

Journal Pre-proof

Better maternal quality of life in pregnancy yields better offspring respiratory outcomes: a birth cohort

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PII: S1081-1206(21)00137-X

DOI: <https://doi.org/10.1016/j.anai.2021.02.019>

Reference: ANAI 3511

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 28 October 2020

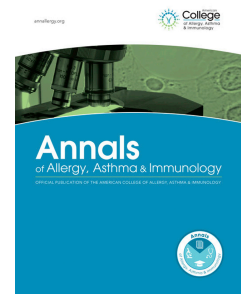
Revised Date: 28 January 2021

Accepted Date: 22 February 2021

Please cite this article as: Yamamoto-Hanada K, Pak K, Saito-Abe M, Sato M, Ohya Y, for the Japan Environment and Children's Study (JECS) Group, Better maternal quality of life in pregnancy yields better offspring respiratory outcomes: a birth cohort, *Annals of Allergy, Asthma and Immunology* (2021), doi: <https://doi.org/10.1016/j.anai.2021.02.019>.

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TITLE PAGE

Original Article

**Better maternal quality of life in pregnancy yields better offspring
respiratory outcomes: a birth cohort**

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Competing interests: None

Declaration of funding: This study was funded and supported by the Ministry of the
Environment, Japan.

Key words

Anxiety; asthma; child; depression; epidemiology; food allergy; quality of life; wheeze

Abbreviations

DOHaD, Developmental Origins of Health and Disease; ISAAC, The International Study of Asthma and Allergies in Childhood; JECS, Japan Environment and Children's Study; MCS, mental component summary; PCS, physical component summary; QoL, quality of life; SF-8, Medical Outcomes Survey Short Form-8 questionnaire; UMIN, University Hospital Medical Information Network

Word count: 2546

Figures:0

Tables:8

e-Supplement, Figure: 1

e-Supplement, Tables: 2

20-10-0703R1

Background: It is suggested that maternal mental health during pregnancy may affect offspring immune and respiratory features, based on the Developmental Origins of Health and Disease hypothesis.

Objective: In this study, we examined whether maternal quality of life (QoL) and depression during pregnancy leads to offspring's wheeze, asthma, and food allergy at 3 years old.

Methods: We conducted a nationwide, multicentre, prospective birth cohort study, Japan Environment and Children's Study. All variables were collected from questionnaires. Health-related QoL was measured using the Medical Outcomes Survey Short Form-8 questionnaire (SF-8) with a physical component summary (PCS) and a mental component summary (MCS) score. We conducted logistic regression analyses to examine the associations of offspring's wheeze, asthma, and food allergy with maternal QoL and depression.

Results: There were 72,685 participants with no missing variables. Maternal PCS scores of the SF-8 was negatively associated with offspring's asthma (adjusted odds ratio [aOR] 0.99, 95% confidence interval [CI] 0.99–1.00), current wheeze (aOR 0.99, 95% CI 0.99–0.99), and food allergy diagnoses (aOR 0.99, 95% CI 0.98–0.99) in children. Offspring's wheeze and asthma were also associated with maternal depression and anxiety during pregnancy.

Conclusion:

Poor maternal prenatal QoL increased a risk of wheeze, asthma, and food allergy in offspring. In addition, maternal depression and anxiety increased the risk of offspring's wheeze, asthma, and food allergy.

Introduction

The World Health Organization defines quality of life (QoL) as an individual's perception of their position in life within the context of the culture and value system in which they live and in relation to their goals, expectations, standards, and concerns. It is a wide-ranging concept affected by a person's psychological state, physical health, personal beliefs, social relationships, and their relationship with their environment. Therefore, QoL is important in daily life. Stucly *et al.*¹ demonstrated that asthma severity and symptoms were strongly related to asthma-specific QoL, and Chen *et al.*² demonstrated that poor asthma control led to impairment of a patient's QoL. The emerging concept of the Developmental Origins of Health and Disease (DOHaD) hypothesis states that various exposures during the preconception and postconception period in the embryo and fetus can contribute to the development of noncommunicable diseases in children.³ Epigenetic modifications such as DNA methylation can occur due to early life environmental exposures, including medication, chemicals, nutritional factors, and stressors. These modifications can have an impact on children's subsequent health. A systematic review reported that maternal psychological stress during pregnancy increased the risk of wheezing and asthma in the offspring.⁴ Based on the DOHaD hypothesis, maternal mental health during pregnancy could affect the offspring's immune system and allergic symptoms.

In Japan, mental health is a serious and alarming issue among pregnant women, with suicide the top cause of death during pregnancy.⁵ Approximately 70% of schoolchildren in Tokyo were found to have IgE sensitization,⁶ indicating an epidemic of allergic symptoms among Japanese children. To the best of our knowledge, no study has yet examined how prenatal maternal QoL influences allergic traits in children. In this study, we examined whether maternal QoL and depression led to wheezing, asthma, and food allergy in offspring at 3 years of age.

Methods

Study design, setting, and participants

We performed a nationwide, multicenter, prospective, birth cohort study: the Japan Environment and Children's Study (JECS),⁷⁻¹⁰ which was conducted by the Ministry of the Environment, Japan. A general population of 103,060 pregnant women was registered in the JECS in 15 regional centers, covering a broad geographic region from the north of Japan (Hokkaido) to the south (Okinawa), 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 August 1, 2011 and mid-2014; and (4) ability to understand the Japanese language. In total, 104,062 newborns were enrolled in the JECS. The JECS registry is the University Hospital Medical Information Network

(UMIN) 000030786 (UMIN Clinical Trials Registry). JECS protocols for the main study and the subcohort study are described on the website of the Japanese Ministry of the Environment.^{11, 12}

Ethics statement

The JECS protocol was reviewed and approved by the Ministry of the Environment Institutional Review Board on Epidemiological Studies and by the ethics committees of all participating institutions. Written informed consent was obtained from all participants. The JECS was conducted in accordance with the principles laid out in the Declaration of Helsinki and other national regulations and guidelines.

Data collection

All variables were collected from written questionnaires that were provided to caregivers during pregnancy and when the child was aged 6 months and 1, 1.5, 2, 2.5, and 3 years. Caregivers answered questions regarding the child and the family. Information on each child's background, lifestyle, and nutrition was assessed using the questionnaires. All the questionnaires were in Japanese.

Exposures

In this study, we established depression, QoL, and a doctor's diagnosis of depression or anxiety disorder as exposures. Depression was defined based on the Kessler Screening Scale for Psychological Distress (K-6) scores.¹³⁻¹⁶ The total K-6 score ranges from 0 to 24. Scores of 13 or

higher indicate severe depression, and scores of 5 or higher indicate any depression. Health-related QoL was measured using the Medical Outcomes Survey Short Form-8 questionnaire (SF-8).^{17, 18} The SF-8 items assess general health, physical functioning, role-physical, bodily pain, vitality, social functioning, mental health, and role-emotional. Two summary scores of the physical component summary (PCS) and mental component summary (MCS), indicating physical and mental functioning, respectively, were shown as standard deviation scores (the national standard score is 50). These scores were calculated using a validated scoring program for Japanese populations. Higher scores indicate a higher-quality health status. The K-6 and SF-8 were assessed during the first trimester (MT1). A doctor's diagnosis of depression or anxiety disorder was also assessed during MT1.

Outcomes

All outcomes were evaluated using the questionnaire administered when the child was 3 years of age; caregiver-reported medical diagnoses of asthma and food allergy were obtained using questionnaires administered at this time. These physician diagnoses were defined as a positive answer from the caregiver to the question: "Has your child ever been diagnosed by a physician as having asthma and/or food allergy in the past 12 months?" Caregiver-reported wheezing and sleep disturbance due to wheezing were evaluated based on a modified International Study of Asthma and Allergies in Childhood questionnaire for children aged 6–7 years, which was translated and validated

in Japanese.¹⁹⁻²¹ Caregiver-reported food allergy was defined as a history of reactions to and

avoidance of causal foods; both were evaluated using a questionnaire.

Statistical analyses

Questionnaire data concerning 104,062 fetuses from mothers who were enrolled in the study and did

not withdraw their consent were included in the analysis (see eFigure 1). As the population of

interest, we analyzed data from 3-year-old children born as a singleton after 37 weeks' gestation and

with questionnaire responses for outcome and exposure variables (eFigure 1). We used a fixed data

set (jecs-ta-201901930-qsn, released in October 2019) in this study. Based on clinical experience and

a review of past reports, we assessed the following factors as possible confounders in the regression

analyses: maternal age, maternal allergy history, maternal body mass index, maternal education level,

annual family income, family smoking when the child was 3 years of age, pet ownership at 6 months

of age, child's sex, nursery school attendance, and the place of recruitment. We checked the

collinearity of preliminarily selected confounders and included all available variables in the model,

without performing variable selection. For each binary outcome variable of allergic symptoms, we

conducted logistic regression analyses and performed a multinomial logistic regression analysis for

the outcome of sleep disturbance due to wheezing (with 4 categories). We evaluated the odds ratios

(ORs) and adjusted odds ratios (aORs) as measures of association and calculated 95% confidence

intervals (CIs) and p-values. We estimated aORs by implementing a multivariate imputation by

chained equations (MICE) algorithm with 20 iterations, using the R package MICE, version 3.9.0. The e-value represents the minimum magnitude of association required between an unmeasured confounder and the exposure and outcome, conditional on measured covariates, to fully attenuate the observed exposure-outcome association. We provided e-values as a sensitivity analysis to unknown and unmeasured confounding variables. All the statistical analyses were performed using R statistical software, version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Participant characteristics

Of the fixed data set at 3 years of age ($N = 104,062$), a total of 72,685 participants had no missing information (see eFigure 1). Mean maternal age at the child's birth was 30.9 (± 4.9) years. Among the total, 10.6% of mothers had an asthma history (Table 1). Passive smoking exposure was present in 44.4% of children at 3 years. A depression diagnosis by a doctor was recorded for 2.9% of the mothers (Table 2). Mean PCS and MCS scores of the SF-8 were 45.8 and 49.2, respectively. As for the children's outcomes, 7.6% of the children had an asthma diagnosis and 30.1% had a lifetime wheezing history (Table 3). The frequency of childhood asthma, wheezing, and food allergy for the SF-8 categories is shown in Table 4.

Maternal quality of life during pregnancy and offspring outcomes

Table 5 demonstrates the associations between offspring's wheezing, asthma, and food allergy at 3 years of age and maternal QoL during pregnancy and the results of those sensitivity analyses as e-values. SF-8 maternal PCS scores were negatively associated with the offspring's asthma (aOR 0.99, 95% CI 0.99–1.00), current wheezing (aOR 0.99, 95% CI 0.99–0.99), and food allergy diagnosis (aOR 0.99, 95% CI 0.98–0.99) in 3-year-old children, based on the complete case analysis. SF-8 MCS scores were also negatively associated with asthma (aOR 0.98, 95% CI 0.98–0.99) and current wheezing (aOR 0.99, 95% CI 0.99–0.99) in 3-year old children based on the complete case analysis. However, there was no association between maternal MCS scores and a food allergy diagnosis.

As for sleep disturbance due to wheezing (Table 6), SF-8 PCS scores were significantly associated with sleep disturbance less than 1 night per week and 1 or more nights per week. SF-8 MCS scores were also negatively associated with sleep disturbance less than 1 night per week and 1 or more nights per week. The results by multiple imputation analysis were almost the same as the results by complete case analysis, as we described earlier. The only different results were that the PCS and MCS scores were not associated with sleep frequency disturbance caused by wheezing in the multiple imputation data analysis.

Maternal depression during pregnancy and offspring outcomes

Table 7 demonstrates the associations between the offspring's wheezing, asthma, and food allergy at 3 years of age and maternal depression and anxiety during pregnancy and shows the results of those sensitivity analyses as e-values. Current wheezing was positively associated with severe depression status (aOR 1.22, 95% CI 1.07–1.38), depressive status (aOR 1.18, 95% CI 1.12–1.24), a doctor's diagnosis of depression (aOR 1.21, 95% CI 1.07–1.37), and a doctor's diagnosis of anxiety disorder (aOR 1.27, 95% CI 1.12–1.44). Asthma diagnosis was also associated with maternal depression status and doctor's diagnosis of anxiety disorder. Food allergy diagnosis in children was positively associated with any depression K-6 scores ≥ 5 (aOR 1.08, 95% CI 1.01–1.16), doctor's diagnosis of maternal depression (aOR 1.28, 95% CI 1.05–1.53), and doctor's diagnosis of anxiety disorder (aOR 1.38 95% CI 1.15–1.65).

