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# Hypertensive disorders of pregnancy and risk of allergic conditions in children: Findings from the Japan Environment and Children's study (JECS)

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## ABSTRACT

**Background:** Hypertensive disorders of pregnancy (HDP) are one of the most common medical conditions that women encounter during pregnancy. Whether or not hypertensive disorders of pregnancy (HDP) are associated with allergic conditions in the offspring is unclear. This study used data from a large Japanese birth cohort to investigate whether HDP contributes to the development of allergic conditions in the offspring at 3 years. We also assessed the effect of blood pressure at different pregnancy trimesters on children's allergies.

**Methods:** We obtained data from the Japan Environment and Children's Study (JECS), which included 104 062 fetal records. After data selection, we analyzed 77 505 mother–child pairs, using logistic regression models to examine the relationships between HDP or the mother's blood pressure and their children's allergic conditions. In addition, we also evaluated the effect of HDP during pregnancy on allergies with a propensity score matched dataset, using a logistic regression model that predicts the conditional probability of whether a mother belonged to the HDP or non-HDP group.

**Results:** Among the 77 505 mothers eligible for analysis, 2334 (3.0%) had HDP. Percentages of women with hypertension were 1.7% in early gestation, 1.0% in mid-gestation, and 1.6% in late gestation. After adjusting for multiple potential confounders, HDP contributed nothing to allergy development in offspring. Children born to women with hypertension were no more likely than those without to have allergic conditions at 3 years of age. The propensity score matched dataset showed similar findings.

**Conclusion:** HDP and high blood pressure during pregnancy are apparently not risk factors for developing allergy in offspring. This information may help clinicians in counseling women who suffered HDP during pregnancy.

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## BACKGROUND

Hypertensive disorders of pregnancy (HDP) are one of the most common medical conditions that women encounter during pregnancy. HDP affects up to 10% of pregnancies and contributes to 7%–12% of pregnancy-related maternal deaths in the United States.[1] HDP includes chronic hypertension (diagnosed before 20 weeks' gestation or persisting longer than 12 weeks after delivery), gestational hypertension, (occurring after 20 weeks' gestation), preeclampsia, and preeclampsia superimposed on chronic hypertension.[2] It is an important risk factor for several adverse maternal and perinatal outcomes.

Increased prevalence of allergic conditions, such as asthma, rhinitis, eczema, and atopic diseases has been well documented. Genetic susceptibility and environmental factors are thought to cause development of these conditions, but their etiologic pathways are complex, and many details remain controversial.[3–7]

The relationship between HDP and early childhood health problems has been the focus of several studies. However, the observed associations have been inconsistent. In some studies, researchers reported increased risks of impaired lung function, asthma, eczema, and aeroallergen and food allergies in women who developed gestational hypertension or preeclampsia.[8,9] However, other studies did not show any of these risks in these women. A Norwegian historical cohort study showed that preeclampsia was not associated with atopic dermatitis, asthma, or altered lung function in late childhood (10 years old).[10] Moreover, in the Avon Longitudinal Study of Parents and Children (ALSPAC), no association was found between HDP and atopy at 7 years.[11] These inconsistent results indicate that studies in different populations with different methodological approaches need to be performed, and confounders and mediating factors need to be carefully assessed.

This study aimed to provide epidemiological evidence on the relationship between HDP and early childhood allergic outcomes in the Japanese population. Our study used data from a large Japanese birth cohort to investigate whether HDP/blood pressure (BP) at different trimesters in pregnancy increases the risk of development of allergies in children. In addition, the effect of HDP on allergic outcomes was assessed with a propensity score-matched approach.

## MATERIALS AND METHODS

### Study design

Data used for analysis was obtained from the Japan Environment and Children's Study (JECS), a nation-wide, government-funded birth cohort study. The aim of JECS is to explore associations between environmental factors and children's health and development. The design of this study has been described in detail elsewhere.[12] The JECS included 104 062 fetal records. Data selection processes used the jecs-ta-201901930-qsn dataset, released by the Program Office in October 2019.

