**Associations of maternal and fetoplacental factors with prehypertension/hypertension in early childhood**

Navin Michaela, Suresh Anand Sadananthana, Wen LunYuanb, Yi Ying Ongc, See Ling Loyn,p, Jonathan Y. Huanga, Mya-Thway Tinta, Natarajan Padmapriyad,e, Jonathan Chook, Lieng Hsi Lingf,g, Michael S Kramerd,i, Keith M. Godfreyo, Peter D. Gluckmana,u, Kok Hian Tanl,p, Johan G. Erikssona,d,r,s, Yap-Seng Chonga,d, Yung Seng Leea,c,h, Neerja Karnania, Fabian Yapj,p,q, Lynette Pei-Chi Sheka, Marielle V.Fortiera,m, Karen M. Moritzt, Shiao-Yng Chana,d, S. Sendhil Velana, Mary E. Wlodeka,d,v

**Short Title: ‘**Childhood Prehypertension Risk Factors’

aSingapore Institute for Clinical Sciences, Agency for Science, Technology, and Research, Singapore.

bUniversité de Paris, CRESS, Inserm, INRAE, F-75004 Paris, France.

cDepartment of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

dDepartment of Obstetrics & Gynaecology and Human Potential Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

eSaw Swee Hock School of Public Health, National University of Singapore, Singapore.

fDept of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

gDepartment of Cardiology, National University Heart Centre, Singapore.

hKhoo Teck Puat-National University Children’s Medical Institute, National University Health System, Singapore.

iDepartments of Epidemiology and Biostatistics and of Pediatrics, Faculty of Medicine, McGill University, Montreal, Canada.

jDepartment of Pediatric Endocrinology, KK Women’s and Children’s Hospital, Singapore.

kCardiology Service, KK Women’s and Children’s Hospital, Singapore.

lDepartment of Maternal Fetal Medicine, KK Women’s and Children’s Hospital, Singapore.

mDepartment of Diagnostic and Interventional Imaging, KK Women’s and Children’s Hospital, Singapore.

nDepartment of Reproductive Medicine, KK Women’s and Children’s Hospital, Singapore.

oMedical Research Council Lifecourse Epidemiology Unit and National Institute for Health Research Southampton Biomedical Research Centre, University of Southampton and University Hospital, Southampton National Health Service Foundation Trust, Southampton, United Kingdom.

pDuke-National University of Singapore Medical School, Singapore.

qLee Kong Chian School of Medicine, Nanyang Technological University, Singapore.

rDept of General Practice and Primary Health Care, University of Helsinki and Helsinki University Hospital, Helsinki, Finland.

sFolkhälsan Research Center, Helsinki, Finland.

tUniversity of Queensland, St Lucia, Australia.

uLiggins Institute, University of Auckland, Auckland, New Zealand.

vUniversity of Melbourne, Parkville, Australia.

**Funding:** This work was supported by the Singapore National Research Foundation under its Translational and Clinical Research (TCR) Flagship Programme and administered by the Singapore Ministry of Health’s National Medical Research Council (NMRC), Singapore [NMRC/TCR/004-NUS/2008, NMRC/TCR/012-NUHS/2014]. Additional funding is provided by the Singapore Institute for Clinical Sciences, Agency for Science Technology and Research, Singapore. KMG is supported by the UK Medical Research Council (MC\_UU\_12011/4), the National Institute for Health Research (NIHR Senior Investigator (NF-SI-0515-10042), NIHR Southampton 1000DaysPlus Global Nutrition Research Group (17/63/154) and NIHR Southampton Biomedical Research Centre (IS-BRC-1215-20004), the European Union (Erasmus+ Programme Early Nutrition eAcademy Southeast Asia-573651-EPP-1-2016-1-DE-EPPKA2-CBHE-JP and ImpENSA 598488-EPP-1-2018-1-DE-EPPKA2-CBHE-JP) and the British Heart Foundation (RG/15/17/3174).

**Conflicts of Interests:** Chong, Godfrey, and Chan are part of an academic consortium that has received research funding from companies selling nutritional products and have received reimbursements for speaking at conferences sponsored by companies selling nutritional products. All other authors have nothing to disclose.

**Corresponding author:**

**Dr Navin Michael**

30 Medical Drive

Brenner Centre for Molecular Medicine

Singapore 117609

Phone: (+65) 6407 0680

navin\_michael@sics.a-star.edu.sg

**Word Count:**

 **Abstract:** 250 words

 **Main Text:** 3398 words (only manuscript text), 5002 (including references)

 **Figures/Tables:** 3 Figures, 1 Table

 **Supplementary:** 1 file (includes 3 Figures, 3 Tables)

**ABSTRACT**

**Objective**: To evaluate whether characterization of maternal and fetoplacental factors beyond birthweight can enable early identification of children at risk of developing prehypertension/hypertension.

**Methods:** We recruited 693 mother-offspring dyads from the GUSTO prospective mother-offspring cohort. Prehypertension/hypertension at age 6y was identified using the simplified paediatric threshold of 110/70 mmHg. We evaluated the associations of pregnancy complications (gestational diabetes, excessive/inadequate gestational weight gain, hypertensive disorders of pregnancy), fetal growth deceleration (decline in fetal abdominal circumference ≥0.67 standard deviations between 2nd and 3rd trimesters), high fetoplacental vascular resistance (3rd trimester umbilical artery systolic-to-diastolic ratio ≥90th centile), preterm birth, small-for-gestational age and neonatal kidney volumes with risk of prehypertension/hypertension at age 6y, after adjusting for sex, ethnicity, maternal education and pre-pregnancy BMI.