Table 8 show the associations between offspring's sleep disturbance caused by wheezing with maternal depression and anxiety during pregnancy and the results of those sensitivity analyses as e-values. The aOR of sleep disturbance 1 or more nights per week was larger than that of sleep disturbance less than 1 night per week with respect to severe depression status, any depression status, and doctor's diagnosis of anxiety disorder.

Discussion

From a large-scale national birth cohort study, we found significant evidence that poor maternal prenatal QoL increased the risk of offspring having wheezing, asthma, and food allergy at 3 years of age. In addition, maternal depression and anxiety during pregnancy also increased the risk of wheezing, asthma, and food allergy in offspring. Our findings are consistent with the DOHaD theory.³ We believe that prenatal maternal mental health can contribute to altering the programming of the respiratory and immunological systems in the fetus before birth. The strength of this study was that our results are based on real-world evidence with a large longitudinal data set.

The results for quality of life showed a weaker association with asthma and food allergy than did the presence of depression. The ORs in all cases were close to 1. The OR 0.99 is certainly close to 1, but they showed that the OR for each increased in SF-8 by 1 unit. In other words, "By increasing the SF-8 by 1 unit, the odds of developing allergies were reduced by approximately 1%." Whether the association is small or large depends on the interpretation of how these associations could impact clinical outcomes. We consider that reducing the odds of developing allergies approximately 1% by increasing the SF-8 by 1 unit would have a significant impact on the public. Furthermore, we believe that the robustness of the associations between maternal mental status and the child's allergic outcomes can be confirmed by evaluating e-values.

To the best of our knowledge, this report is the first to demonstrate associations between offspring's wheezing, asthma, and food allergy and maternal QoL. Our study results suggest that better maternal

QoL during pregnancy leads to better respiratory outcomes in their offspring. A past systematic review found that the physical component of QoL decreased during pregnancy.²² The mother's QoL should be carefully assessed and warrants increased attention. Furthermore, a past review indicated that the factors associated with better QoL were the absence of social and economic problems, feeling happiness, having social connections, and physical exercise.²² A randomized controlled trial demonstrated that a relaxation program was effective for pregnant women with psychological stress.²³ To obtain better maternal QoL, mothers need various types of support and modification of risk factors related to poor QoL during pregnancy.

As for the associations with maternal psychosocial stress, Flanigan *et al.*⁴ performed a systematic review and meta-analysis regarding prenatal maternal stress and the offspring's allergy using data from 22 observational studies. The results of the meta-analysis demonstrated that prenatal maternal stress²⁴⁻³¹ and anxiety^{24, 25, 27} increased the risk of the offspring having asthma. Maternal depression^{24, 25, 27, 32} and anxiety^{27, 32, 33} during pregnancy also increased the risk of the offspring having wheezing.

Our study results concurred with the results of these past studies. As for food allergy outcomes, we found no observational studies that have examined the association between food allergy and maternal depression, anxiety, and stress. Our results, therefore, represent the first to reveal that food allergy in offspring is influenced by prenatal psychosocial stress.

Considering the mechanism of stress and the immune system, a proposed mechanism is that stress perception due to various external stressors alters the hypophyseal–pituitary–adrenal axis and autonomic nervous systems, producing an altered immune balance and having a negative impact on immune system molecules such as cytokines, chemokines, and immune cells.³⁴ Another meta-analysis reported that major depression increased the level of interleukin-6 and tumor necrosis factor-alpha.³⁵ In a birth cohort in Germany, Trump *et al.*³⁶ identified that alterations in DNA methylation in mothers and their offspring due to prenatal psychological stress were associated with the development of wheezing in children. These study results support our findings. We speculate that our study population might have experienced epigenetic changes during pregnancy.

The present study has several limitations to consider. First, the prevalence of doctors' diagnoses might be underestimated because we could not use medical chart data and/or other patient registry data. Furthermore, we did not examine the medications for depression and anxiety. Therefore, we could not evaluate how medications could influence maternal health and child outcomes. However, we used validated questionnaires to assess wheezing, depression status, and QoL, as have been used in various past studies. Second, some participants were lost during the follow-up period. However, we believe that the rate of loss to follow-up was low. Third, we did not conduct a molecular epidemiology investigation using genetic data. Although we speculate that epigenetic changes might

192 have occurred during pregnancy, we cannot confirm genetic alterations. In a future study, we hope to
193 validate our study results using genetic data.

194 In summary, poor maternal prenatal QoL increased the risk of the offspring having wheezing, asthma,
195 and food allergy at 3 years of age. In addition, maternal depression and anxiety during pregnancy
196 increased the risk of wheezing, asthma, and food allergy in the offspring.

References

1. Stucky BD, Sherbourne CD, Edelen MO, Eberhart NK. Understanding asthma-specific quality of life: moving beyond asthma symptoms and severity. *European Respiratory Journal*. 2015;46:680-687.
2. Chen H, Gould MK, Blanc PD, et al. Asthma control, severity, and quality of life: quantifying the effect of uncontrolled disease. *J Allergy Clin Immunol*. 2007;120:396-402.
3. Wadhwa PD, Buss C, Entringer S, Swanson JM. Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. *Semin Reprod Med*. 2009;27:358-368.
4. Flanigan C, Sheikh A, DunnGalvin A, Brew BK, Almqvist C, Nwaru BI. Prenatal maternal psychosocial stress and offspring's asthma and allergic disease: A systematic review and meta-analysis. *Clin Exp Allergy*. 2018;48:403-414.
5. Takeda S, Takeda J, Murakami K, et al. Annual Report of the Perinatology Committee, Japan Society of Obstetrics and Gynecology, 2015: Proposal of urgent measures to reduce maternal deaths. *J Obstet Gynaecol Res*. 2017;43:5-7.
6. Yamamoto-Hanada K, Borres MP, Åberg MK, et al. IgE responses to multiple allergen components among school-aged children in a general population birth cohort in Tokyo. *World Allergy Organization Journal*. 2020;13:100105.
7. Kawamoto T, Nitta H, Murata K, et al. Rationale and study design of the Japan environment and children's study (JECS). *BMC Public Health*. 2014;14:25.
8. Yamamoto-Hanada K, Ishitsuka K, Pak K, et al. Allergy and mental health among pregnant women in the Japan Environment and Children's Study. *J Allergy Clin Immunol Pract*. 2018;6:1421-1424 e1422.
9. Saito M, Yamamoto-Hanada K, Pak K, et al. Having small-for-gestational-age infants was associated with maternal allergic features in the JECS birth cohort. *Allergy*. 2018;73:1908-1911.
10. Yamamoto-Hanada K, Pak K, Saito-Abe M, et al. Cumulative inactivated vaccine exposure and allergy development among children: a birth cohort from Japan. *Environ Health Prev Med*. 2020;25:27.
11. Programme Office of Japan Environment and Children's Study NifES. Japan Environment and Children's Study (JECS) Study Protocol.
12. Programme Office of Japan Environment and Children's Study NifES. Japan Environment and Children's Study (JECS) Sub-Cohort Study Protocol.

13. Kessler RC, Andrews G, Colpe LJ, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. *Psychol Med.* 2002;32:959-976.
14. Kessler RC, Barker PR, Colpe LJ, et al. Screening for serious mental illness in the general population. *Arch Gen Psychiatry.* 2003;60:184-189.
15. Sakurai K, Nishi A, Kondo K, Yanagida K, Kawakami N. Screening performance of K6/K10 and other screening instruments for mood and anxiety disorders in Japan. *Psychiatry Clin Neurosci.* 2011;65:434-441.
16. Furukawa TA, Kawakami N, Saitoh M, et al. The performance of the Japanese version of the K6 and K10 in the World Mental Health Survey Japan. *International journal of methods in psychiatric research.* 2008;17:152-158.
17. Ware JE KM, Dewey JE, Gandek B. *How to score and interpret singleitem health status measures: a manual for users of the SF-8 health survey.* : Lincoln, RI: QualityMetric Inc; 2001.
18. Fukuhara S SY. *Manual of the SF-8 Japanese Version.* Kyoto: Institute for Health Outcome and Process Evaluation Research. 2004.
19. Asher M, Keil U, Anderson H, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *European respiratory journal.* 1995;8:483-491.
20. Weiland SK, Björkstén B, Brunekreef B, Cookson WO, von Mutius E, Strachan DP. Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): rationale and methods. *Eur Respir J.* 2004;24:406-412.
21. Ellwood P, Asher MI, Beasley R, Clayton TO, Stewart AW. The international study of asthma and allergies in childhood (ISAAC): phase three rationale and methods. *Int J Tuberc Lung Dis.* 2005;9:10-16.
22. Lagadec N, Steinecker M, Kapassi A, et al. Factors influencing the quality of life of pregnant women: a systematic review. *BMC Pregnancy Childbirth.* 2018;18:455.
23. Tragea C, Chrousos GP, Alexopoulos EC, Darviri C. A randomized controlled trial of the effects of a stress management programme during pregnancy. *Complement Ther Med.* 2014;22:203-211.
24. Bandoli G, von Ehrenstein O, Ghosh JKC, Flores MES, Dunkel Schetter C, Ritz B. Prenatal Maternal Stress and the Risk of Lifetime Wheeze in Young Offspring: An Examination by Stressor and Maternal Ethnicity. *J Immigr Minor Health.* 2016;18:987-995.

25. Cookson H, Granell R, Joinson C, Ben-Shlomo Y, Henderson AJ. Mothers' anxiety during pregnancy is associated with asthma in their children. *J Allergy Clin Immunol.* 2009;123:847-853.e811.
26. Fang F, Höglund CO, Arck P, et al. Maternal bereavement and childhood asthma-analyses in two large samples of Swedish children. *PLoS One.* 2011;6:e27202.
27. Guxens M, Sonnenschein-van der Voort AM, Tiemeier H, et al. Parental psychological distress during pregnancy and wheezing in preschool children: the Generation R Study. *J Allergy Clin Immunol.* 2014;133:59-67.e51-12.
28. Hartwig IR, Sly PD, Schmidt LA, et al. Prenatal adverse life events increase the risk for atopic diseases in children, which is enhanced in the absence of a maternal atopic predisposition. *J Allergy Clin Immunol.* 2014;134:160-169.
29. Lee A, Mathilda Chiu YH, Rosa MJ, et al. Prenatal and postnatal stress and asthma in children: Temporal- and sex-specific associations. *J Allergy Clin Immunol.* 2016;138:740-747 e743.
30. Radhakrishnan DK, Shariff S, Richard L, To T. Does maternal stress influence the development of asthma in childhood? A63. *PEDIATRIC ASTHMA: PREDICTORS AND OUTCOMES*: American Thoracic Society; 2016:A2158-A2158.
31. Turcotte-Tremblay AM, Lim R, Laplante DP, Kobzik L, Brunet A, King S. Prenatal maternal stress predicts childhood asthma in girls: project ice storm. *Biomed Res Int.* 2014;2014:201717.
32. Cheng TS, Chen H, Lee T, et al. An independent association of prenatal depression with wheezing and anxiety with rhinitis in infancy. *Pediatr Allergy Immunol.* 2015;26:765-771.
33. Reyes M, Perzanowski MS, Whyatt RM, et al. Relationship between maternal demoralization, wheeze, and immunoglobulin E among inner-city children. *Ann Allergy Asthma Immunol.* 2011;107:42-49.e41.
34. Marshall GD. Psychological stress, immunity, and asthma: developing a paradigm for effective therapy and prevention. *Current Opinion in Behavioral Sciences.* 2019;28:14-19.
35. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry.* 2010;67:446-457.
36. Trump S, Bieg M, Gu Z, et al. Prenatal maternal stress and wheeze in children: novel insights into epigenetic regulation. *Sci Rep.* 2016;6:28616.

