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Early View

Original article

Maternal blood pressure and hypertensive disorders during pregnancy and childhood respiratory morbidity. The Generation R Study

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Maternal blood pressure and hypertensive disorders during pregnancy and childhood respiratory morbidity. The Generation R Study.

Freke A. Wilmink, MD[1,2,3], Herman T. den Dekker, MD[2,4,5], Johan C. de Jongste, MD PhD[2,5], I. Reiss[2,6], Vincent W.V. Jaddoe, MD PhD[2,4,5], Eric A. Steegers, MD, PhD[2,3], Liesbeth Duijts, MD PhD[2,5,6]

[1]Department of Obstetrics and Neonatology, Radboudumc, Nijmegen, the Netherlands, [2]The Generation R Study Group, [3]Department of Gynaecology and Obstetrics, [4]Department of Epidemiology, [5]Department of Paediatrics, Division of Respiratory Medicine and Allergology, [6]Department of Paediatrics, Division of Neonatology; Erasmus MC, University Medical Centre, Rotterdam, the Netherlands.

Corresponding author

Dr. Liesbeth Duijts, MD, PhD, Erasmus MC, University Medical Centre Rotterdam, Sp-3435; PO Box 2060, 3000 CB Rotterdam, The Netherlands. Tel: *31 10 7036263, Fax: *31 10 7036811, E-mail: l.duijts@erasmusmc.nl

Contribution of authors to the study

FW, HD, LD contributed to the conception and design, acquisition of data, analyses and interpretation of the data, drafted the article, revised it critically for important intellectual content, and gave final approval of the version to be published.

JJ, VJ, ES contributed to the conception and design, acquisition of data, revised the drafted manuscript critically for important intellectual content, and gave final approval of the version to be published.

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ABSTRACT

Preeclampsia is associated with an increased risk of bronchopulmonary dysplasia, wheezing and asthma in later childhood. Currently, there are no studies available investigating maternal blood pressure measurements during multiple time points in pregnancy and respiratory outcome measures in the child. We examined the associations of maternal blood pressure and hypertensive disorders with the risk of lower lung function, wheezing and asthma in children aged 10 years. This study among 4,894 children was embedded in a population-based prospective cohort study. We used multivariate analyses, taking lifestyle and socio-economic factors into account. We observed consistent associations per 5 mmHg higher maternal blood pressure in early pregnancy with a lower FEV_1/FVC (Z-score (95% CI) -0,03 (-0,05, -0,01)), and per 5 mmHg higher blood pressure in late pregnancy with a higher risk for current wheezing and current asthma: (odds ratios (95% CI): 1.07 (1.02, 1.12) and 1.06 (1.00, 1.11), respectively). We found no associations of maternal hypertensive disorders during pregnancy with child lung function, current wheezing or current asthma.

Our results suggest that higher blood pressure in pregnant women is associated with lower lung function and increased risks of current wheezing and current asthma in children. The associations may be trimester specific.

Keywords: asthma, spirometry, wheezing, maternal blood pressure, preeclampsia, pregnancy.

INTRODUCTION

Maternal hypertensive disorders during pregnancy, including preeclampsia, are associated with adverse neonatal outcomes such as a two- to five-fold increased risk of preterm birth or low birth weight.(1-3) Lower gestational age and birth weight across the full range are independently associated with a higher risk for lower lung function and asthma in later life.(4-7) Next to this indirect effect, maternal hypertensive disorders during pregnancy, which are usually accompanied with poorer maternal vascular health, could also have a direct effect on respiratory morbidity through disturbed placental function and an altered angiogenic status, affecting lung growth and lung maturation.(8-11) Hospital-based studies observed that preeclampsia is associated with a two- to four-fold increased risk of bronchopulmonary dysplasia. (8, 12-14) Several former cohort studies examined the association of preeclampsia with wheezing and asthma.(15-20) One case control and two cohort studies report a positive association, although part of the association could be explained by preterm birth and confounders shared by siblings.(16, 19, 20) One prospective cohort study found no association between preeclampsia and lower lung function or early wheezing, but did found an association of pre-existing hypertension with an up to1.6 fold increased risk of childhood wheezing and asthma.(18) We hypothesized that on a population-based level more common, small adverse changes in maternal blood pressure during pregnancy or gestational hypertension might increase the risk of chronic obstructive lung diseases such as asthma in childhood Furthermore, it is unclear if a critical window exists during pregnancy and what the potential influence is of lifestyle, socio-economic factors, growth and atopy.

Therefore, we examined the associations of maternal blood pressure during early, mid and late pregnancy, gestational hypertension, and preeclampsia with the risks of lower lung function, wheezing and childhood asthma in a population-based prospective cohort study among 4,894 children. We also explored if any association could be explained by lifestyle and socio-economic factors, or modified by child's gestational age, weight at birth or atopic mechanisms.

METHODS

Design This study was embedded in the Generation R Study, a population-based prospective cohort study from early fetal life onwards.(21) For the current study we used the data of women enrolled during pregnancy with a live born singleton who participated in the postnatal phase at 10 years of age and included only one child per mother (n=6,168). After applying exclusion criteria, our final population for analysis existed of n=4,894 children (Figure 1).

Maternal hypertensive disorders during pregnancy Maternal systolic and diastolic blood pressures in early (<18 weeks), mid (18-25 weeks) and late pregnancy (>25 weeks) were measured with the validated Omron 907® automated digital oscillometric sphygmomanometer (OMRON Healthcare Europe B.V., Hoofddorp, the Netherlands), as described previously.(22) Gestational hypertension and preeclampsia were defined according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria and according to those of the American College of Obstetricians and Gynaecologists (ACOG)(23, 24). **Childhood lung function, current wheezing and current asthma**

Children visited our dedicated research centre at a mean age of 9.8 years (range 8.6 to 12.0 years). Spirometry was performed according to the American Thoracic Society and European Respiratory Society recommendations.(25) All spirometric variables were converted into sex-, height-, age-, and ethnicity-adjusted z-scores according to the Global Lung Initiative reference data.(26) Current wheezing, physician diagnosed asthma ever and use of inhaled medication (bronchodilators, corticosteroids) in the past 12 months was assessed by parental questionnaire at age 10 years. Current asthma was defined as physician diagnosed asthma ever, with either current wheezing or the use of inhaled medication in the past 12 months. Response rate for questionnaires ranged from 68 to 75%.

Covariates See our supplementary material.

Statistical analysis We used multivariate linear and binary logistic regression models to examine the associations of maternal blood pressure and hypertensive disorders during pregnancy with lung function, current wheezing or current asthma. Selection of covariates

was based on literature and if the effect estimate of the unadjusted analyses changed ≥10% when additionally was adjusted for a covariate. First, models were adjusted for child's sex only (crude analysis). Second, we adjusted for potential lifestyle and socio-economic confounders including maternal age, ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid and child's sex, which we considered the main model. Third, we adjusted our main model for potential intermediates, including maternal psychological distress during pregnancy, mode of delivery, and child's gestational age at delivery and birth weight, to observe whether changes in the effect estimates occurred. Adjusting for intermediates in the main analyses can cause overcorrection, and we therefore considered the confounder model as our main model.(27, 28) In addition we performed a mediation analysis. Finally, we applied conditional regression analyses to our main model, to take account for the correlation between blood pressures measured at multiple time points in pregnancy.(29) We performed a sensitivity analysis excluding all woman who were treated with medication for high blood pressure during pregnancy. The modifying effects of a maternal history of asthma and atopy, children's gestational age at birth, birth weight, inhalant allergic sensitization and current eczema were tested. For additional explanation about intermediates, our mediation and conditional analyses, imputation and testing effect modification, see the supplementary material. All measures of association were analyzed per 5mmHg and presented as z-score differences for lung function and odds ratios (ORs) for current wheezing or asthma, with corresponding 95% confidence intervals (95% CI). Analyses were performed using SPSS version 21.0 for Windows (IBM, Chicago, Ill, USA) and with R version 3.0.0.

.

RESULTS

Maternal and child characteristics are presented in Table 1. Of n=4,894 woman eligible for analyses, 206 (4.2%) had gestational hypertension and 1.9% (n=91) preeclampsia or HELLP syndrome. Current wheezing and asthma were reported in 18.1% (n=692) and 8.3% (n=313) at age 10 years. Loss-to-follow-up analysis showed that mothers not included in the analysis were younger, lower educated, smoked more and used less folic acid before and during pregnancy, had more psychological distress and were more often of non-Western origin. Their children were more often male, were born at a shorter gestational age with a lower birth weight (Table S1).

Maternal blood pressure and hypertensive disorders during pregnancy and child lung function Crude analyses showed that higher maternal blood pressures in early, mid and late pregnancy were associated with lower FEV_1/FVC and FEF_{75} (Table S2). After adjusting for lifestyle and socio-economic factors, higher maternal systolic, diastolic and mean arterial blood pressure in early pregnancy (per 5 mmHg) were associated with lower FEV_1/FVC (Z-score (95% CI) -0.02 (-0.04, -0.01), -0.02 (-0.04, -0.01) and -0.03 (-0.05, -0.01), respectively), higher diastolic pressure in mid pregnancy with lower FEV_1 (-0.02 (-0.04, -0.00)), and higher systolic pressure in late pregnancy with lower FEV_1/FVC (-0.01 (-0.03, -0.00)) (Table 2). Effect estimates attenuated into non-significant when we additionally adjusted for intermediating factors (Table S3a). Psychological distress during pregnancy explained 13 to 39% of the associations between blood pressure and FEV_1/FVC in early pregnancy. Gestational age at delivery explained 9 to 11% of the associations between blood pressure and FEV_1/FVC in early pregnancy. Associations between blood pressure and lung function in late pregnancy were not significantly explained by one of the intermediates (Table S3b) Only the associations of maternal blood pressure in early pregnancy with FEV_1/FVC remained significant when conditional analyses adjusted for lifestyle and socio-economic factors were applied (Figure 2 and Table S4). Hypertensive disorders during pregnancy were not associated with any lung function measure.