**Results:** Pregnancy complications, small-for-gestational age, preterm birth, and low neonatal kidney volume were not associated with an increased risk of prehypertension/hypertension at age 6y. In contrast, fetal growth deceleration was associated with a 72% higher risk (risk ratio [RR] = 1.72, 95%CI 1.18 to 2.52). High fetoplacental vascular resistance was associated with a 58% higher risk (RR = 1.58, 95%CI 0.96 to 2.62). Having both these characteristics, relative to having neither, was associated with over 2-fold higher risk (RR = 2.55, 95%CI 1.26 to 5.16). Over 85% of the fetuses with either of these characteristics were born appropriate or large for gestational age.

**Conclusion:** Fetal growth deceleration and high fetoplacental vascular resistance may be helpful in prioritizing high-risk children for regular blood pressure monitoring and preventive interventions, across the birthweight spectrum.

**Keywords:** Low birthweight, childhood prehypertension, fetal growth, placental insufficiency, pregnancy complications, mother-offspring cohort study

**Introduction**

The increasing prevalence of hypertension in children is a growing concern, particularly as elevated blood pressure tracks from childhood to adulthood [1,2]. Children with elevated blood pressure have a 2-3 fold higher high risk of progressing to hypertension in adulthood [3]. Hypertension is a major cause of premature death and one of the most important modifiable risk factors for cardiovascular and chronic kidney disease [4]. The underlying aetiology of hypertension is complex and multifactorial [5]. Multiple epidemiological studies have shown associations of low birth weight with increased adult blood pressure, suggesting an important role of the intrauterine environment in programming the risk of hypertension [6,7].

The mechanisms linking low birthweight to later hypertension remain to be fully elucidated. Given the kidney’s role in the regulation of blood pressure, perinatal influences on nephron endowment have received considerable attention. Given that nephrogenesis in humans ceases by about 36 weeks, perinatal perturbations like maternal undernutrition, hypertensive disorders of pregnancy and placental insufficiency that impair fetal growth can result in persistent nephron deficits [8]. At the other extreme, maternal hyperglycaemia and gestational diabetes, that are generally linked to fetal over-nutrition and fetal overgrowth have also been linked to impaired fetal kidney development and reduced nephrogenesis [6]. Low birth weight is commonly caused by prematurity, which can result in underdeveloped kidneys at birth. While some degree of extrauterine nephrogenesis can occur in preterm infants, they tend to have a high proportion of abnormal glomeruli in the outer renal cortex. Brenner hypothesized that the reduced filtration surface area due to low nephron endowment and the resultant compensatory mechanisms to maintain adequate filtration, may predispose to hypertension [9]. This has been supported by human autopsy studies showing only half the nephron number and marked glomerular hypertrophy in hypertensives relative to normotensives [10]. Independent of nephron endowment, other pathways have also been hypothesized linking low birthweight to later hypertension, including increased sodium reabsorption due to increased sympathetic nervous system (SNS) [11] or glucocorticoid activity [12], arterial stiffening, aortic wall thickening, altered endothelium-dependent vasodilation and microvascular rarefaction [13].

Birthweight is a convenient and widely available surrogate for an unfavourable intrauterine environment. However, the link between impaired fetal growth and cardiovascular disease extends across the entire birthweight spectrum [14,15]. Emerging evidence suggests that reductions in nephron endowment due to prenatal insults and programming of hypertension can occur even without a reduction in birthweight [16]. Up to 70% of the infants who are born small for gestational age (SGA) are small owing to constitutional factors [17]. Since not all fetuses experiencing a stressed intrauterine milieu are born SGA, we hypothesized that a detailed characterization of suboptimal fetal environments and maternal-fetal stressors [7,18,19] could help in early identification of children at risk of developmentally programmed hypertension. We evaluated the association of early childhood prehypertension/hypertension with gestational diabetes, inadequate gestational weight gain (marker of maternal undernutrition), hypertensive disorders of pregnancy, excessive gestational weight gain (risk factor for hypertensive disorders of pregnancy and gestational diabetes), fetal growth deceleration measured by longitudinal fetal ultrasound, high fetoplacental vascular resistance measured by Doppler velocimetry (marker of placental insufficiency), preterm birth, SGA, and reduced neonatal kidney volume (proxy for nephron number) in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) prospective mother-offspring cohort. Identifying the factors showing the strongest association with early childhood prehypertension/hypertension may aid early risk stratification and permit the development and testing of interventions in mothers and children.

**Materials and Methods**

***Study Population***

Pregnant women (N=1450) were recruited (2009-2010) in the first trimester from two public maternity hospitals in Singapore (National University Hospital and KK Women and Children’s Hospital) into the GUSTO prospective mother-offspring cohort, resulting in 1178 singleton pregnancies [20]. The children had homogeneous parental ethnicities (Chinese, Malay or Indian). The current study was limited to 693 mother-offspring dyads who had offspring blood pressure measurements at age 6y. The recruitment criteria have been shown in Supplementary Fig. S1. The recruitment flowchart and data availability of exposures/covariates are shown in Fig. 1.