Table 1. Baseline characteristic of the study

	Category	Analysis set	Excluded
Mothers		72685	15589
Study Prefectures	Hokkaido, n(%)	5750 (7.9%)	1294 (8.3%)
	Miyagi, n(%)	6287 (8.6%)	1532 (9.8%)
	Fukushima, n(%)	9373 (12.9%)	2198 (14.1%)
	Chiba, n(%)	4078 (5.6%)	1095 (7.0%)
	Kanagawa, n(%)	4762 (6.6%)	982 (6.3%)
	Yamanashi, n(%)	3055 (4.2%)	856 (5.5%)
	Koshin(nagano), n(%)	2137 (2.9%)	239 (1.5%)
	Toyama, n(%)	4184 (5.8%)	629 (4.0%)
	Aichi, n(%)	4128 (5.7%)	751 (4.8%)
	Kyoto, n(%)	2978 (4.1%)	500 (3.2%)
	Osaka, n(%)	5700 (7.8%)	1140 (7.3%)
	Hyogo, n(%)	3767 (5.2%)	735 (4.7%)
	Tottori, n(%)	2283 (3.1%)	381 (2.4%)
	Kochi, n(%)	4800 (6.6%)	1209 (7.8%)
	Fukuoka, n(%)	5533 (7.6%)	1038 (6.7%)
	Kumamoto, n(%)	1908 (2.6%)	655 (4.2%)
	Miyazaki, n(%)	1395 (1.9%)	169 (1.1%)
	Okinawa, n(%)	567 (0.8%)	186 (1.2%)
Age at birth, year	Mean (SD)	30.9 (4.9)	29.4 (5.4)
	Minimum	14	14
	25%ile	28	26
	50%ile	31	29
	75%ile	34	33
	Max	48	46

Past medical history	Missing, n(%)	1357 (1.9%)	401 (2.6%)
	Any allergic diseases, n(%)	40492 (55.7%)	7900 (50.7%)
	Asthma, n(%)	7689 (10.6%)	1863 (12.0%)
	Hayfever, allergic rhinitis, n(%)	26520 (36.5%)	4970 (31.9%)
	Atopic dermatitis, n(%)	11650 (16.0%)	2217 (14.2%)
	Allergic conjunctivitis, n(%)	7373 (10.1%)	1341 (8.6%)
	Food allergy, n(%)	3477 (4.8%)	753 (4.8%)
	Drug allergy, n(%)	1925 (2.6%)	341 (2.2%)
	Urticaria, n(%)	11248 (15.5%)	2101 (13.5%)
	Contact dermatitis, n(%)	1449 (2.0%)	243 (1.6%)
Highest graduation	Middle school, n(%)	2702 (3.7%)	1422 (9.1%)
	High school, n(%)	21623 (29.7%)	5487 (35.2%)
	Technical school, n(%)	1176 (1.6%)	240 (1.5%)
	College of technology, n(%)	16567 (22.8%)	3165 (20.3%)
	Junior college, n(%)	13257 (18.2%)	1950 (12.5%)
	University, n(%)	15601 (21.5%)	1931 (12.4%)
	Graduate school, n(%)	1158 (1.6%)	142 (0.9%)
	Missing, n(%)	601 (0.8%)	1252 (8.0%)
BMI before pregnancy	Mean (SD)	21.1 (3.2)	21.5 (3.7)
	Minimum	13.3	14.3
	25%ile	19.1	19.1
	50%ile	20.5	20.7
	75%ile	22.4	23.0
	Max	48.8	45.9
	Missing, n(%)	37 (0.1%)	71 (0.5%)
Children			
Child's sex	Boy, n(%)	37054 (51.0%)	7937 (50.9%)

	Girl, n(%)	35631 (49.0%)	7644 (49.0%)
	Unclear/Missing, n(%)	0 (0.0%)	8 (0.1%)
Sibling at one month	yes, n(%)	37701 (51.9%)	
	no, n(%)	34690 (47.7%)	
	Missing, n(%)	294 (0.4%)	
Passive smoking at 3y	yes, n(%)	32253 (44.4%)	
	no, n(%)	38915 (53.5%)	
	Missing, n(%)	1517 (2.1%)	
Pet at 6 months	yes, n(%)	17467 (24.0%)	
	no, n(%)	53979 (74.3%)	
	Missing, n(%)	1239 (1.7%)	
Daycare center at 3y	yes, n(%)	44165 (60.8%)	
	no, n(%)	26327 (36.2%)	
	Missing, n(%)	2193 (3.0%)	
Annual household income, yen	<2,000,000, n(%)	3343 (4.6%)	1178 (7.6%)
	2,000,000-3,999,999, n(%)	22881 (31.5%)	4900 (31.4%)
	4,000,000-5,999,999, n(%)	22682 (31.2%)	3947 (25.3%)
	6,000,000-7,999,999, n(%)	11206 (15.4%)	1703 (10.9%)
	8,000,000-9,999,999, n(%)	4647 (6.4%)	722 (4.6%)
	10,000,000-11,999,999, n(%)	1717 (2.4%)	240 (1.5%)
	12,000,000-14,999,999, n(%)	673 (0.9%)	103 (0.7%)
	15,000,000-19,999,999, n(%)	375 (0.5%)	64 (0.4%)
	20,000,000-, n(%)	207 (0.3%)	53 (0.3%)
	Missing, n(%)	4954 (6.8%)	2679 (17.2%)

Table 2. Maternal mental status (depression and quality of life) during pregnancy (N=72685)

	Category	Statistics
Doctor's depression diagnosis	yes, n (%)	2086 (2.9%)
Doctor's diagnosis of anxiety disorder	yes, n (%)	1897 (2.6%)
K-6 scores	Mean (SD)	3.3 (3.6)
	minimum, 25th, 50th, 75th, max	0, 1, 2, 5, 24
K-6 score ≥ 13 , severe depressive status	≥ 13 , n (%)	2067 (2.8%)
	< 13 , n (%)	70198 (96.6%)
K-6 score ≥ 5 , any depressive status	≥ 5 , n (%)	19947 (27.4%)
	< 5 , n (%)	52318 (72.0%)
SF-8 (PCS)	Mean (SD)	45.8 (6.1)
	minimum, 25th, 50th, 75th, max	5.72, 42.13, 46.15, 50.06, 66.10
SF-8 (MSC)	Mean (SD)	49.2 (6.1)
	minimum, 25th, 50th, 75th, max	12.87, 45.74, 49.68, 53.59, 73.33

Table 3. Wheeze, asthma, and food allergy in 3-year-old children (N=72685)

	Category	Statistics
Doctor's diagnosis		
Asthma diagnosis	yes, n (%)	5522 (7.6%)
Food allergy diagnosis	yes, n (%)	4643 (6.4%)
Allergic symptoms		
Respiratory		
Ever wheeze	yes, n (%)	21853 (30.1%)
Current wheeze	yes, n (%)	12423 (17.1%)
Frequency of wheeze	None, n (%)	4969 (6.8%)
	1–3 times, n (%)	9095 (12.5%)
	4–12 times, n (%)	1930 (2.7%)
	13 times and more, n (%)	346 (0.5%)
Sleep disturbance caused by wheeze	No wheeze, n (%)	59766 (82.2%)
	Never woken with wheezing, n (%)	6197 (8.5%)
	Less than one night per week, n (%)	4805 (6.6%)
	One or more nights per week, n (%)	1415 (1.9%)
Speech difficulty caused by wheeze	yes, n (%)	805 (1.1%)
Wheeze caused by physical activity and crying	yes, n (%)	1635 (2.2%)
Night cough	yes, n (%)	5858 (8.1%)
Food allergy symptoms reported by caregiver	yes, n (%)	5497 (7.6%)

Table 4 frequency of childhood asthma, wheeze, food allergy for SF-8 categories

SF-8 (PCS)	Allergy features (Outcome)	No. of Yes / N (%)	SF-8 (MCS)	Allergy features (Outcome)	No. of Yes / N (%)
<25	Asthma diagnosis	43 / 414 (10.39%)	<25	Asthma diagnosis	18 / 151 (11.92%)
>=25, <30		59 / 727 (8.12%)	>=25, <30		38 / 445 (8.54%)
>=30, <35		194 / 2149 (9.03%)	>=30, <35		120 / 1266 (9.48%)
>=35, <40		600 / 7358 (8.15%)	>=35, <40		300 / 3182 (9.43%)
>=40, <45		1479 / 18995 (7.79%)	>=40, <45		850 / 9997 (8.50%)
>=45, <50		1740 / 23701 (7.34%)	>=45, <50		1717 / 22271 (7.71%)
>=50, <55		1083 / 15197 (7.13%)	>=50, <55		1505 / 21401 (7.03%)
>=55, <60		221 / 3012 (7.34%)	>=55, <60		816 / 12050 (6.77%)
>=60		11 / 124 (8.87%)	>=60		66 / 913 (7.23%)
<25	Current wheeze	94 / 411 (22.87%)	<25	Current wheeze	38 / 151 (25.17%)
>=25, <30		139 / 716 (19.41%)	>=25, <30		76 / 437 (17.39%)
>=30, <35		441 / 2136 (20.65%)	>=30, <35		254 / 1250 (20.32%)
>=35, <40		1389 / 7311 (19.00%)	>=35, <40		652 / 3152 (20.69%)
>=40, <45		3373 / 18863 (17.88%)	>=40, <45		1772 / 9914 (17.87%)
>=45, <50		3894 / 23534 (16.55%)	>=45, <50		3925 / 22122 (17.74%)
>=50, <55		2392 / 15101 (15.84%)	>=50, <55		3541 / 21263 (16.65%)
>=55, <60		494 / 2993 (16.51%)	>=55, <60		1823 / 11989 (15.21%)
>=60		19 / 124 (15.32%)	>=60		154 / 910 (16.92%)
<25	ever wheeze	147 / 413 (35.59%)	<25	ever wheeze	61 / 151 (40.40%)
>=25, <30		244 / 722 (33.80%)	>=25, <30		137 / 441 (31.07%)
>=30, <35		721 / 2139 (33.71%)	>=30, <35		434 / 1261 (34.42%)
>=35, <40		2416 / 7347 (32.88%)	>=35, <40		1121 / 3172 (35.34%)
>=40, <45		5859 / 18945 (30.93%)	>=40, <45		3167 / 9962 (31.79%)
>=45, <50		7033 / 23640 (29.75%)	>=45, <50		6878 / 22220 (30.95%)

>=50, <55		4199 / 15167 (27.69%)	>=50, <55		6197 / 21354 (29.02%)
>=55, <60		883 / 3003 (29.40%)	>=55, <60		3273 / 12025 (27.22%)
>=60		35 / 124 (28.23%)	>=60		269 / 913 (29.46%)
<25	food allergy diagnosis	41 / 414 (9.90%)	<25	food allergy diagnosis	13 / 151 (8.61%)
>=25, <30		49 / 727 (6.74%)	>=25, <30		21 / 445 (4.72%)
>=30, <35		171 / 2149 (7.96%)	>=30, <35		95 / 1266 (7.50%)
>=35, <40		499 / 7358 (6.78%)	>=35, <40		210 / 3182 (6.60%)
>=40, <45		1228 / 18995 (6.46%)	>=40, <45		631 / 9997 (6.31%)
>=45, <50		1540 / 23701 (6.50%)	>=45, <50		1472 / 22271 (6.61%)
>=50, <55		889 / 15197 (5.85%)	>=50, <55		1343 / 21401 (6.28%)
>=55, <60		164 / 3012 (5.44%)	>=55, <60		737 / 12050 (6.12%)
>=60		5 / 124 (4.03%)	>=60		64 / 913 (7.01%)
<25	food allergy symptoms	42 / 414 (10.14%)	<25	food allergy symptoms	12 / 151 (7.95%)
>=25, <30		66 / 727 (9.08%)	>=25, <30		32 / 445 (7.19%)
>=30, <35		204 / 2149 (9.49%)	>=30, <35		92 / 1266 (7.27%)
>=35, <40		639 / 7358 (8.68%)	>=35, <40		260 / 3182 (8.17%)
>=40, <45		1486 / 18995 (7.82%)	>=40, <45		753 / 9997 (7.53%)
>=45, <50		1763 / 23701 (7.44%)	>=45, <50		1738 / 22271 (7.80%)
>=50, <55		1029 / 15197 (6.77%)	>=50, <55		1571 / 21401 (7.34%)
>=55, <60		193 / 3012 (6.41%)	>=55, <60		901 / 12050 (7.48%)
>=60		8 / 124 (6.45%)	>=60		71 / 913 (7.78%)

Table 5. Logistic regression results for offspring's asthma, wheeze, and food allergy associated with maternal quality of life during pregnancy

