significant, except for the distribution of maternal age and the ratio of parity and

200   childhood eczema. The ratio of all outcome measures indicating childhood asthma was

201   significantly higher in the MRA group than in the reference group.

202   Table 2 presents the cORs and aORs for wheezing ever, diagnosis of asthma in the

203   last 12 months, and asthma ever. The cORs and aORs for all outcomes in Models 1 and

204   2 significantly increased compared to those in the reference group. Although aORs for

205 wheezing ever in Model 3 significantly increased, aORs for the other outcomes did not

206 significantly increase. Analysis performed using gestational age of delivery and birth

207 weight as confounding factors rather than PTB and low birth weight, respectively,

208 revealed a similar tendency (data not shown).

209   Table 3 presents the cORs and aORs for wheezing ever, diagnosis of asthma in the

210 last 12 months, and asthma ever in participants without PTB. The cORs and aORs for

211 all outcomes in Models 1 and 2 significantly increased compared to the reference group.

212 Although aORs for wheezing ever in Model 3 significantly increased in Model 3, aORs

213 for the other outcomes did not significantly increase. Analysis performed using

214 gestational age of delivery and birth weight as confounding factors rather than PTB and

215 low birth weight, respectively, revealed a similar tendency (data not shown).

216

217 **DISCUSSION**

218 In summary, MRA was associated with an increased incidence of childhood wheezing

219 up to three years of age even considering childhood factors, although there was only a

220 slight increase in the aOR. In a recent study, there was a significant association between

221 MRA and childhood asthma considering only confounding factors during pregnancy.[12]

222 This previous study concluded that exposure to ritodrine hydrochloride *in utero* was a

223 risk factor for childhood asthma, with a dose-dependent association. In contrast, our

224 study is considered the confounding factors with the childhood factors affecting the

225 incidence of wheezing because childhood factors are strong determinants of the

226 incidence of childhood wheezing.[13-15] Immune responses to airway exposures including

227 tobacco smoke, allergens, and viruses can stimulate prolonged pathogenic inflammation

228 and aberrant repair of injured pulmonary tissues. Although MRA seems to affect

229 childhood condition during pregnancy or a short period after MRA due to its half-life,

230 we revealed the significant association between MRA and childhood wheezing while

231 considering childhood factors in a relatively large sample.

232   As another strength, the present study analyzed both total participants with term

233 births and PTB and stratified participants with term births. The previous study excluded

234 participants with PTB before 34 weeks and did not perform stratification.[12] Since PTB

235 was independently positively associated with childhood asthma,[22] the stratified analysis

236 strengthened the association between MRA and incidence of childhood wheezing,

237 regardless of gestational age of birth. The reason PTB increased the likelihood of

238 childhood wheezing is unclear; however, long-term bronchopulmonary dysplasia may

239 increase impedance and resistance of the small airways.[30,31] Regarding term births in

240 which gestational age was forcefully prolonged by MRA, infants from mothers who

241   received long-term MRA might have suffered from "excessive" uterine contractions that

242   were not completely controlled by MRA; this may result in fetal stress and influence the

243   secretion of fetal pituitary adrenocorticotropic hormone, potentially leading to future

244   asthma development in the offspring.[32]

245   Childhood asthma is a heterogeneous disease characterized by chronic airway

246   inflammation and a history of respiratory symptoms due to restricted expiratory

247   airflow.[33] The association of MRA with an increased incidence of childhood wheezing

248   remains unclear; the underlying mechanism regarding the MRA-associated childhood

249   wheezing may be associated with pathological impairment in the trachea of children,

250   hyper-responsiveness, and beta-receptor desensitization.[34-36] As maternal inflammation

251   increases the risk of childhood asthma via maternal type-2 cytokines in maternal asthma

252   cases,[37] II, which frequently coexists in mothers with PTL, may affect the incidence of

253   childhood wheezing via changing the maternal and children's inflammatory condition.[38]

254   Further studies investigating the biological effects of MRA on fetal trachea or fetal

255   inflammatory condition are necessary to clarify the mechanism. Since JECS is a

256   prospective birth cohort study, future research may clarify the effect of MRA on older

257   children's respiratory health, leading to more reliable results.