***Maternal Assessments***

Self-reported ethnicity, education and pre-pregnancy weight were collected through questionnaires administered on enrolment. Mothers underwent an oral glucose tolerance test and anthropometric assessments at 26th-28th weeks gestation. Gestational diabetes mellitus (GDM) was diagnosed using the WHO 1999 criteria, which was being used at the time of recruitment (fasting glucose ≥7.0 mmol/l and/or 2-h glucose ≥7.8 mmol/l) [21]. Self-reported pre-pregnancy weight and recorded height were used to compute pre-pregnancy body mass index (ppBMI). Serial measurements of maternal weights obtained from clinical records were used in a linear mixed-effects model with the best linear unbiased prediction to estimate the individual rate of gestational weight gain (GWG) per week between 15 to 35 weeks of gestation, during which the weight gain is approximately linear [22]. The Institute of Medicine (IOM) 2009 Gestational Weight Gain Guidelines were used to classify the computed GWG rate as adequate, inadequate or excessive for the corresponding ppBMI [23]. Based on their clinical records, mothers were classified as having a hypertensive disorder of pregnancy if they were diagnosed with either pregnancy-induced hypertension (*de novo* gestational hypertension (blood pressure ≥140/90 mmHg) after 20 weeks of gestation, based on at least two readings spread four hours apart) or pre-eclampsia (pregnancy-induced hypertension with at least one of the following additional features: urine dipstick reading of ≥1+, proteinuria ≥300 mg/24h, elevated uric acid or elevated liver enzymes). Mothers with pre-eclampsia super-imposed on chronic hypertension were also classified as having a hypertensive disorder of pregnancy. Details of drug treatments offered to mothers with hypertensive disorders of pregnancy are shown in supplementary table S2.

***Ultrasound Assessments***

Ultrasound scans were performed using a GE Voluson 730 Expert transabdominal probe (AB2-7, 2-7 MHz broadband curved array transducer) or a GE Voluson 730 PRO transabdominal probe (4CA, broadband curved array transducer). Fetal growth was assessed using longitudinal fetal abdominal circumference measurements performed in ultrasound scan visits in the second (19-21 weeks) and third (32-34 weeks) trimesters. Abdominal circumference measurements were made on standard views at the level of the stomach, where the umbilical vein enters the portal sinus. These measurements were converted to z-scores using the INTERGROWTH-21 fetal growth standards [24]. Fetal growth deceleration (FGD) was defined as downward crossing of the fetal abdominal circumference by at least one major centile band between the second and third trimester [25], which corresponds to a z-score decline ≥0.67. At the third trimester scan, umbilical artery Doppler waveforms were measured in a free cord loop. Resistance to blood flow in the umbilical artery was assessed using the systolic to diastolic (S/D) ratio [26]. An umbilical artery S/D ratio ≥90th percentile was used to identify fetuses with high fetoplacental vascular resistance [27].

***Birthweight for gestational age and Anthropometric Assessments***

Cohort-specific birthweight percentiles adjusted for sex and gestational age were derived using a customizable birthweight reference[28]. Infants were classified as large for gestational age (LGA, birthweight >90th percentile), small for gestational age (SGA, birthweight <10th percentile) or appropriate for gestational age (AGA, birthweight between the 10th and 90th percentiles). At age 6y, height and weight were measured to compute BMI.

***Neonatal Kidney Volume***

Abdominal magnetic resonance imaging (MRI) was performed without sedation within the first 2 weeks of life in neonates delivered at gestational age ≥ 34 weeks. Axial fast-spin echo sequences covering the entire abdomen were acquired using a Signa HDxt 1.5 Tesla scanner (GE Medical Systems, Milwaukee, USA). Orthogonal dimensions of the right kidney were measured using ITK-SNAP [29]. At the axial slice with the biggest cross-sectional area, we approximated the kidney cross-section as an ellipse and measured the major and minor axes. The image slices at which the superior and inferior tips of the kidney were visible were recorded. The number of slices spanning the kidney length was multiplied by the slice thickness to calculate the length of the kidney. Kidney volume was calculated using the ellipsoid approximation as: Volume = π/6 × Length × Width × Depth [30].

***Blood Pressure Assessment***

At age 6y, peripheral systolic and diastolic blood pressure (SBP and DBP) were measured on the right arm using a Dinamap CARESCAPE V100 (GE Healthcare, Milwaukee, WI) BP monitor, with an appropriate cuff size, in a quiet room after a five-minute rest. The children were in a seated position with their legs uncrossed and their arms resting at the level of the heart. BP was measured in duplicate, with a third measurement performed if either of the two SBP or DBP measurements differed by greater than 10 mmHg. The average of the two lowest BP readings was recorded to account for child anxiety. Prehypertension/hypertension was defined if either SBP or DBP crossed the simplified paediatric prehypertension threshold of 110/70 mmHg [31]. Prehypertension/hypertension was treated as a single category to increase statistical power. Xi et al. found that the simplified paediatric thresholds for prehypertension and hypertension of 110/70 and 120/80 mmHg, respectively, for ages 6-11y did as well in predicting adulthood hypertension and cardiovascular alterations as complex thresholds derived from age-, sex- and height-standardized BP percentiles, which are more cumbersome to use in clinical practice [31].

