Maternal blood pressure and hypertensive disorders during pregnancy and childhood respiratory morbidity: the Generation R Study

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ABSTRACT Pre-eclampsia 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 4894 children was embedded in a population-based prospective cohort study. We used multivariate analyses, taking lifestyle and socioeconomic factors into account.

We observed consistent associations per 5 mmHg higher maternal blood pressure in early pregnancy with a lower forced expiratory volume in 1 s/forced vital capacity ratio (z-score −0.03 (95% CI −0.05–−0.01)) and per 5 mmHg higher blood pressure in late pregnancy with a higher risk for current wheezing and current asthma (OR 1.07 (95% CI 1.02–1.12) and 1.06 (95% CI 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.

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Introduction

Maternal hypertensive disorders during pregnancy, including pre-eclampsia, are associated with adverse neonatal outcomes such as a 2- to 5-fold increased risk of pre-term birth or low birthweight [1–3]. Lower gestational age and birthweight 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 pre-eclampsia is associated with a 2- to 4-fold increased risk of bronchopulmonary dysplasia [8, 12–14]. Several former cohort studies examined the association of pre-eclampsia 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 pre-term birth and confounders shared by siblings [16, 19, 20]. One prospective cohort study found no association between pre-eclampsia and lower lung function or early wheezing, but did find an association of pre-existing hypertension with an up to 1.6-fold increased risk of childhood wheezing and asthma [18]. We hypothesised 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 influences are of lifestyle, socioeconomic factors, growth and atopy.

Therefore, we examined the associations of maternal blood pressure during early, mid and late pregnancy, gestational hypertension, and pre-eclampsia with the risks of lower lung function, wheezing and childhood asthma in a population-based prospective cohort study among 4894 children. We also explored if any association could be explained by lifestyle and socioeconomic factors, or modified by a 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 post-natal phase at 10 years of age and included only one child per mother (n=6168). After applying exclusion criteria, our final population for analysis consisted of n=4894 children (figure 1).

Maternal hypertensive disorders during pregnancy

Maternal systolic and diastolic blood pressures in early (<18 weeks), mid (18–25 weeks) and late (>25 weeks) pregnancy were measured with the validated HEM-907 automated digital oscillometric sphygmomanometer (OMRON Healthcare Europe, Hoofddorp, The Netherlands), as described previously [22]. Gestational hypertension and pre-eclampsia were defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy and the American College of Obstetricians and Gynaecologists [23, 24].

Childhood lung function, current wheezing and current asthma

Children visited our dedicated research centre at a mean (range) age of 9.8 (8.6–12.0) years. Spirometry was performed according to American Thoracic Society/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 use of inhaled medication in the past 12 months. The response rate for the questionnaires ranged from 68% to 75%.

Covariates

See the 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 the literature and if the effect estimate of the unadjusted analyses changed ⩾10% when additionally adjusted for a covariate. First, models were adjusted for child's sex only (crude analysis). Second, we adjusted for potential lifestyle and socioeconomic