Maternal blood pressure and hypertensive disorders during pregnancy and current wheezing or current asthma Crude analyses showed that higher maternal blood pressure

in early and late pregnancy was associated with an increased risk of current wheezing and current asthma (Table S5). After adjusting for lifestyle and socio-economic factors, higher systolic and mean arterial pressure in early pregnancy and a higher diastolic and mean arterial pressure in late pregnancy were associated with an increased risk of current wheezing (ORs (95% CI) 1.05 (1.01, 1.10), 1.07 (1.01, 1.13), 1.06 (1.01, 1.11) and 1.06 (1.01, 1.12), respectively). A higher systolic blood pressure in late pregnancy was associated with an increased risk of current asthma (1.06 (1.00, 1.12), Table 3). After additionally adjusting for intermediating factors, only the association of a higher systolic pressure in early pregnancy with a higher risk for current wheezing at the age of 10 years remained significant (1.05 (1.00, 1.09), Table S6a). Mediation analyses did not show that one of the intermediates significantly explained the associations found (Table S6b). When conditional analyses were applied, associations of maternal blood pressure with current wheezing attenuated into non-significant. The association of a higher systolic pressure with a higher risk for current asthma remained consistent (1.16 (1.01, 1.33), Figure 2 and Table S7). Hypertensive disorders during pregnancy were not associated with current wheezing or current asthma. For all associations, we did not observe modifying effects of maternal history of asthma and atopy, child's gestational age at birth, birth weight, inhalant allergic sensitization and current eczema (P-values for interaction > 0.05), (Table S8 and S9).

As the effect estimates were small, we performed several sensitivity analyses. Analysis of the complete case dataset showed no major differences in the magnitude or direction of the effect estimates (Table S11 and S12). After exclusion of women who were treated with medication for high blood pressure during pregnancy (n=39), the size and the direction of the effect estimates of the observed associations remained similar.

DISCUSSION

In this population-based prospective cohort study we observed that higher maternal blood pressure in early pregnancy was associated with a lower FEV_1/FVC in the child at 10 years, and higher pressure in late pregnancy was associated with a higher risk for current wheezing

and current asthma in the child, taking lifestyle and socioeconomic factors into account. Results did not change after conditional analysis in which the measurements at multiple time points during pregnancy were taken into account. In the intermediate model results attenuated into non-significant, most probably by over-adjustment. Mediation analysis showed that psychological distress and gestational age at birth explained part of the associations found. Hypertensive disorders during pregnancy were not associated with lung function, current wheezing or current asthma. Results were not modified by atopic mechanisms, gestational age or birth weight Z-score.

Comparison with previous studies Currently, there are no studies available to compare the results of our association analyses between maternal blood pressure measurements during multiple time points in pregnancy and respiratory outcome measures in the child. A large prospective cohort study, examining the ALSPAC cohort, assessed associations of maternal hypertension before pregnancy, gestational hypertension and preeclampsia with lung function, wheezing or asthma in children at 18 months and age 7-9 years.(18) They observed that pre-existing hypertension, and not gestational hypertension or preeclampsia, may be a risk factor for childhood wheezing and asthma with ORs (95% CI): 1.63 (1.16, 2.31) and 1.34 (1.00-1.79), respectively.(18) The associations we found of higher blood pressure measures in early pregnancy with lower lung function, represents, equal to the ALSPAC cohort, women with hypertension before pregnancy as gestational hypertensive disorders do not reveal itself before 20 weeks of gestation. The effect estimates we found were relatively small compared to the effect estimates found in the ALSPAC cohort. However, we report our estimates per 5mmHg maternal blood pressure change which is quite smaller than the difference between normotensive woman and woman with hypertensive diseases. In addition, they present results at a different child age.

Other population-based studies demonstrated inconsistent associations of gestational hypertension or preeclampsia with altered lung function or asthma in early or late

childhood.(15-17, 19, 20, 30, 31) A pooled analysis of 14 birth cohorts (n = 85,509) demonstrated that preeclampsia is associated with an increased risk for wheezing between birth up to 12-24 months.(31) They did not found associations for other hypertensive disorders.(31) One historically matched cohort study, assessing if maternal preeclampsia was associated with atopy, asthma and altered lung function in late childhood, did not find these associations, but might have lacked power due to the small sample size (n=617). (15) A Norwegian study among 406,907 subjects of a registry-based study and 45,028 subjects of a cohort-based study examined the associations between preeclampsia and asthma at age 7 years.(19) The registry-based results did show a positive association (OR (95% CI) 1.31 (1.22-1.41)), however this was largely explained by preterm birth and confounders shared by siblings. The cohort-based results did not show an association.(19) A Danish case control study, nested in a cohort based on national registers among 115,522 subjects, found an association of early onset preeclampsia before 34 weeks gestation with asthma (incidence rate ratio (IRR) (95% CI): 1.88 (1.67, 2.11)).(16) A case-sibling analysis (n=65,041 cases and n=82,271 controls) showed that part of the association of early onset preeclampsia with asthma (IRR (95% CI) 1.15 (1.02, 1.29) may be due to confounding by factors shared by siblings.(16)

Another Danish registry-based cohort study (n=1,698,638) showed a higher risk for asthma in children born to mothers with preeclampsia (n= 62,728), (adjusted IRR (95%CI), 1.09 (1.05, 1.12)).(20) This risk increased when the duration of preeclampsia was ≥ 14 days, (1.17 (1.11, 1.25)).(20) Our study consisted of a relatively healthy population with a relatively low prevalence of gestational hypertension or preeclampsia. However, the effect estimates for the associations of higher maternal blood pressure in early pregnancy with lung function, and higher maternal blood pressure in late pregnancy with a higher risk for wheezing and asthma were consistent and might have a potential large impact on a population level. Given the consistency of our results it is not likely that the associations are due to chance.

Potential underlying mechanisms Preeclampsia is strongly associated with (iatrogenic) preterm birth and being born small for gestational age with an increased risk for subsequent wheezing, asthma and lower lung function in childhood.(2) We can only speculate about the explanations of the differences in associations being depended on the trimester of pregnancy. Different pathophysiological mechanisms affecting development of the lungs and related vasculature may play a role or changing magnitudes of the same mechanisms throughout pregnancy. Higher blood pressure in pregnancy may reflect diminished maternal vascular health with subsequent suboptimal placentation and maternal adaptation to pregnancy as well as related increased risks of placental insufficiency. Resulting fetal growth restriction and prematurity are related with lower lung function in childhood. Higher blood pressure may also be associated with an anti-angiogenic maternal and fetal environment directly affecting the developing fetal lungs.(32) This may give rise not only to decreased lung function but also to increased risks of wheezing and asthma in childhood. Unknown epigenetic mechanisms may obviously also be involved in all suggested pathophysiological mechanisms.(33) The physiological mid pregnancy drop in blood pressure in many pregnancies might explain why we did not found consistent associations of blood pressure in the second trimester with child's respiratory morbidity.

A prospective cohort study (n=69 preterm infants) showed that an anti-angiogenic status of the mother is reflected in the neonate, as neonates of mothers with preeclampsia had higher cord blood soluble fms-like tyrosine kinase-1 (sFlt-1) and lower Placental growth factor (PLGF) and vascular endothelial growth factor (VEGF) levels.(34) A high concentration of endostatin, an anti-angiogenic growth factor, in human cord plasma predicts the development of bronchopulmonary dysplasia in very low birth weight infants.(11) In animal studies, inhibiting of VEGF resulted in reduced alveolarization and persistent abnormalities of pulmonary vascular structures.(9, 10) Additionally, administering of sFlt into the amnionic sac of pregnant rats, at a stage of lung development corresponding 24 to 26 weeks of human gestation, decreased VEGF signalling and increased apoptosis. Subsequently, reduced alveolarization and pulmonary vascular growth was observed during infancy of the

offspring.(32) Whether this hypothesis applies to less extreme conditions in a relatively healthy cohort remains to be shown.

Early and late pregnancy seemed critical windows, as we did not find any associations with maternal blood pressure measurements in mid-pregnancy, which in most pregnancies is characterized by the mid pregnancy drop.

Strengths and limitations The strength of the current study is the population-based prospective cohort design from early pregnancy onwards, with detailed information on maternal and child characteristics and validated maternal blood pressure measures throughout all stages of pregnancy. Spirometry is the preferred and robust method to assess lung function.(35) Some limitations need to be addressed. Mothers who were lost to follow up showed marked differences with mothers included in our study population. This could have lead to selection bias if associations of maternal blood pressure and hypertensive disorders with child lung function, wheezing and asthma would have been different between the groups included and lost to follow-up. As adjustment for potential lifestyle and socio-economic confounders, which were the marked differences in the two groups, did not change the direction of the statistically significant effects, selection bias seems not very likely, but cannot fully be excluded. Extensive analysis of selection bias in a comparable birth cohort showed that selection bias by loss to follow up seems limited and adding further statistical measures, as inverse probability weighting, do not seem to further reduce bias.(36, 37)

The information we have on hypertension before pregnancy is based on self reported questionnaires without a clear definition (n=48). However, our blood pressure measurement in early pregnancy is representative of hypertension before pregnancy. We also performed a sensitivity analysis excluding all woman (n=39) using anti hypertensive medication. Results were similar. Our late pregnancy measurements were rather early (median 30.4 weeks) and this could have resulted in underestimated associations, as maternal blood pressures usually rise during the third trimester of pregnancy. However, we examined gestational hypertensive disorders at the end of pregnancy, and these were not associated with respiratory morbidity

of the child. Part of our respiratory data were self-reported by questionnaires, and therefore we cannot exclude under- or overestimations of the observed associations.