***Kidney Function***

At age 6y, blood samples were collected after an overnight fast (N=332). Creatinine was measured using creatininase (endpoint) method (Beckman AU 5800, Beckman Coulter, Inc., USA). The creatinine assay calibration was traceable to an isotope dilution mass spectrometry (IDMS) reference method using the National Institutes of Standards and Technology (NIST) Standard Reference Material 967. The estimated glomerular filtration rate (eGFR) was calculated using the Bedside Schwartz formula [32].

***Statistical Analysis***

Poisson regression with robust error variance was used to calculate the risk ratio (RR) [33] for developing prehypertension/hypertension at age 6y associated with GDM, hypertensive disorders of pregnancy, rate of gestational weight gain category, fetal growth deceleration, high fetoplacental vascular resistance, preterm birth, SGA, and neonatal kidney volume in separate models, adjusted for sex, ethnicity, maternal education and maternal ppBMI. Additionally, we evaluated if fetuses experiencing both fetal growth deceleration and high fetoplacental vascular resistance have elevated risk, as well as the individual associations of these fetal characteristics with child prehypertension/hypertension in a mutually adjusted model. We only included baseline confounders in our models and did not include adjustments for current body size (weight, height or BMI) or postnatal growth since adjustments for variables on causal pathways can result in biased estimates for the early life exposures [34-36]. Additionally, we evaluated the associations of fetal growth deceleration and high fetoplacental vascular resistance with eGFR at age 6y, after adjusting for the same set of confounders.

We performed the following sensitivity analyses. The association of maternal and fetoplacental factors with child prehypertension/hypertension was evaluated after removing cases with only maternal chronic hypertension without superimposed preeclampsia. We also repeated the analyses after accounting for missingness in covariates. Multiple imputation (20 imputations) of covariates was performed using fully conditional specification with all variables (exposures, covariates, outcomes) included as predictors.

**Results**

Characteristics of mother-offspring dyads with blood pressure data at age 6y were comparable to those of mother-offspring dyads without blood pressure data at age 6y (Supplementary Table S1). At age 6y, BP in 14.4% of the cohort crossed the simplified prehypertension threshold. Table 1 shows the maternal and offspring characteristics of prehypertensive/hypertensive children and their normotensive counterparts.

The associations of maternal and fetoplacental factors with childhood prehypertension/hypertension, after adjustment for covariates are shown in Fig. 1A (unadjusted estimates are shown in Supplementary Fig. S2). Among the various early-life risk factors investigated, fetal growth deceleration and high fetoplacental vascular resistance showed the strongest association with child prehypertension/hypertension. Fetal growth deceleration was associated with a 72% higher risk (RR = 1.72, 95% CI 1.18 to 2.52, p = 0.005), while fetoplacental vascular resistance was associated with a 58% higher risk (RR = 1.58, 95% CI 0.96 to 2.62, p = 0.074). Having both these fetal characteristics (relative to having neither) was associated with over 2-fold higher risk (RR = 2.55, 95%CI 1.26 to 5.16, p = 0.009). These trends were similar after removing cases with maternal chronic hypertension without superimposed preeclampsia (Fig 1B) and after accounting for missingness in covariates (Fig. 1C). Mutually adjusting for these two fetal characteristics did not alter their associations with child prehypertension/hypertension (Supplementary Fig. S3). Both these characteristics were not associated with eGFR at age 6y (Supplementary Table S3). Of note, 85.1% of the infants exposed to either fetal growth deceleration or high fetoplacental vascular resistance were born AGA or LGA (Fig. 3A). The prevalences of fetal growth deceleration and high fetoplacental vascular resistance were 26.2% and 11.0%, respectively, with only 3.9% of the fetuses having both characteristics (Fig. 3B). The prevalence of fetal growth deceleration assessed by downward centile crossing in the current cohort was comparable to the 30% prevalence observed by Lampl, et al. in uncomplicated pregnancies in a Chilean cohort[25].

**Discussion**

We found that 14.4% of the children had blood pressure levels at age 6y which crossed the simplified paediatric threshold for prehypertension [31]. A key finding was that neither SGA nor preterm birth was associated with increased risk of prehypertension/hypertension at age 6y, in contrast to the epidemiological evidence linking low birthweight [37,38] and preterm birth [39] to adult blood pressure and cardiovascular disease. Similarly, we found no associations with inadequate/excessive rates of GWG, GDM or hypertensive disorders of pregnancy. Treatments offered to mothers diagnosed with GDM or hypertensive disorders of pregnancy may have partly attenuated their associations with child prehypertension/hypertension. It is possible that the associations of SGA, preterm birth and pregnancy complications with later hypertension, that have been reported earlier [37,40-43], may vary in different populations or may only be unmasked with additional secondary insults over the life-course, such as excessive weight gain, sedentary lifestyle or high salt intake. We expected neonatal kidney volume to be a better proxy for nephron endowment than birthweight [44], but surprisingly, it was also not associated with child prehypertension/hypertension. Compensatory renal growth has been reported *in utero*, in adaptation to reduced nephron numbers [45]. Thus, neonatal kidney volumes may not be a reliable marker of nephron endowment and tracking of fetal kidney volumes may be more important.