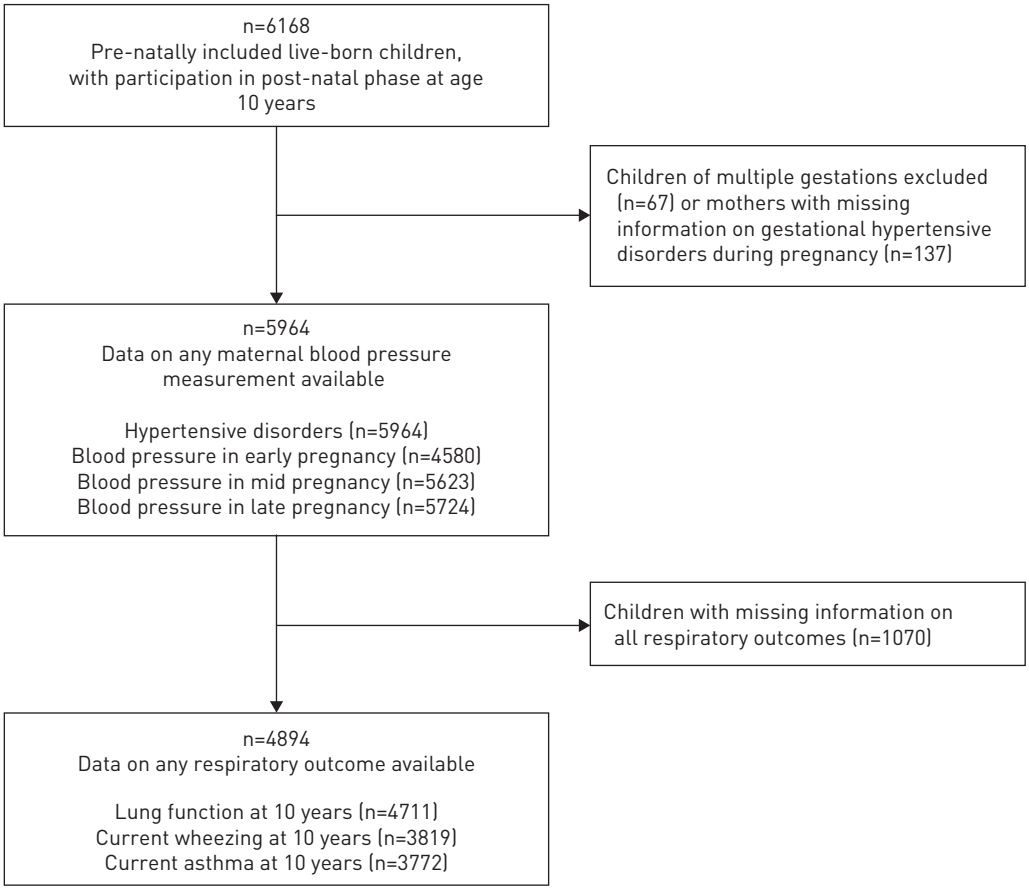

FIGURE 1 Flowchart of participants included for analysis.

confounders, including maternal age, ethnicity, pre-pregnancy body mass index, 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 birthweight, 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 of the correlation between blood pressures measured at multiple time-points in pregnancy [29]. We performed a sensitivity analysis excluding all women who were treated with medication for high blood pressure during pregnancy. The modifying effects of a maternal history of asthma and atopy, child's gestational age at birth, birthweight, inhalant allergic sensitisation, and current eczema were tested. For additional explanations about intermediates, our mediation and conditional analyses, imputation, and testing effect modification, see the supplementary material. All measures of association were analysed per 5 mmHg and presented as z-score differences for lung function and odds ratios for current wheezing or asthma, with corresponding 95% confidence intervals. Analyses were performed using SPSS version 21.0 for Windows (IBM, Armonk, NY, USA) and R version 3.0.0 (https://cran.r-project.org).

Results

Maternal and child characteristics are presented in table 1. Of 4894 women eligible for analyses, 4.2% (206) had gestational hypertension and 1.9% (n=91) had pre-eclampsia or HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome. Current wheezing and asthma were reported in 18.1% (n=692) and 8.3% (n=313) at age 10 years, respectively. Loss-to-follow-up analysis showed that mothers not included in the analysis were younger, less 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 and were born at a shorter gestational age with a lower birthweight (supplementary table S1).

