

Immunoglobulin E Levels and Hypertensive Disorders of Pregnancy: Japan Environment and Children's Study

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Abstract

High serum immunoglobulin E (IgE) levels are associated with cardiovascular events. We aimed to evaluate the association between total IgE levels during the first trimester of pregnancy and hypertensive disorders of pregnancy (HDP) development in a large Japanese cohort. We analysed data pertaining to singleton primipara pregnancies recorded in the Japan Environment and Children's Study involving births in 2011–2014. First trimester's serum IgE levels were determined using the immunonephelometric technique. High serum IgE was defined as IgE levels ≥ 170 IU/ml. A multiple logistic regression model was used to estimate the risk of high serum IgE levels on HDP, comprising early-onset and late-onset hypertension. A total of 32,518 participants were enrolled. The prevalence of total, early-onset, and late-onset HDP was 3.2%, 0.6%, and 2.3%, respectively. Patients with high serum IgE levels had an increased risk of late-onset hypertension (adjusted odds ratio [aOR]: 1.19, 95% confidence interval: 1.01–1.40). No correlation was found with either HDP (total) or early-onset hypertension (aOR: 1.15 and 0.85, 95% confidence interval: 0.99–1.32 and 0.60–1.21, respectively). High serum IgE levels during the first trimester are associated with late-onset hypertension. Our results could influence and shape further research regarding the pathogenesis of late-onset hypertension.

Introduction

Hypertensive disorders of pregnancy (HDP) occur in approximately 2.5% of all pregnancies in Japan¹. HDP is a public health burden, because it is the direct cause of approximately 30,000 maternal deaths per year and accounts for 14% of maternal deaths worldwide^{2,3}. Pre-eclampsia (PE) and gestational hypertension (GH) are the main forms of HDP, which are conventionally defined as new onset hypertension after 20 weeks of gestation, with (in cases of PE) or without (in cases of GH) signs of dysfunction in organs including the kidney, liver, and placenta⁴. HDP can also be categorised into early-onset (Eo)-HDP (onset hypertension before 34 weeks) and late-onset (Lo)-HDP (onset of hypertension after 34 weeks)⁵. These conditions have different clinical implications. Eo-HDP but not Lo-HDP is a high-risk factor for foetal death (adjusted odds ratio [aOR], 5.8; 95% confidence interval [CI], 4.0–8.3 vs aOR, 1.3; 95% CI, 0.8–2.0, respectively)⁶. However, both Eo- and Lo-HDP result in 10- and two-fold increase in perinatal maternal death, respectively, compared with that in pregnant women without HDP⁵. Although there are distinct perinatal differences between Eo-HDP and Lo-HDP, the exact mechanisms leading to Eo- and Lo-HDP remain unknown. The clinical burden of HDP necessitates that the mechanisms underlying the pathophysiology of HDP are elucidated in order to implement preventative strategies.

Mast cells are essential components of asthma and allergic responses^{7,8}. One of the best-known mechanisms for mast cell activation is the binding of immunoglobulin E (IgE) to its high-affinity receptor FcεR1 on the mast cell surface. After IgE binding, mast cells release histamine, mast cell protease, proteoglycan, cytokines, and chemokines^{9,10}. Many of these inflammatory mediators are associated with the development of pregnancy-related hypertension^{11–14}. Therefore, high serum IgE levels during pregnancy could be associated with Lo maternal cardiovascular events such as HDP. Nevertheless, little

is known about the relationship between serum total IgE levels during the first trimester of pregnancy and the development of HDP.

Therefore, the aim of this study was to evaluate the association between serum IgE levels during the first trimester and the development of HDP using nationally representative data from the Japan Environmental and Children's Study (JECS)¹⁵. The present study was conducted to examine the hypothesis that high serum IgE levels during the first trimester are associated with the development of HDP. Specifically, we sought answers to the two following questions in this study: (i) Is HDP associated with high serum IgE levels during the first trimester? (ii) If so, which type of HDP (Eo or Lo) is associated with high levels of serum IgE during the first trimester?