We found that fetal growth deceleration and fetoplacental vascular resistance were associated with 72% and 58% higher risks, respectively, of child prehypertension/hypertension, while having both characteristics resulted in over 2-fold higher risk. These associations were not significantly altered after removing cases with maternal chronic hypertension. Hence, the observed trends are unlikely to be driven by maternal chronic hypertension. Downward fetal abdominal circumference centile crossing in prenatal life has been previously shown to be an indicator for an adverse prenatal environment [25]. Early fetal biometry studies by Grannum et al [46] found fetal abdominal circumference to closely track kidney development, with the ratio of kidney to abdominal circumferences remaining constant throughout pregnancy at ~0.3. Downward centile crossing of the fetal abdominal circumference is a fetal response to prenatal constraints in maternal-fetal nutrient and oxygen delivery, elevated glucocorticoid exposure or physical size constraints of the uterus [25,47], which may affect the development of visceral organs, especially nephrogenesis. High fetoplacental vascular resistance reflects increased impedance to blood flow in the umbilical artery and can result from impaired placental villous development or chronic exposure to elevated glucocorticoids [26,48]. This can result in inadequate delivery of oxygen to the fetus, leading to adaptive changes in the fetal circulation that spare the brain at the expense of the visceral organs [49,50]. Reduced oxygen supply to the metanephric mesenchyme can result in impaired nephrogenesis through pathways involving hypoxia-inducible factors [51]. Our findings are consistent with prior findings linking high fetoplacental vascular resistance to increased blood pressure in childhood [52]. Neither fetal growth deceleration nor high fetoplacental vascular resistance were associated with eGFR at age 6y. Hence, the associations of these fetal characteristics with prehypertension/hypertension in early childhood do not yet seem to involve any alterations in the kidney’s filtration function.

A surprising finding was the relatively small overlap between children who experienced either fetal growth deceleration or high fetoplacental vascular resistance and being born SGA. Over 85% of the fetuses with either of these characteristics were born AGA or LGA and would not be considered at increased risk of developmentally programmed hypertension if birthweight was the sole basis for characterizing an adverse intrauterine environment. Thus, these characteristics may program later hypertension across the birthweight spectrum and not just at the lower ranges. Although fetoplacental vascular resistance has been commonly linked to slowed fetal growth [52], less than 4% of the children had both these characteristics, and mutual adjustment did not change their individual associations with child prehypertension/hypertension. Our findings suggest that these two fetal features may be acting through different pathways to influence risk of later hypertension and may need to be monitored separately.

Our study, leveraging data from a well phenotyped prospective mother-offspring cohort, has several key strengths. Most studies on the effects of early-life risk factors have focused on health in adulthood, where the effects of later life influences on the cardiovascular phenotype may be more dominant. Our study contributes to the limited evidence base on the associations of the maternal and fetoplacental factors with blood pressure regulation in early childhood. A key strength was the comparison of prehypertension/hypertension risk associated with multiple markers of suboptimal intrauterine environments, beyond just birthweight. The Asian ethnic groups we included (Indian, Chinese and Malay) make up nearly half of the global population and live in regions where the healthcare burdens of hypertension-related comorbidities are high [53]. Our findings may aid better identification of children in these regions who are at risk of developing hypertension.

Several study limitations should be noted. The simplified prehypertension threshold [31] was derived using BP data from American children, whereas our study involved Asian children (Chinese, Malay and Indian ethnic groups). Ethnic differences have been reported in both childhood BP levels and the relationship between body size and BP [54,55], which suggest that customized approaches for assessing childhood prehypertension/hypertension in different populations may be preferable. It is unclear if our findings in an urban Asian cohort can be extrapolated to other populations with different ethnic compositions and sociodemographic profiles; validation studies in other mother-offspring cohorts are warranted. A systematic review investigating the accuracy of oscillometric devices relative to the auscultatory method found that oscillometric devices tend to overestimate systolic blood pressure in children [56]. However, since this overestimation is systematic, we do not expect it to bias the reported phenotypic associations. Nearly 90% of the preterms in this study were moderate or late preterms, so it may not be possible to extrapolate our findings to extreme/very preterms. We do recognize that performing ultrasound based serial fetal monitoring for assessing fetal growth deceleration and fetoplacental vascular resistance may not be feasible in many low-resource settings. Even in high-resource settings, cost-effectiveness studies are needed to evaluate the value of incorporating serial fetal ultrasound biometry and Doppler scans into early CVD prevention strategies.

**Conclusion**

Published epidemiological studies of the association between low birthweight and hypertension have not yet led to actionable public health strategies. Birthweight is a crude proxy for the intrauterine environment, with most of the birthweight variation linked to factors such as sex, parity, and maternal age, height and weight. Moreover, not all prenatal perturbations result in lower birthweight. A key finding from our study is that children who experienced fetal growth deceleration or high fetoplacental vascular resistance are at higher risk of developing hypertension across the birthweight spectrum. These factors were found to be more strongly associated with child prehypertension/hypertension than SGA, preterm birth, neonatal kidney volume and pregnancy complications (GDM, hypertensive disorders of pregnancy and inadequate/excessive rate of GWG). Since less than 15% of children who experienced either fetal growth deceleration or fetoplacental vascular resistance were born SGA, these children would be missed by risk stratification approaches being developed that target the lower ranges of birthweight [57]. Further follow-up of kidney and cardiac function and blood pressure in these children is warranted, and a better understanding of the aetiology of these early changes in blood pressure is needed. Currently, in many high-resource settings, serial fetal biometry scans and umbilical artery Dopplers are typically performed when an elevated risk of fetal morbidity/mortality is perceived. Our findings suggest a case for expanding their use beyond just guiding obstetric care to help identify children at risk of developing hypertension. This would be useful for assessing the benefits of regular monitoring of BP as well as kidney/cardiac function, and the development and testing of early interventions for preventing hypertension and its related comorbidities in high-risk children.