TABLE 1 Baseline characteristics of mothers and their children

Maternal characteristics	
Subjects	4894
Age years	30.7±4.8
Ethnicity: Western	65.4 (3201)
BMI kg·m^{-2}	23.7 (18.8–35.7)
Educational level: higher	49.2 (2408)
Nulliparity: yes	62.3 (3049)
Psychological distress: yes	9.2 (448)
Smoking during pregnancy	
No	74.6 (3.650)
Yes: stopped	9.5 (465)
Yes: continued	15.9 (779)
Folic acid use	
No	22.5 (1101)
Start before 10 weeks	32.5 (1593)
Pre-conception start	45.0 (2200)
Caesarean section: yes	13.0 (637)
History of asthma or atopy: yes	41.1 (2.013)
Blood pressure	
Early pregnancy weeks	13.2 (10.5–17.5)
SBP mmHg	116±12
DBP mmHg	69±9
MAP mmHg	84±9
Mid pregnancy weeks	20.5 (18.6–23.3)
SBP mmHg	117±12
DBP mmHg	67±9
MAP mmHg	84±9
Late pregnancy weeks	30.4 (28.5–32.9)
SBP mmHg	119±12
DBP mmHg	69±9
MAP mmHg	85±9
Hypertensive disorder	
Gestational hypertension	4.2 (206)
Pre-eclampsia/HELLP	1.9 (91)
Child characteristics	
Sex: female	50.4 (2467)
Birthweight g	3428±553
Gestational age at birth weeks	40.1 (35.7–42.4)
Inhalant allergies: yes	34.2 (1673)
Current eczema: yes	9.0 (439)
Spirometry	
FEV_1 L	2.01±0.30
FVC L	2.33±0.37
FEV_1/FVC	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	9.7 (368)
Current wheezing	18.1 (692)
Current asthma	8.3 (313)

Data are presented as n, mean±SD, % (n) or median (95% range) based on imputed data; data on maternal blood pressure, hypertensive disorders, lung function, wheezing and asthma were not imputed. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HELLP: haemolysis, elevated liver enzymes and low platelets; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25–75\%}$: mean forced expiratory flow between 25% and 75% of FVC; $FEF_{75\%}$: forced expiratory flow at 75% of FVC.

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 forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio and forced expiratory flow at 75% of FVC ($FEF_{75\%}$) (supplementary table S2). After adjusting for lifestyle and socioeconomic 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 −0.02 (95% CI −0.04–−0.01),

−0.02 (95% CI −0.04–−0.01) and −0.03 (95% CI −0.05–−0.01), respectively), higher diastolic pressure in mid pregnancy was associated with lower FEV_1 (z-score −0.02 (95% CI −0.04–−0.00)), and higher systolic pressure in late pregnancy was associated with lower FEV_1/FVC (z-score −0.01 (95% CI −0.03–−0.00)) (table 2). Effect estimates attenuated into nonsignificant when we additionally adjusted for intermediating factors (supplementary table S3a). Psychological distress during pregnancy explained 13–39% of the associations between blood pressure and FEV_1/FVC in early pregnancy. Gestational age at delivery explained 9–11% 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 any of the intermediates (supplementary 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 socioeconomic factors were applied (figure 2 and supplementary 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 (supplementary table S5). After adjusting for lifestyle and socioeconomic factors, higher systolic and mean arterial pressure in early pregnancy and higher diastolic and mean arterial pressure in late pregnancy were associated with an increased risk of current wheezing (OR 1.05 (95% CI 1.01–1.10), 1.07 (95% CI 1.01–1.13), 1.06 (95% CI 1.01–1.11) and 1.06 (95% CI 1.01–1.12), respectively). Higher systolic blood pressure in late pregnancy was associated with an increased risk of current asthma (OR 1.06 (95% CI 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 (OR 1.05 (95% CI 1.00–1.09)) (supplementary table S6a). Mediation analyses did not show that any of the intermediates significantly explained the associations found (supplementary table S6b). When conditional analyses were applied, associations of maternal blood pressure with current wheezing attenuated into nonsignificant. The association of a higher systolic pressure with a higher risk for current asthma remained consistent (OR 1.16 (95% CI 1.01–1.33)) (figure 2 and supplementary 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, birthweight, inhalant allergic sensitisation, and current eczema ($p_{interaction}>0.05$) (supplementary table S8 and S9).

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

	FEV_1	FVC	FEV_1/FVC	$FEF_{25–75\%}$	$FEF_{75\%}$
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
Gestational hypertension	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)

Data are presented as change in z-score (95% CI) from linear regression models. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25–75\%}$: mean forced expiratory flow between 25% and 75% of FVC; $FEF_{75\%}$: forced expiratory flow at 75% of FVC; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PE/HELLP: pre-eclampsia/haemolysis, elevated liver enzymes and low platelets. The z-scores of spirometry are standardised by fetal sex, age, ethnicity and height. Maternal blood pressure is analysed per 5 mmHg. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy body mass index, educational level, nulliparity, smoking habits during pregnancy, folic acid use and child's sex. *: $p<0.05$.