The data selection process in our study is shown in Fig. 1. The study was limited to live births. We also excluded children who, by 3 years of age, had been lost to follow-up, or for whom data on allergic diseases was missing. The remaining 77 505 mother–child pairs were left for analysis.

### Ethics statement

The JECS study was approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and by the Ethics Committees of all participating units and institutions. Written informed consent was signed from all participants.

### Allergies in children

The outcomes investigated in this study include wheezing, asthma, atopic dermatitis, rhinitis, hay

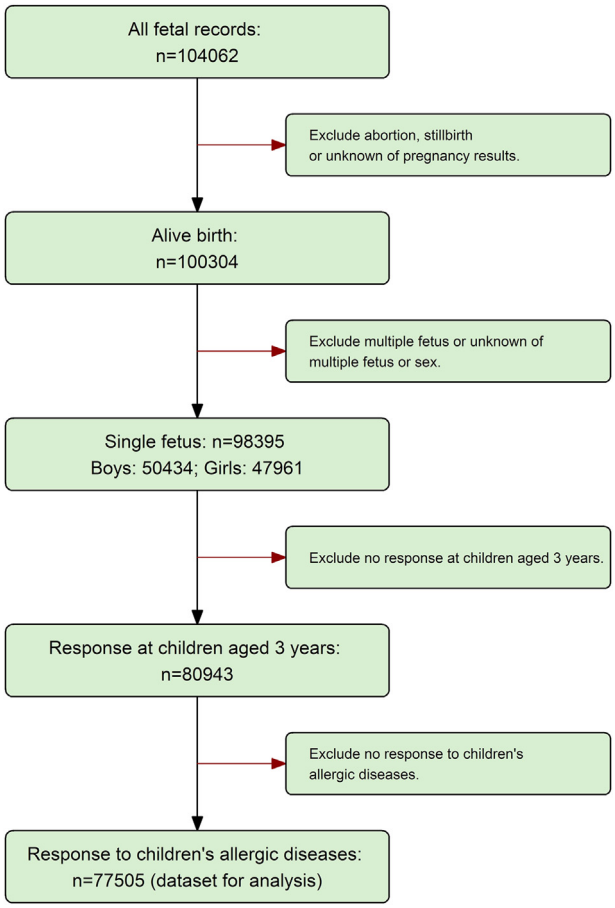


**Fig. 1** Flow chart of data selection.

fever and food allergy in 3-year-old children. Information on these allergic conditions was obtained from the answered questionnaires. Definitions (Table 1) of wheezing, asthma, atopic dermatitis, rhinitis, and hay fever are based on the International Study of Asthma and Allergies in Childhood (ISAAC).[13,14] A Japanese-translated version of ISAAC was used in JECS, which was validated based on the ISAAC protocol for 6–7 years children with part of modification.

## Blood pressure and gestational hypertensive complications

Maternal systolic and diastolic BPs (SBP, DBP) in early (≤14 weeks), mid- (14–28 weeks) and late (≥28 weeks) pregnancy were collected from medical records by doctors, nurses, midwives or Research Co-ordinators. Blood pressure was reclassified as normal, hypertension (SBP ≥140 and/or DBP ≥90 mm Hg) and hypotension (SBP <90 and/or DBPs <60 mm Hg).

Information on HDP was obtained from medical records transcribed during pregnancy and after delivery. HDP was defined as hypertension (SBP ≥140 mm Hg and/or DBP ≥90 mm Hg) with or without proteinuria (≥300 mg/24 h) after 20 weeks' gestation but resolving by 12 weeks postpartum, based on the guideline of Japanese Society for Study of Hypertension in Pregnancy in Japan. However, JECS did not provide further detailed classification for HDP (ie, gestational hypertension, preeclampsia, superimposed preeclampsia or eclampsia).[15]

## Covariates in models

Most covariates were derived from self-administered questionnaires completed at the time of study registration (MT1 questionnaire) and during mid-to late pregnancy (MT2 questionnaire). Information about mothers' age, height and weight before pregnancy, history of pregnancy abnormality, maternal smoking, paternal smoking, and mothers' allergy history were also collected from MT1 questionnaires. BMI was calculated as (weight)/(height$^2$). Information on maternal and paternal education levels, income, pet keeping and maternal drinking were obtained from MT2 questionnaires. Data on mode of delivery, birth weight, sex, and parity were from the Dr_0m data, and data on breastfeeding were from a questionnaire answered by the mothers at 6–8 months postpartum.