 **References**

1. Song P, Zhang Y, Yu J, Zha M, Zhu Y, Rahimi K, et al. Global prevalence of hypertension in children: a systematic review and meta-analysis. JAMA pediatrics2019; 173:1154-1163.

2. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. Circulation2008; 117:3171.

3. Bao W, Threefoot SA, Srinivasan SR, Berenson GS. Essential hypertension predicted by tracking of elevated blood pressure from childhood to adulthood: the Bogalusa Heart Study. American journal of hypertension1995; 8:657-665.

4. He FJ, MacGregor GA. Blood pressure is the most important cause of death and disability in the world. European heart journal supplements2007; 9:B23-B28.

5. Carretero OA, Oparil S. Essential hypertension: part I: definition and etiology. Circulation2000; 101:329-335.

6. Aisa MC, Cappuccini B, Barbati A, Clerici G, Torlone E, Gerli S, et al. Renal consequences of gestational diabetes mellitus in term neonates: a multidisciplinary approach to the DOHaD perspective in the prevention and early recognition of neonates of GDM mothers at risk of hypertension and chronic renal diseases in later life. Journal of clinical medicine2019; 8:429.

7. Briffa JF, Wlodek ME, Moritz KM. Transgenerational programming of nephron deficits and hypertension. Seminars in cell & developmental biology: Elsevier; 2020. pp. 94-103.

8. Hoy WE, Hughson MD, Bertram JF, Douglas-Denton R, Amann K. Nephron number, hypertension, renal disease, and renal failure. Journal of the American Society of Nephrology2005; 16:2557-2564.

9. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure: less of one, more the other? American journal of hypertension1988; 1:335-347.

10. Keller G, Zimmer G, Mall G, Ritz E, Amann K. Nephron number in patients with primary hypertension. New England Journal of Medicine2003; 348:101-108.

11. IJzerman RG, Stehouwer CD, de Geus EJ, van Weissenbruch MM, Delemarre-van de Waal HA, Boomsma DI. Low birth weight is associated with increased sympathetic activity: dependence on genetic factors. Circulation2003; 108:566-571.

12. Anagnostis P, Athyros VG, Tziomalos K, Karagiannis A, Mikhailidis DP. The pathogenetic role of cortisol in the metabolic syndrome: a hypothesis. The Journal of Clinical Endocrinology & Metabolism2009; 94:2692-2701.

13. Ligi I, Grandvuillemin I, Andres V, Dignat-George F, Simeoni U. Low birth weight infants and the developmental programming of hypertension: a focus on vascular factors. Seminars in perinatology: Elsevier; 2010. pp. 188-192.

14. Barker D. Mothers, babies and health in adult life. Edinburgh: Churchill Livingstone1998:66-74.

15. Gluckman PD, Pinal CS. Regulation of fetal growth by the somatotrophic axis. The Journal of nutrition2003; 133:1741S-1746S.

16. Moritz KM, Singh RR, Probyn ME, Denton KM. Developmental programming of a reduced nephron endowment: more than just a baby's birth weight. American Journal of Physiology-Renal Physiology2009; 296:F1-F9.

17. Alberry M, Soothill P. Management of fetal growth restriction. Archives of Disease in Childhood-Fetal and Neonatal Edition2007; 92:F62-F67.

18. Barker DJ. The fetal origins of adult hypertension. Journal of hypertension Supplement: official journal of the International Society of Hypertension1992; 10:S39-44.

19. Morton JS, Cooke C-L, Davidge ST. In utero origins of hypertension: mechanisms and targets for therapy. Physiological reviews2016; 96:549-603.

20. Soh S-E, Tint MT, Gluckman PD, Godfrey KM, Rifkin-Graboi A, Chan YH, et al. Cohort profile: Growing Up in Singapore Towards healthy Outcomes (GUSTO) birth cohort study. International journal of epidemiology2014; 43:1401-1409.

21. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabetic medicine1998; 15:539-553.

22. Cheung YB. Statistical analysis of human growth and development. CRC Press; 2013.

23. Council NR. Weight gain during pregnancy: reexamining the guidelines. National Academies Press; 2010.

24. Papageorghiou AT, Kennedy SH, Salomon LJ, Altman DG, Ohuma EO, Stones W, et al. The INTERGROWTH-21st fetal growth standards: toward the global integration of pregnancy and pediatric care. American journal of obstetrics and gynecology2018; 218:S630-S640.

25. Lampl M, Gotsch F, Kusanovic JP, Espinoza J, Goncalves L, Gomez R, et al. Downward percentile crossing as an indicator of an adverse prenatal environment. Annals of human biology2008; 35:462-474.

26. GILES WB, TRUDINGER BJ, BAIRD PJ. Fetal umbilical artery flow velocity waveforms and placental resistance: pathological correlation. BJOG: An International Journal of Obstetrics & Gynaecology1985; 92:31-38.

27. Baschat AA, Weiner CP. Umbilical artery Doppler screening for detection of the small fetus in need of antepartum surveillance. American journal of obstetrics and gynecology2000; 182:154-158.