258   The present study has several limitations. First, diagnosis of childhood asthma is

259 often unsatisfactory;[16] the diagnosis of asthma in the last 12 months and ''asthma ever''

260 using questionnaires may be less accurate than ''wheezing ever'' because of the

261 ambiguities regarding the classification and diagnosis of childhood asthma. Although

262 the information regarding ''wheezing ever'' and ''asthma ever'' are based on the ISAAC

263 questionnaire, results should be interpreted carefully. Second, this study did not account

264 for MRA details. The dosage, duration, and purpose of MRA use were not included in

265 the dataset. Specifically, MRA could not be divided based on the method of

266 administration (intravenous or oral administration). Since a dose-dependent effect of

267 MRA on childhood asthma was reported,[12] the dosage and duration of MRA may

268 significantly impact the grade of childhood effects. This was a retrospective

269 observational study, we could not clarify a cause-and-effect relationship. Further studies

270 examining the detailed effects of MRA on childhood asthma with stratified analysis of

271 the dosage and duration of MRA are necessary. Third, the present study did not include

272 data on PTL severity, such as cervical dilatation, frequency of uterine contractions, fetal

273 fibronectin, or II severity, because these data were lacking. Although PTB was

274 considered a confounding factor in this study and stratified analysis was performed,

275 further studies clarifying the association between PTL severity and incidence of

276 childhood asthma are required. Finally, data on daily maternal use of drugs such as anti-

277   asthmatic medications, antioxidative supplements, and antipyretic analgesics were not

278   included. Because these drugs may influence the incidence of childhood wheezing,

279   further studies including these clinical factors may strengthen our results.

280   In conclusion, MRA was associated with an increased incidence of childhood

281   wheezing, regardless of term births or PTB. It is important that perinatal physicians

282   consider both the adverse maternal side effects of MRA and its potential effects on the

283   offspring's childhood, especially for long-term MRA use.

284

52

ACKNOWLEDGMENTS

ETHICAL APPROVAL

303 The JECS was conducted according to the Declaration of Helsinki and local regulations.

304 The JECS protocol was reviewed and approved by the Ministry of the Environment's

305 Institutional Review Board on Epidemiological Studies (100910001) and by the ethics

306 committees of all participating institutions. All participants provided written informed

307 consent.

308

309 **AUTHOR CONTRIBUTIONS**

310 All authors approved the final manuscript. T.M. initiated the concept and designed the

311 study. T.M., H.K., S.Y., T.F., A.Y., H.M., K.H., H.N., and K.F. provided advice on the

312 study design. K.S., A.S., and Y.O. collected the data. T.M. analyzed the data and wrote

313 the manuscript. M.H., S.Y., K.H., K.S., A.S., Y.O., H.N., K.F., and the JECS Group

314 reviewed the manuscript and provided critical advice.

315

316 **KEY MESSAGE**

317 The effects of maternal ritodrine hydrochloride administration during pregnancy on

318 fetuses and offspring are not entirely clear. The present study revealed maternal

319 ritodrine administration was associated with an increased incidence of childhood

320 wheezing up to three years. It is important that perinatal physicians consider both the

321 adverse maternal side effects of MRA and its potential effects on the offspring's

322 childhood.

58

323

REFERENCES

1. Barden TP, Peter JB, Merkatz IR. Ritodrine hydrochloride: a betamimetic agent for use in preterm labor. I. pharmacology, clinical history, administration, side effects, and safety. Obstet Gynecol 1980;56:1-6.

2. Kerem E, Dollberg S, Paz I, et al. Prenatal ritodrine administration and the incidence of respiratory distress syndrome in premature infants. J Perinatol 1997;17:101-106.

3. Weintraub Z, Solovechick M, Reichman B, et al. Effect of maternal tocolysis on the incidence of severe periventricular/intraventricular haemorrhage in very low birthweight infants. Arch Dis Child Fetal Neonatal Ed 2001;85:F13-17.

4. Takagi K, Satoh T, Multicentre Premature Labour Study Group. Is long-term tocolysis effective for threatened premature labour? J Int Med Res 2009;37:227-239.

5. Shigemi D, Aso S, Yasunaga H. Inappropriate use of ritodrine hydrochloride for threatened preterm birth in Japan: a retrospective cohort study using a national inpatient database. BMC Pregnancy Childbirth 2019;19:204.

6. Minakami H, Maeda T, Fujii T, et al. Guidelines for obstetrical practice in Japan: Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG) 2014 edition. J Obstet Gynaecol Res 2014;40:1469-1499.