In conclusion, our study shows that higher blood pressures in pregnancy were associated with lower FEV_1/FVC, and increased risks of current wheezing and current asthma in children at the age of 10 years. We did not show associations of specific gestational hypertensive disorders with childhood respiratory morbidity.

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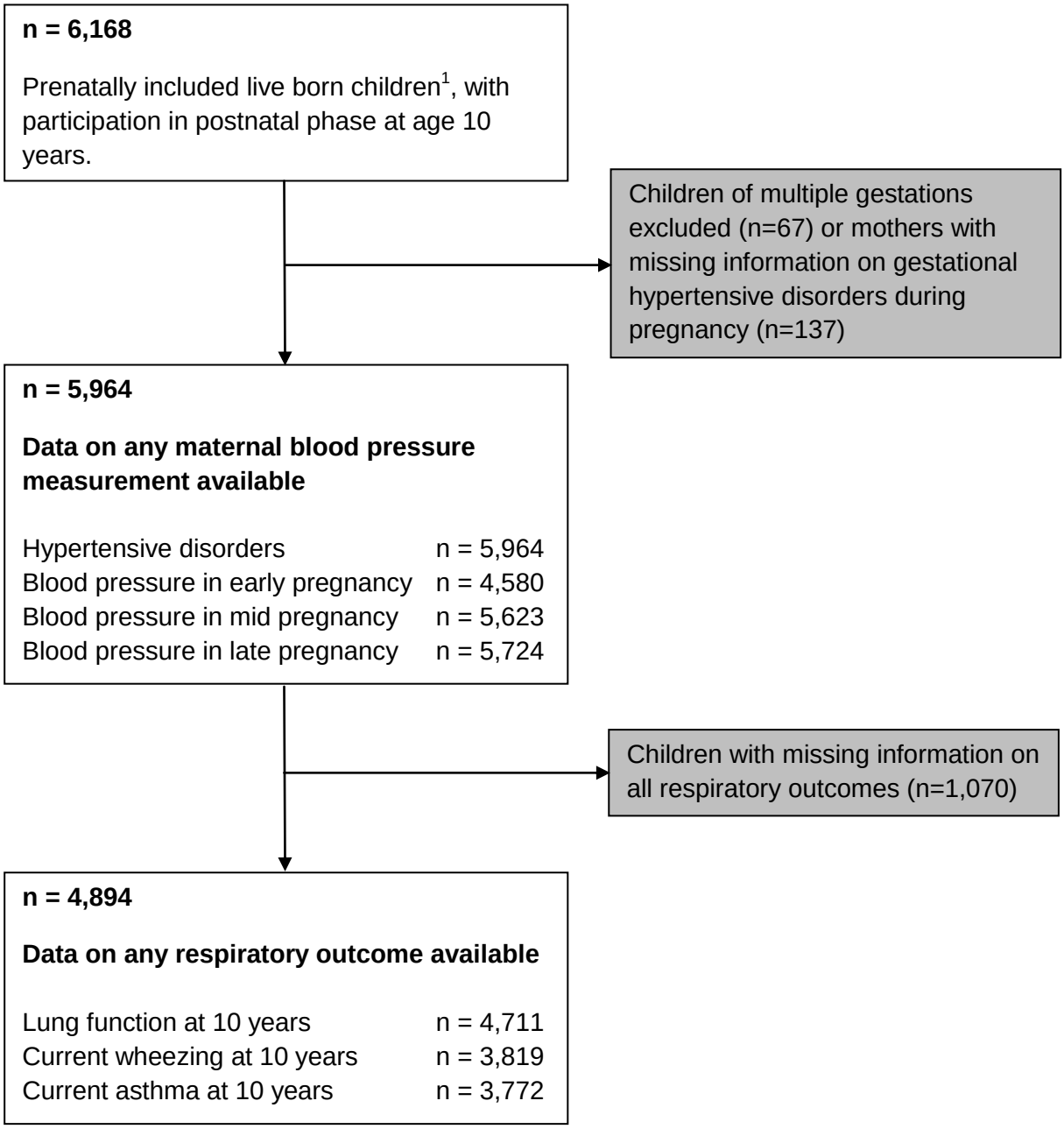
Figure captions

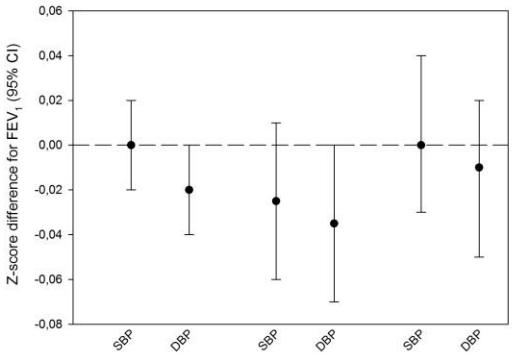
Figure 1. Flow chart of participants included for analysis

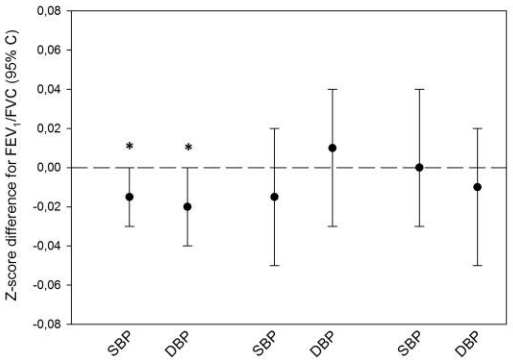
Figure 2. Associations of maternal blood pressure during pregnancy with lung function, current wheezing and current asthma at age 10 years, conditional regression analyses

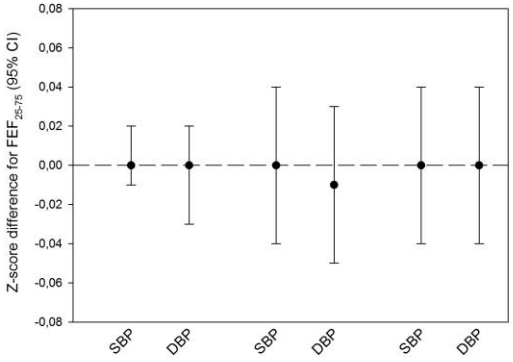
Figure legend for Figure 2.

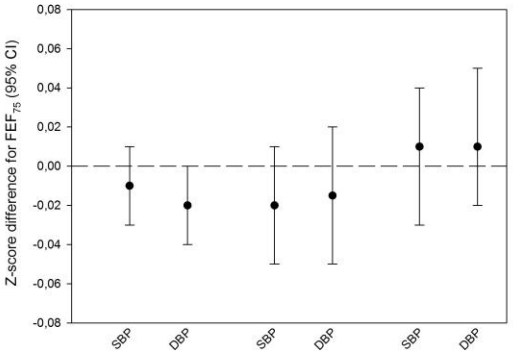
Abbreviations: Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Forced expiratory volume in 1 sec (FEV_1), forced vital capacity (FVC), mean forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}) and forced expiratory flow at 75% of FVC (FEF_{75}).

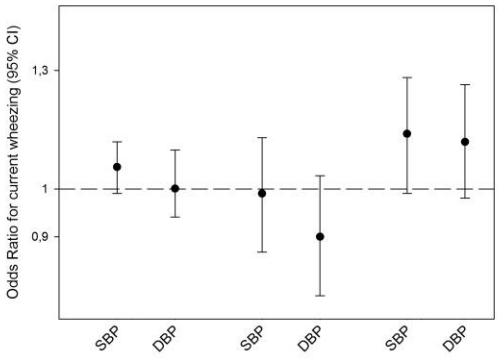

n = 6,168
Prenatally included live born children[1], with participation in postnatal phase at age 10 years.
Children of multiple gestations excluded (n=67) or mothers with missing information on gestational hypertensive disorders during pregnancy (n=137)
n = 5,964
Data on any maternal blood pressure measurement available
Hypertensive disorders n = 5,964
Blood pressure in early pregnancy n = 4,580
Blood pressure in mid pregnancy n = 5,623
Blood pressure in late pregnancy n = 5,724
Children with missing information on all respiratory outcomes (n=1,070)
n = 4,894
Data on any respiratory outcome available
Lung function at 10 years n = 4,711
Current wheezing at 10 years n = 3,819
Current asthma at 10 years n = 3,772


Z-score difference for FEV1 (95% CI)
0,06
0,04
0,02
0,00
-0,02
-0,04
-0,06
-0,08
SBP
DBP
SBP
DBP
SBP
DBP


Z-score difference for FEV1/FVC (95% C)
0,08
0,06
0,04
0,02
0,00
-0,02
-0,04
-0,06
-0,08
*
*
SBP
DBP
SBP
DBP
SBP
DBP


Z-score difference for FEF25-75 (95% CI)
0,08
0,06
0,04
0,02
0,00
-0,02
-0,04
-0,06
-0,08
SBP
DBP
SBP
DBP
SBP
DBP


Z-score difference for FEF75 (95% CI)
0,08
0,06
0,04
0,02
0,00
-0,02
-0,04
-0,06
-0,08
SBP
DBP
SBP
DBP
SBP
DBP


Odds Ratio for current wheezing (95% CI)
1,3
1
0,9
SBP
DBP
SBP
DBP
SBP
DBP

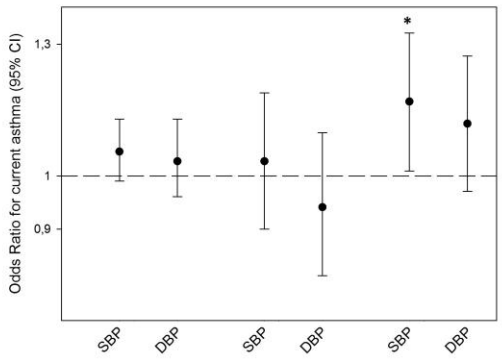

Odds Ratio for current asthma (95% CI)
1,3
1
0,9
*
SBP
DBP
SBP
DBP
SBP
DBP

Table 1. Baseline characteristics of mothers and their children.