## Statistical analysis

We used multivariable logistic regression models to assess associations between HDP/BP and children's allergies, and adjusted for confounding factors (maternal age, maternal education level, maternal BMI, maternal history of pregnancy abnormality, maternal allergy history, maternal smoking, maternal drinking, paternal smoking, education level, family income, pet keeping, parity, and sex). All continuous variables or ordinal variables were regrouped as dichotomous variables. Confounders were identified, according to published literature, biological plausibility, and their availability in the JECS, as those known to be associated with HDP or childhood allergy. The variables cesarean delivery, birthweight, and gestational age were treated as

| | |
|---|---|
| Current wheeze | A positive answer to the question, "Has your child ever had wheezing or whistling in the past 12 months?" |
| Ever wheeze | A positive answer to the question at 3 years old of the children: "Has your child ever had wheezing or whistling in the chest at any time in the past?" |
| Ever asthma | A positive answer to the question "Has your children ever been diagnosed as asthma by a doctor?" |
| Ever rhinitis | A positive answer to the question: "Has your child ever had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or theu?" |
| Rhinitis | A positive answer for both of the following questions: "In the past 12 months, has your child had a problem with sneezing, or a runny or blocked nose when he/she did not have a cold or the flu?" |
| Ever atopic dermatitis | A positive answer to the question: "Has your child ever had atopic dermatitis?" |
| Current atopic dermatitis | A positive answer to both the following question:<br>1) "Has your child had this itchy rash at any time in the past 12 months?"<br>2) "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?" |
| Hay fever | A positive answer to both the following question: "Has your child ever had hay fever at any time in the past?" |
| Food allergy | A positive answer to the question, "Has your child experienced any allergic symptom in 3 h since food intake, as follows: urticaria, swelling, sneezing, runny nose, itchy in mouth, wheezing, cough, vomiting, abdominal pains, fainting, or becoming unconscious?" |

**Table 1.** Definitions of allergic conditions.

mediators in this study, which were further adjusted for sensitivity analyses.

We show adjusted odd ratios (ORs) with their corresponding 95% confidence intervals (CIs). We checked the collinearity of these confounders with the variance inflation factor of 5. We did not perform a model selection to reduce variables in current study.

To deal with missing values, we performed a multiple imputation (MI) analysis with a chained equation algorithm. We assumed that the missing data in the model was random and generated 20 data sets with the missing data imputed. All available confounders were used in the imputation processes.

With regard to the relationship between mothers' HDP and children's allergies, we also built a generalized estimating equation (GEE) model with a propensity score matched dataset, using a logistic regression model that predicts the conditional probability of whether a mother belonged to the HDP or non-HDP group. Covariates in the logistic model to calculate propensity

scores included maternal age, parity, BMI before pregnancy, history of pregnancy abnormality, maternal smoking, and maternal drinking. We assessed covariate imbalances before and after propensity score matching. Estimated propensity scores were compared between the 2 groups, using histogram plots.

We performed several sensitivity analyses to evaluate the robustness of our results. We added cesarean delivery, birthweight, and gestational age to the logistic models to examine the potential mediator effect, as mentioned above. In addition, we checked the interaction effect between maternal history of allergy and HDP in the logistic models. Finally, we built a logistic regression model using systolic and diastolic BPs as continuous variables. Restricted cubic splines, with 3 knots at the 10%, 50%, and 90% empirical quantiles, were used to relax linearity assumptions for SBP and DBP.