Methods

Study design

The present study utilised data from the JECS, a government-funded birth cohort study that commenced in January 2011. The JECS investigated the effects of several environmental factors, such as heavy metals and allergens, on children's health¹⁵. Pregnant women were eligible for participation in the JECS: (1) if lived in the study area at the time of the application and expected to live in Japan in the near future; (2) if they had an expected delivery date between 1 August 2011 and mid-2014; and (3) if they were able to participate without difficulty (i.e. they could complete the self-management questionnaires). The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and by the Ethics Committees of all participating institutions. The study was conducted in accordance with the Helsinki Declaration and other nationally valid regulations and guidelines. Written informed consent was obtained from all participants.

Data collection

The current analysis utilised the JECS data set released in March 2018 (data set: jecs-an-20180131), from which we used the following information: (1) a self-reported questionnaire completed in the first trimester, including details about medical conditions before pregnancy, number of previous deliveries, and smoking status; (2) a self-reported questionnaire completed during the second/third trimester, which included particulars regarding socioeconomic data; (3) obstetrics outcomes and maternal medical background data, retrieved from the medical records of each participant's institution; and (4) maternal blood sample records, collected during the first trimester. This study only involved primipara women since the risk of HDP is much higher in primipara women than in multipara women³². In the present study, we excluded cases with insufficient data, multiple pregnancies, or hypertension before pregnancy, and multipara.

Measurement of total IgE, obstetrics outcomes, and confounding factors

Blood samples were obtained from the mother during the first trimester of pregnancy. Serum total IgE titres were analysed in a contract clinical laboratory by immunological assays. Serum total IgE titres were assayed by ImmunoCAP (Thermo Fisher Scientific, Inc., Sweden)³³. A high serum IgE level was defined as IgE \geq 170 IU/ml based on the results of a Japanese cross-sectional study in pregnant women³¹. Maternal systolic and diastolic blood pressures were measured at the time of blood sample collection.

Obstetrics outcomes included HDP, gestational age at birth, and birth weight. HDP was defined as new onset hypertension (\geq 140/90 mmHg) after conception⁴. HDP was further classified into two categories: Eo-HDP (HDP onset before 34 weeks of gestation) and Lo-HDP (HDP onset after 34 weeks of gestation). SGA was defined as a birth weight less than -1.5 SDs below the population mean, corrected for gestational age and sex according to the 'New Japanese neonatal anthropometric charts for gestational age at birth'³⁴. PTB was defined as delivery before 37 gestational weeks. LBW was defined as birth weight <2500 g.

The following parameters were considered to be confounding factors: maternal age at delivery, BMI before pregnancy, maternal smoking status, maternal educational status, and SLE. The mothers were categorised into four age groups: <20, 20–29, 30–39, or \geq 40 years. The maternal BMI before pregnancy was calculated by dividing the mother's weight (kg) by the square of the mother's height (m). BMI was categorised into <18.5, 18.5–25.0, or >25.0 kg/m² ¹.

A self-reported questionnaire during first trimester had the following options regarding smoking history: 'Never', 'Previously did. Quit prior to current pregnancy', 'Previously did. Quit during this pregnancy', and 'Currently smoking'. Women who chose 'Currently smoking' were considered smokers (smoking category); otherwise, they were considered non-smokers (non-smoking category).

Based on the Japanese educational system, maternal education was categorised into the following four groups: junior high school: <10, high school: 10–12, professional school or university: 13–16, and graduate school: \geq 17 years of education¹.

Maternal participants were requested to provide the following information regarding SLE: 'Have you ever been diagnosed with SLE at a medical institution?'. The maternal participants who answered 'Yes' were classified into the SLE group³⁵. The confounding factors in this study were determined based on previously identified risk factors for HDP^{36–39}.