28. Mikolajczyk RT, Zhang J, Betran AP, Souza JP, Mori R, Gülmezoglu AM, et al. A global reference for fetal-weight and birthweight percentiles. The Lancet2011; 377:1855-1861.

29. Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage2006; 31:1116-1128.

30. Jones TB, Riddick L, Harpen M, Dubuisson RL, Samuels D. Ultrasonographic determination of renal mass and renal volume. Journal of Ultrasound in Medicine1983; 2:151-154.

31. Xi B, Zhang T, Li S, Harville E, Bazzano L, He J, et al. Can pediatric hypertension criteria be simplified? A prediction analysis of subclinical cardiovascular outcomes from the Bogalusa Heart Study. Hypertension2017; 69:691-696.

32. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. Clinical Journal of the American Society of Nephrology2009; 4:1832-1843.

33. Zou G. A modified poisson regression approach to prospective studies with binary data. American journal of epidemiology2004; 159:702-706.

34. Gilthorpe M, Jiang T, Tilling K, Ellison G, Baxter P. Common Statistical Errors: Over-Adjustment for Confounders and Mediators in Lifecourse Research. International Journal of Epidemiology2015; 44:i36-i37.

35. Tu Y-K, West R, Ellison GT, Gilthorpe MS. Why evidence for the fetal origins of adult disease might be a statistical artifact: the “reversal paradox” for the relation between birth weight and blood pressure in later life. American journal of epidemiology2005; 161:27-32.

36. Kramer MS, Zhang X, Dahhou M, Yang S, Martin RM, Oken E, et al. Does fetal growth restriction cause later obesity? Pitfalls in analyzing causal mediators as confounders. American journal of epidemiology2017; 185:585-590.

37. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth M. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. British Medical Journal1989; 298:564-567.

38. Davies AA, Smith GD, May MT, Ben-Shlomo Y. Association between birth weight and blood pressure is robust, amplifies with age, and may be underestimated. Hypertension2006; 48:431-436.

39. Lewandowski AJ, Levy PT, Bates ML, McNamara PJ, Nuyt AM, Goss KN. Impact of the vulnerable preterm heart and circulation on adult cardiovascular disease risk. Hypertension2020; 76:1028-1037.

40. Bertagnolli M, Luu TM, Lewandowski AJ, Leeson P, Nuyt AM. Preterm birth and hypertension: is there a link? Current hypertension reports2016; 18:28.

41. Tam WH, Ma RCW, Ozaki R, Li AM, Chan MHM, Yuen LY, et al. In utero exposure to maternal hyperglycemia increases childhood cardiometabolic risk in offspring. Diabetes care2017; 40:679-686.

42. Øglænd B, Forman MR, Romundstad PR, Nilsen ST, Vatten LJ. Blood pressure in early adolescence in the offspring of preeclamptic and normotensive pregnancies. Journal of hypertension2009; 27:2051-2054.

43. Tam CH, Ma RC, Yuen LY, Ozaki R, Li AM, Hou Y, et al. The impact of maternal gestational weight gain on cardiometabolic risk factors in children. Diabetologia2018; 61:2539-2548.

44. Tsuboi N, Kanzaki G, Koike K, Kawamura T, Ogura M, Yokoo T. Clinicopathological assessment of the nephron number. Clinical kidney journal2014; 7:107-114.

45. Chevalier RL. The life cycle of the kidney: implications for CKD. Am Soc Nephrol; 2014.

46. Grannum P, Bracken M, Silverman R, Hobbins JC. Assessment of fetal kidney size in normal gestation by comparison of ratio of kidney circumference to abdominal circumference. American journal of obstetrics and gynecology1980; 136:249-254.

47. Sato N, Miyasaka N. Heterogeneity in fetal growth velocity. Scientific reports2019; 9:1-9.

48. Nugent J, Wareing M, Palin V, Sibley C, Baker P, Ray D, et al. Chronic glucocorticoid exposure potentiates placental chorionic plate artery constriction: implications for aberrant fetoplacental vascular resistance in fetal growth restriction. Endocrinology2013; 154:876-887.

49. Verburg BO, Geelhoed J, Steegers E, Hofman A, Moll H, Witteman J, et al. Fetal kidney volume and its association with growth and blood flow in fetal life: The Generation R Study. Kidney international2007; 72:754-761.

50. Godfrey KM, Haugen G, Kiserud T, Inskip HM, Cooper C, Harvey NC, et al. Fetal liver blood flow distribution: role in human developmental strategy to prioritize fat deposition versus brain development. PloS one2012; 7:e41759.

51. Buchholz B, Schley G, Eckardt K-U. The impact of hypoxia on nephrogenesis. Current opinion in nephrology and hypertension2016; 25:180-186.

52. Gaillard R, Steegers EA, Tiemeier H, Hofman A, Jaddoe VW. Placental vascular dysfunction, fetal and childhood growth, and cardiovascular development: the generation R study. Circulation2013; 128:2202-2210.

53. Lim CC, Teo BW, Ong PG, Cheung CY, Lim SC, Chow KY, et al. Chronic kidney disease, cardiovascular disease and mortality: a prospective cohort study in a multi-ethnic Asian population. European journal of preventive cardiology2015; 22:1018-1026.

54. Ke L, Brock KE, Cant RV, Li Y, Morrell SL. The relationship between obesity and blood pressure differs by ethnicity in Sydney school children. American journal of hypertension2009; 22:52-58.