The logistic regression model and MI were performed using R version 4.0.3 software (Institute for Statistics and Mathematics, Vienna, Austria; www.r-project.org). The R packages "MatchIt", "MICE" and "rms" were used for the PS, MI processes and building the GLM model, respectively.

## RESULTS

### Characteristics of the study population

Maternal characteristics are listed in Table E1. When children with complete data were compared with those who were excluded because of incomplete data or loss to follow-up, rates of history of abnormal pregnancy, maternal asthma history, sex, birth weight, gestational weeks, BP in pregnancy, HDP, and Cesarean delivery were similar. However, participants with complete data tended to belong to families with higher socioeconomic status or parental educational levels, and to have lower prevalence of parental smoking. In addition, older mothers, nulliparous mothers, living without a pet, and breastfeeding were slightly more common in participants with complete data (Table E2).

Among the 77 505 mothers eligible for analysis, 2334 (3.0%) had HDP. Percentages of women with hypertension were 1.7% in early gestation, 1.0% in mid-gestation, and 1.6% in late gestation. Among the children, percentages of current allergy symptoms were wheezing: 17.2%, atopic dermatitis: 12.2%, rhinitis: 29.8%, and food allergy: 7.0%. Compared with non-HDP mothers, women who had HDP were older, more likely to have histories of pregnancy abnormalities, be nulliparous, and to

| Allergic conditions | | OR[#1] | 95% CI | OR[#2] | 95% CI | OR[&] | 95% CI |
|---|---|---|---|---|---|---|---|
| Ever wheeze | HDP (yes) | 1.05 | 0.96–1.16 | 0.99 | 0.90–1.08 | 1.02 | 0.90–1.16 |
| Current wheeze | HDP (yes) | 1.09 | 0.97–1.21 | 1.01 | 0.90–1.13 | 1.08 | 0.93–1.26 |
| Ever asthma | HDP (yes) | 1.03 | 0.90–1.19 | 0.98 | 0.85–1.13 | 0.97 | 0.79–1.20 |
| Atopic dermatitis | HDP (yes) | 0.87 | 0.76–1.00 | 0.91 | 0.79–1.04 | 0.88 | 0.73–1.07 |
| Ever atopic dermatitis | HDP (yes) | 0.89 | 0.77–1.02 | 0.91 | 0.79–1.05 | 0.89 | 0.73–1.08 |
| Ever rhinitis | HDP (yes) | 1.08 | 0.99–1.18 | 1.08 | 0.99–1.18 | 1.03 | 0.91–1.17 |
| Rhinitis | HDP (yes) | 1.08 | 0.98–1.18 | 1.08 | 0.99–1.18 | 1.05 | 0.92–1.19 |
| Hay fever | HDP (yes) | 1.20 | 0.98–1.48 | 1.20 | 0.97–1.48 | 1.19 | 0.89–1.60 |
| Food allergy | HDP (yes) | 0.84 | 0.71–1.01 | 0.88 | 0.73–1.05 | 0.88 | 0.69–1.11 |

**Table 2.** Association of hypertensive disorders of pregnancy with allergic outcomes among children at age 3 years *CI: confidence interval; HDP: hypertensive disorder of pregnancy; ORs: odds ratios.*[#1,#2] *Multivariable logistic regression model with multiple imputation dataset (*N = *77505,* M = *20).*[&] *Generalized estimating equation (GEE) with propensity score matched dataset (*N = *18235).*[#1,&] *The models were adjusted by maternal age, maternal education level, maternal BMI, maternal history of pregnancy abnormality, maternal allergy history, maternal smoking, maternal drinking, paternal smoking and education level, family income, pet keeping, parity and sex..*[#2]*The models were adjusted by maternal age, maternal education level, maternal BMI, maternal history of pregnancy abnormality, maternal allergy history, maternal smoking, maternal drinking, paternal smoking and education level, family income, pet keeping, parity and sex, Cesarean delivery, birthweight and gestational age.The non-HDP group was the reference group.*