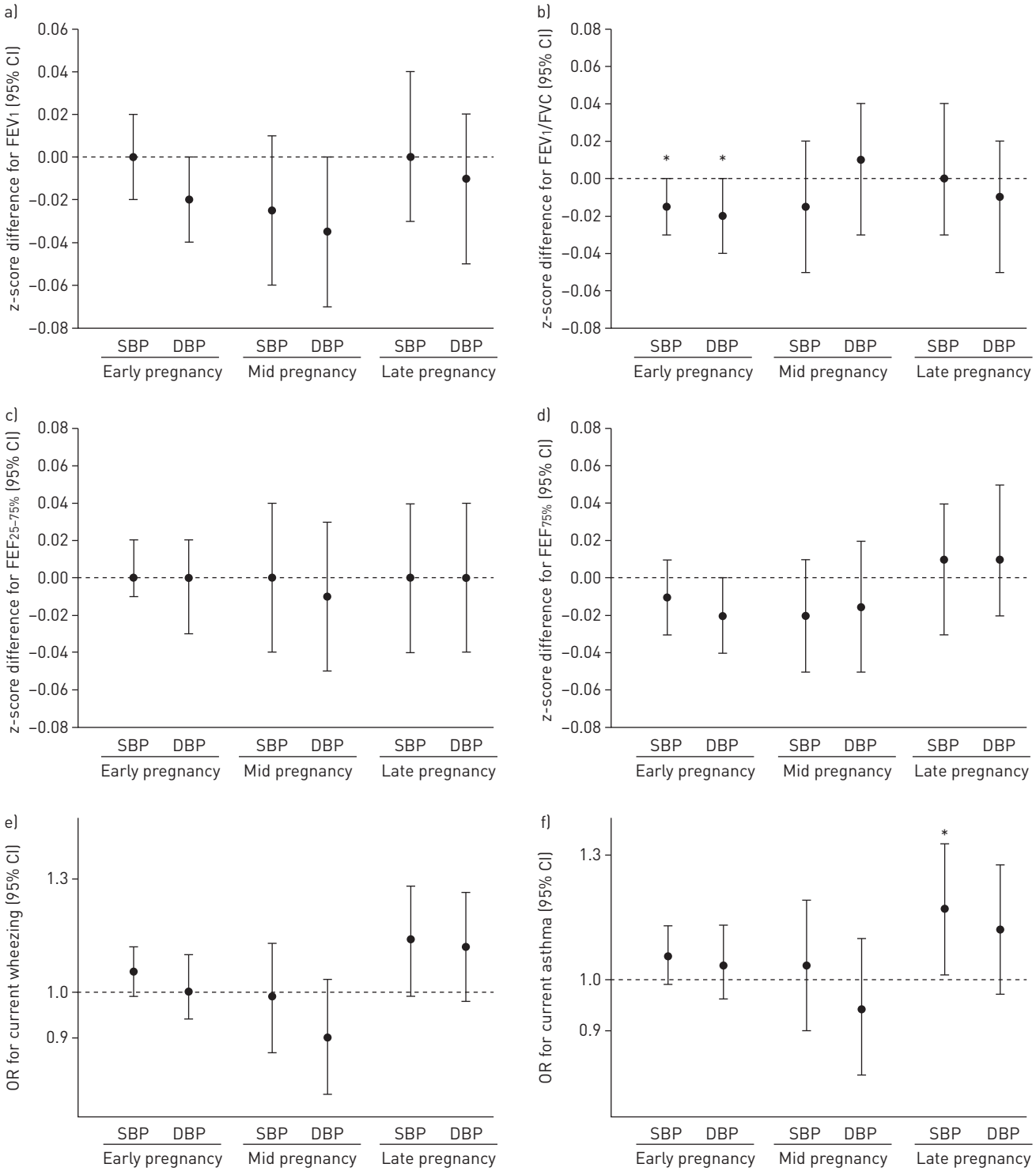

FIGURE 2 Associations of maternal systolic blood pressure (SBP) and diastolic blood pressure (DBP) during early, mid and late pregnancy with a–d) lung function, e) current wheezing and f) current asthma at age 10 years (conditional regression analyses). FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{25–75\%}$: forced expiratory flow at 25–75% of FVC; $FEF_{75\%}$: forced expiratory flow at 75% of FVC. *: p<0.05.

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 (supplementary table S11 and S12). After exclusion of women who were treated with medication for high blood pressure during pregnancy (n=39), the size and direction of the effect estimates of the observed associations remained similar.

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
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
Gestational hypertension	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)

Data are presented as OR (95% CI) from logistic binary and multinomial regression models. SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PE/HELLP: pre-eclampsia/haemolysis, elevated liver enzymes and low platelets. Maternal blood pressure is analysed per 5 mmHg. Models were adjusted for possible confounders: maternal age, maternal ethnicity, pre-pregnancy body mass index, educational level, nulliparity, smoking habits during pregnancy, folic acid use and child's sex. *: $p<0.05$.

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 age 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 the results attenuated into nonsignificant, most probably by overadjustment. 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 birthweight 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 children. A large prospective cohort study, examining the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, assessed associations of maternal hypertension before pregnancy, gestational hypertension and pre-eclampsia with lung function, wheezing or asthma in children at age 18 months and 7–9 years [18]. They observed that pre-existing hypertension, and not gestational hypertension or pre-eclampsia, may be a risk factor for childhood wheezing and asthma with OR 1.63 (95% CI 1.16–2.31) and 1.34 (95% CI 1.00–1.79), respectively [18]. The associations we found of higher blood pressure measures in early pregnancy with lower lung function represent, equal to the ALSPAC cohort, women with hypertension before