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Maternal Blood Pressure During Pregnancy and Early Childhood Blood Pressures in the Offspring

The GUSTO Birth Cohort Study

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Abstract: Although epidemiological studies suggest that offspring of women with preeclampsia are at increased risk to higher blood pressures and cardiovascular disease, little is known about the nature of blood pressures between the mother and her offspring. As blood pressures comprise of both pulsatile (systolic blood pressure [SBP] and pulse pressure [PP]) and stable (diastolic blood pressure [DBP]) components, and they differ between central and peripheral sites, we sought to examine maternal peripheral and central blood pressure components in relation to offspring early childhood blood pressures.

A prospective birth cohort of 567 Chinese, Malay, and Indian mother–offspring with complete blood pressure information were studied. Maternal brachial artery SBP, DBP, and PP were measured at 26 to 28 weeks gestation; and central SBP and PP were estimated from radial artery waveforms. Offspring brachial artery SBP, DBP, and PP were measured at 3 years of age. Associations between continuous variables of maternal blood pressures (peripheral SBP, DBP, PP, central SBP, and PP) and offspring blood pressures (peripheral SBP, DBP, and PP) were examined using multiple linear regression with adjustment for maternal characteristics (age, education level, parity, smoking status, alcohol consumption and physical activity during pregnancy, and pre-pregnancy BMI) and offspring characteristics (sex, ethnicity, BMI, and height at 3 years of age).

In the multivariate models, offspring peripheral SBP increased by 0.08 (95% confidence interval 0.00–0.17, $P = 0.06$) mmHg with every 1-mmHg increase in maternal central SBP, and offspring peripheral PP increased by 0.10 (0.01–0.18, $P = 0.03$) mmHg for every 1-mmHg increase in maternal central PP. The relations of maternal-offspring peripheral blood pressures (SBP, DBP, and PP) were positive but not statistically significant, and the corresponding values were 0.05 (−0.03 to 0.13; $P = 0.21$), 0.03 (−0.04 to 0.10; $P = 0.35$), and 0.05 (−0.02 to 0.13; $P = 0.14$), respectively.

Maternal central pulsatile blood pressure components (SBP and PP) during pregnancy are associated with higher blood pressures in the offspring. This positive correlation is already evident at 3-years old. Studies are needed to further evaluate the effects of maternal central pulsatile blood pressure components during pregnancy and long-term cardiovascular health in the offspring.

(*Medicine* 94(45):e1981)

Abbreviations: AGA = appropriate for gestational age, BMI = body mass index, CI = confidence interval, DBP = diastolic blood pressure, GUSTO = Growing Up in Singapore Towards Healthy Outcomes, PP = pulse pressure, SBP = systolic blood pressure, SD = standard deviation, SGA = small for gestational age.

INTRODUCTION

Findings from epidemiological studies suggest that in-utero exposure to preeclampsia is associated with higher blood pressures and an increased risk of hypertension and cardiovascular complications later in life.[1–13] For example, meta-analyses of observational studies reported about 2.28 to 2.35 and 1.35 to 1.68 mmHg higher systolic (SBP) and diastolic

Editor: Chun Gao.
Received: July 22, 2015; revised: September 23, 2015; accepted: October 11, 2015.
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Supplemental Digital Content is available for this article.

This work is supported by the Translational Clinical Research (TCR) Flagship Program on Developmental Pathways to Metabolic Disease funded by the National Research Foundation (NRF) and administered by the National Medical Research Council (NMRC), Singapore (NMRC/TCR/004-NUS/2008). Additional funding is provided by the Singapore Institute for Clinical Sciences and A*STAR. KMG is supported by the National Institute for Health Research through the NIHR Southampton Biomedical Research Centre.