		Univariable(Complete Case)			Multivariable (Complete Case)			Multivariable (Multiple Imputation)		
Maternal mental health status (Exposure)	Allergy features (Outcome)	N	OR (95%CI)	p-value	aOR (95%CI)	p-value	E-value		aOR (95%CI)	p-value
							for the	for the		
							limit of	the CI		
SF-8 (PCS)	Asthma diagnosis	61283	0.99 (0.99 - 1.00)	0.0002	0.99 (0.99 - 1.00)	0.0025	1.096	1.055	0.99 (0.99 - 1.00)	0.0001
	Current wheeze	60912	0.99 (0.98 - 0.99)	<0.0001	0.99 (0.99 - 0.99)	<0.0001	1.082	1.068	0.99 (0.99 - 0.99)	<0.0001
	ever wheeze	61159	0.99 (0.98 - 0.99)	<0.0001	0.99 (0.99 - 0.99)	<0.0001	1.082	1.070	0.99 (0.99 - 0.99)	<0.0001
	food allergy diagnosis	61283	0.99 (0.98 - 0.99)	<0.0001	0.99 (0.98 - 0.99)	<0.0001	1.119	1.085	0.99 (0.98 - 0.99)	<0.0001
	food allergy symptoms	61283	0.98 (0.98 - 0.99)	<0.0001	0.98 (0.98 - 0.99)	<0.0001	1.144	1.118	0.98 (0.98 - 0.99)	<0.0001
SF-8 (MCS)	Asthma diagnosis	61283	0.98 (0.98 - 0.99)	<0.0001	0.98 (0.98 - 0.99)	<0.0001	1.143	1.116	0.99 (0.98 - 0.99)	<0.0001
	Current wheeze	60912	0.99 (0.98 - 0.99)	<0.0001	0.99 (0.99 - 0.99)	<0.0001	1.083	1.069	0.99 (0.99 - 0.99)	<0.0001
	ever wheeze	61159	0.99 (0.98 - 0.99)	<0.0001	0.99 (0.99 - 0.99)	<0.0001	1.086	1.075	0.99 (0.99 - 0.99)	<0.0001
	food allergy diagnosis	61283	1.00 (0.99 - 1.00)	0.5002	1.00 (0.99 - 1.00)	0.4063	1.050	1.000	1.00 (0.99 - 1.00)	0.2943
	food allergy symptoms	61283	1.00 (1.00 - 1.01)	0.9704	1.00 (0.99 - 1.00)	0.6015	1.037	1.000	1.00 (0.99 - 1.00)	0.3247

Table 6. Maternal quality of life sleep during pregnancy disturbance caused by wheeze at 3 years of age

			Univariable (Complete case)			Multivariable (Complete cases)			E-value for the limit of the	
Maternal mental health status (Exposure)	Allergy features (Outcome)	Allergy features (Category)	N	OR (95% CI)	p-value	aOR (95% CI)	p-value	E-value for the aOR	CI	
SF-8 (PCS)	Sleep disturbance caused by wheeze	No wheeze (Ref)	50498	-	-	-	-	-	-	-
		Never woken with wheezing	5192	0.99 (0.99–1.00)	0.0027	1.00 (0.99–1.00)	0.0638	1.072	1.000	
		Less than 1 night per week	4037	0.98 (0.98–0.99)	<0.0001	0.98 (0.98–0.99)	<0.0001	1.153	1.126	
		One or more nights per week	1175	0.98 (0.97–0.99)	<0.0001	0.98 (0.97–0.99)	<0.0001	1.168	1.121	
SF-8 (MCS)		No wheeze (Ref)	50498	-	-	-	-	-	-	-
		Never woken with wheezing	5192	1.00(0.99–1.00)	0.2569	1.00 (0.99–1.00)	0.5957	1.037	1.000	
		Less than one night per week	4037	0.98 (0.98–0.99)	<0.0001	0.99 (0.98–0.99)	<0.0001	1.142	1.113	
		One or more nights per week	1175	0.96 (0.95–0.97)	<0.0001	0.96 (0.95–0.97)	<0.0001	1.246	1.212	

Table 7. Logistic regression results for association of offspring's asthma, wheeze, and food allergy with maternal depression during pregnancy

Multivariable (Multiple Imputation)											
Univariable (Complete Case)						Multivariable (Complete Case)			Imputation)		
Maternal mental health status (Exposure)	Maternal mental health	Allergy features (Outcome)	No. of Yes / N (%)	OR (95%CI)	p-value	aOR (95%CI)	p-value	E-value for the aOR CI	E-value for the limit of the CI	aOR (95%CI)	p-value
	Category										
K-6 (>=13) severe depression											
depression	No	Asthma diagnosis	4434 / 60101 (7.38%)	-	-	-	-	-	-	-	-
	Yes		170 / 1628 (10.44%)	1.46 (1.25 - 1.72)	<0.0001	1.37 (1.16 - 1.61)	0.0002	2.072	1.586	1.36 (1.17 - 1.57)	<0.0001
	No	Current wheeze	10161 / 59737 (17.01%)	-	-	-	-	-	-	-	-
	Yes		333 / 1616 (20.61%)	1.27 (1.12 - 1.43)	0.0002	1.22 (1.07 - 1.38)	0.0021	1.440	1.229	1.23 (1.10 - 1.37)	0.0003
	No	ever wheeze	17845 / 59979 (29.75%)	-	-	-	-	-	-	-	-
	Yes		584 / 1626 (35.92%)	1.32 (1.19 - 1.47)	<0.0001	1.27 (1.15 - 1.42)	<0.0001	1.508	1.343	1.28 (1.16 - 1.40)	<0.0001
	No	food allergy diagnosis	3870 / 60101 (6.44%)	-	-	-	-	-	-	-	-
	Yes		101 / 1628 (6.20%)	0.96 (0.78 - 1.18)	0.7027	0.97 (0.79 - 1.19)	0.7796	1.205	1.000	0.99 (0.83 - 1.19)	0.9296
	No	food allergy symptoms	4622 / 60101 (7.69%)	-	-	-	-	-	-	-	-
	Yes		129 / 1628 (7.92%)	1.03 (0.86 - 1.24)	0.7273	1.05 (0.87 - 1.26)	0.6290	1.267	1.000	1.01 (0.86 - 1.20)	0.8837
K-6 (>=5) any depression											
K-6 (>=5) any depression	No	Asthma diagnosis	1452 / 16566 (8.76%)	-	-	-	-	-	-	-	-
	Yes		3152 / 45163 (6.98%)	1.28 (1.20 - 1.37)	<0.0001	1.23 (1.148 - 1.31)	<0.0001	1.755	1.561	1.21 (1.14 - 1.29)	<0.0001
	No	Current wheeze	3146 / 16434 (19.14%)	-	-	-	-	-	-	-	-
	Yes		7348 / 44919 (16.36%)	1.21 (1.16 - 1.27)	<0.0001	1.18 (1.12 - 1.24)	<0.0001	1.391	1.313	1.18 (1.13 - 1.24)	<0.0001
	No	ever wheeze	5494 / 16527 (33.24%)	-	-	-	-	-	-	-	-
	Yes		12935 / 45078 (28.69%)	1.24 (1.19 - 1.29)	<0.0001	1.21 (1.16 - 1.26)	<0.0001	1.427	1.364	1.21 (1.17 - 1.25)	<0.0001
	No	food allergy diagnosis	1121 / 16566 (6.77%)	-	-	-	-	-	-	-	-
	Yes		2850 / 45163 (6.31%)	1.08 (1.00 - 1.16)	0.0406	1.08 (1.01 - 1.16)	0.0331	1.380	1.086	1.08 (1.01 - 1.15)	0.0347

	No	food allergy symptoms	1332 / 16566 (8.04%)	-	-	-	-	-	-	-	-
	Yes		3419 / 45163 (7.57%)	1.068 (1.00 - 1.14)	0.0521	1.07 (1.00 - 1.15)	0.0409	1.351	1.057	1.07 (1.01 - 1.14)	0.0307
Doctor's diagnosis											
depression	No	Asthma diagnosis	4449 / 60026 (7.41%)	-	-	-	-	-	-	-	-
	Yes		157 / 1756 (8.94%)	1.23 (1.04 - 1.45)	0.0164	1.17 (0.99 - 1.39)	0.0684	1.617	1.000	1.24 (1.07 - 1.45)	0.0049
	No	Current wheeze	10144 / 59668 (17.00%)	-	-	-	-	-	-	-	-
	Yes		357 / 1738 (20.54%)	1.22 (1.12 - 1.42)	0.0001	1.21 (1.03 - 1.37)	0.0019	1.433	1.229	1.21 (1.09 - 1.36)	0.0006
	No	ever wheeze	17849 / 59908 (29.79%)	-	-	-	-	-	-	-	-
	Yes		592 / 1750 (33.83%)	1.21 (1.09 - 1.33)	0.0003	1.18 (1.06 - 1.31)	0.0018	1.391	1.210	1.16 (1.04 - 1.28)	0.0023
	No	food allergy diagnosis	3830 / 60026 (6.38%)	-	-	-	-	-	-	-	-
	Yes		143 / 1756 (8.14%)	1.30 (1.09 - 1.55)	0.0031	1.28 (1.08 - 1.53)	0.0056	1.883	1.360	1.25 (1.06 - 1.47)	0.0081
	No	food allergy symptoms	4585 / 60026 (7.64%)	-	-	-	-	-	-	-	-
	Yes		168 / 1756 (9.57%)	1.28 (1.09 - 1.50)	0.0029	1.23 (1.05 - 1.45)	0.0119	1.770	1.270	1.25 (1.08 - 1.46)	0.0037
Doctor's diagnosis anxiety											
disorder	No	Asthma diagnosis	4454 / 60201 (7.40%)	-	-	-	-	-	-	-	-
	Yes		152 / 1581 (9.61%)	1.33 (1.12 - 1.58)	0.0010	1.29 (1.09 - 1.54)	0.0034	1.910	1.399	1.41 (1.21 - 1.64)	<0.0001
	No	Current wheeze	10174 / 59841 (17.00%)	-	-	-	-	-	-	-	-
	Yes		327 / 1565 (20.89%)	1.29 (1.14 - 1.46)	<0.0001	1.27 (1.12 - 1.44)	0.0002	1.504	1.304	1.33 (1.19 - 1.49)	<0.0001
	No	ever wheeze	17881 / 60081 (29.76%)	-	-	-	-	-	-	-	-
	Yes		560 / 1577 (35.51%)	1.30 (1.17 - 1.44)	<0.0001	1.30 (1.17 - 1.45)	<0.0001	1.537	1.372	1.34 (1.21 - 1.48)	<0.0001
	No	food allergy diagnosis	3838 / 60201 (6.38%)	-	-	-	-	-	-	-	-
	Yes		135 / 1581 (8.54%)	1.37 (1.15 - 1.64)	0.0006	1.38 (1.15 - 1.65)	0.0005	2.099	1.564	1.37 (1.16- 1.62)	0.0002
	No	food allergy symptoms	4597 / 60201 (7.64%)	-	-	-	-	-	-	-	-
	Yes		156 / 1581 (9.87%)	1.32 (1.12 - 1.57)	0.0011	1.31 (1.10 - 1.55)	0.0020	1.940	1.440	1.39 (1.19 - 1.62)	<0.0001

Table 8. Maternal depression during pregnancy and sleep disturbance caused by wheeze in 3-year-old children

		Univariable (Complete cases)				Multivariable (Complete cases)			
		Maternal mental health status						E-value for the limit of the	E-value for the limit of the
Allergy features (Outcome)	Allergy features (Category)	(Exposure)	No. of "yes" / N (%)	OR (95% CI)	p-value	aOR (95% CI)	p-value	aOR	CI
Sleep disturbance caused by wheeze	No wheeze (Ref)	K-6 (≥ 13) severe depression	1283 / 50859 (2.52%)	-	-	-	-	-	-
	Never woken with wheezing		127 / 5230 (2.43%)	0.96 (0.80–1.16)	0.6781	0.94 (0.78 - 1.13)	0.5171	1.324	1.000
	Less than one night per week		140 / 4069 (3.44%)	1.38 (1.15–1.64)	0.0004	1.31 (1.1 - 1.57)	0.0032	1.948	1.417
	One or more nights per week		66 / 1185 (5.57%)	2.28 (1.77–2.94)	<0.0001	2.1. (1.62 - 2.72)	<0.0001	3.619	2.630
	No wheeze (Ref)	K-6 (≥ 5) any depression	13288 / 50859 (26.13%)	-	-	-	-	-	-
	Never woken with wheezing		1365 / 5230 (26.10%)	1.00 (0.94–1.07)	0.9654	0.98 (0.92 - 1.05)	0.5878	1.155	1.000
	Less than one night per week		1332 / 4069 (32.74%)	1.38 (1.29–1.47)	<0.0001	1.33 (1.24 - 1.43)	<0.0001	1.994	1.788
	One or more nights per week		444 / 1185 (37.47%)	1.69 (1.50–1.91)	<0.0001	1.61 (1.43 - 1.82)	<0.0001	2.610	2.215
	No wheeze (Ref)	Doctor's diagnosis of depression	1381 / 50905 (2.71%)	-	-	-	-	-	-
	Never woken with wheezing		184 / 5233 (3.52%)	1.31 (1.12–1.53)	0.0008	1.26 (1.08–1.48)	0.0038	1.843	1.370
	Less than one night per week		137 / 4073 (3.36%)	1.25 (1.00–1.49)	0.0149	1.20 (1.00–1.43)	0.0522	1.680	1.000
	One or more nights per week		38 / 1185 (3.21%)	1.19 (0.86–1.65)	0.3025	1.10 (0.79–1.54)	0.5567	1.442	1.000
	No wheeze (Ref)	Doctor's diagnosis of anxiety disorder	1238 / 50905 (2.43%)	-	-	-	-	-	-
	Never woken with wheezing		158 / 5233 (3.02%)	1.25 (1.06–1.48)	0.0095	1.24 (1.05–1.48)	0.0120	1.795	1.276
	Less than one night per week		122 / 4073 (3.00%)	1.24 (1.03–1.50)	0.0262	1.22 (1.01–1.47)	0.0442	1.730	1.077
	One or more nights per week		53 / 1185 (4.47%)	1.88 (1.42–2.49)	<0.0001	1.77 (1.33–2.34)	<0.0001	2.927	1.992