pregnancy as gestational hypertensive disorders do not reveal themselves before 20 weeks of gestation. The effect estimates we found were relatively small compared with the effect estimates found in the ALSPAC cohort. However, we report our estimates per 5 mmHg maternal blood pressure change, which is quite a lot smaller than the difference between normotensive women and women with hypertensive diseases. In addition, the cohort study presents results at a different child age.

Other population-based studies demonstrated inconsistent associations of gestational hypertension or pre-eclampsia 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 pre-eclampsia is associated with an increased risk for wheezing from birth up to 12–24 months [31]. The analysis did not find associations for other hypertensive disorders [31]. One historically matched cohort study, assessing if maternal

pre-eclampsia 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 pre-eclampsia and asthma at age 7 years [19]. The registry-based results did show a positive association (OR 1.31 (95% CI 1.22–1.41)), although this was largely explained by pre-term birth and confounders shared by siblings; the cohort-based results did not show any 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 pre-eclampsia before 34 weeks gestation with asthma (incidence rate ratio (IRR) 1.88 (95% CI 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 pre-eclampsia with asthma (IRR 1.15 (95% CI 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 pre-eclampsia (n=62 728) (adjusted IRR 1.09 (95% CI 1.05–1.12)) [20]. This risk increased when the duration of pre-eclampsia was ⩾14 days (adjusted IRR 1.17 (95% CI 1.11–1.25)) [20].

Our study consisted of a relatively healthy population with a relatively low prevalence of gestational hypertension or pre-eclampsia. 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 potentially 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

Pre-eclampsia is strongly associated with (iatrogenic) pre-term 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 dependent 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 early 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 to lower lung function in childhood. Higher blood pressure may also be associated with an antiangiogenic 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 find consistent associations of blood pressure in the second trimester with child respiratory morbidity.