Statistical analyses

First, maternal characteristics and obstetric factors were summarised according to serum IgE levels. Then, participants were categorised into one of the three following groups, the non-HDP group (defined as control), Eo-HDP group, or Lo-HDP group. The prevalence of obstetric outcomes in HDP, including PTB, LBW, and SGA, were compared across the three groups. T-test and chi-square tests were performed to compare continuous and categorical variables, respectively. To compare more than three variables, the Kruskal-Wallis (one-way analysis of variance) and chi-square tests were used. Finally, logistic regression

models were used to calculate the aORs and 95% CI for HDP, Eo-HDP, and Lo-HDP. An aOR was calculated after adjusting for maternal age, BMI before pregnancy, maternal smoking during pregnancy, SLE, and maternal education. Logistic regression model analysis was performed using dummy variables for categorical variables composed of more than three categories (e.g. BMI could be categorised as <18.5, 18.5–25.0, and >25). SPSS version 26 (IBM Corp., Armonk, NY) was used for the statistical analyses. A p-value <0.05 was deemed to be statistically significant.

Data availability

The datasets analysed during the current study are not publicly available due to confidentiality/research subject protections. The authors, with permission of the Eco-child Study Investigation Committee and the Japan government, can make the datasets available upon reasonable request.

Results

In the JECS dataset, the total number of records for infants delivered between 2011 and 2014 was 104,065. Of these, 1,994 infants were delivered as a result of multiple gestation, 1,222 participants had maternal chronic hypertension, 16,307 participants had insufficient data, and 49,783 multiparous participants were excluded. After applying our inclusion criteria, 32,518 participants were eligible for enrolment in this study and were subsequently categorised into two groups according to positive IgE sensitisation (IgE < 170 IU/ml or IgE \geq 170 IU/ml) (Fig. 1). The median [interquartile (IQR)] serum IgE level for all participants was 60.0 (range, 21.5–159.0) IU/ml. In total, 1,067 cases (3.2%) developed HDP (Eo-HDP: 196 cases (0.6%), Lo-HDP: 769 cases (2.3%)). For 102 cases of HDP, the gestational age at onset of hypertension was unknown.

Maternal medical and socioeconomic background and obstetric outcomes

Table 1 summarises the maternal medical background data and the obstetric outcomes for the groups classified according to the IgE levels. The mean maternal age significantly differed between the two groups ($p < 0.01$), with women in the IgE < 170 IU/ml group being older. Neither the mean maternal systolic nor the diastolic blood pressure measured during blood sample collection was remarkably different (mean \pm standard deviation [SD], 111 ± 15 mmHg vs 111 ± 12 mmHg, $p = 0.232$; and 64 ± 13 mmHg vs 64 ± 14 mmHg, $p = 0.098$; respectively). Body mass index (BMI) categories and maternal education levels were significantly different between the participants in the two groups ($p < 0.001$ and $p < 0.001$, respectively), with the participants in the IgE \geq 170 IU/ml group having a higher BMI and lower educational level. The ratio of smokers was higher in the \geq 170 IU/ml group than in the IgE < 170 IU/ml group (4.8% and 3.2%, respectively, $p < 0.01$). There was no significant difference with respect to prevalence of systemic lupus erythematosus (SLE) (0.1% and 0.1%, $p = 0.698$) between the groups. Regarding the obstetric outcomes, no pertinent differences were found in the development of HDP ($p = 0.114$), Eo-HDP ($p = 0.351$), and Lo-HDP ($p = 0.058$).