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Table 1. Baseline characteristic of the study

	Category	Analysis set	Excluded
Mothers		72685	15589
Study Prefectures	Hokkaido, n(%)	5750 (7.9%)	1294 (8.3%)
	Miyagi, n(%)	6287 (8.6%)	1532 (9.8%)
	Fukushima, n(%)	9373 (12.9%)	2198 (14.1%)
	Chiba, n(%)	4078 (5.6%)	1095 (7.0%)
	Kanagawa, n(%)	4762 (6.6%)	982 (6.3%)
	Yamanashi, n(%)	3055 (4.2%)	856 (5.5%)
	Koshin(nagano), n(%)	2137 (2.9%)	239 (1.5%)
	Toyama, n(%)	4184 (5.8%)	629 (4.0%)
	Aichi, n(%)	4128 (5.7%)	751 (4.8%)
	Kyoto, n(%)	2978 (4.1%)	500 (3.2%)
	Osaka, n(%)	5700 (7.8%)	1140 (7.3%)
	Hyogo, n(%)	3767 (5.2%)	735 (4.7%)
	Tottori, n(%)	2283 (3.1%)	381 (2.4%)
	Kochi, n(%)	4800 (6.6%)	1209 (7.8%)
	Fukuoka, n(%)	5533 (7.6%)	1038 (6.7%)
	Kumamoto, n(%)	1908 (2.6%)	655 (4.2%)
	Miyazaki, n(%)	1395 (1.9%)	169 (1.1%)
	Okinawa, n(%)	567 (0.8%)	186 (1.2%)
Age at birth, year	Mean (SD)	30.9 (4.9)	29.4 (5.4)
	Minimum	14	14
	25%ile	28	26
	50%ile	31	29
	75%ile	34	33
	Max	48	46

Children	Past medical history	Missing, n(%)	1357 (1.9%)	401 (2.6%)
		Any allergic diseases, n(%)	40492 (55.7%)	7900 (50.7%)
		Asthma, n(%)	7689 (10.6%)	1863 (12.0%)
		Hayfever, allergic rhinitis, n(%)	26520 (36.5%)	4970 (31.9%)
		Atopic dermatitis, n(%)	11650 (16.0%)	2217 (14.2%)
		Allergic conjunctivitis, n(%)	7373 (10.1%)	1341 (8.6%)
		Food allergy, n(%)	3477 (4.8%)	753 (4.8%)
		Drug allergy, n(%)	1925 (2.6%)	341 (2.2%)
		Urticaria, n(%)	11248 (15.5%)	2101 (13.5%)
		Contact dermatitis, n(%)	1449 (2.0%)	243 (1.6%)
	Highest graduation	Middle school, n(%)	2702 (3.7%)	1422 (9.1%)
		High school, n(%)	21623 (29.7%)	5487 (35.2%)
		Technical school, n(%)	1176 (1.6%)	240 (1.5%)
		College of technology, n(%)	16567 (22.8%)	3165 (20.3%)
		Junior college, n(%)	13257 (18.2%)	1950 (12.5%)
		University, n(%)	15601 (21.5%)	1931 (12.4%)
		Graduate school, n(%)	1158 (1.6%)	142 (0.9%)
		Missing, n(%)	601 (0.8%)	1252 (8.0%)
	BMI before pregnancy	Mean (SD)	21.1 (3.2)	21.5 (3.7)
		Minimum	13.3	14.3
		25%ile	19.1	19.1
		50%ile	20.5	20.7
		75%ile	22.4	23.0
		Max	48.8	45.9
		Missing, n(%)	37 (0.1%)	71 (0.5%)
Children	Child's sex	Boy, n(%)	37054 (51.0%)	7937 (50.9%)

	Girl, n(%)	35631 (49.0%)	7644 (49.0%)
	Unclear/Missing, n(%)	0 (0.0%)	8 (0.1%)
Sibling at one month	yes, n(%)	37701 (51.9%)	
	no, n(%)	34690 (47.7%)	
	Missing, n(%)	294 (0.4%)	
Passive smoking at 3y	yes, n(%)	32253 (44.4%)	
	no, n(%)	38915 (53.5%)	
	Missing, n(%)	1517 (2.1%)	
Pet at 6 months	yes, n(%)	17467 (24.0%)	
	no, n(%)	53979 (74.3%)	
	Missing, n(%)	1239 (1.7%)	
Daycare center at 3y	yes, n(%)	44165 (60.8%)	
	no, n(%)	26327 (36.2%)	
	Missing, n(%)	2193 (3.0%)	
Annual household income, yen	<2,000,000, n(%)	3343 (4.6%)	1178 (7.6%)
	2,000,000-3,999,999, n(%)	22881 (31.5%)	4900 (31.4%)
	4,000,000-5,999,999, n(%)	22682 (31.2%)	3947 (25.3%)
	6,000,000-7,999,999, n(%)	11206 (15.4%)	1703 (10.9%)
	8,000,000-9,999,999, n(%)	4647 (6.4%)	722 (4.6%)
	10,000,000-11,999,999, n(%)	1717 (2.4%)	240 (1.5%)
	12,000,000-14,999,999, n(%)	673 (0.9%)	103 (0.7%)
	15,000,000-19,999,999, n(%)	375 (0.5%)	64 (0.4%)
	20,000,000-, n(%)	207 (0.3%)	53 (0.3%)
	Missing, n(%)	4954 (6.8%)	2679 (17.2%)

Table 2. Maternal mental status (depression and quality of life) during pregnancy (N=72685)

	Category	Statistics
Doctor's depression diagnosis	yes, n (%)	2086 (2.9%)
Doctor's diagnosis of anxiety disorder	yes, n (%)	1897 (2.6%)
K-6 scores	Mean (SD)	3.3 (3.6)
	minimum, 25th, 50th, 75th, max	0, 1, 2, 5, 24
K-6 score ≥ 13 , severe depressive status	≥ 13 , n (%)	2067 (2.8%)
	< 13 , n (%)	70198 (96.6%)
K-6 score ≥ 5 , any depressive status	≥ 5 , n (%)	19947 (27.4%)
	< 5 , n (%)	52318 (72.0%)
SF-8 (PCS)	Mean (SD)	45.8 (6.1)
	minimum, 25th, 50th, 75th, max	5.72, 42.13, 46.15, 50.06, 66.10
SF-8 (MSC)	Mean (SD)	49.2 (6.1)
	minimum, 25th, 50th, 75th, max	12.87, 45.74, 49.68, 53.59, 73.33

Table 3. Wheeze, asthma, and food allergy in 3-year-old children (N=72685)

	Category	Statistics
Doctor's diagnosis		
Asthma diagnosis	yes, n (%)	5522 (7.6%)
Food allergy diagnosis	yes, n (%)	4643 (6.4%)
Allergic symptoms		
Respiratory		
Ever wheeze	yes, n (%)	21853 (30.1%)
Current wheeze	yes, n (%)	12423 (17.1%)
Frequency of wheeze	None, n (%)	4969 (6.8%)
	1–3 times, n (%)	9095 (12.5%)
	4–12 times, n (%)	1930 (2.7%)
	13 times and more, n (%)	346 (0.5%)
Sleep disturbance caused by wheeze	No wheeze, n (%)	59766 (82.2%)
	Never woken with wheezing, n (%)	6197 (8.5%)
	Less than one night per week, n (%)	4805 (6.6%)
	One or more nights per week, n (%)	1415 (1.9%)
Speech difficulty caused by wheeze	yes, n (%)	805 (1.1%)
Wheeze caused by physical activity and crying	yes, n (%)	1635 (2.2%)
Night cough	yes, n (%)	5858 (8.1%)
Food allergy symptoms reported by caregiver	yes, n (%)	5497 (7.6%)

Table 4 frequency of childhood asthma, wheeze, food allergy for SF-8 categories

SF-8 (PCS)	Allergy features (Outcome)	No. of Yes / N (%)	SF-8 (MCS)	Allergy features (Outcome)	No. of Yes / N (%)
<25	Asthma diagnosis	43 / 414 (10.39%)	<25	Asthma diagnosis	18 / 151 (11.92%)
>=25, <30		59 / 727 (8.12%)	>=25, <30		38 / 445 (8.54%)
>=30, <35		194 / 2149 (9.03%)	>=30, <35		120 / 1266 (9.48%)
>=35, <40		600 / 7358 (8.15%)	>=35, <40		300 / 3182 (9.43%)
>=40, <45		1479 / 18995 (7.79%)	>=40, <45		850 / 9997 (8.50%)
>=45, <50		1740 / 23701 (7.34%)	>=45, <50		1717 / 22271 (7.71%)
>=50, <55		1083 / 15197 (7.13%)	>=50, <55		1505 / 21401 (7.03%)
>=55, <60		221 / 3012 (7.34%)	>=55, <60		816 / 12050 (6.77%)
>=60		11 / 124 (8.87%)	>=60		66 / 913 (7.23%)
<25	Current wheeze	94 / 411 (22.87%)	<25	Current wheeze	38 / 151 (25.17%)
>=25, <30		139 / 716 (19.41%)	>=25, <30		76 / 437 (17.39%)
>=30, <35		441 / 2136 (20.65%)	>=30, <35		254 / 1250 (20.32%)
>=35, <40		1389 / 7311 (19.00%)	>=35, <40		652 / 3152 (20.69%)
>=40, <45		3373 / 18863 (17.88%)	>=40, <45		1772 / 9914 (17.87%)
>=45, <50		3894 / 23534 (16.55%)	>=45, <50		3925 / 22122 (17.74%)
>=50, <55		2392 / 15101 (15.84%)	>=50, <55		3541 / 21263 (16.65%)
>=55, <60		494 / 2993 (16.51%)	>=55, <60		1823 / 11989 (15.21%)
>=60		19 / 124 (15.32%)	>=60		154 / 910 (16.92%)
<25	ever wheeze	147 / 413 (35.59%)	<25	ever wheeze	61 / 151 (40.40%)
>=25, <30		244 / 722 (33.80%)	>=25, <30		137 / 441 (31.07%)
>=30, <35		721 / 2139 (33.71%)	>=30, <35		434 / 1261 (34.42%)
>=35, <40		2416 / 7347 (32.88%)	>=35, <40		1121 / 3172 (35.34%)
>=40, <45		5859 / 18945 (30.93%)	>=40, <45		3167 / 9962 (31.79%)
>=45, <50		7033 / 23640 (29.75%)	>=45, <50		6878 / 22220 (30.95%)

>=50, <55		4199 / 15167 (27.69%)	>=50, <55		6197 / 21354 (29.02%)
>=55, <60		883 / 3003 (29.40%)	>=55, <60		3273 / 12025 (27.22%)
>=60		35 / 124 (28.23%)	>=60		269 / 913 (29.46%)
<25	food allergy diagnosis	41 / 414 (9.90%)	<25	food allergy diagnosis	13 / 151 (8.61%)
>=25, <30		49 / 727 (6.74%)	>=25, <30		21 / 445 (4.72%)
>=30, <35		171 / 2149 (7.96%)	>=30, <35		95 / 1266 (7.50%)
>=35, <40		499 / 7358 (6.78%)	>=35, <40		210 / 3182 (6.60%)
>=40, <45		1228 / 18995 (6.46%)	>=40, <45		631 / 9997 (6.31%)
>=45, <50		1540 / 23701 (6.50%)	>=45, <50		1472 / 22271 (6.61%)
>=50, <55		889 / 15197 (5.85%)	>=50, <55		1343 / 21401 (6.28%)
>=55, <60		164 / 3012 (5.44%)	>=55, <60		737 / 12050 (6.12%)
>=60		5 / 124 (4.03%)	>=60		64 / 913 (7.01%)
<25	food allergy symptoms	42 / 414 (10.14%)	<25	food allergy symptoms	12 / 151 (7.95%)
>=25, <30		66 / 727 (9.08%)	>=25, <30		32 / 445 (7.19%)
>=30, <35		204 / 2149 (9.49%)	>=30, <35		92 / 1266 (7.27%)
>=35, <40		639 / 7358 (8.68%)	>=35, <40		260 / 3182 (8.17%)
>=40, <45		1486 / 18995 (7.82%)	>=40, <45		753 / 9997 (7.53%)
>=45, <50		1763 / 23701 (7.44%)	>=45, <50		1738 / 22271 (7.80%)
>=50, <55		1029 / 15197 (6.77%)	>=50, <55		1571 / 21401 (7.34%)
>=55, <60		193 / 3012 (6.41%)	>=55, <60		901 / 12050 (7.48%)
>=60		8 / 124 (6.45%)	>=60		71 / 913 (7.78%)