Maternal characteristics	**n=4,894**
Age (years)[1]	30.7 (4.8)
Ethnicity, western, % (n)	65.4 (3,201)
Body mass index (kg/m2)[2]	23.7 (18.8, 35.7)
Educational level, higher, % (n)	49.2 (2,408)
Nulliparity, yes, % (n)	62.3 (3,049)
Psychological distress, yes	9.2 (448)
Smoking during pregnancy, % (n)	
No	74.6 (3.650)
Yes – stopped	9.5 (465)
Yes – continued	15.9 (779)
Folic acid use, % (n)	
No	22.5 (1,101)
Start before 10 weeks	32.5 (1,593)
Preconception start	45.0 (2,200)
Caesarean section, yes, % (n)	13.0 (637)
History of asthma or atopy, yes, % (n)	41.1 (2.013)
Blood pressure	
Early pregnancy (weeks)[2]	13.2 (10.5, 17.5)
SBP (mmHg)[1]	116 (12)
DBP (mmHg)[1]	69 (9)
MAP (mmHg)[1]	84 (9)
Mid pregnancy (weeks)[2]	20.5 (18.6, 23.3)
SBP (mmHg)[1]	117 (12)
DBP (mmHg)[1]	67 (9)
MAP (mmHg)[1]	84 (9)
Late pregnancy (weeks)[2]	30.4 (28.5, 32.9)
SBP (mmHg)[1]	119 (12)
DBP (mmHg)[1]	69 (9)

MAP (mmHg)[1]	85 (9)
Hypertensive disorder, % (n)	
Gestational hypertension	4.2 (206)
Preeclampsia / HELLP[7]	1.9 (91)
Child characteristics	
Sex, female, % (n)	50.4 (2,467)
Birth weight (grams)[1]	3428 (553)
Gestational age at birth (weeks)[2]	40.1 (35.7, 42.4)
Inhalant allergies, yes, % (n)	34.2 (1,673)
Current eczema, yes, % (n)	9.0 (439)
Spirometry	
FEV_1 (L/s)[1]	2.01 (0.30)
FVC (L)[1]	2.33 (0.37)
FEV_1/FVC (s)[1]	0.87 (0.06)
FEF_{25-75} (L/s)[1]	2.69 (0.65)
FEF_{75} (L/s)[1]	1.14 (0.35)
Ever asthma, % (n)	9.7 (368)
Current wheezing, % (n)	18.1 (692)
Current asthma, % (n)	8.3 (313)

Values are valid percentages (absolute numbers), [1]means (SD) or [2]medians (95% range) based on imputed data. Data on maternal blood pressure, hypertensive disorders, lung function, wheezing and asthma were not imputed.

Abbreviations: Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), Haemolysis Elevated liverenzymes Low platelets (HELLP), Forced expiratory volume in 1 sec (FEV_1), forced vital capacity (FVC), FEV_1/FVC, mean forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}) and forced expiratory flow at 75% of FVC (FEF_{75}).

Table 2. Multivariate analysis of maternal blood pressure and hypertensive disorders during pregnancy with spirometry in children at age 10 years.

	Spirometry				
	FEV_1	**FVC**	**FEV_1/FVC**	**FEF_{25-75}**	**FEF_{75}**
	Z-score (95%CI)	**Z-score (95%CI)**	**Z-score (95%CI)**	**Z-score (95%CI)**	**Z-score (95%CI)**
Early pregnancy					
SBP	-0.00 (-0.02, 0.01)	0.01 (-0.00, 0.03)	**-0.02 (-0.04, -0.01)***	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.00)
DBP	-0.02 (-0.04, 0.00)	-0.00 (-0.02, 0.02)	**-0.02 (-0.04, -0.01)***	-0.00 (-0.03, 0.02)	-0.02 (-0.04, 0.00)
MAP	-0.01 (-0.03, 0.00)	0.01 (-0.01, 0.02)	**-0.03 (-0.05, -0.01)***	-0.00 (-0.03, 0.02)	-0.02 (-0.04, 0.00)
Mid pregnancy					
SBP	0.01 (-0.02, 0.01)	0.00 (-0.01, 0.02)	-0.01 (-0.03, 0.00)	0.00 (-0.02, 0.02)	-0.01 (-0.02, 0.01)
DBP	**-0.02 (-0.04, -0.00)***	-0.01 (-0.03, 0.00)	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.01)
MAP	-0.02 (-0.03 ,0.00)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.00)
Late pregnancy					
SBP	-0.00 (-0.02, 0.01)	0.01 (-0.01, 0.02)	**-0.01 (-0.03, -0.00)***	0.01 (-0.01, 0.02)	-0.01 (-0.02, 0.01)
DBP	-0.02 (-0.03, 0.00)	-0.01 (-0.03, 0.01)	-0.01 (-0.02, 0.01)	0.01 (-0.02, 0.02)	-0.01 (-0.02, 0.01)
MAP	-0.01 (-0.03, 0.01)	-0.01 (-0.02, 0.01)	-0.01 (-0.03, 0.00)	0.01 (-0.02, 0.03)	-0.01 (-0.03, 0.01)
Hypertensive disorder					
None	*reference*	*reference*	*reference*	*reference*	*reference*
GH	0.05 (-0.11, 0.20)	0.44 (-0.10, 0.19)	0.02 (-0.12, 0.17)	0.01 (-0.16, 0.18)	0.02 (-0.13, 0.16)
PE/ HELLP	-0.16 (-0.38, 0.06)	-0.10 (-0.31, 0.11)	-0.05 (-0.27, 0.16)	-0.11 (-0.35, 0.14)	-0.10 (0.31, 0.11)

Values reflect the change in Z-score (95% confidence interval) from linear regression models. The Z-scores of spirometry are standardized by fetal sex, age, ethnicity and height. Maternal blood pressure is analysed per 5mmHg. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid use and child's sex. *p-value < 0.05.

Abbreviations: Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), Gestational hypertension (GH), Preeclampsia/ Haemolysis Elevated liverenzymes Low platelets (PE/ HELLP).

Table 3. Multivariate analysis of maternal blood pressure and hypertensive disorders during pregnancy with current wheezing or asthma at age 10 years.

	Current wheezing	**Current asthma**
	Odds ratio (95%CI)	**Odds ratio (95%CI)**
Early pregnancy		
SBP	**1.05 (1.01, 1.10)***	1.04 (0.98, 1.10)
DBP	1.05 (0.99, 1.11)	1.03 (0.96, 1.11)
MAP	**1.07 (1.01, 1.13)***	1.04 (0.97, 1.13)
Mid pregnancy		
SBP	1.00 (0.96, 1.04)	1.00 (0.95, 1.05)
DBP	1.01 (0.97, 1.07)	0.95 (0.89, 1.02)
MAP	1.01 (0.96, 1.06)	0.96 (0.90, 1.04)
Late pregnancy		
SBP	1.04 (1.00, 1.08)	**1.06 (1.00, 1.12)***
DBP	**1.06 (1.01, 1.11)***	1.02 (0.96, 1.10)
MAP	**1.06 (1.01, 1.12)***	1.05 (0.98, 1.13)
Hypertensive disorder		
None	*Reference*	*Reference*
GH	0.95 (0.63, 1.42)	0.99 (0.57, 1.73)
PE/ HELLP	0.70 (0.36, 1.39)	0.80 (0.32, 2.01)

Values are Odds ratio's (95% confidence interval) from logistic binary and multinomial regression models. Maternal blood pressure is analysed per 5mmHg. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid use and child's sex. *p-value < 0.05.

Abbreviations: Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), Gestational hypertension (GH), Preeclampsia/ Haemolysis Elevated liverenzymes Low platelets (PE/ HELLP).

Supplementary material

Methods – more extensive description

Statistical analyses – additional explanation about intermediates, mediation analysis, conditional regression analyses, imputation and testing effect modification

Methods – more extensive description

Design The study has been approved by the Medical Ethical Committee of the Erasmus MC, University Medical Centre in Rotterdam, the Netherlands (MEC 40020.078.12/2012/165). Written informed consent was obtained from either parents or legal guardians.

Maternal hypertensive disorders during pregnancy Maternal systolic and diastolic blood pressures in early (<18 weeks), mid (18-25 weeks) and late pregnancy (>25 weeks) were measured with the validated Omron 907® automated digital oscillometric sphygmomanometer (OMRON Healthcare Europe B.V., Hoofddorp, the Netherlands), as described previously.(22) Evidence of gestational hypertension or preeclampsia based on information in the clinical records was crosschecked with the original hospital charts. Details of these procedures have been described elsewhere.(23) Gestational hypertension and preeclampsia were defined according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) criteria and according to those of the American College of Obstetricians and Gynaecologists (ACOG)(24, 25). Haemolysis Elevated Liver enzymes and Low Platelet syndrome (HELLP syndrome) was defined as thrombocytes less than 100 × 10^9/L, both aspartate aminotransferase and alanine aminotransferase more than 70 U/L, and lactate dehydrogenase more than 600 U/L.(26)

Childhood lung function, current wheezing and current asthma Spirometry was performed according to the American Thoracic Society and European Respiratory Society recommendations.(27)Quality criteria required three reproducible curves and no use of inhalant bronchodilators or corticosteroids within 48 hours before spirometry. Lung function variables tested were forced expiratory volume in 1 sec (FEV_1), forced vital capacity (FVC), FEV_1/FVC, mean forced expiratory flow between 25% and 75% of FVC (FEF_{25-75}) and forced expiratory flow at 75% of FVC (FEF_{75}).