Table 1
Maternal background and obstetric outcomes based on serum IgE levels

Variable	Participants		P-value
	Total IgE < 170 IU/ml n = 24,878	Total IgE ≥ 170 IU/ml n = 7,640	
Maternal medical background			
Maternal age, years mean ± SD	30.1 (5.1)	29.3 (5.2)	< 0.01 ^a
Maternal age category, %			
≤ 19	1.3	2.4	< 0.01 ^b
20–29	46.1	51.3	
30–39	48.7	43.7	
≥ 40	4.0	2.6	
Systolic blood pressure in the first trimester, mean ± SD mmHg	111 ± 15	111 ± 12	0.232 ^a
Diastolic blood pressure in the first trimester, mean ± SD mmHg	64 ± 13	64 ± 14	0.098 ^a
BMI before pregnancy (kg/m ²), %			
< 18.5	17.7	16.9	< 0.01 ^b
18.5–25.0	74.0	73.4	
> 25.0	8.3	9.7	
Smoking during pregnancy, %	3.2	4.8	< 0.01 ^b
SLE, %	0.1	0.1	0.698 ^b
Maternal education, year, %			
< 10	3.3	4.7	< 0.01 ^b
10–12	28.8	30.3	
13–16	43.0	41.1	
≥ 17	24.9	23.9	
Obstetric outcomes			

	Participants		
HDP, %	3.2	3.6	0.114 ^b
Eo-HDP, %	0.6	0.5	0.351 ^b
Lo-HDP, %	2.3	2.7	0.058 ^b

IgE: immunoglobulin E, SD: standard deviation, BMI: body mass index, SLE: systemic lupus erythematosus, HDP: hypertensive disorders of pregnancy, Eo: early-onset, Lo: late-onset. ^ap-value, t-test. ^bp-value, chi-square test.

Maternal background and obstetrics outcomes among those with Eo and Lo HDP

Table 2 summarises the maternal background data and obstetrics outcomes among the control, Eo-HDP, and Lo-HDP groups. The mean maternal age (SD) among the control, Eo-HDP, and Lo-HDP groups was 29.9 (\pm 5.1), 32.1 (\pm 5.8), and 31.1 (\pm 5.4), respectively, and was found to be significantly different among the three groups ($p < 0.01$). There was no notable difference in gestational age among the three groups ($p = 0.700$).

Table 2
Maternal background and obstetric outcomes for Eo-HDP and Lo-HDP

Variable	Participants			P-value
	Control n = 31,451	Eo-HDP n = 196	Lo-HDP n = 769	
Maternal medical background				
Maternal age, years mean \pm SD	29.9 \pm 5.1	32.1 \pm 5.8	31.0 \pm 5.4	< 0.01 ^a
Maternal age category, %				
\leq 19	1.5	0.5	1.2	< 0.01 ^b
20–29	47.6	35.7	39.0	
30–39	47.3	55.1	52.7	
\geq 40	3.5	8.7	7.2	
Gestational age at blood sample, mean \pm SD weeks	15.6 \pm 3.4	15.5 \pm 3.5	15.5 \pm 3.2	0.700 ^a
Total IgE IU/ml median (interquartile)	60.2 (21.5–158.0)	57.4 (18.3–139.3)	62.6 (25.2–179.5)	0.190 ^c
Total IgE \geq 170 (IU/ml), %	23.4	20.9	26.5	0.090 ^b
BMI before pregnancy (kg/m ²), %				
< 18.5	17.7	7.7	13.0	< 0.01 ^b
18.5–25.0	74.2	61.7	67.5	
> 25.0	8.2	30.6	19.5	
Smoking during pregnancy, %	3.6	4.1	3.6	0.934 ^b
SLE, %	0.1	0.5	0.0	0.167 ^b
Maternal education, year, %				
< 10	3.6	5.1	4.4	< 0.05 ^b
10–12	29.1	29.6	29.3	
13–16	42.5	45.4	46.6	
\geq 17	24.8	19.9	19.8	
Obstetric outcomes				

	Participants			
PTB < 37 weeks, %	3.9	43.9	8.2	< 0.01 ^b
LBW < 2500 g, %	8.5	48.7	20.5	< 0.01 ^b
SGA, %	4.9	26.2	11.6	< 0.01 ^b

Eo: early-onset, Lo: late-onset, HDP: hypertensive disorders of pregnancy, SD: standard deviation, IgE: immunoglobulin E, BMI: body mass index, SLE: systemic lupus erythematosus, PTB: preterm birth, LBW; low birth weight, SGA: small for gestational age. ^ap-value, one-way analysis of variance. ^bp-value, chi-square test. ^cp-value, Kruskal-Wallis test