The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000001981

(DBP) blood pressures, respectively, in offspring whose mothers had preeclampsia.[12,13]

Although there is evidence to suggest that maternal hypertension is associated with higher offspring blood pressures, little is known on how the pulsatile (SBP and pulse pressure [PP]) and stable [DBP] components of maternal blood pressures from peripheral or central sites may affect offspring blood pressures. Assessing the various components of maternal blood pressures are important as they reflect different cardiovascular adaptation[14,15] and there is evidence to suggest that central SBP or PP is more strongly associated with cardiovascular outcomes compared to its peripheral measures.[16,17] Moreover, as blood pressure has a unimodal distribution in the population and has been shown to have a graded relationship with cardiovascular disease,[18,19] assessment of maternal blood pressures using predetermined blood pressure cut-offs may be suboptimal in elucidating its influence on offspring blood pressure.

Therefore in the present study, we examined the relation between the maternal blood pressure components during pregnancy and offspring blood pressures during early childhood in a prospective mother–offspring cohort of Southeast Asian Chinese, Malay and Indian participants.

METHODS

Study Population

The Growing Up in Singapore Towards Healthy Outcomes (GUSTO) study is a prospective mother–offspring cohort study where 1162 pregnant women less than 14 weeks gestation were recruited at 2 public tertiary hospitals with maternity care in Singapore from 2009 to 2010.[20] Women who were enrolled into the GUSTO study were free of type 1 diabetes and were not on chemotherapy treatment or on psychotropic drugs. From the GUSTO study cohort, there were 1152 women with singleton pregnancies and 10 with twin pregnancies. Of the 1152 women with singleton pregnancies, 829 women had mid-pregnancy blood pressure measurements and were eligible for the present study. Among the offspring of women with mid-pregnancy blood pressure measurements, 567 had blood pressure measurements at age 3 years and these 567 maternal–offspring pairs with complete blood pressure information were included in the present study (Fig. 1). The women included in the analysis tended to be older, had higher education, and were less likely to smoke and consume alcohol compared to the 262 women excluded. Maternal blood pressures during pregnancy and offspring blood pressures at 3-years old were similar between women who were included and excluded in the analysis (Supplemental Table 1, http://links.lww.com/MD/A505). The study was approved by the SingHealth Centralised Institutional Review Board and National Healthcare Group Domain Specific Review Board. Written informed consent was obtained from the study participants.

Maternal Blood Pressure Measurements

Based on a standardized protocol, maternal blood pressures were taken by trained research coordinators who were blinded to the maternal status of preeclampsia or gestational hypertension during the GUSTO mid-pregnancy follow-up visits at a median gestation of 27 weeks (interquartile range 26–29 weeks). Mothers were rested for at least 10 minutes prior to blood pressure measurement, and the peripheral SBP and DBP were measured thrice from the brachial artery at 30 to 60 second intervals with an oscillometric device (MC3100, HealthSTATS International Pte Ltd, Singapore). An average of these 3 readings was calculated if the difference between readings was less than 10 mmHg; otherwise, measurements were repeated. Central blood pressures were determined by the radial artery pressure waveforms measured from the A-pulse tonometer (BPro, HealthSTATS International Pte Ltd, Singapore), having calibrated with the average of peripheral SBP and DBP, respectively. From the calibrated radial artery pressure waveforms, central SBP would be estimated as the maximum value of the average data points generated incrementally over a sampling fraction of n/4.[21] Peripheral and central PP were calculated as the difference between peripheral or central SBP and peripheral DBP.