| Allergic conditions | Blood pressure[a] | Early pregnancy | | Mid-pregnancy | | Late pregnancy | |
|---|---|---|---|---|---|---|---|
| | | OR[b] | 95% CI | OR[b] | 95% CI | OR[b] | 95% CI |
| Ever wheeze | Hypertension | 0.85 | 0.74–0.96 | 0.91 | 0.77–1.08 | 1.00 | 0.88–1.14 |
| | Hypotension | 1.03 | 0.99–1.06 | 1.06 | 1.03–1.09 | 1.07 | 1.04–1.11 |
| Current wheeze | Hypertension | 0.94 | 0.80–1.10 | 0.97 | 0.80–1.19 | 1.04 | 0.89–1.21 |
| | Hypotension | 1.03 | 0.99–1.07 | 1.09 | 1.05–1.14 | 1.09 | 1.05–1.14 |
| Ever asthma | Hypertension | 0.91 | 0.74–1.11 | 0.94 | 0.73–1.22 | 1.00 | 0.82–1.22 |
| | Hypotension | 1.10 | 1.04–1.16 | 1.09 | 1.03–1.14 | 1.18 | 1.12–1.25 |
| Atopic dermatitis | Hypertension | 0.84 | 0.69–1.02 | 0.74 | 0.57–0.97 | 0.79 | 0.65–0.95 |
| | Hypotension | 1.10 | 1.05–1.15 | 1.06 | 1.01–1.11 | 1.04 | 1.00–1.10 |
| Ever atopic dermatitis | Hypertension | 1.17 | 0.98–1.39 | 0.72 | 0.54–0.94 | 0.81 | 0.66–0.98 |
| | Hypotension | 1.06 | 1.00–1.11 | 1.06 | 1.01–1.11 | 0.97 | 0.92–1.02 |
| Ever rhinitis | Hypertension | 0.90 | 0.79–1.02 | 0.91 | 0.78–1.07 | 1.00 | 0.89–1.13 |
| | Hypotension | 1.04 | 1.01–1.08 | 1.02 | 0.99–1.05 | 1.01 | 0.97–1.04 |
| Rhinitis | Hypertension | 0.93 | 0.81–1.06 | 0.95 | 0.81–1.11 | 1.04 | 0.92–1.17 |
| | Hypotension | 1.05 | 1.02–1.09 | 1.03 | 1.00–1.06 | 1.02 | 0.98–1.05 |
| Hay fever | Hypertension | 1.01 | 0.74–1.37 | 1.07 | 0.73–1.56 | 1.21 | 0.92–1.60 |
| | Hypotension | 1.02 | 0.94–1.11 | 0.91 | 0.84–0.99 | 0.98 | 0.90–1.06 |
| Food allergy | Hypertension | 0.91 | 0.71–1.17 | 0.72 | 0.50–1.02 | 0.76 | 0.59–0.98 |
| | Hypotension | 1.00 | 0.94–1.07 | 1.03 | 0.97–1.09 | 1.00 | 0.94–1.07 |

**Table 3.** Association of maternal blood pressure during pregnancy with allergic outcomes among children at age 3 years *CI: confidence interval; ORs: odds ratios. [a]Reference group: Normal blood pressure. [b]Multivariable logistic regression model with multiple imputation dataset (N = 77,505, M = 20).The models were adjusted by maternal age, maternal education level, maternal BMI, maternal history of pregnancy abnormality, maternal allergy history, maternal smoking, maternal drinking, paternal smoking, paternal education level, family income, pet keeping, parity and sex.*

have Cesarean deliveries, premature birth, and low birth weight, and were less likely to breastfeed. However, we found no meaningful differences between the HDP group and the non-HDP groups with respect to children's allergic conditions (Table E3).

### Associations between HDP/BP during pregnancy and children's allergic conditions

Table 2 shows the associations between maternal HDP and children's allergies. After confounding factors were taken into account, HDP did not contribute to the development of children's allergies. Table 3 shows the associations between BP during pregnancy and children's allergic conditions. We calculated ORs against the intermediate category (normal BP) as the reference group to detect a U-shaped association with BP and outcomes. After adjusting for multiple potential confounders, children born to women with hypertension were no more likely to have allergic conditions at 3 years old than those without allergic conditions.