Covariates Information on maternal age, ethnicity, pre-pregnancy body mass index (BMI), educational level, parity, psychological distress, smoking habits during pregnancy, folic acid use and a history of asthma and atopy were collected by multiple questionnaires during

pregnancy. Child's sex, birth weight, gestational age and mode of delivery were obtained from midwife and hospital records at birth. Birth weight was adjusted for gestational age.(29) Child's ethnicity was defined by country of birth of the parents and classified according to the GLI definitions.(28) Inhalant allergic sensitization for *Dermatophagoides pteronyssinus*, 5-grass mixture (*Dactylis glomerata, Festuca pratensis, Lolium perenne, Phleum pratense, Poa pratensis*), bird (*Betula verrucosa*), cat (*Felis catus*) and dog (*Canis familiaris*) (ALK-Abelló B.V., Almere, The Netherlands) was measured by skin prick test using the 'scanned area method' at a median age of 9.7 years (range 8.6, 12.0 years).(30) Information on eczema was collected by a questionnaire at age 10 years.

Statistical analyses – additional explanation about intermediates, mediation analysis, conditional regression analyses, imputation and testing effect modification

Intermediates In our third model we adjusted our main model (confounder model) for potential intermediates, including maternal psychological distress during pregnancy, mode of delivery, and child's gestational age at delivery and birth weight, to observe whether changes in the effect estimates occurred. Intermediates are cofactors in between the pathway from determinant to outcome measure. Adjusting for intermediates in the main analyses can cause overcorrection, and we therefore considered the confounder model as our main model.(1, 2)

Mediation analysis In addition we performed a mediation analysis. The difference between the original effect estimates and the effect estimates after additional adjustment for potential mediators was expressed as percentage change. The percentage change was calculated by using the following formula: $100 \times (\text{Effect estimate}_{\text{mediator}} - \text{Effect estimate}_{\text{original model}})/(\text{Effect estimate}_{\text{original model}} - 1)$. A 95% CI for the percentage change of the effect estimate was calculated by using a bootstrap method with 1000 resamplings.(3-5)

Conditional regression analysis Finally, we applied conditional regression analyses to our main model, to take account for the correlation between blood pressures measured at multiple time points in pregnancy.(16) Variables for sequential blood pressure measurements that were statistically independent of each other were constructed, allowing inclusion of these variables together in one regression model. Thus, the influence of blood pressure in specific periods could then be assessed in comparison with, and adjusted for, blood pressure measurements in other periods of pregnancy. Hypertensive disorders were not measured at multiple time points in pregnancy and therefore conditional analyses were not applied on their association with lung function, current wheezing or current asthma.

The main advantages of conditional models are removal of strong correlation between different blood pressure measurements allowing large numbers of related variables to be included in a single regression model and facilitation of interpretation of the results. Conditional models are build using stepwise linear regression analyses. Blood pressure at time 1 was the starting point. Conditional change in blood pressure from time 1 to time 2 was equivalent to the standardized residuals resulting from the linear regression model of blood pressure at time 2 on blood pressure at time 1. Accordingly, the conditional change in blood pressure from time 2 to time 3 was given as the standardized residuals obtained from regressing blood pressure measurements at time 3 on blood pressure measurements at both time 2 and time 1, simultaneously. This process was continued for each subsequent time point.

Imputation Missing data for covariates within the population for analysis was <20%, except for maternal folic acid use (22.4%), inhalant allergies of the child (30.8%), and current eczema (21.0%). Missing data from covariates were imputed to reduce bias and improve efficiency using the Markov Chain Monte Carlo method to select the most likely value for a missing response.(34) Ten new datasets were constructed. No major differences in the magnitude or direction of the effect estimates were observed between analyses with imputed missing data and complete cases only.

Testing effect modification The modifying effects of a maternal history of asthma and atopy, children's gestational age at birth, birth weight, inhalant allergic sensitization and current eczema were tested by adding them as product terms with blood pressure and gestational hypertensive disorders in the models

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Table S1. Comparison of the study population with individuals lost to follow-up.

Original data	**Included**	**Lost to follow up**	***P*-value**
Maternal characteristics	**n=4,984**	**n=1,070**	
Age (years)[1]	30.7 (4.8)	27.8 (5.5)	**<0.001**
Ethnicity, western	65.9 (3,173)	37.0 (362)	**<0.001**
Missing, % (n)[2]	*1.7 (81)*	*8.6 (92)*	
Body mass index (kg/m2)[3]	23.7 (18.8-35.6)	24.6 (18.5-37.0)	**<0.001**
Missing, % (n)[2]	*0.6 (30)*	*1.21 (13)*	
Educational level, higher	50.1 (2,342)	19.8 (178)	**<0.001**
Missing, % (n)[2]	*4.5 (222)*	*15.8 (169)*	
Nulliparity	62.5 (3,046)	51.3 (542)	**<0.001**
Missing, % (n)[2]	*0.5 (22)*	*1.21 (13)*	
Psychological distress, yes	8.1 (331)	17.5 (121)	**<0.001**
Missing, % (n)[2]	*16.1 (790)*	*35.5 (380)*	
Smoking during pregnancy			**<0.001**
No	75.4 (3,334)	66.7 (607)	
Yes – stopped	8.4 (409)	6.7 (61)	
Yes – continued	13.9 (678)	26.6 (242)	
Missing, % (n)[2]	*9.7 (473)*	*15.0 (160)*	
Folic acid use			**<0.001**
No	20.9 (793)	47.2 (345)	
Start before 10 weeks	32.2 (1224)	28.3 (207)	
Preconception start	46.9 (1,781)	24.5 (179)	
Missing, % (n)[2]	*22.4 (1,096)*	*31.7 (339)*	
Caesarean section, yes	12.8 (582)	12.0 (117)	0.52
Missing, % (n)[2]	*7.2 (351)*	*9.1 (97)*	

History of asthma or atopy, yes	40.0 (1,625)	36.6 (287)	0.08
Missing, % (n)[2]	*17.0 (830)*	*26.7 (286)*	
Hypertensive disorder			0.88
Gestational hypertension	4.2 (206)	3.8 (41)	
Preeclampsia / HELLP	1.9 (91)	2.1 (22)	
Child characteristics			
Sex, female	50.4 (2,467)	47.6 (509)	0.10
Gestational age at birth (weeks)[3]	40.1 (35.7-42.4)	40.1 (36.3-42.3)	0.38
Birth weight (grams)[1]	3428 (553)	3389 (548)	0.04
Inhalant allergies, yes	33.8 (1,147)	37.1 (33)	0.57
Missing, % (n)[2]	*30.8 (1,505)*	*91.7 (981)*	

Values are valid percentages (absolute numbers), [1]means (SD), [2]total percentages (absolute numbers) or [3]medians (95% range). Differences in baseline characteristics were tested using Student's *t*, Mann-Whitney *U* and Chi-square tests.

Table S2. Crude analysis of maternal blood pressure and hypertensive disorders during pregnancy with spirometry in children at age 10 years.

	Spirometry				
	FEV_1	**FVC**	**FEV_1/FVC**	**FEF_{25-75}**	**FEF_{75}**
	Z-score (95%CI)	**Z-score (95%CI)**	**Z-score (95%CI)**	**Z-score (95%CI)**	**Z-score (95%CI)**
Early pregnancy					
SBP	-0.00 (-0.17, 0.01)	0.01 (-0.00, 0.03)	**-0.03 (-0.04, -0.02)***	-0.01 (-0.02, 0.01)	**-0.02 (-0.03, -0.01)***
DBP	-0.01 (-0.28, 0.01)	0.01 (-0.01, 0.02)	**-0.03 (-0.05, -0.01)***	-0.01 (-0.03, 0.01)	**-0.02 (-0.04, -0.00)***
MAP	-0.01 (-0.03, 0.01)	0.01 (-0.01, 0.03)	**-0.04 (-0.05, -0.02)***	-0.01 (-0.03, 0.01)	**-0.03 (-0.04, -0.01)***
Mid pregnancy					
SBP	-0.01 (-0.02, 0.01)	0.01 (-0.01, 0.02)	**-0.02 (-0.03, -0.01)***	-0.01 (-0.02, 0.01)	**-0.02 (-0.03, -0.01)***
DBP	-0.01 (-0.03, 0.01)	-0.00 (-0.02, 0.01)	-0.02 (0.03, 0.00)	0.00 (-0.02, 0.02)	-0.02 (-0.03, -0.00)
MAP	-0.01 (-0.03, 0.01)	0.00 (-0.01, 0.02)	**-0.02 (-0.04, -0.01)***	-0.00 (-0.02, 0.02)	**-0.02 (-0.04, -0.00)***
Late pregnancy					
SBP	-0.01 (-0.02, 0.01)	0.00 (-0.01, 0.02)	**-0.02 (-0.03, -0.01)***	-0.01 (-0.02, 0.01)	**-0.02 (-0.03, -0.01)***
DBP	-0.01 (-0.03, 0.01)	-0.00 (-0.02, 0.01)	-0.02 (-0.03, -0.00)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.00)
MAP	-0.01 (-0.03, 0.01)	0.00 (-0.01, 0.02)	**-0.02 (-0.04, -0.01)***	-0.00 (-0.02, 0.02)	**-0.02 (-0.03, 0.00)***

Hypertensive disorder					
None	*reference*	*reference*	*reference*	*reference*	*reference*
GH	0.05 (-0.10, 0.20)	0.07 (-0.07, 0.22)	-0.03 (-0.18, 0.11)	-0.03 (-0.20, 0.13)	-0.04 (-0.18, 0.10)
PE/ HELLP	-0.17 (-0.39, 0.06)	-0.09 (-0.03, 0.12)	-0.08 (-0.30, 0.13)	-0.12 (-0.36, 0.13)	-0.12 (-0.33, 0.09)

Values reflect the change in Z-score (95% confidence interval) from linear regression models. The Z-scores of spirometry values are standardized for fetal sex, age, ethnicity and height. Models were adjusted for child's sex. *p-value < 0.05.

Abbreviations: Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), Gestational hypertension (GH), Preeclampsia/ Haemolysis Elevated liver enzymes Low platelets (PE/ HELLP).