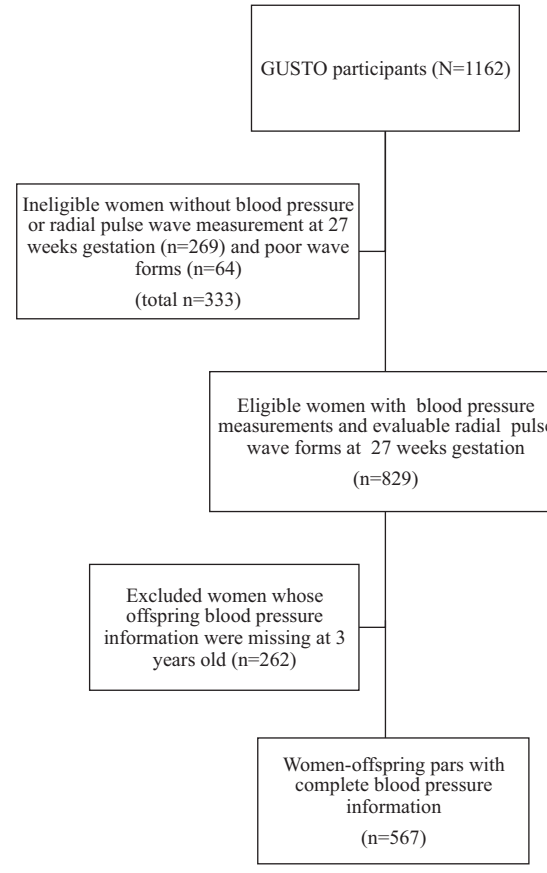

FIGURE 1. Flow chart of women in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study selected for analysis.

Offspring Blood Pressure Outcomes

At the age of 3 years, offspring blood pressure outcomes were measured by trained research personnel at outpatient clinics. Prior to blood pressure taking, the child was required to seat with the mother for at least 5 minutes in a quiet room. Peripheral SBPs and DBPs were taken twice from the right brachial artery using a Dynamap CARESCAPE V100 (GE Healthcare, Milwaukee, WI) with the arm resting at the chest level. An average of the 2 blood pressure readings was calculated if the difference between readings were less than 10 mmHg; otherwise, a 3rd reading was taken and an average of the 3 readings was taken instead. The coefficients of variation

of SBP and DBP were less than 12%. Offspring peripheral PP was calculated as the difference between peripheral SBP and DBP.

Covariates

Information on maternal age, ethnicity and education level, smoking status, alcohol and coffee consumption and physical activity during pregnancy, family history of hypertension, number of living children, and pre-pregnancy weight was obtained via questionnaires, and maternal height was measured by trained research coordinators at GUSTO mid-pregnancy follow-up. Maternal pre-pregnancy body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Women who had chronic hypertension or were diagnosed as gestational hypertension or preeclampsia (de novo hypertension with or without proteinuria after 20 weeks gestation) were classified as maternal hypertension during pregnancy.[22] Information on the offspring's sex, weight, and gestation at birth were retrieved from medical records. Offspring who were born before 37 weeks gestation would be considered premature and those who were below the 10th percentile for gestational age adjusted birth weight (based on the GUSTO cohort) would be considered as small for gestational age (SGA). At 3 years of age, offspring weight and height were measured at the same time of their blood pressure measurements.

Statistical Analysis

Maternal blood pressures differences between characteristics of eligible mother–offspring pairs were examined using one way analysis of variance test. Partial correlations between maternal and offspring blood pressures were performed using Pearson correlations, adjusted for offspring sex and ethnicity.

Selection of confounders (maternal or offspring) were based on their biological importance or known confounding from the literature. For example, maternal age, race, BMI, parity and offspring BMI, and height were considered as biologically important covariates;[8] whereas maternal education, smoking status, alcohol consumption, and physical activity were considered as known confounders.[23] As these covariates may be intercorrelated, a conceptual framework[24] was developed to examine their pathways in the maternal–offspring blood pressure relations (Supplemental Figure 1, http://links.lww.com/MD/A505). Maternal socio-economic factors (age, race, and education) may affect parity, BMI, lifestyle (smoking status, alcohol consumption, and physical activity), and blood pressures during pregnancy. These maternal factors may in turn affect offspring BMI and height at 3-years old and therein offspring blood pressures. Maternal blood pressure and other maternal factors may also affect offspring weight and gestation at birth, which in turn affects offspring BMI and blood pressures at 3-years old.