The median (IQR) serum total IgE level among the control, Eo-HDP, and Lo-HDP groups was not significantly different (60.2 (21.5–158.0) IU/ml, 57.4 (18.3-139.3) IU/ml, and 62.6 (25.2-179.5) IU/ml, respectively, $p = 0.190$). The proportion of positive serum IgE cases in the control, Eo-HDP, and Lo-HDP groups was not also significantly different (23.4% vs 29.0% vs 26.5%, respectively, $p = 0.090$).

The ratio of smokers and those with SLE were not significantly different among the three groups ($p = 0.934$, $p = 0.167$, respectively). The proportion of women with a BMI > 25.0 kg/m² and the proportion of women with an education level < 10 years were significantly higher in the Lo-HDP group ($p < 0.01$ and $p < 0.01$, respectively).

Regarding obstetrics outcomes in HDP, the prevalence of preterm birth (PTB) < 37 weeks, low birth weight (LBW) < 2500 g, and small for gestational age (SGA) were significantly different among the three groups ($p < 0.01$, $p < 0.01$, and $p < 0.01$, respectively). The prevalence of PTB < 37 weeks, LBW < 2500 g, and SGA was highest in the Eo-HDP group. Overall, the incidence of these outcomes was highest in the Eo-HDP group, followed by the Lo-HDP group, and lowest in the control group.

Association between IgE positivity and occurrence of HDP

Table 3 summarises the association between serum IgE levels ≥ 170 IU/ml and the prevalence of HDP (total), Eo-HDP, and Lo-HDP. Using the IgE < 170 IU/ml group as reference, multiple logistic regression analyses were performed which showed that IgE ≥ 170 IU/ml was associated with an increased risk of developing Lo-HDP (aOR: 1.19, 95% CI: 1.01–1.40). However, IgE levels ≥ 170 IU/ml were not associated with the onset of either HDP (total) or Eo-HDP (aOR: 1.15, 95% CI: 0.99–1.32 and aOR: 0.85, 95% CI: 0.60–1.21, respectively).

Table 3
Relationship between IgE levels ≥ 170 IU/ml and HDP, Eo-HDP, and Lo-HDP

	HDP	Eo-HDP	Lo-HDP
Number	1067	196	769
Case, %	3.2	0.6	2.3
IgE (-)	Ref	Ref	Ref
IgE (+) OR (95% CI)	1.14 (0.99–1.31)	0.86 (0.61–1.22)	1.18 (1.01–1.39)
IgE (+) aOR (95% CI)	1.15 (0.99–1.32)	0.85 (0.60–1.21)	1.19 (1.01–1.40)

IgE: immunoglobulin E, HDP: hypertensive disorders of pregnancy, Eo: early-onset, Lo: late-onset, OR: odds ratio, CI: confidence interval, aOR: adjusted odds ratio, Ref: reference. aOR was calculated by logistic regression analysis, using maternal age, body mass index before pregnancy, systemic lupus erythematosus, maternal smoking status, and maternal education.

Discussion

In this study, although we assessed data pertaining to maternal background (such as maternal age, BMI before pregnancy, maternal education, and smoking habit) and analysed the differences between participants with serum IgE levels < 170 IU/ml and ≥ 170 IU/ml, we found no differences regarding the onset of HDP (total), Eo-HDP, and Lo-HDP between the two groups. We also compared maternal background variables with obstetric outcomes such as PTB, LBW, and SGA in those without HDP and in participants with Eo-HDP and Lo-HDP. Our findings indicated significant differences in adverse obstetrics outcomes and maternal background between the three groups. Multiple logistic regression analyses found that high serum IgE levels during first trimester were a risk factor for development of Lo-HDP.