A prospective cohort study (n=69 pre-term infants) showed that the antiangiogenic status of the mother is reflected in the neonate, as neonates of mothers with pre-eclampsia had higher cord blood soluble fms-like tyrosine kinase-1 (sFlt-1) levels, and lower placental growth factor and vascular endothelial growth factor (VEGF) levels [34]. A high concentration of endostatin, an antiangiogenic growth factor, in human cord plasma predicts the development of bronchopulmonary dysplasia in very-low-birthweight infants [11]. In animal studies, inhibition of VEGF resulted in reduced alveolarisation and persistent abnormalities of pulmonary vascular structures [9, 10]. Additionally, administering sFlt into the amnionic sac of pregnant rats, at a stage of lung development corresponding to 24–26 weeks of human gestation, decreased VEGF signalling and increased apoptosis. Subsequently, reduced alveolarisation and pulmonary vascular growth were observed during infancy in 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 to be critical windows, as we did not find any associations with maternal blood pressure measurements in mid pregnancy, which in most pregnancies is characterised 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 to mothers included in our study population. This could have led 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 socioeconomic 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 be fully 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, *e.g.* inverse probability weighting, does 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 women (n=39) using antihypertensive 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. As part of our respiratory data were self-reported by questionnaires, we cannot exclude under- or overestimations of the observed associations.

Conclusions

Our study shows that higher blood pressures in pregnancy were associated with lower FEV_1/FVC, and with 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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References

1 Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* 2009; 33: 130–137.
2 Ray JG, Burrows RF, Burrows EA, *et al.* MOS HIP: McMaster outcome study of hypertension in pregnancy. *Early Hum Dev* 2001; 64: 129–143.
3 Bakker R, Steegers EA, Hofman A, *et al.* Blood pressure in different gestational trimesters, fetal growth, and the risk of adverse birth outcomes: the Generation R study. *Am J Epidemiol* 2011; 174: 797–806.
4 Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, *et al.* Preterm birth, infant weight gain, and childhood asthma risk: a meta-analysis of 147,000 European children. *J Allergy Clin Immunol* 2014; 133: 1317–1329.
5 Lum S, Kirkby J, Welsh L, *et al.* Nature and severity of lung function abnormalities in extremely pre-term children at 11 years of age. *Eur Respir J* 2011; 37: 1199–1207.
6 Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med* 2007; 357: 1946–1955.
7 Kotecha SJ, Edwards MO, Watkins WJ, *et al.* Effect of preterm birth on later FEV_1: a systematic review and meta-analysis. *Thorax* 2013; 68: 760–766.
8 Gagliardi L, Rusconi F, Da Fre M, *et al.* Pregnancy disorders leading to very preterm birth influence neonatal outcomes: results of the population-based ACTION cohort study. *Pediatr Res* 2013; 73: 794–801.
9 Le Cras TD, Markham NE, Tuder RM, *et al.* Treatment of newborn rats with a VEGF receptor inhibitor causes pulmonary hypertension and abnormal lung structure. *Am J Physiol Lung Cell Mol Physiol* 2002; 283: L555–L562.
10 Jakkula M, Le Cras TD, Gebb S, *et al.* Inhibition of angiogenesis decreases alveolarization in the developing rat lung. *Am J Physiol Lung Cell Mol Physiol* 2000; 279: L600–L607.