342   7. Kawaguchi R, Matsumoto K, Akira S, et al. Guidelines for obstetrical practice in

343   Japan: Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of

344   Obstetricians and Gynecologists (JAOG) 2017 edition. J Obstet Gynaecol Res

345   2019;45:766-786.

346   8. American College of Obstetricians and Gynecologists' Committee on Practice

347   Bulletins—Obstetrics. Practice Bulletin No. 171: Management of Preterm Labor. Obstet

348   Gynecol 2016;128:e155-164.

349   9. Neilson JP, West HM, Dowswell T. Betamimetics for inhibiting preterm labour.

350   Cochrane Database Syst Rev 2014;5:CD004352.

351   10. Murata T, Kyozuka H, Shiraiwa A, et al. Maternal pulmonary edema after 46 h of

352   ritodrine hydrochloride administration: a case report. Case Rep Womens Health

353   2020;25:e00173.

354   11. Lamont CD, Jørgensen JS, Lamont RF. The safety of tocolytics used for the

355   inhibition of preterm labour. Expert Opin Drug Saf 2016;15:1163-1173.

356   12. Ogawa K, Tanaka S, Limin Y, et al. Beta-2 receptor agonist exposure in the uterus

357   associated with subsequent risk of childhood asthma. Pediatr Allergy Immunol

358   2017;28:746-753.

359   13. Yu B, Dai L, Chen J, et al. Prenatal and neonatal factors involved in the

360   development of childhood allergic diseases in Guangzhou primary and middle school

361   students. BMC Pediatr 2019;19:479.

362   14. Furuhata M, Otsuka Y, Kaneita Y, et al. Factors associated with the development of

363   childhood asthma in Japan: a nationwide longitudinal study. Matern Child Health J

364   2020;24:911-922.

365   15. Owora AH, Zhang Y. Childhood wheeze trajectory-specific risk factors: a systematic

366   review and meta-analysis. Pediatr Allergy Immunol 2020:e13313.

367   https://doi.org/10.1111/pai.13313.

368   16. Kothalawala DM, Kadalayil L, Weiss VBN, et al. Prediction models for childhood

369   asthma: a systematic review. Pediatr Allergy Immunol 2020;31:616-627.

370   17. Kawamoto T, Nitta H, Murata K, et al. Rationale and study design of the Japan

371   Environment and Children's Study (JECS). BMC Public Health 2014;14:25.

372   18. Michikawa T, Nitta H, Nakayama SF, et al. Baseline profile of participants in the

373   Japan Environment and Children's Study (JECS). J Epidemiol 2018;28:99-104.

374   19. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies

375   in Childhood (ISAAC): rationale and methods. Eur Respir J 1995;8:483-491.

376 20. Weiland SK, Björkstén B, Brunekreef B, et al. Phase II of the International Study of

377 Asthma and Allergies in Childhood (ISAAC II): rationale and methods. Eur Respir J

378 2004;24:406-412.

379 21. Ellwood P, Asher MI, Beasley R, Clayton TO, Stewart AW, and the ISAAC Steering

380 Committee. The International Study of Asthma and Allergies in Childhood (ISAAC):

381 Phase Three rationale and methods. Int J Tuberc Lung Dis 2005;9:10-16.

382 22. Takata N, Tanaka K, Nagata C, Arakawa M, Miyake Y. Preterm birth is associated

383 with higher prevalence of wheeze and asthma in a selected population of Japanese

384 children aged three years. Allergol Immunopathol (Madr) 2019;47:425-430.

385 23. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis

386 of the association between Caesarean section and childhood asthma. Clin Exp Allergy

387 2008;38:629-633.

388 24. Güngör D, Nadaud P, LaPergola CC, et al. Infant milk-feeding practices and food

389 allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span: a

390 systematic review. Am J Clin Nutr 2019;109:772S-799S.

391 25. Martinez FD. Viral infections and the development of asthma. Am J Respir Crit

392 Care Med 1995;151:1644-1648.

73

393   26. Kyozuka H, Fujimori K, Hosoya M, et al. The effect of maternal age at the first

394   childbirth on gestational age and birth weight: the Japan Environment and Children's

395   Study (JECS). J Epidemiol 2019;29:187-191.

396   27. Kyozuka H, Fujimori K, Hosoya M, et al. The Japan Environment and Children's

397   Study (JECS) in Fukushima Prefecture: pregnancy outcome after the Great East Japan

398   Earthquake. Tohoku J Exp Med 2018;246:27-33.

399   28. Murata T, Kyozuka H, Yamaguchi A, et al. Maternal pre-pregnancy body mass index

400   and foetal acidosis in vaginal and caesarean deliveries: The Japan Environment and

401   Children's Study. Sci Rep 2021;11:4350.

402   29. Lencki SG, Maciulla MB, Eglinton GS. Maternal and umbilical cord serum

403   interleukin levels in preterm labor with clinical chorioamnionitis. Am J Obstet Gynecol

404   1994;170:1345-1351.