### Associations between HDP and children's allergic conditions with the propensity score-matched dataset

Histograms of propensity scores before and after matching are shown in Fig. E1. Histograms after matching were similar to those before matching, which indicated successful matching. Effect estimates based on the propensity score-matched dataset in GEE models are shown in Table 2. The ORs do not suggest that children born to mothers with HDP had a higher risk of developing allergic conditions at 3 years old. The ORs are similar to those listed in Table 2 (without a propensity score-matched approach).

### Sensitivity analysis

ORs from complete data (Tables E4 and E5) were similar with those from MI We did not find a meaningful mediating effect. Adding mediators (cesarean delivery, birthweight, and gestational age) to the models did not affect the ORs (Table 2 and Table E6). HDP was not associated with asthma/wheezing with atopic dermatitis (data not shown). There were no interactions between HDP and a maternal history of allergic diseases (data not shown). We also built models for childhood allergies based on SBP and DBP as continuous variables. The ORs were plotted in Figs. E2–3 (online only). No obviously positive association was observed between high BP during late gestation and childhood allergies. Similar results also were observed for early and middle pregnancy (data not shown).

## DISCUSSION

In this large cohort, we did not observe an association between hypertension during pregnancy and childhood allergic conditions, after adjusting for potential confounders; or between HDP and childhood allergy.

Previous studies have assessed the associations between hypertensive disorders and childhood allergy. For example, a Danish study with registry-based data observed an incidence rate ratio of 1.19 (95% CI: 1.15–1.24) between pre-eclampsia and asthma.[16] A large Norwegian registry study also indicated that pre-eclampsia could be a risk factor for childhood asthma.[6] Another study further explained this association with preterm birth by using a mediation analysis.[17] A prospective study with large cohort (Avon Longitudinal Study of Parents and Children), which assessed the associations between HDP (including maternal hypertension before pregnancy, gestational hypertension and pre-eclampsia) and childhood lung function, wheezing or asthma in children at 18 months and 7–9 years of age, indicated increased risk for developing childhood wheezing and asthma among children born to women with pre-existing hypertension, but not those with gestational hypertension.[11] In contrast, a Norwegian study reported no association between pre-eclampsia and children's asthma at the age of 10 years, and found no association between pre-eclampsia and atopic dermatitis in late childhood.[10] Different study design hampered making a direct comparison between our study and these published studies. Most studies that suggested an increased risk of wheezing/asthma focused on pre-eclampsia. We were not able to perform this type of study because the JECS did not include separate data on gestational hypertension and pre-eclampsia.

Some of our findings are in accordance with results of a UK study, which investigated whether *in utero* and perinatal influences contribute to the development of asthma in childhood, with a large birth cohort of 4065 natural children and 2583 mothers.[18] No significant relationship was observed for HDP. A population-based cohort study in Netherlands investigated the role of maternal BP in developing childhood respiratory and atopic outcomes.[11] They found that each 5-mm Hg in increased BP in late pregnancy led to increased risk for wheezing (OR 1.07, 95% CI: 1.02–1.12) and asthma (OR 1.06, 95% CI 1.00–1.11). No similar relationship was found between BP and children's allergic diseases in our study. Differences in children's ages and analytic approaches between the 2 studies might partly explain their inconsistency. A population-based study that explored the role of maternal complications during pregnancy in wheezing phenotypes in 15 609 children aged 6–7 years suggested that maternal hypertension or preeclampsia (analyzed in combination) contributes to an increased risk of transient early wheezing, persistent wheezing and late-onset wheezing.[19] Whether HDP is positively associated with wheezing phenotypes in childhood in Japanese children needs further analysis.