11 Janer J, Andersson S, Kajantie E, *et al.* Endostatin concentration in cord plasma predicts the development of bronchopulmonary dysplasia in very low birth weight infants. *Pediatrics* 2009; 123: 1142–1146.
12 Gagliardi L, Rusconi F, Bellu R, *et al.* Association of maternal hypertension and chorioamnionitis with preterm outcomes. *Pediatrics* 2014; 134: e154–e161.
13 Hansen AR, Barnes CM, Folkman J, *et al.* Maternal preeclampsia predicts the development of bronchopulmonary dysplasia. *J Pediatr* 2010; 156: 532–536.
14 Gortner L, Misselwitz B, Milligan D, *et al.* Rates of bronchopulmonary dysplasia in very preterm neonates in Europe: results from the MOSAIC cohort. *Neonatology* 2011; 99: 112–117.
15 Byberg KK, Ogland B, Eide GE, *et al.* Birth after preeclamptic pregnancies: association with allergic sensitization and allergic rhinoconjunctivitis in late childhood; a historically matched cohort study. *BMC Pediatr* 2014; 14: 101.
16 Liu X, Olsen J, Agerbo E, *et al.* Maternal preeclampsia and childhood asthma in the offspring. *Pediatr Allergy Immunol* 2015; 26: 181–185.
17 Nafstad P, Magnus P, Jaakkola JJ. Risk of childhood asthma and allergic rhinitis in relation to pregnancy complications. *J Allergy Clin Immunol* 2000; 106: 867–873.
18 Shaheen SO, Macdonald-Wallis C, Lawlor DA, *et al.* Hypertensive disorders of pregnancy, respiratory outcomes and atopy in childhood. *Eur Respir J* 2016; 47: 156–165.
19 Magnus MC, Haberg SE, Magnus P, *et al.* Pre-eclampsia and childhood asthma. *Eur Respir J* 2016; 48: 1622–1630.
20 Stokholm J, Sevelsted A, Anderson UD, *et al.* Preeclampsia associates with asthma, allergy, and eczema in childhood. *Am J Respir Crit Care Med* 2017; 195: 614–621.
21 Kooijman MN, Kruithof CJ, van Duijn CM, *et al.* The Generation R Study: design and cohort update 2017. *Eur J Epidemiol* 2016; 31: 1243–1264.
22 Gaillard R, Bakker R, Willemsen SP, *et al.* Blood pressure tracking during pregnancy and the risk of gestational hypertensive disorders: the Generation R Study. *Eur Heart J* 2011; 32: 3088–3097.
23 ACOG Committee on Practice Bulletins – Obstetrics. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstet Gynecol* 2002; 99: 159–167.
24 Brown MA, Lindheimer MD, de Swiet M, *et al.* The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* 2001; 20: IX–XIV.
25 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
26 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.
27 Gagliardi L, Bellu R, Rusconi F, *et al.* Antenatal steroids and risk of bronchopulmonary dysplasia: a lack of effect or a case of over-adjustment? *Paediatr Perinat Epidemiol* 2007; 21: 347–353.
28 VanderWeele TJ, Mumford SL, Schisterman EF. Conditioning on intermediates in perinatal epidemiology. *Epidemiology* 2012; 23: 1–9.
29 Keijzer-Veen MG, Euser AM, van Montfoort N, *et al.* A regression model with unexplained residuals was preferred in the analysis of the fetal origins of adult diseases hypothesis. *J Clin Epidemiol* 2005; 58: 1320–1324.
30 Rusconi F, Gagliardi L. Pregnancy complications and wheezing and asthma in childhood. *Am J Respir Crit Care Med* 2018; 197: 580–588.
31 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: 199–208.
32 Tang JR, Karumanchi SA, Seedorf G, *et al.* Excess soluble vascular endothelial growth factor receptor-1 in amniotic fluid impairs lung growth in rats: linking preeclampsia with bronchopulmonary dysplasia. *Am J Physiol Lung Cell Mol Physiol* 2012; 302: L36–L46.
33 Herzog EM, Eggink AJ, Willemsen SP, *et al.* Early- and late-onset preeclampsia and the tissue-specific epigenome of the placenta and newborn. *Placenta* 2017; 58: 122–132.
34 Tsao PN, Wei SC, Su YN, *et al.* Excess soluble fms-like tyrosine kinase 1 and low platelet counts in premature neonates of preeclamptic mothers. *Pediatrics* 2005; 116: 468–472.
35 Francisco B, Ner Z, Ge B, *et al.* Sensitivity of different spirometric tests for detecting airway obstruction in childhood asthma. *J Asthma* 2015; 52: 505–511.
36 Bliddal M, Liew Z, Pottegard A, *et al.* Examining nonparticipation in the maternal follow-up within the Danish National Birth Cohort. *Am J Epidemiol* 2018; 187: 1511–1519.
37 Nohr EA, Liew Z. How to investigate and adjust for selection bias in cohort studies. *Acta Obstet Gynecol Scand* 2018; 97: 407–416.