To the best of our knowledge, only one study has examined the association between maternal serum IgE levels and obstetric outcomes. This study suggested that IgE levels in the third trimester of pregnancy and cord blood were strongly related to birth outcomes and foetal growth restriction¹⁶. Most previous studies that measured serum IgE levels have focused on cardiovascular events such as hypertension or coronary artery disease in the general population^{17,18}. A study including 156 patients with coronary heart disease showed a significantly higher total IgE concentration in patients with unstable angina and acute myocardial infarction than in those with stable angina or those in the control group¹⁹. In another study, 195 patients with any form of ischemic heart disease had significantly higher total IgE levels than those in the control group²⁰. Guo et al. reported that serum IgE levels were significantly higher in patients with multi-vessel disease than in those with single vessel disease, suggesting that a higher serum IgE level was an independent predictor for acquiring multi vessel disease [21]. On the contrary, a cross sectional study that included 315 women showed no significant positive correlation between increased serum IgE levels and cardiovascular disease²². Despite evidence that high total IgE levels are associated with

cardiovascular disease, an important question remains; do increased total IgE levels precede or result from cardiovascular events?

The exact cause of HDP also remains unclear. Eo-HDP is reportedly caused by the failure of the trophoblasts to invade the maternal spiral artery, resulting in a high maternal vascular resistance^{23,24}. As a result, foetal growth restriction or SGA usually occurs^{25,26}, frequently requiring preterm delivery for maternal and/or foetal indications. On the contrary, Lo-HDP is considered to be more of a maternal constitutional disorder²⁷ due to underlying maternal microvascular disorders or sustained maternal stress²⁸, in which poor trophoblast invasion is less likely to play a significant role. Lo-HDP is more common than Eo-HDP and often has a mild course but can be associated with significant clinical morbidities²⁹. Consistent with previous studies, in the present study, the prevalence of PTB < 37 weeks, LBW < 2500 g, and SGA in the Eo-HDP group (43.9%, 48.7%, and 216.2%, respectively) was higher than that in the LO-HDP group (8.2%, 20.5%, and 11.6%, respectively). High IgE levels are associated with microvascular disorders, and maternal microvascular disorders could result in Lo-HDP. Therefore, our results that maternal high serum IgE levels are a risk factor for Lo-HDP are biologically plausible.

This was the first large-scale study conducted in Japan by the Japanese government with meticulous attention to data collection. Therefore, this study is considered to be representative of the general pregnant population in Japan³⁰. Additionally, we only included primipara cases and had a sufficiently large number of the same in the ethnic population. Nevertheless, this study also has potential limitations. First, although we accounted for some confounding factors in large portions of the questionnaire, unknown factors that could affect the occurrence of HDP might have existed. Second, although obstetric outcomes were based on medical records, this study focused on HDP, which does not differentiate between GH and PE as we did not have information regarding the severity of hypertension, presence of urine protein, or any organ dysfunction. Finally, since there are very few previous studies on serum IgE levels during pregnancy³¹, the cut-off value for positive IgE (IU/ml) was defined as 170 IU/ml. The cut-off value of serum IgE levels may have affected the results of the logistic regression analysis. Thus, further studies that examine the relationship between serum IgE levels and the risk of Lo-HDP occurrence, are warranted.

Our findings indicate that high serum IgE levels (≥ 170 IU/ml) during the first trimester are associated with the risk of Lo-HDP. The results of this study may provide novel insights into the pathogenesis of new onset hypertension during pregnancy. However, only a few studies have previously measured maternal serum IgE levels, and hence additional studies are needed to confirm or refute our findings.

Declarations

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Author contributions

All authors approved the final manuscript. H.K. initiated the concept and designed the study to which Y.E., H.K., T.M., T.F., K.A., A.Y., K.F., and K.H. gave advice. A.S., and Y.O., collected the data. H.K. analyzed the data and wrote the manuscript. H.N., Sh.Y., M.H., K.F., Se.Y., A.S., Y.O., K.H., and the JECS group reviewed the manuscript and gave critical advice.