Our data did not permit us to clarify the mechanisms of HDP with respect to children's allergic conditions. Some published studies have given possible explanations for the association between pre-eclampsia and wheezing or asthma, such as the effects of pre-term birth and being born small for gestational age. However, gestational hypertension is unlikely to be a risk factor for small for gestational age. This might explain lack of relation between gestational hypertension and children's allergies.[11]

One strength of this study was its prospective design. In addition, as the JECS dataset did not specifically focus on HDP or allergic diseases, participants were less likely to be affected by the current study's objective. Third, data used for analysis were obtained from a large nationwide cohort, and included most of the potential risk factors for childhood allergy, which allowed us to control a large number of confounders. JECS data covered about 45% of live births within the Study Areas of the Regional Centres, and characteristics of the JECS participants were similar to those of other women in Japanese Vital Statistics; thus the cohort was representative of the Japanese population.[20] We also used a propensity score approach to our dataset. Propensity score approach is widely used in childhood asthma epidemiology,[21] and is useful for addressing covariate imbalances in observation studies.[21] To our knowledge, this is the first study to evaluate the effect of HDP on childhood allergic disorders using propensity score matching.

Despite our results from the larger prospective dataset, some limitations must also be considered. First, information based on questionnaires may lead to recall bias. Blood pressures were obtained from medical records by physicians or nurses, but JECS did not set a special guide for BP measurement, such as standardized sphygmomanometers, rest time before measurement, or number of measurements. Measuring variations may therefore exist among different regional medical centers.[15] Although recall bias may have been present owing to the questionnaire-based definition for allergy, the ISAAC questionnaire is a validated questionnaire, which is used extensively for allergy research. Second, as described above, HDP in the JECS study represents a mix of gestational hypertension, pre-pregnancy hypertension and pre-eclampsia. Thus, we cannot provide separate evaluations for gestational hypertension and pre-eclampsia; this complicates comparisons with most published studies, which specifically focus on maternal preeclampsia and allergy in children. Finally, we did not adjust for all potential confounders, such as air quality index.

In summary, high BP during pregnancy and HDP are apparently not risk factors for allergies in young children. Different from methods used by other published studies on this topic, we further fitted model with PS matching dataset. The PS matching is a valuable approach in addressing covariate imbalance in observational studies for allergy. Our results may help clinicians in counseling women who suffered HDP during pregnancy.

## Abbreviations

HDP, hypertensive disorder of pregnancy; BP: blood pressure; ISAAC, the International Study of Asthma and Allergies in Childhood; JECS, Japan Environment and

Children's Study; SBP: systolic blood pressure; DBP: diastolic blood pressure; OR, odds ratio; CI: confidence interval; MI, multiple imputation; GEE, generalized estimating equation.


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## Availability of data and materials
Data sharing not applicable.

## Author contributions
All authors approved the final manuscript. L.M. initiated the concept and designed the study to which M.S, M. S.-A., M.I., M.N. H.S., M.K., K.I., H.M., K.Y.-H., K.M. and Y.O. gave advice. L.M., M.S, M. S.-A., M.I., M.N. H.S., M.K., K.I., H.M., K.Y.-H., K.M. and Y.O collected the data. L.M. analyzed the data and wrote the manuscript. L.M., M.S, M. S.-A., M.I., M.N. H.S., M.K., K.I., H.M., K.Y.-H., K.M., Y.O and the JECS group reviewed the manuscript and gave critical advice.

## Author agreement
All authors have seen and approved the final version of the manuscript being submitted. They warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

## Institutional Review Board statement
The study was conducted according to the guidelines of the Declaration of Helsinki. The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (No.100406001, April 6, 2010) and by the Ethics Committees of all participating institutions. Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Funding: The Japan Environment and Children's Study was funded by the Ministry of the Environment, Japan. The findings and conclusions of this article are solely the responsibility of the authors and do not represent the official views of the above funder.

## Declaration of competing interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.


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## Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2021.100581.