55. Harding S, Whitrow M, Lenguerrand E, Maynard M, Teyhan A, Cruickshank JK, et al. Emergence of ethnic differences in blood pressure in adolescence: the determinants of adolescent social well-being and health study. Hypertension2010; 55:1063-1069.

56. Duncombe SL, Voss C, Harris KC. Oscillometric and auscultatory blood pressure measurement methods in children: a systematic review and meta-analysis. Journal of hypertension2017; 35:213-224.

57. Weight TLB, Group NNW. The impact of kidney development on the life course: a consensus document for action. Nephron Clinical Practice2017; 136:3.

**Figures**

Fig 1. Recruitment flowchart with data availability for exposures and covariates.

****

Fig 2. Adjusted risk of child prehypertension/hypertension at age 6y associated with maternal and fetoplacental factors, evaluated in separate models (A) Complete case analysis (B) Complete case analysis, after excluding cases with chronic hypertension but without superimposed preeclampsia (C) With multiple imputation to account for missingness in covariates. All models included sex, ethnicity, maternal education and ppBMI as covariates. Number of cases included in each model is shown.



Fig 3. (A) Birthweight for gestational age distribution in infants exposed to either fetal growth deceleration (FGD) or high fetoplacental vascular resistance (HFPVR), or neither of these characteristics (SGA: Small for gestational age, AGA: Appropriate for gestational age, LGA: Large for gestational age). (B) Distribution of fetoplacental characteristics in the cohort



**Tables**

Table 1. Demographic and clinical characteristics (mean (sd) for continuous variables and N (%) for categorical variables, percentages calculated across columns to indicate % of children who were prehypertensive/hypertensive or normotensive at age 6y, in each category) of mother-offspring dyads with blood pressure data available at age 6y (N=693), stratified by prehypertension/hypertension status at age 6y.

|  |  |
| --- | --- |
| **Characteristics** | **Mean (SD) / N (%)** |
| **Prehypertensive/Hypertensive** | **Normotensive** |
| (N=100, 14.4%) | (N=593, 85.6%) |
| **Mother/Fetus** |
| **Age (years)** | 30.5 (5.9) | 30.8 (5.1) |
| **ppBMI, kg/m2** | 23.4 (4.7) | 22.6 (4.3) |
| **Height, cm** | 159.2 (5.3) | 158.1 (5.7) |
| **Race/Ethnicity** |  |  |
| * Chinese
 | 50 (12.7%) | 345 (87.3%) |
| * Malay
 | 27 (15.1%) | 152 (84.9%) |
| * Indian
 | 23 (19.5%) | 95 (80.5%) |
| **Education Level** |  |  |
| * Secondary
 | 49 (16.8%) | 243 (83.2%) |
| * Diploma
 | 24 (14.6%) | 140 (85.4%) |
| * University
 | 26 (11.3%) | 205 (88.7%) |
| **Gestational Diabetes** |  |  |
| * Yes
 | 22 (18.0%) | 100 (82.0%) |
| * No
 | 73 (13.4%) | 470 (86.6%) |
| **Hypertensive Disorders of Pregnancy** |  |  |
| * Preeclampsia
 | 1 (6.3%) | 15 (93.7%) |
| * Preeclampsia superimposed on chronic hypertension
 | 0 (0%) | 1 (100%) |
| * Eclampsia
 | 0 (0%) | 1 (100%) |
| * Pregnancy Induced Hypertension
 | 6 (33.3%) | 12 (66.7%) |
| * None
 | 93 (14.2%) | 564 (85.8%) |
| **GWG Rate Category (IOM 2009)** |  |  |
| * Inadequate
 | 15 (16.9%) | 74 (83.1%) |
| * Adequate
 | 26 (12.1%) | 188 (87.9%) |
| * Excessive
 | 49 (16.4%) | 250 (83.6%) |
| **Fetal Growth Deceleration** |  |  |
| * Deceleration
 | 35 (20.7%) | 134 (79.3%) |
| * No Deceleration
 | 60 (12.6%) | 415 (87.4%) |
| **Fetoplacental Vascular Resistance** |  |  |
| * High
 | 15 (21.4%) | 55 (78.6%) |
| * Normal
 | 76 (13.5%) | 489 (86.5%) |
| **Offspring** |
| **Gestational Age, weeks** | 39.0 (1.2) | 38.7 (1.6) |
| **Birthweight, kg** | 3.1 (0.4) | 3.1 (0.5) |
| **Birthweight-for-GA** |  |  |
| * SGA
 | 11 (15.1%) | 62 (84.9%) |
| * AGA
 | 74 (14.6%) | 432 (85.4%) |
| * LGA
 | 15 (13.2%) | 99 (86.8%) |
| **Sex** |  |  |
| * Boys
 | 57 (16.1%) | 298 (83.9%) |
| * Girls
 | 43 (12.7%) | 295 (87.3%) |
| **Weight, kg (6y)** | 23.1 (5.3) | 20.5 (3.9) |
| **Height, cm (6y)** | 117.6 (5.2) | 115.2 (4.9) |
| **BMI, kg/m2 (6y)** | 16.5 (2.8) | 15.4 (2.1) |
| **eGFR, mL/min/1.73 m2 (6y)** | 121.1 (15.3) | 121.6 (17.4) |