Table S3a. Multivariate analysis of maternal blood pressure and hypertensive disorders during pregnancy with spirometry in children at age 10 years, additionally adjusted for intermediates

	Spirometry				
	FEV_1	**FVC**	**FEV_1/FVC**	**FEF_{25-75}**	**FEF_{75}**
	Z-score (95%CI)	**Z-score (95%CI)**	**Z-score (95%CI)**	**Z-score (95%CI)**	**Z-score (95%CI)**
Early pregnancy					
SBP	0.00 (-0.02, 0.02)	0.01 (-0.01, 0.02)	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.01 (-0.02, 0.01)
DBP	-0.01 (-0.04, 0.01)	-0.00 (-0.02, 0.02)	-0.02 (-0.04, 0.00)	-0.01 (-0.03, 0.02)	-0.02 (-0.04, 0.00)
MAP	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.02 (-0.04, 0.00)	-0.00 (-0.03, 0.02)	-0.01 (-0.03, 0.01)
Mid pregnancy					
SBP	-0.01 (-0.02, 0.01)	0.00 (-0.01, 0.02)	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.01 (-0.02, 0.01)
DBP	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.01)
MAP	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.01)
Late pregnancy					
SBP	-0.00 (-0.02, 0.02)	-0.01 (-0.01, 0.02)	-0.01 (-0.03, 0.00)	0.01 (-0.01, 0.02)	-0.01 (-0.02, 0.01)
DBP	-0.00 (-0.02, 0.02)	-0.00 (-0.02, 0.02)	-0.00 (-0.02, 0.02)	0.01 (-0.02, 0.03)	0.00 (-0.02, 0.02)
MAP	-0.00 (-0.02, 0.02)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.01)	0.01 (-0.02, 0.03)	-0.00 (-0.02, 0.02)

Hypertensive disorder					
None	*reference*	*reference*	*reference*	*reference*	*reference*
GH	0.11 (-0.06, 0.27)	0.10 (-0.05, 0.26)	0.02 (-0.14, 0.18)	0.02 (-0.16, 0.21)	0.03 (-0.12, 0.19)
PE/ HELLP	-0.03 (-0.27, 0.22)	-0.03 (-0.26, 0.21)	0.03 (-0.21, 0.26)	0.02 (00.25, 0.30)	-0.05 (-0.28, 0.18)

Values reflect the change in Z-score (95% confidence interval) from linear regression models. The Z-scores of spirometry values are standardized for fetal sex, age, ethnicity and height. Maternal blood pressure is analysed per 5mmHg. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid use, child's sex and additionally for possible intermediates: psychological distress during pregnancy, mode of delivery, gestational age at delivery and birth weight Z-score. *p-value < 0.05.

Abbreviations: Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), Gestational hypertension (GH), Preeclampsia/ Haemolysis Elevated liver enzymes Low platelets (PE/ HELLP).

Table S3b. Mediation analysis of maternal blood pressure and hypertensive disorders during pregnancy with spirometry in children at age 10 years.

	Spirometry				
	FEV_1	**FVC**	**FEV_1/FVC**	**FEF_{25-75}**	**FEF_{75}**
	Z-score (95%CI)	**Z-score (95%CI)**	**Z-score (95%CI)**	**Z-score (95%CI)**	**Z-score (95%CI)**
Early pregnancy					
SBP	-0.00 (-0.02, 0.01)	0.01 (-0.00, 0.03)	**-0.02 (-0.04, -0.01)***	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.00)
+ Psychological distress %	*97.5 (-913, 732)*		*-39.1 (-49.0, -27.2)***		
+ Mode of delivery %			*-0.25 (-1.93, 1.54)*		
+ Gestational age at birth %			*-8.51 (-11.90, -6.47)***		
+ Birth weight Z-score %			*0.05 (-0.11, 0.25)*		
DBP	-0.02 (-0.04, 0.00)	-0.00 (-0.02, 0.02)	**-0.02 (-0.04, -0.01)***	-0.00 (-0.03, 0.02)	-0.02 (-0.04, 0.00)
+ Psychological distress %			*-12.6 (-26.6, -1.8)**		
+ Mode of delivery %			***-**1.0 (-2.3, 0.9)*		
+ Gestational age at birth %			*-11.2 (-15.6, -9.0)***		
+ Birth weight Z-score %			*0.81 (-0.49, 2.56)*		
MAP	-0.01 (-0.03, 0.00)	0.01 (-0.01, 0.02)	**-0.03 (-0.05, -0.01)***	-0.00 (-0.03, 0.02)	-0.02 (-0.04, 0.00)

+ Psychological distress %			*-23.1 (-35.1, -15.3)***		
+ Mode of delivery %			*-0.7 (-2.4, 0.9)*		
+ Gestational age at birth %			*-10.0 (-13.9, -7.8)***		
+ Birth weight Z-score %			*0.5 (-0.7, 1.7)*		
Mid pregnancy					
SBP	0.01 (-0.02, 0.01)	0.00 (-0.01, 0.02)	-0.01 (-0.03, 0.00)	0.00 (-0.02, 0.02)	-0.01 (-0.02, 0.01)
DBP	**-0.02 (-0.04, -0.00)***	-0.01 (-0.03, 0.00)	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.01)
+ Psychological distress %	*-6.7 (-21.3, 7.8)*				
+ Mode of delivery %	*-1.3 (-0.6, 3.9)*				
+ Gestational age at birth %	*-9.8 (-15.3, -7.3)***				
+ Birth weight Z-score %	*-12.2 (-17.7, -8.8)***				
MAP	-0.02 (-0.03 ,0.00)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	-0.01 (-0.03, 0.00)
Late pregnancy					
SBP	-0.00 (-0.02, 0.01)	0.01 (-0.01, 0.02)	**-0.01 (-0.03, -0.00)***	0.01 (-0.01, 0.02)	-0.01 (-0.02, 0.01)
+ Psychological distress %			*4.9 (-223, 313)*		
+ Mode of delivery %			*-13.9 (-178, 89.5)*		

+ Gestational age at birth %			*-70.4 (-683, 207)*		
+ Birth weight Z-score %			*3.9 (-40.4, 64.0)*		
DBP	-0.02 (-0.03, 0.00)	-0.01 (-0.03, 0.01)	-0.01 (-0.02, 0.01)	0.01 (-0.02, 0.02)	-0.01 (-0.02, 0.01)
MAP	-0.01 (-0.03, 0.01)	-0.01 (-0.02, 0.01)	-0.01 (-0.03, 0.00)	0.01 (-0.02, 0.03)	-0.01 (-0.03, 0.01)
Hypertensive disorder					
None	*reference*	*reference*	*reference*	*reference*	*reference*
GH	0.05 (-0.11, 0.20)	0.44 (-0.10, 0.19)	0.02 (-0.12, 0.17)	0.01 (-0.16, 0.18)	0.02 (-0.13, 0.16)
PE/ HELLP	-0.16 (-0.38, 0.06)	-0.10 (-0.31, 0.11)	-0.05 (-0.27, 0.16)	-0.11 (-0.35, 0.14)	-0.10 (0.31, 0.11)

Values reflect the change in Z-score (95% confidence interval) from linear regression models. The Z-scores of spirometry are standardized by fetal sex, age, ethnicity and height. Maternal blood pressure is analysed per 5mmHg. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid use and child's sex. *p-value < 0.05. **p-value < 0,01.

Abbreviations: Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), Gestational hypertension (GH), Preeclampsia/ Haemolysis Elevated liver enzymes Low platelets (PE/ HELLP).

Table S4. Conditional analysis of maternal blood pressure and hypertensive disorders during pregnancy with spirometry in children at age 10 years.

	Spirometry				
	FEV_1	**FVC**	**FEV_1/FVC**	**FEF_{25-75}**	**FEF_{75}**
	Z-score	**Z-score**	**Z-score**	**Z-score**	**Z-score**
Early pregnancy					
SBP	0.00 (-0.02, 0.02)	0.01 (-0.00, 0.03)	**-0.02 (-0.03, -0.00)***	0.00 (-0.01, 0.02)	-0.01 (-0.03, 0.01)
DBP	-0.02 (-0.04, 0.00)	-0.01 (-0.02, 0.02)	**-0.02 (-0.04, -0.00)***	-0.00 (-0.03, 0.02)	-0.02 (-0.04, 0.00)
MAP	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	**-0.03 (-0.05, -0.01)***	0.00 (-0.02, 0.02)	-0.02 (-0.04, 0.00)
Mid pregnancy					
SBP	-0.02 (-0.06, 0.01)	-0.01 (-0.05, 0.02)	-0.01 (-0.05, 0.02)	-0.00 (-0.04, 0.04)	-0.02 (-0.05, 0.01)

DBP	-0.03 (-0.07, 0.00)	-0.03 (-0.07, 0.00)	0.01 (-0.03, 0.04)	-0.01 (-0.05, 0.03)	-0.02 (-0.05, 0.02)
MAP	-0.03 (-0.07, 0.00)	-0.03 (-0.06, 0.00)	0.01 (-0.04, 0.03)	-0.01 (-0.05, 0.03)	-0.02 (-0.05, 0.01)
Late pregnancy					
SBP	0.00 (-0.03, 0.04)	0.00 (-0.03, 0.04)	0.00 (-0.03, 0.04)	0.00 (-0.04, 0.04)	0.01 (-0.03, 0.04)
DBP	-0.01 (-0.05, 0.02)	-0.01 (-0.05, 0.02)	0.01 (-0.03, 0.04)	0.00 (-0.04, 0.04)	0.01 (-0.02, 0.05)
MAP	-0.01 (-0.04, 0.03)	-0.01 (-0.04, 0.03)	0.01 (-0.03, 0.04)	0.00 (-0.04, 0.04)	0.01 (-0.02, 0.05)

Values reflect the change in Z-score (95% confidence interval) from conditional regression models. The Z-scores of spirometry values are standardized for fetal sex, age, ethnicity and height. Maternal blood pressure is analysed per 5mmHg. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid use and child's sex. *p-value < 0.05.