405   30. Manti S, Galdo F, Parisi GF, et al. Long-term effects of bronchopulmonary dysplasia

406   on lung function: a pilot study in preschool children's cohort. J Asthma 2020;1-8.

407   31. Day CL, Ryan RM. Bronchopulmonary dysplasia: new becomes old again! Pediatr

408   Res. 2017;81:210-213.

409   32. Matsubara S, Takahashi H, Ohkuchi A, Kumagai H, Ishikawa S. Intrauterine

410   ritodrine exposure and childhood asthma: is ritodrine a real culprit? Pediatr Allergy

411   Immunol 2018;29:332-333.

74   25
75

412   33. Reddel HK, Bateman ED, Becker A, et al. A summary of the new GINA strategy: a

413   roadmap to asthma control. Eur Respir J 2015;46:622-639.

414   34. Verberne AA, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF. One year

415   treatment with salmeterol compared with beclomethasone in children with asthma. The

416   Dutch Paediatric Asthma Study Group. Am J Respir Crit Care Med 1997;156:688-695.

417   35. Turki J, Pak J, Green SA, Martin RJ, Liggett SB. Genetic polymorphisms of the beta

418   2-adrenergic receptor in nocturnal and nonnocturnal asthma. Evidence that Gly16

419   correlates with the nocturnal phenotype. J Clin Invest 1995;95:1635-1641.

420   36. Sano Y, Watt G, Townley RG. Decreased mononuclear cell beta-adrenergic receptors

421   in bronchial asthma: parallel studies of lymphocyte and granulocyte desensitization. J

422   Allergy Clin Immunol 1983;72:495-503.

423   37. Lebold KM, Jacoby DB, Drake MG. Inflammatory mechanisms linking maternal

424   and childhood asthma. J Leukoc Biol 2020;108:113-121.

425   38. Goldenberg RL, McClure EM, Saleem S, Reddy UM. Infection-related stillbirths.

426   Lancet 2010;375:1482-1490.

427

428   **TABLE 1** Demographic and clinical characteristics of participants stratified by MRA status

Variable	Total participants n = 68,123	MRA group n = 18,141	Reference group n = 49,982	P value
Maternal age, % (n)				0.075
<20 years	0.4 (247)	0.4 (76)	0.3 (171)	
20–34 years	70.6 (48,125)	71.1 (12,899)	70.5 (35,226)	
≥35 years	29.0 (19,751)	28.5 (5,166)	29.2 (14,585)	
Maternal BMI before pregnancy, % (n)				<0.001
<18.5 kg/m^2	15.9 (10,859)	18.5 (3,348)	15.0 (7,511)	
18.5–24.9 kg/m^2	74.1 (50,508)	72.5 (13,148)	74.7 (37,360)	
≥25.0 kg/m^2	9.9 (6,756)	9.1 (1,645)	10.2 (5,111)	
Nulliparous, % (n)	41.6 (28,337)	41.4 (7,513)	41.7 (20,824)	0.561
Maternal smoking during pregnancy, % (n)	3.5 (2,401)	3.8 (693)	3.4 (1,708)	0.012
Maternal educational status, % (n)				<0.001
<10 years	3.4 (2,320)	3.5 (633)	3.4 (1,687)	
10–12 years	29.1 (19,828)	29.4 (5,339)	29.0 (14,489)	
13–16 years	43.5 (29,617)	44.8 (8,123)	43.0 (21,494)	
>17 years	24.0 (16,358)	22.3 (4,046)	24.6 (12,312)	
Annual household income, % (n)				<0.001
<2,000,000 JPY	4.8 (3,290)	4.6 (840)	4.9 (2,450)	
2,000,000–5,999,999 JPY	67.4 (45,930)	66.3 (12,024)	67.8 (33,906)	
6,000,000–9,999,999 JPY	23.3 (15,896)	24.4 (4,430)	22.9 (11,466)	