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## REFERENCES

1. Creanga AA, Syverson C, Seed K, Callaghan WM. Pregnancy-related mortality in the United States, 2011-2013. *Obstet Gynecol*. 2017;130(2):366–373.
2. Bridwell M, Handzel E, Hynes M, et al. Hypertensive disorders in pregnancy and maternal and neonatal outcomes in Haiti: the importance of surveillance and data collection. *BMC Pregnancy Childbirth*. 2019;19(1):208.
3. Waked M, Salameh P. Risk factors for asthma and allergic diseases in school children across Lebanon. *J Asthma Allergy*. 2008;2:1–7.
4. Rusconi F, Galassi C, Forastiere F, et al. Maternal complications and procedures in pregnancy and at birth and wheezing phenotypes in children. *Am J Respir Crit Care Med*. 2007;175(1):16–21.
5. Zugna D, Galassi C, Annesi-Maesano I, et al. Maternal complications in pregnancy and wheezing in early childhood: a pooled analysis of 14 birth cohorts. *Int J Epidemiol*. 2015;44(1):199–208.
6. Nafstad P, Samuelsen SO, Irgens LM, Bjerkedal T. Pregnancy complications and the risk of asthma among Norwegians born between 1967 and 1993. *Eur J Epidemiol*. 2003;18(8):755–761.
7. Nafstad P, Magnus P, Jaakkola JJ. Risk of childhood asthma and allergic rhinitis in relation to pregnancy complications. *J Allergy Clin Immunol*. 2000;106(5):867–873.
8. Stokholm J, Sevelsted A, Anderson UD, Bisgaard H. Preeclampsia associates with asthma, allergy, and eczema in childhood. *Am J Respir Crit Care Med*. 2017;195(5):614–621.
9. Stick SM, Burton PR, Gurrin L, Sly PD, LeSouef PN. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. *Lancet*. 1996;348(9034):1060–1064.
10. Byberg KK, Ogland B, Eide GE, Oymar K. Birth after preeclamptic pregnancies: association with allergic sensitization and allergic rhinoconjunctivitis in late childhood; a historically matched cohort study. *BMC Pediatr*. 2014;14:101.
11. Shaheen SO, Macdonald-Wallis C, Lawlor DA, Henderson AJ. Hypertensive disorders of pregnancy, respiratory outcomes and atopy in childhood. *Eur Respir J*. 2016;47(1):156–165.
12. 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.
13. Weiland SK, Bjorksten B, Brunekreef B, Cookson WO, von Mutius E, Strachan DP, International Study of A, Allergies in Childhood Phase IISG. Phase II of the international study of asthma and allergies in childhood (ISAAC II): rationale and methods. *Eur Respir J*. 2004;24(3):406–412.
14. Ellwood P, Asher MI, Beasley R, Clayton TO, Stewart AW, Committee IS. The international study of asthma and allergies in childhood (ISAAC): phase three rationale and methods. *Int J Tuberc Lung Dis*. 2005;9(1):10–16.
15. Iwama N, Metoki H, Nishigori H, et al. Blood pressure changes during twin pregnancies: the Japan Environment and Children's Study. *J Hypertens*. 2019;37(1):206–215.
16. Liu X, Olsen J, Agerbo E, Yuan W, Wu CS, Li J. Maternal preeclampsia and childhood asthma in the offspring. *Pediatr Allergy Immunol*. 2015;26(2):181–185.
17. Magnus MC, Haberg SE, Magnus P, et al. Pre-eclampsia and childhood asthma. *Eur Respir J*. 2016;48(6):1622–1630.
18. Annesi-Maesano I, Moreau D, Strachan D. In utero and perinatal complications preceding asthma. *Allergy*. 2001;56(6):491–497.
19. Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. *Stat Med*. 2007;26(4):734–753.
20. Yamamoto M, Sakurai K, Eguchi A, et al. Association between blood manganese level during pregnancy and birth size: the Japan environment and children's study (JECS). *Environ Res*. 2019;172:117–126.
21. Juhn YJ, Qin R, Urm S, Katusic S, Vargas-Chanes D. The influence of neighborhood environment on the incidence of childhood asthma: a propensity score approach. *J Allergy Clin Immunol*. 2010;125(4):838–843 e832.