Abbreviations: Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP).

Table S5. Crude analysis of maternal blood pressure and hypertensive disorders during pregnancy with current wheezing or asthma at age 10 years.

	Current wheezing	**Current asthma**
	Odds ratio (95%CI)	**Odds ratio (95%CI)**
Early pregnancy		
SBP	**1.06 (1.02, 1.10)***	1.04 (0.99, 1.10)
DBP	**1.06 (1.01, 1.12)***	1.04 (0.97, 1.12)
MAP	**1.08 (1.02, 1.13)***	1.05 (0.98, 1.13)
Mid pregnancy		
SBP	1.01 (0.98, 1.05)	1.01 (0.96, 1.060
DBP	1.04 (0.99, 1.08)	0.97 (0.91, 1.04)
MAP	1.03 (0.99, 1.08)	0.99 (0.92, 1.05)
Late pregnancy		
SBP	**1.04 (1.01, 1.08)***	**1.06 (1.00, 1.11)***
DBP	**1.07 (1.02, 1.12)***	1.03 (0.97, 1.10)
MAP	**1.07 (1.02, 1.12)***	1.05 (0.99, 1.12)
Hypertensive disorder		
None	*reference*	*reference*
GH	1.03 (0.70, 1.53)	1.06 (0.61, 1.82)
PE/ HELLP	0.75 (0.38, 1.48)	0.85 (0.34, 2.12)

Values are Odds ratio's (95% confidence interval) from logistic binary and multinomial regression models. Maternal blood pressure is analysed per 5mmHg. Models were adjusted for child's sex. *p-value < 0.05.

Abbreviations: Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), Gestational hypertension (GH), Preeclampsia/ Haemolysis Elevated liver enzymes Low platelets (PE/ HELLP).

Table S6a. Multivariate analysis of maternal blood pressure and hypertensive disorders during pregnancy with current wheezing or asthma at age 10 years, additionally adjusted for intermediates.

	Current wheezing	**Current asthma**
	Odds ratio (95%CI)	**Odds ratio (95%CI)**
Early pregnancy		
SBP	**1.05 (1.00, 1.09)***	1.05 (0.99, 1.12)
DBP	1.05 (0.99, 1.11)	1.04 (0.96, 1.13)
MAP	1.06 (1.00, 1.12)	1.06 (0.97, 1.15)
Mid pregnancy		
SBP	1.00 (0.96, 1.04)	0.99 (0.93, 1.05)
DBP	1.02 (0.97, 1.08)	0.96 (0.89, 1.03)
MAP	1.01 (0.96, 1.07)	0.97 (0.89, 1.04)
Late pregnancy		
SBP	1.04 (0.99, 1.08)	1.06 (1.00, 1.12)
DBP	1.04 (0.99, 1.10)	1.0 (0.93, 1.07)
MAP	1.05 (1.00, 1.11)	1.03 (0.95, 1.11)
Hypertensive disorder		
None	*reference*	*reference*
GH	1.00 (0.65, 1.53)	1.02 (0.57, 1.84)
PE/ HELLP	0.71 (0.35, 1.44)	0.75 (0.29, 1.97)

Values are Odds ratio's (95% confidence interval) from logistic binary and multinomial regression models. Maternal blood pressure is analysed per 5mmHg. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy BMI, educational

level, nulliparity, smoking habits during pregnancy, folic acid use, child's sex and additionally for possible intermediates: psychological distress during pregnancy, mode of delivery, gestational age at delivery and birth weight Z-score. *p-value < 0.05.

Abbreviations: Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), Gestational hypertension (GH), Preeclampsia/ Haemolysis Elevated liver enzymes Low platelets (PE/ HELLP).

Table S6b. Mediation analysis of maternal blood pressure and hypertensive disorders during pregnancy with current wheezing or asthma at age 10 years.

	Current wheezing	**Current asthma**
	Odds ratio (95%CI)	**Odds ratio (95%CI)**
Early pregnancy		
SBP	**1.05 (1.01, 1.10)***	1.04 (0.98, 1.10)
+ *Psychological distress %*	*-15.1 (-358, 135)*	
+ *Mode of delivery %*	*-33.9 (-109, 586)*	
+ *Gestational age at birth %*	*-12.0 (-90.7, 326)*	
+ *Birth weight Z-score %*	*-13.7 (-124, 153)*	
DBP	1.05 (0.99, 1.11)	1.03 (0.96, 1.11)
MAP	**1.07 (1.01, 1.13)***	1.04 (0.97, 1.13)
+ *Psychological distress %*	*8.5 (-1058, 427)*	
+ *Mode of delivery %*	*-13.6 (-83.3, 284)*	
+ *Gestational age at birth %*	*-18.1 (-106, 276)*	
+ *Birth weight Z-score %*	*31.7 (-75.0, 328)*	
Mid pregnancy		
SBP	1.00 (0.96, 1.04)	1.00 (0.95, 1.05)
DBP	1.01 (0.97, 1.07)	0.95 (0.89, 1.02)
MAP	1.01 (0.96, 1.06)	0.96 (0.90, 1.04)
Late pregnancy		
SBP	1.04 (1.00, 1.08)	**1.06 (1.00, 1.12)***
+ *Psychological distress %*		*-20.4 (-244, 34.5)*
+ *Mode of delivery %*		*34.3 (-70.9, 169)*
+ *Gestational age at birth %*		*29.6 (-123, 164)*
+ *Birth weight Z-score %*		*1.0 (-48.8, 90.2)*

DBP	**1.06 (1.01, 1.11)***	1.02 (0.96, 1.10)
+ *GSI%*	*-36.5 (-690, 225)*	
+ *Mode of delivery %*	*-36.5 (-89.5, 67.9)*	
+ *Gestational age at birth %*	*-33.6 (-167, 356)*	
+ *Birth weight Z-score %*	*-0.78 (-294, 342)*	
MAP	**1.06 (1.01, 1.12)***	1.05 (0.98, 1.13)
+ *Psychological distress %*	*15.4 (-460, 106)*	
+ *Mode of delivery %*	*-84.6 (-526, 122)*	
+ *Gestational age at birth %*	*39.0 (-144, 166)*	
+ *Birth weight Z-score %*	*-7.4 (-134, 126)*	
Hypertensive disorder		
None	*Reference*	*Reference*
GH	0.95 (0.63, 1.42)	0.99 (0.57, 1.73)
PE/ HELLP	0.70 (0.36, 1.39)	0.80 (0.32, 2.01)

Values are Odds ratio's (95% confidence interval) from logistic binary and multinomial regression models. Maternal blood pressure is analysed per 5mmHg. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid use and child's sex. *p-value < 0.05.

Abbreviations: Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), Gestational hypertension (GH), Preeclampsia/ Haemolysis Elevated liver enzymes Low platelets (PE/ HELLP).

Table S7. Conditional analysis of maternal blood pressure during pregnancy with current wheezing or asthma at age 10 years.

	Current wheezing	**Current asthma**
	Odds ratio (95%CI)	**Odds ratio (95%CI)**
Early pregnancy		
SBP	1.05 (0.99, 1.11)	1.05 (0.99, 1.12)
DBP	1.01 (0.94, 1.09)	1.03 (0.96, 1.12)
MAP	1.04 (0.96, 1.12)	1.06 (0.97,1.14)
Mid pregnancy		
SBP	0.99 (0.87, 1.12)	1.03 (0.90, 1.18)
DBP	0.90 (0.79, 1.03)	0.94 (0.82, 1.09)
MAP	0.93 (0.81, 1.06)	0.97 (0.84, 1.12)
Late pregnancy		
SBP	1.13 (0.99, 1.28)	**1.16 (1.01, 1.33)***
DBP	1.11 (0.98, 1.26)	1.11 (0.97, 1.27)
MAP	1.13 (1.00, 1.29)	**1.15 (1.00, 1.32)***

Values are Odds ratio's (95% confidence interval) from logistic binary and multinomial regression models. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid use and child's sex. *p-value < 0.05.

Abbreviations: Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP).

Table S8. Associations of early pregnancy blood pressure and hypertensive diseases with childhood lung function, and interaction of potential effect modifiers

	Lung function Z-score	$P_{interaction}$
SBP		
Maternal atopy or asthma	FEV_1/FVC	0.89
	FEF_{75}	0.22
Inhalant allergies at child's age 10 years	FEV_1/FVC	0.52
	FEF_{75}	0.93
Doctor-diagnosed eczema in the past 12 months at age 10 years	FEV_1/FVC	0.46
	FEF_{75}	0.65
Gestational age adjusted birth weight	FEV_1/FVC	0.82
	FEF_{75}	0.82
Gestational age at birth	FEV_1/FVC	0.24
	FEF_{75}	0.22
DBP		
Maternal atopy or asthma	FEV_1/FVC	0.22
	FEF_{75}	0.90

Inhalant allergies at child's age 10 years	FEV_1/FVC	0.91
	FEF_{75}	0.88
Doctor-diagnosed eczema in the past 12 months at age 10 years	FEV_1/FVC	0.20
	FEF_{75}	0.83
Gestational age adjusted birth weight	FEV_1/FVC	0.79
	FEF_{75}	0.19
Gestational age at birth	FEV_1/FVC	0.31
	FEF_{75}	0.61
MAP		
Maternal atopy or asthma	FEV_1/FVC	0.45
	FEF_{75}	0.64
Inhalant allergies at child's age 10 years	FEV_1/FVC	0.73
	FEF_{75}	0.94
Doctor-diagnosed eczema in the past 12 months at age 10 years	FEV_1/FVC	0.23
	FEF_{75}	0.74
Gestational age adjusted birth weight	FEV_1/FVC	0.96

	FEF_{75}	0.34
Gestational age at birth	FEV_1/FVC	0.24
	FEF_{75}	0.39
Hypertensive disorders		
Maternal atopy or asthma	FEV_1/FVC	0.30
	FEF_{75}	0.82
Inhalant allergies at child's age 10 years	FEV_1/FVC	0.59
	FEF_{75}	0.96
Doctor-diagnosed eczema in the past 12 months at age 10 years	FEV_1/FVC	0.75
	FEF_{75}	0.85
Gestational age adjusted birth weight	FEV_1/FVC	0.15
	FEF_{75}	0.24
Gestational age at birth	FEV_1/FVC	0.53
	FEF_{75}	0.64

Pinteraction: P-value for the statistical interaction of early pregnancy blood pressure and hypertensive disorders for lung function measures with effect modifiers.

Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP)

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF_{75}, forced expiratory flow at 75% of FVC.

Table S9. Associations of early pregnancy blood pressure and hypertensive diseases with current asthma at age 10 years, and interaction of potential effect modifiers

	Current asthma (Odds ratio) $P_{interaction}$
SBP	
Maternal atopy or asthma	0.76
Inhalant allergies at child's age 10 years	0.29
Doctor-diagnosed eczema in the past 12 months at age 10 years	0.40
Gestational age adjusted birth weight	0.84
Gestational age at birth	0.60
DBP	
Maternal atopy or asthma	0.82
Inhalant allergies at child's age 10 years	0.07
Doctor-diagnosed eczema in the past 12 months at age 10 years	0.84

Gestational age adjusted birth weight	0.15
Gestational age at birth	0.87
MAP	
Maternal atopy or asthma	0.77
Inhalant allergies at child's age 10 years	0.09
Doctor-diagnosed eczema in the past 12 months at age 10 years	0.62
Gestational age adjusted birth weight	0.38
Gestational age at birth	0.36
Hypertensive disorders	
Maternal atopy or asthma	0.57
Inhalant allergies at child's age 10 years	0.12
Doctor-diagnosed eczema in the past 12 months at age 10 years	0.03*
Gestational age adjusted birth weight	0.58

Gestational age at birth	0.98

Pinteraction: P-value for the statistical interaction of early pregnancy blood pressure and hypertensive disorders for Current asthma at age 10 years with effect modifiers.

Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP)

*P-value < 0.05, however, due to multiple testing, this is not significant.

Table S10. Baseline characteristics of mothers and their children in complete cases and imputed dataset.

	Original data	Imputed data
Maternal characteristics	**n=4,894**	**n=4,894**
Age (years)[1]	30.7 (4.8)	30.7 (4.8)
Ethnicity, western	65.9 (3,173)	65.4 (3,201)
Missing, %(n)[2]	*1.7 (81)*	-
Body mass index (kg/m2)[3]	23.7 (18.8-35.6)	23.7 (18.8-35.7)
Missing, %(n)[2]	*0.6 (30)*	-
Educational level, higher	50.1 (2,342)	49.2 (2,408)
Missing, %(n)[2]	*4.5 (222)*	-
Nulliparity	62.5 (3,046)	62.3 (3,049)
Missing, %(n)[2]	*0.5 (22)*	-
Psychological distress, yes	8.1 (331)	9.2 (448)
Missing, %(n)[2]	*16.1 (790)*	-
Smoking during pregnancy		
No	75.4 (3,334)	74.6 (3.650)
Yes – stopped	8.4 (409)	9.5 (465)
Yes – continued	13.9 (678)	15.9 (779)
Missing, %(n)[2]	*9.7 (473)*	-
Folic acid use		
No	20.9 (793)	22.5 (1,101)
Start before 10 weeks	32.2 (1224)	32.5 (1,593)
Preconception start	46.9 (1,781)	45.0 (2,200)
Missing, %(n)[2]	*22.4 (1,096)*	-
Caesarean section, yes	12.8 (582)	13.0 (637)
Missing, %(n)[2]	*7.2 (351)*	-
History of asthma or atopy, yes	40.0 (1,625)	41.1 (2.013)

Missing, %(n)[2]	*17.0 (830)*	-
Children's characteristics		
Sex, female	50.4 (2,467)	50.4 (2,467)
Birth weight (grams)[1]	3428 (553)	3428 (553)
Gestational age at birth (weeks)[3]	40.1 (35.7-42.4)	40.1 (35.7-42.4)
Inhalant allergies, yes	33.8 (1,147)	34.2 (1,673)
Missing, %(n)[2]	*30.8 (1,505)*	-
Current eczema, yes	7.3 (281)	9.0 (439)
Missing, %(n)[2]	*21.0 (1,026)*	-
Eczema ever[6]**, yes**	23.2 (874)	26.7 (1,308)
Missing, %(n)[2]	*23.1 (1,129)*	-

Values are valid percentages (absolute numbers), [1]means (SD) or [2]percentages (absolute numbers) or [3]medians (95% range).

Table S11. Sensitivity analysis. Multivariate analysis of maternal blood pressure and hypertensive disorders during pregnancy with spirometry in children at age 10 years in complete case dataset.

	Spirometry				
	FEV_1	**FVC**	**FEV_1/FVC**	**FEF_{25-75}**	**FEF_{75}**
	Z-score (95%CI)	**Z-score (95%CI)**	**Z-score (95%CI)**	**Z-score (95%CI)**	**Z-score (95%CI)**
Early pregnancy					
SBP	-0.00 (-0.02, 0.01)	0.01 (-0.00, 0.03)	**-0.02 (-0.03, -0.01)***	0.01 (-0.03, 0.00)	-0.00 (-0.02, 0.02)
DBP	-0.02 (-0.04, 0.00)	-0.01 (-0.02, 0.01)	**-0.02 (-0.04, -0.01)***	-0.02 (-0.04, 0.00)	-0.01 (-0.03, 0.02)
MAP	-0.01 (-0.03, 0.01)	0.00 (-0.02, 0.02)	**-0.03 (-0.05, -0.01)***	**-0.02 (-0.04, 0.00)***	-0.00 (-0.03, 0.02)
Mid pregnancy					
SBP	-0.01 (-0.02, 0.01)	0.00 (-0.01, 0.02)	-0.01 (-0.03, 0.00)	0.01 (-0.02, 0.00)	-0.00 (-0.02, 0.01)
DBP	**-0.02 (-0.04, -0.00)***	-0.02 (-0.03, 0.00)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.01)
MAP	-0.02 (-0.04 ,0.00)	-0.01 (-0.03, 0.01)	-0.01 (-0.03, 0.00)	-0.02 (-0.03, 0.00)	-0.01 (-0.03, 0.02)
Late pregnancy					
SBP	-0.00 (-0.02, 0.01)	0.01 (-0.01, 0.02)	**-0.02 (-0.03, -0.00)***	0.01 (-0.02, 0.00)	-0.01 (-0.01, 0.02)
DBP	-0.01 (-0.03, 0.00)	-0.01 (-0.03, 0.01)	-0.01 (-0.02, 0.01)	0.01 (-0.02, 0.01)	-0.00 (-0.02, 0.02)
MAP	-0.01 (-0.03, 0.01)	-0.00 (-0.02, 0.01)	-0.01 (-0.03, 0.00)	0.01 (-0.03, 0.01)	-0.01 (-0.01, 0.03)

Hypertensive disorder					
None	*reference*	*reference*	*reference*	*reference*	*reference*
GH	0.04 (-0.11, 0.20)	0.04 (-0.10, 0.19)	0.02 (-0.13, 0.17)	0.01 (-0.14, 0.15)	-0.01 (-0.18, 0.16)
PE/ HELLP	-0.15 (-0.37, 0.07)	-0.09 (-0.31, 0.12)	-0.07 (-0.28, 0.15)	-0.10 (-0.30, 0.11)	-0.11 (0.35, 0.14)

Values reflect the change in Z-score (95% confidence interval) from linear regression models. The Z-scores of spirometry are standardized by fetal sex, age, ethnicity and height. Maternal blood pressure is analysed per 5mmHg. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid use and child's sex. *p-value < 0.05.

Abbreviations: Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), Gestational hypertension (GH), Preeclampsia/ Haemolysis Elevated liver enzymes Low platelets (PE/ HELLP).

Table S12. Sensitivity analysis. Multivariate analysis of maternal blood pressure and hypertensive disorders during pregnancy with current wheezing or asthma at age 10 years in complete case dataset.

	Current wheezing	**Current asthma**
	Odds ratio (95%CI)	**Odds ratio (95%CI)**
Early pregnancy		
SBP	**1.05 (1.01, 1.10)***	1.03 (0.98, 1.09)
DBP	1.04 (0.99, 1.11)	1.00 (0.93, 1.07)
MAP	**1.06 (1.00, 1.12)***	1.02 (0.95, 1.10)
Mid pregnancy		
SBP	1.00 (0.96, 1.04)	0.98 (0.93, 1.03)
DBP	1.02 (0.97, 1.07)	0.93 (0.87, 1.00)
MAP	1.01 (0.96, 1.06)	0.94 (0.88, 1.01)
Late pregnancy		
SBP	1.04 (1.00, 1.08)	1.04 (0.99, 1.09)
DBP	**1.06 (1.01, 1.11)***	1.02 (0.96, 1.09)
MAP	**1.07 (1.01, 1.12)***	1.04 (0.97, 1.11)
Hypertensive disorder		
None	*Reference*	*Reference*
GH	0.95 (0.63, 1.42)	0.86 (0.49, 1.50)
PE/ HELLP	0.69 (0.35, 1.36)	0.96 (0.43, 2.13)

Values are Odds ratio's (95% confidence interval) from logistic binary and multinomial regression models. Maternal blood pressure is analysed per 5mmHg. Models were adjusted

for possible confounders: maternal age, maternal ethnicity, pre-pregnancy BMI, educational level, nulliparity, smoking habits during pregnancy, folic acid use and child's sex. *p-value < 0.05.

Abbreviations: Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), Gestational hypertension (GH), Preeclampsia/ Haemolysis Elevated liver enzymes Low platelets (PE/ HELLP).