Table 5. Logistic regression results for offspring's asthma, wheeze, and food allergy associated with maternal quality of life during pregnancy

Maternal mental health status (Exposure)	Allergy features (Outcome)	N	Univariable(Complete Case)		Multivariable (Complete Case)		Multivariable (Multiple Imputation)		E-value for the limit of the CI	p-value
			OR (95%CI)	p-value	aOR (95%CI)	p-value	aOR	aOR (95%CI)		
SF-8 (PCS)	Asthma diagnosis	61283	0.99 (0.99 - 1.00)	0.0002	0.99 (0.99 - 1.00)	0.0025	1.096	1.055	0.99 (0.99 - 1.00)	0.0001
	Current wheeze	60912	0.99 (0.98 - 0.99)	<0.0001	0.99 (0.99 - 0.99)	<0.0001	1.082	1.068	0.99 (0.99 - 0.99)	<0.0001
	ever wheeze	61159	0.99 (0.98 - 0.99)	<0.0001	0.99 (0.99 - 0.99)	<0.0001	1.082	1.070	0.99 (0.99 - 0.99)	<0.0001
	food allergy diagnosis	61283	0.99 (0.98 - 0.99)	<0.0001	0.99 (0.98 - 0.99)	<0.0001	1.119	1.085	0.99 (0.98 - 0.99)	<0.0001
	food allergy symptoms	61283	0.98 (0.98 - 0.99)	<0.0001	0.98 (0.98 - 0.99)	<0.0001	1.144	1.118	0.98 (0.98 - 0.99)	<0.0001
SF-8 (MCS)	Asthma diagnosis	61283	0.98 (0.98 - 0.99)	<0.0001	0.98 (0.98 - 0.99)	<0.0001	1.143	1.116	0.99 (0.98 - 0.99)	<0.0001
	Current wheeze	60912	0.99 (0.98 - 0.99)	<0.0001	0.99 (0.99 - 0.99)	<0.0001	1.083	1.069	0.99 (0.99 - 0.99)	<0.0001
	ever wheeze	61159	0.99 (0.98 - 0.99)	<0.0001	0.99 (0.99 - 0.99)	<0.0001	1.086	1.075	0.99 (0.99 - 0.99)	<0.0001
	food allergy diagnosis	61283	1.00 (0.99 - 1.00)	0.5002	1.00 (0.99 - 1.00)	0.4063	1.050	1.000	1.00 (0.99 - 1.00)	0.2943
	food allergy symptoms	61283	1.00 (1.00 - 1.01)	0.9704	1.00 (0.99 - 1.00)	0.6015	1.037	1.000	1.00 (0.99 - 1.00)	0.3247

Table 6. Maternal quality of life sleep during pregnancy disturbance caused by wheeze at 3 years of age

				Univariable (Complete case)		Multivariable (Complete cases)		E-value for the limit of the CI	
Maternal mental health status (Exposure)	Allergy features (Outcome)	Allergy features (Category)	N	OR (95% CI)	p-value	aOR (95% CI)	p-value	E-value for the aOR	E-value for the limit of the CI
SF-8 (PCS)	Sleep disturbance caused by wheeze	No wheeze (Ref)	50498	-	-	-	-	-	-
		Never woken with wheezing	5192	0.99 (0.99–1.00)	0.0027	1.00 (0.99–1.00)	0.0638	1.072	1.000
		Less than 1 night per week	4037	0.98 (0.98–0.99)	<0.0001	0.98 (0.98–0.99)	<0.0001	1.153	1.126
		One or more nights per week	1175	0.98 (0.97–0.99)	<0.0001	0.98 (0.97–0.99)	<0.0001	1.168	1.121
SF-8 (MCS)		No wheeze (Ref)	50498	-	-	-	-	-	-
		Never woken with wheezing	5192	1.00(0.99–1.00)	0.2569	1.00 (0.99–1.00)	0.5957	1.037	1.000
		Less than one night per week	4037	0.98 (0.98–0.99)	<0.0001	0.99 (0.98–0.99)	<0.0001	1.142	1.113
		One or more nights per week	1175	0.96 (0.95–0.97)	<0.0001	0.96 (0.95–0.97)	<0.0001	1.246	1.212

Table 7. Logistic regression results for association of offspring's asthma, wheeze, and food allergy with maternal depression during pregnancy

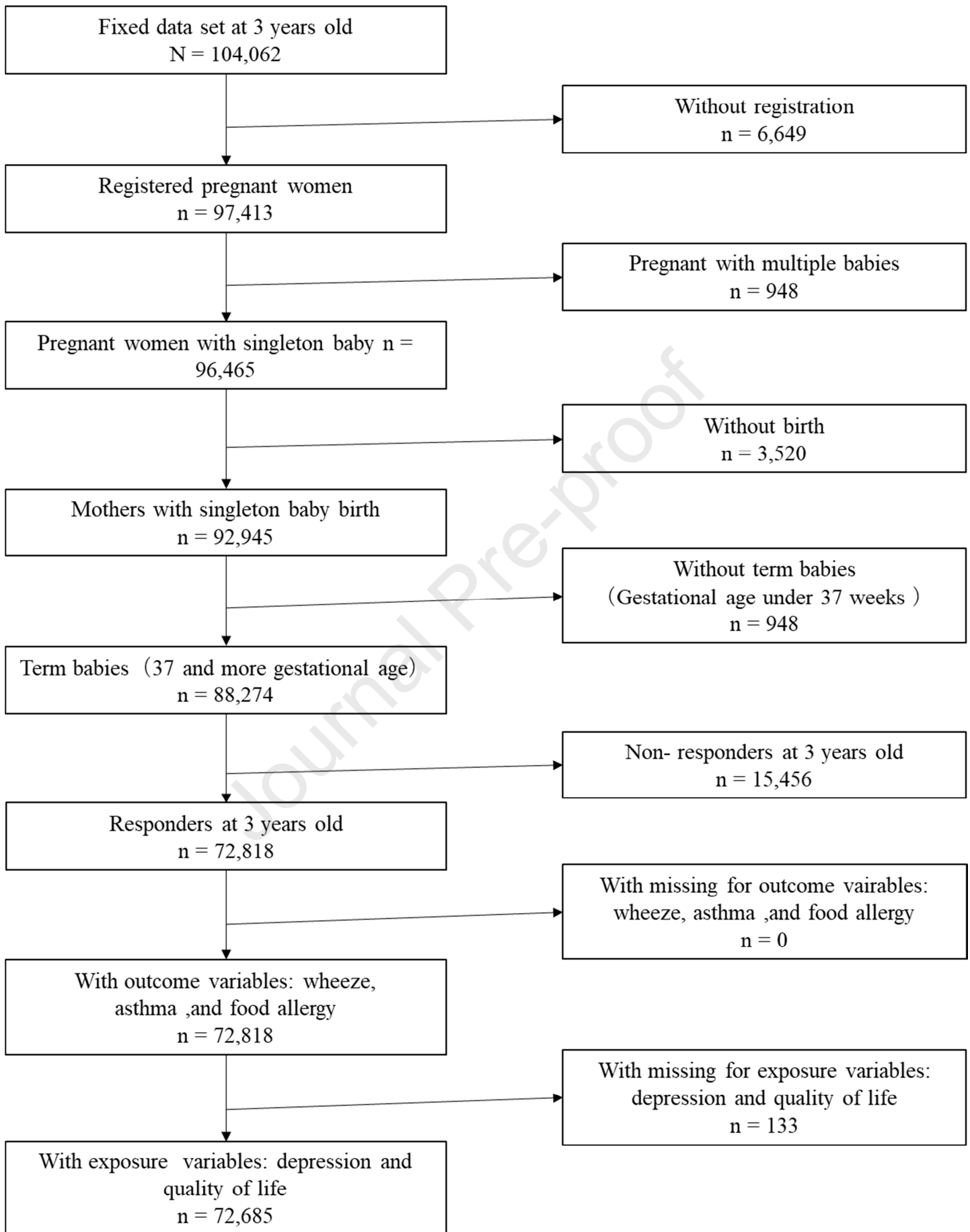
Maternal mental health status (Exposure)	Maternal mental health Category	Allergy features (Outcome)	No. of Yes / N (%)	Univariable (Complete Case)		Multivariable (Complete Case)		Multivariable (Multiple Imputation)		E-value for the limit of the CI
				OR (95%CI)	p-value	aOR (95%CI)	p-value	aOR (95%CI)	p-value	
K-6 (≥ 13) severe depression	No	Asthma diagnosis	4434 / 60101 (7.38%)							
	Yes		170 / 1628 (10.44%)	1.46 (1.25 - 1.72)	<0.0001	1.37 (1.16 - 1.61)	0.0002	2.072	1.586	1.36 (1.17 - 1.57) <0.0001
	No	Current wheeze	10161 / 59737 (17.01%)							
	Yes		333 / 1616 (20.61%)	1.27 (1.12 - 1.43)	0.0002	1.22 (1.07 - 1.38)	0.0021	1.440	1.229	1.23 (1.10 - 1.37) 0.0003
	No	ever wheeze	17845 / 59979 (29.75%)							
	Yes		584 / 1626 (35.92%)	1.32 (1.19 - 1.47)	<0.0001	1.27 (1.15 - 1.42)	<0.0001	1.508	1.343	1.28 (1.16 - 1.40) <0.0001
	No	food allergy diagnosis	3870 / 60101 (6.44%)							
	Yes		101 / 1628 (6.20%)	0.96 (0.78 - 1.18)	0.7027	0.97 (0.79 - 1.19)	0.7796	1.205	1.000	0.99 (0.83 - 1.19) 0.9296
	No	food allergy symptoms	4622 / 60101 (7.69%)							
	Yes		129 / 1628 (7.92%)	1.03 (0.86 - 1.24)	0.7273	1.05 (0.87 - 1.26)	0.6290	1.267	1.000	1.01 (0.86 - 1.20) 0.8837
K-6 (≥ 5) any depression	No	Asthma diagnosis	1452 / 16566 (8.76%)							
	Yes		3152 / 45163 (6.98%)	1.28 (1.20 - 1.37)	<0.0001	1.23 (1.148 - 1.31)	<0.0001	1.755	1.561	1.21 (1.14 - 1.29) <0.0001
	No	Current wheeze	3146 / 16434 (19.14%)							
	Yes		7348 / 44919 (16.36%)	1.21 (1.16 - 1.27)	<0.0001	1.18 (1.12 - 1.24)	<0.0001	1.391	1.313	1.18 (1.13 - 1.24) <0.0001
	No	ever wheeze	5494 / 16527 (33.24%)							
	Yes		12935 / 45078 (28.69%)	1.24 (1.19 - 1.29)	<0.0001	1.21 (1.16 - 1.26)	<0.0001	1.427	1.364	1.21 (1.17 - 1.25) <0.0001
	No	food allergy diagnosis	1121 / 16566 (6.77%)							
	Yes		2850 / 45163 (6.31%)	1.08 (1.00 - 1.16)	0.0406	1.08 (1.01 - 1.16)	0.0331	1.380	1.086	1.08 (1.01 - 1.15) 0.0347