430   Abbreviations: BMI, body mass index; JPY, Japanese yen; MRA, maternal ritodrine administration; SD, standard deviation

431

432

433 **TABLE 2** Odds ratios for obstetric complications in the maternal ritodrine administration group

Childhood outcomes	Wheezing ever	Diagnosis of asthma in the last 12 months	Asthma ever
		Odds ratios (95% CI)	
Ritodrine hydrochloride usage			
cORs	1.24 (1.19–1.28)	1.16 (1.09–1.23)	1.15 (1.09–1.21)
aORs (Model 1)	1.20 (1.16–1.25)	1.12 (1.05–1.19)	1.11 (1.05–1.17)
aORs (Model 2)	1.19 (1.15–1.24)	1.10 (1.03–1.17)	1.09 (1.03–1.16)
aORs (Model 3)	1.16 (1.11–1.20)	1.06 (0.99–1.13)	1.06 (0.99–1.12)

434 Abbreviations: aOR, adjusted odds ratio; cOR, crude odds ratio; CI, confidence interval

435 In Model 1, multivariate logistic regression analyses were adjusted for maternal age, maternal body mass index before pregnancy, parity,

436 maternal smoking status, maternal educational status, annual household income, mode of delivery, preterm births before 37 weeks, low-

437 birth-weight infants (below 2500 g), maternal asthma, and intrauterine infection

438   In Model 2, multivariate logistic regression analyses were adjusted for maternal age, maternal body mass index before pregnancy, parity,

439   maternal smoking status, maternal educational status, annual household income, mode of delivery, preterm births before 37 weeks, low

440   birth weight <2500 g, maternal asthma, intrauterine infection, smoking environment around the children, milk feeding, male newborn,

441   childhood eczema, childhood rhinitis, and pet breeding

442   In Model 3, multivariate logistic regression analyses were adjusted for maternal age, maternal body mass index before pregnancy, parity,

443   maternal smoking status, maternal educational status, annual household income, mode of delivery, preterm births before 37 weeks, low

444   birth weight <2500 g, maternal asthma, intrauterine infection, smoking environment around the children, milk feeding, male newborn,

445   childhood eczema, childhood rhinitis, pet breeding, and childhood viral infection

446

447 **TABLE 3** Odds ratios for obstetric complications in the maternal ritodrine administration group without preterm births

Childhood outcomes	Wheezing ever	Diagnosis of asthma in the last 12 months	Asthma ever
		Odds ratios (95% CI)	
Ritodrine hydrochloride usage			
cORs	1.21 (1.17–1.26)	1.13 (1.06–1.21)	1.13 (1.06–1.19)
aORs (Model 1)	1.20 (1.16–1.25)	1.11 (1.04–1.19)	1.11 (1.05–1.18)
aORs (Model 2)	1.19 (1.15–1.24)	1.10 (1.02–1.17)	1.09 (1.03–1.16)
aORs (Model 3)	1.16 (1.11–1.20)	1.06 (0.99–1.13)	1.06 (0.99–1.13)

448 Abbreviations: aOR, adjusted odds ratio; cOR, crude odds ratio; CI, confidence interval

449 In Model 1, multivariate logistic regression analyses were adjusted for maternal age, maternal body mass index before pregnancy, parity,

450 maternal smoking status, maternal educational status, annual household income, mode of delivery, low-birth-weight infants (below 2500

451 g), maternal asthma, and intrauterine infection

452 In Model 2, multivariate logistic regression analyses were adjusted for maternal age, maternal body mass index before pregnancy, parity,

453 maternal smoking status, maternal educational status, annual household income, mode of delivery, preterm births before 37 weeks, low

454 birth weight <2500 g, maternal asthma, intrauterine infection, smoking environment around the children, milk feeding, male newborn,

455 childhood eczema, childhood rhinitis, and pet breeding

456 In Model 3, multivariate logistic regression analyses were adjusted for maternal age, maternal body mass index before pregnancy, parity,

457 maternal smoking status, maternal educational status, annual household income, mode of delivery, preterm births before 37 weeks, low

458 birth weight <2500 g, maternal asthma, intrauterine infection, smoking environment around the children, milk feeding, male newborn,

459 childhood eczema, childhood rhinitis, pet breeding, and childhood viral infection

460
461

462 **FIGURE LEGENDS**

463 **FIGURE 1** Study enrollment flowchart

464 Abbreviations: BMI: body mass index; MRA: maternal ritodrine hydrochloride

465 administration