Additional Information

Competing interests

The authors declare no competing interests

Consortium

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Figures

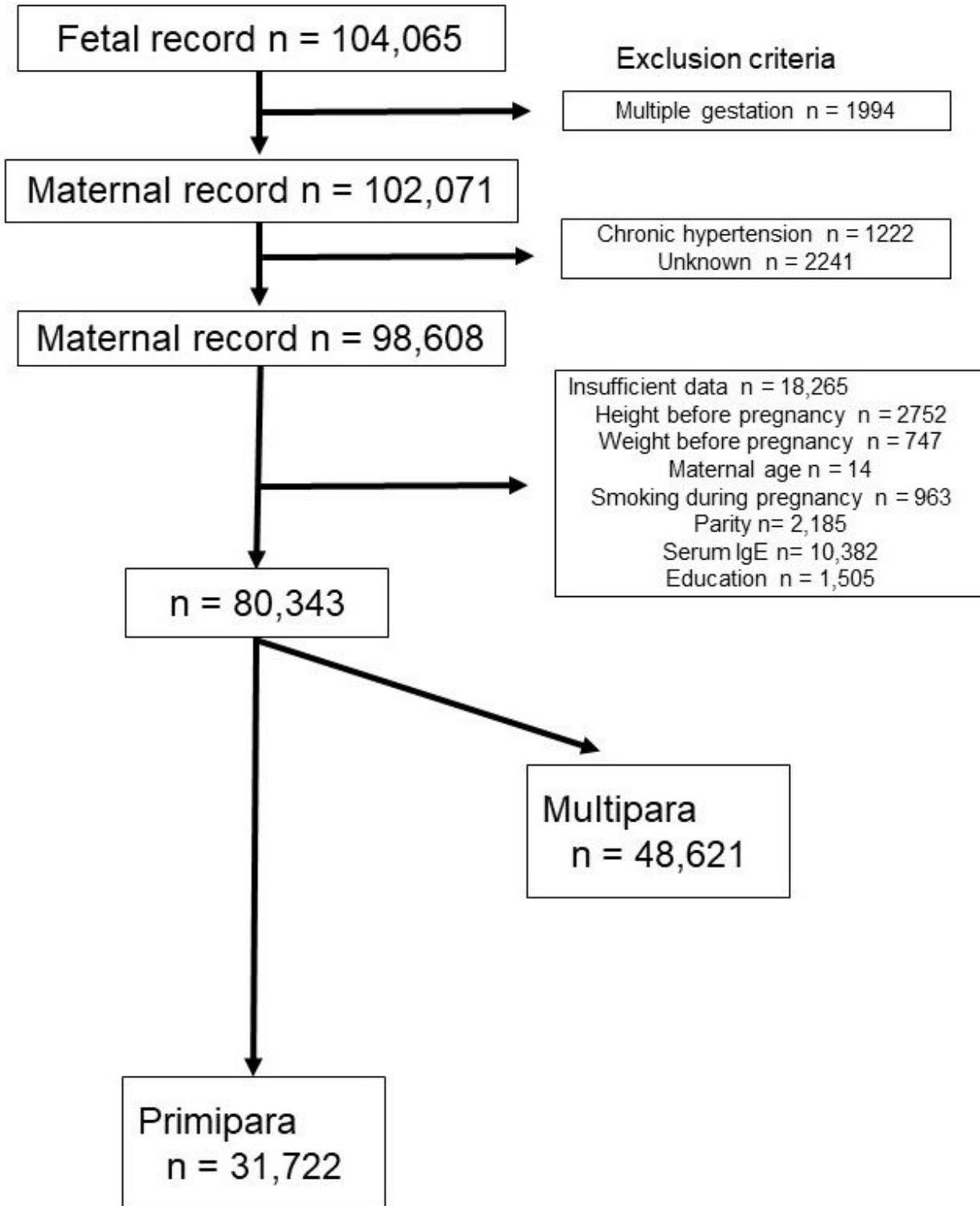


Figure 1

Flow chart of the study participants. IgE: immunoglobulin E.