	No	food allergy symptoms	1332 / 16566 (8.04%)								
	Yes		3419 / 45163 (7.57%)	1.068 (1.00 - 1.14)	0.0521	1.07 (1.00 - 1.15)	0.0409	1.351	1.057	1.07 (1.01 - 1.14)	0.0307
Doctor's diagnosis											
depression	No	Asthma diagnosis	4449 / 60026 (7.41%)								
	Yes		157 / 1756 (8.94%)	1.23 (1.04 - 1.45)	0.0164	1.17 (0.99 - 1.39)	0.0684	1.617	1.000	1.24 (1.07 - 1.45)	0.0049
	No	Current wheeze	10144 / 59668 (17.00%)								
	Yes		357 / 1738 (20.54%)	1.22 (1.12 - 1.42)	0.0001	1.21 (1.03 - 1.37)	0.0019	1.433	1.229	1.21 (1.09 - 1.36)	0.0006
	No	ever wheeze	17849 / 59908 (29.79%)								
	Yes		592 / 1750 (33.83%)	1.21 (1.09 - 1.33)	0.0003	1.18 (1.06 - 1.31)	0.0018	1.391	1.210	1.16 (1.04 - 1.28)	0.0023
	No	food allergy diagnosis	3830 / 60026 (6.38%)								
	Yes		143 / 1756 (8.14%)	1.30 (1.09 - 1.55)	0.0031	1.28 (1.08 - 1.53)	0.0056	1.883	1.360	1.25 (1.06 - 1.47)	0.0081
	No	food allergy symptoms	4585 / 60026 (7.64%)								
	Yes		168 / 1756 (9.57%)	1.28 (1.09 - 1.50)	0.0029	1.23 (1.05 - 1.45)	0.0119	1.770	1.270	1.25 (1.08 - 1.46)	0.0037
Doctor's diagnosis anxiety											
disorder	No	Asthma diagnosis	4454 / 60201 (7.40%)								
	Yes		152 / 1581 (9.61%)	1.33 (1.12 - 1.58)	0.0010	1.29 (1.09 - 1.54)	0.0034	1.910	1.399	1.41 (1.21 - 1.64)	<0.0001
	No	Current wheeze	10174 / 59841 (17.00%)								
	Yes		327 / 1565 (20.89%)	1.29 (1.14 - 1.46)	<0.0001	1.27 (1.12 - 1.44)	0.0002	1.504	1.304	1.33 (1.19 - 1.49)	<0.0001
	No	ever wheeze	17881 / 60081 (29.76%)								
	Yes		560 / 1577 (35.51%)	1.30 (1.17 - 1.44)	<0.0001	1.30 (1.17 - 1.45)	<0.0001	1.537	1.372	1.34 (1.21 - 1.48)	<0.0001
	No	food allergy diagnosis	3838 / 60201 (6.38%)								
	Yes		135 / 1581 (8.54%)	1.37 (1.15 - 1.64)	0.0006	1.38 (1.15 - 1.65)	0.0005	2.099	1.564	1.37 (1.16 - 1.62)	0.0002
	No	food allergy symptoms	4597 / 60201 (7.64%)								
	Yes		156 / 1581 (9.87%)	1.32 (1.12 - 1.57)	0.0011	1.31 (1.10 - 1.55)	0.0020	1.940	1.440	1.39 (1.19 - 1.62)	<0.0001

Table 8. Maternal depression during pregnancy and sleep disturbance caused by wheeze in 3-year-old children

		Univariable (Complete cases)				Multivariable (Complete cases)			
						E-value for the limit of the			
						aOR CI			
Allergy features (Outcome)	Allergy features (Category)	(Exposure)	No. of “yes” / N (%)	OR (95% CI)	p-value	aOR (95% CI)	p-value	aOR	CI
Sleep disturbance caused by wheeze	No wheeze (Ref)	K-6 (≥13) severe depression	1283 / 50859 (2.52%)	-	-	-	-	-	-
	Never woken with wheezing		127 / 5230 (2.43%)	0.96 (0.80–1.16)	0.6781	0.94 (0.78 - 1.13)	0.5171	1.324	1.000
	Less than one night per week		140 / 4069 (3.44%)	1.38 (1.15–1.64)	0.0004	1.31 (1.1 - 1.57)	0.0032	1.948	1.417
	One or more nights per week		66 / 1185 (5.57%)	2.28 (1.77–2.94)	<0.0001	2.1 (1.62 - 2.72)	<0.0001	3.619	2.630
	No wheeze (Ref)	K-6 (≥5) any depression	13288 / 50859 (26.13%)	-	-	-	-	-	-
	Never woken with wheezing		1365 / 5230 (26.10%)	1.00 (0.94–1.07)	0.9654	0.98 (0.92 - 1.05)	0.5878	1.155	1.000
	Less than one night per week		1332 / 4069 (32.74%)	1.38 (1.29–1.47)	<0.0001	1.33 (1.24 - 1.43)	<0.0001	1.994	1.788
	One or more nights per week		444 / 1185 (37.47%)	1.69 (1.50–1.91)	<0.0001	1.61 (1.43 - 1.82)	<0.0001	2.610	2.215
	No wheeze (Ref)	Doctor's diagnosis of depression	1381 / 50905 (2.71%)	-	-	-	-	-	-
	Never woken with wheezing		184 / 5233 (3.52%)	1.31 (1.12–1.53)	0.0008	1.26 (1.08–1.48)	0.0038	1.843	1.370
	Less than one night per week		137 / 4073 (3.36%)	1.25 (1.00–1.49)	0.0149	1.20 (1.00–1.43)	0.0522	1.680	1.000
	One or more nights per week		38 / 1185 (3.21%)	1.19 (0.86–1.65)	0.3025	1.10 (0.79–1.54)	0.5567	1.442	1.000
		Doctor's diagnosis of anxiety disorder							
	No wheeze (Ref)		1238 / 50905 (2.43%)	-	-	-	-	-	-
	Never woken with wheezing		158 / 5233 (3.02%)	1.25 (1.06–1.48)	0.0095	1.24 (1.05–1.48)	0.0120	1.795	1.276
	Less than one night per week		122 / 4073 (3.00%)	1.24 (1.03–1.50)	0.0262	1.22 (1.01–1.47)	0.0442	1.730	1.077
	One or more nights per week		53 / 1185 (4.47%)	1.88 (1.42–2.49)	<0.0001	1.77 (1.33–2.34)	<0.0001	2.927	1.992

eFigure 1. Flow chart of the study



eTable 1 Delivery mode and allergic outcomes

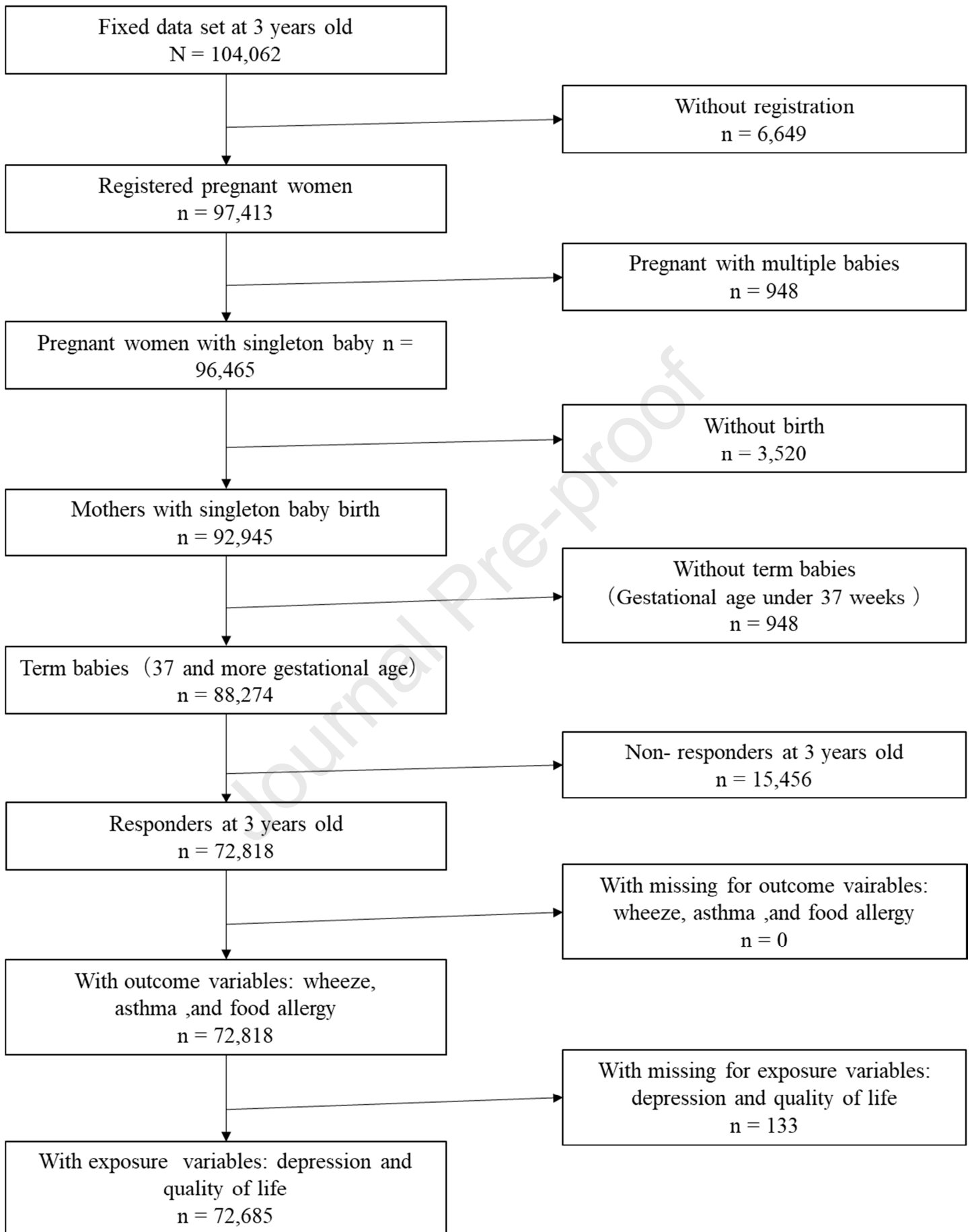
				p-value (Chi-squared test)
Allergic symptoms	Category	C-section (N=12601)	Vaginal delivery (N=59907)	
Doctor's diagnosis				
Asthma	yes, n(%)	1020 (8.1%)	4480 (7.5%)	0.0184
	no, n(%)	11581 (91.9%)	55427 (92.5%)	-
Food allergy	yes, n(%)	778 (6.2%)	3849 (6.4%)	0.3044
	no, n(%)	11823 (93.8%)	56058 (93.6%)	-
Food allergy reported by caregiver				
Caregiver's reported food allergy*	yes, n(%)	902 (7.2%)	4575 (7.6%)	0.0673
	no, n(%)	11699 (92.8%)	55332 (92.4%)	-

* N=177 were excluded from the analysis due to missing delivery method.

Table 2. Maternal quality of life and delivery mode

Maternal mental health status	Group	N	Mean (SD)	Difference of mean (95%CI)	p-value
				(C-section - Vaginal delivery)	(Welch's t-test, two-sided)
SF-8 (PCS)	C-section	12438	45.523 (6.263)	-0.361 (-0.482 - -0.240)	<0.0001
	Vaginal delivery	59073	45.884 (6.100)	-	-
SF-8 (MCS)	C-section	12438	49.129 (6.275)	-0.141 (-0.262 - -0.020)	0.0220
	Vaginal delivery	59073	49.270 (6.087)	-	-

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1 Introduction

2 The World Health Organization defines quality of life (QoL) as an individual's perception of their
3 position in life within the context of the culture and value system in which they live and in relation
4 to their goals, expectations, standards, and concerns. It is a wide-ranging concept affected by a
5 person's psychological state, physical health, personal beliefs, social relationships, and their
6 relationship with their environment. Therefore, QoL is important in daily life. Stucly *et al.*¹
7 demonstrated that asthma severity and symptoms were strongly related to asthma-specific QoL,
8 and Chen *et al.*² demonstrated that poor asthma control led to impairment of a patient's QoL.
9 The emerging concept of the Developmental Origins of Health and Disease (DOHaD) hypothesis
10 states that various exposures during the preconception and postconception period in the embryo and
11 fetus can contribute to the development of noncommunicable diseases in children.³ Epigenetic
12 modifications such as DNA methylation can occur due to early life environmental exposures,
13 including medication, chemicals, nutritional factors, and stressors. These modifications can have an
14 impact on children's subsequent health. A systematic review reported that maternal psychological
15 stress during pregnancy increased the risk of wheezing and asthma in the offspring.⁴ Based on the
16 DOHaD hypothesis, maternal mental health during pregnancy could affect the offspring's immune
17 system and allergic symptoms.

In Japan, mental health is a serious and alarming issue among pregnant women, with suicide the top cause of death during pregnancy.⁵ Approximately 70% of schoolchildren in Tokyo were found to have IgE sensitization,⁶ indicating an epidemic of allergic symptoms among Japanese children. To the best of our knowledge, no study has yet examined how prenatal maternal QoL influences allergic traits in children. In this study, we examined whether maternal QoL and depression led to wheezing, asthma, and food allergy in offspring at 3 years of age.

Methods

Study design, setting, and participants

We performed a nationwide, multicenter, prospective, birth cohort study: the Japan Environment and Children's Study (JECS),⁷⁻¹⁰ which was conducted by the Ministry of the Environment, Japan. A general population of 103,060 pregnant women was registered in the JECS in 15 regional centers, covering a broad geographic region from the north of Japan (Hokkaido) to the south (Okinawa), 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 August 1, 2011 and mid-2014; and (4) ability to understand the Japanese language. In total, 104,062 newborns were enrolled in the JECS. The JECS registry is the University Hospital Medical Information Network

(UMIN) 000030786 (UMIN Clinical Trials Registry). JECS protocols for the main study and the subcohort study are described on the website of the Japanese Ministry of the Environment.^{11, 12}

Ethics statement

The JECS protocol was reviewed and approved by the Ministry of the Environment Institutional Review Board on Epidemiological Studies and by the ethics committees of all participating institutions. Written informed consent was obtained from all participants. The JECS was conducted in accordance with the principles laid out in the Declaration of Helsinki and other national regulations and guidelines.

Data collection

All variables were collected from written questionnaires that were provided to caregivers during pregnancy and when the child was aged 6 months and 1, 1.5, 2, 2.5, and 3 years. Caregivers answered questions regarding the child and the family. Information on each child's background, lifestyle, and nutrition was assessed using the questionnaires. All the questionnaires were in Japanese.

Exposures

In this study, we established depression, QoL, and a doctor's diagnosis of depression or anxiety disorder as exposures. Depression was defined based on the Kessler Screening Scale for Psychological Distress (K-6) scores.¹³⁻¹⁶ The total K-6 score ranges from 0 to 24. Scores of 13 or

higher indicate severe depression, and scores of 5 or higher indicate any depression. Health-related QoL was measured using the Medical Outcomes Survey Short Form-8 questionnaire (SF-8).^{17, 18} The SF-8 items assess general health, physical functioning, role-physical, bodily pain, vitality, social functioning, mental health, and role-emotional. Two summary scores of the physical component summary (PCS) and mental component summary (MCS), indicating physical and mental functioning, respectively, were shown as standard deviation scores (the national standard score is 50). These scores were calculated using a validated scoring program for Japanese populations. Higher scores indicate a higher-quality health status. The K-6 and SF-8 were assessed during the first trimester (MT1). A doctor's diagnosis of depression or anxiety disorder was also assessed during MT1.

Outcomes

All outcomes were evaluated using the questionnaire administered when the child was 3 years of age; caregiver-reported medical diagnoses of asthma and food allergy were obtained using questionnaires administered at this time. These physician diagnoses were defined as a positive answer from the caregiver to the question: "Has your child ever been diagnosed by a physician as having asthma and/or food allergy in the past 12 months?" Caregiver-reported wheezing and sleep disturbance due to wheezing were evaluated based on a modified International Study of Asthma and Allergies in Childhood questionnaire for children aged 6–7 years, which was translated and validated

in Japanese.¹⁹⁻²¹ Caregiver-reported food allergy was defined as a history of reactions to and

avoidance of causal foods; both were evaluated using a questionnaire.

Statistical analyses

Questionnaire data concerning 104,062 fetuses from mothers who were enrolled in the study and did

not withdraw their consent were included in the analysis (see eFigure 1). As the population of

interest, we analyzed data from 3-year-old children born as a singleton after 37 weeks' gestation and

with questionnaire responses for outcome and exposure variables (eFigure 1). We used a fixed data

set (jecs-ta-201901930-qsn, released in October 2019) in this study. Based on clinical experience and

a review of past reports, we assessed the following factors as possible confounders in the regression

analyses: maternal age, maternal allergy history, maternal body mass index, maternal education level,

annual family income, family smoking when the child was 3 years of age, pet ownership at 6 months

of age, child's sex, nursery school attendance, and the place of recruitment. We checked the

collinearity of preliminarily selected confounders and included all available variables in the model,

without performing variable selection. For each binary outcome variable of allergic symptoms, we

conducted logistic regression analyses and performed a multinomial logistic regression analysis for

the outcome of sleep disturbance due to wheezing (with 4 categories). We evaluated the odds ratios

(ORs) and adjusted odds ratios (aORs) as measures of association and calculated 95% confidence

intervals (CIs) and p-values. We estimated aORs by implementing a multivariate imputation by

chained equations (MICE) algorithm with 20 iterations, using the R package MICE, version 3.9.0. The e-value represents the minimum magnitude of association required between an unmeasured confounder and the exposure and outcome, conditional on measured covariates, to fully attenuate the observed exposure-outcome association. We provided e-values as a sensitivity analysis to unknown and unmeasured confounding variables. All the statistical analyses were performed using R statistical software, version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Participant characteristics

Of the fixed data set at 3 years of age ($N = 104,062$), a total of 72,685 participants had no missing information (see eFigure 1). Mean maternal age at the child's birth was 30.9 (± 4.9) years. Among the total, 10.6% of mothers had an asthma history (Table 1). Passive smoking exposure was present in 44.4% of children at 3 years. A depression diagnosis by a doctor was recorded for 2.9% of the mothers (Table 2). Mean PCS and MCS scores of the SF-8 were 45.8 and 49.2, respectively. As for the children's outcomes, 7.6% of the children had an asthma diagnosis and 30.1% had a lifetime wheezing history (Table 3). The frequency of childhood asthma, wheezing, and food allergy for the SF-8 categories is shown in Table 4.

Maternal quality of life during pregnancy and offspring outcomes

Table 5 demonstrates the associations between offspring's wheezing, asthma, and food allergy at 3 years of age and maternal QoL during pregnancy and the results of those sensitivity analyses as e-values. SF-8 maternal PCS scores were negatively associated with the offspring's asthma (aOR 0.99, 95% CI 0.99–1.00), current wheezing (aOR 0.99, 95% CI 0.99–0.99), and food allergy diagnosis (aOR 0.99, 95% CI 0.98–0.99) in 3-year-old children, based on the complete case analysis. SF-8 MCS scores were also negatively associated with asthma (aOR 0.98, 95% CI 0.98–0.99) and current wheezing (aOR 0.99, 95% CI 0.99–0.99) in 3-year old children based on the complete case analysis. However, there was no association between maternal MCS scores and a food allergy diagnosis.

As for sleep disturbance due to wheezing (Table 6), SF-8 PCS scores were significantly associated with sleep disturbance less than 1 night per week and 1 or more nights per week. SF-8 MCS scores were also negatively associated with sleep disturbance less than 1 night per week and 1 or more nights per week. The results by multiple imputation analysis were almost the same as the results by complete case analysis, as we described earlier. The only different results were that the PCS and MCS scores were not associated with sleep frequency disturbance caused by wheezing in the multiple imputation data analysis.

Maternal depression during pregnancy and offspring outcomes

Table 7 demonstrates the associations between the offspring's wheezing, asthma, and food allergy at 3 years of age and maternal depression and anxiety during pregnancy and shows the results of those sensitivity analyses as e-values. Current wheezing was positively associated with severe depression status (aOR 1.22, 95% CI 1.07–1.38), depressive status (aOR 1.18, 95% CI 1.12–1.24), a doctor's diagnosis of depression (aOR 1.21, 95% CI 1.07–1.37), and a doctor's diagnosis of anxiety disorder (aOR 1.27, 95% CI 1.12–1.44). Asthma diagnosis was also associated with maternal depression status and doctor's diagnosis of anxiety disorder. Food allergy diagnosis in children was positively associated with any depression K-6 scores ≥ 5 (aOR 1.08, 95% CI 1.01–1.16), doctor's diagnosis of maternal depression (aOR 1.28, 95% CI 1.05–1.53), and doctor's diagnosis of anxiety disorder (aOR 1.38 95% CI 1.15–1.65).

Table 8 show the associations between offspring's sleep disturbance caused by wheezing with maternal depression and anxiety during pregnancy and the results of those sensitivity analyses as e-values. The aOR of sleep disturbance 1 or more nights per week was larger than that of sleep disturbance less than 1 night per week with respect to severe depression status, any depression status, and doctor's diagnosis of anxiety disorder.

Discussion

From a large-scale national birth cohort study, we found significant evidence that poor maternal prenatal QoL increased the risk of offspring having wheezing, asthma, and food allergy at 3 years of age. In addition, maternal depression and anxiety during pregnancy also increased the risk of wheezing, asthma, and food allergy in offspring. Our findings are consistent with the DOHaD theory.³ We believe that prenatal maternal mental health can contribute to altering the programming of the respiratory and immunological systems in the fetus before birth. The strength of this study was that our results are based on real-world evidence with a large longitudinal data set.

The results for quality of life showed a weaker association with asthma and food allergy than did the presence of depression. The ORs in all cases were close to 1. The OR 0.99 is certainly close to 1, but they showed that the OR for each increased in SF-8 by 1 unit. In other words, "By increasing the SF-8 by 1 unit, the odds of developing allergies were reduced by approximately 1%." Whether the association is small or large depends on the interpretation of how these associations could impact clinical outcomes. We consider that reducing the odds of developing allergies approximately 1% by increasing the SF-8 by 1 unit would have a significant impact on the public. Furthermore, we believe that the robustness of the associations between maternal mental status and the child's allergic outcomes can be confirmed by evaluating e-values.

To the best of our knowledge, this report is the first to demonstrate associations between offspring's wheezing, asthma, and food allergy and maternal QoL. Our study results suggest that better maternal

QoL during pregnancy leads to better respiratory outcomes in their offspring. A past systematic review found that the physical component of QoL decreased during pregnancy.²² The mother's QoL should be carefully assessed and warrants increased attention. Furthermore, a past review indicated that the factors associated with better QoL were the absence of social and economic problems, feeling happiness, having social connections, and physical exercise.²² A randomized controlled trial demonstrated that a relaxation program was effective for pregnant women with psychological stress.²³ To obtain better maternal QoL, mothers need various types of support and modification of risk factors related to poor QoL during pregnancy.

As for the associations with maternal psychosocial stress, Flanigan *et al.*⁴ performed a systematic review and meta-analysis regarding prenatal maternal stress and the offspring's allergy using data from 22 observational studies. The results of the meta-analysis demonstrated that prenatal maternal stress²⁴⁻³¹ and anxiety^{24, 25, 27} increased the risk of the offspring having asthma. Maternal depression^{24, 25, 27, 32} and anxiety^{27, 32, 33} during pregnancy also increased the risk of the offspring having wheezing.

Our study results concurred with the results of these past studies. As for food allergy outcomes, we found no observational studies that have examined the association between food allergy and maternal depression, anxiety, and stress. Our results, therefore, represent the first to reveal that food allergy in offspring is influenced by prenatal psychosocial stress.

Considering the mechanism of stress and the immune system, a proposed mechanism is that stress perception due to various external stressors alters the hypophyseal–pituitary–adrenal axis and autonomic nervous systems, producing an altered immune balance and having a negative impact on immune system molecules such as cytokines, chemokines, and immune cells.³⁴ Another meta-analysis reported that major depression increased the level of interleukin-6 and tumor necrosis factor-alpha.³⁵ In a birth cohort in Germany, Trump *et al.*³⁶ identified that alterations in DNA methylation in mothers and their offspring due to prenatal psychological stress were associated with the development of wheezing in children. These study results support our findings. We speculate that our study population might have experienced epigenetic changes during pregnancy.

The present study has several limitations to consider. First, the prevalence of doctors' diagnoses might be underestimated because we could not use medical chart data and/or other patient registry data. Furthermore, we did not examine the medications for depression and anxiety. Therefore, we could not evaluate how medications could influence maternal health and child outcomes. However, we used validated questionnaires to assess wheezing, depression status, and QoL, as have been used in various past studies. Second, some participants were lost during the follow-up period. However, we believe that the rate of loss to follow-up was low. Third, we did not conduct a molecular epidemiology investigation using genetic data. Although we speculate that epigenetic changes might

192 have occurred during pregnancy, we cannot confirm genetic alterations. In a future study, we hope to
193 validate our study results using genetic data.

194 In summary, poor maternal prenatal QoL increased the risk of the offspring having wheezing, asthma,
195 and food allergy at 3 years of age. In addition, maternal depression and anxiety during pregnancy
196 increased the risk of wheezing, asthma, and food allergy in the offspring.