Therefore, the regression of offspring blood pressures (peripheral SBP, DBP, and PP) on maternal blood pressures (peripheral SBP, DBP, PP, central SBP, and PP) were adjusted for maternal age, education level, parity, smoking status, alcohol consumption and physical activity during pregnancy, and pre-pregnancy BMI; and offspring characteristics (including sex, ethnicity, BMI, and height at 3 years of age). Offspring weight and gestation at delivery were not adjusted as they were considered mediators of the maternal–offspring blood pressure relations. From literature, we also considered maternal hypertension, offspring prematurity, and SGA as potential mediating factors as they may lie in the pathway between maternal and offspring blood pressures.[23,25,26] This is because higher maternal blood pressures during pregnancy are strongly associated with hypertension during pregnancy and can lead to preterm birth and smaller offspring due to shared placental pathophysiology and/or medically indicated birth induction.[27] In turn, prematurity and/or SGA in the offspring are associated with higher blood pressures in later life.[23,25,26] Therefore, we repeated our main analysis in subgroups of women, stratified by maternal hypertension, offspring prematurity, and SGA to test the robustness of our results. For the assessment of offspring's SGA status at birth, we have used the 10th percentile cut-offs weight for gestation at delivery based on the GUSTO and INTERGROWTH – 21st Project[28] for local and international comparisons, respectively. As there were few women with pregnancy hypertension (n = 30), offspring prematurity (n = 47), and SGA (n = 45, GUSTO; n = 34, INTERGROWTH – 21st), analysis were repeated only in women and offspring without these conditions.

We explored effect modifications by offspring sex (male, female) and ethnicity (Chinese, Malay, or Indian) were evaluated from the multiplicative interaction terms between continuous blood pressure variables and the effect modifier added to the main effect model. Ethnicity and sex stratified analyses were performed, respectively, and likelihood ratio testing used to test for interaction effects. Lastly, we examined the differences in characteristics in mother–offspring pairs that were included and excluded from the present study. Analyses were performed using Student's *t*-test and Chi-square test for continuous and categorical variables, respectively. All analyses were performed using Stata version 11.2 (Statacorp, College Station, TX); two-tailed *P* values less than 0.05 were considered statistically significant.

RESULTS

Of the 567 mother–offspring pairs followed up in the present study, 310 (54.7%) were of ethnic Chinese, 157 (27.7%) Malay, and 100 (17.6%) Indian. The mean age of women enrolled was 31.0 (standard deviation 5.1) years. Overall, higher maternal blood pressures were observed in women of Malay ethnicity, lower education, who smoked before, had no or light physical activity during pregnancy, or higher pre-pregnancy BMI. Higher maternal blood pressures also observed in women who developed hypertension in pregnancy and those who had premature deliveries (Table 1).

The mean BMI and height of offspring followed up at the age of 3-years old were 15.8 (95% confidence interval [CI] 15.7–15.9) kg/m^2 and 94.8 (95% CI 94.5–95.1) cm, respectively. The mean peripheral SBP, DBP, and PP of the offspring at 3 years of age were 98.5 (95% CI 97.8–99.2) mmHg, 58.3 (95% CI 57.9–58.8) mmHg, and 40.2 (95% CI 39.7–40.7) mmHg, respectively (Supplemental Table 1, http://links.lww.com/MD/A505). After accounting for offspring sex and ethnicity, maternal blood pressures were weakly correlated with offspring peripheral SBP and PP (adjusted *r* ranged from 0.05 to 0.11), but not with offspring peripheral DBP. Weak correlations were also observed between offspring blood pressures, BMI, and height (*r* ranged from 0.11 to 0.25; Supplemental Figure 2, http://links.lww.com/MD/A505).

In multiple linear regression models, positive maternal–offspring blood pressure relations were observed for the blood pressure measures of SBP and PP (Fig. 2), but not for DBP. Other maternal–offspring blood pressure relations were not statistically significant, except for the relations between

TABLE 1. Distribution of Maternal Blood Pressures by Maternal and Offspring's Characteristics*

		Peripheral Blood Pressures, mmHg						Central Blood Pressures, mmHg			
		SBP		DBP		PP		SBP		PP	
Maternal Characteristics	**Overall n, %**	**Mean (95% CI)**	***P***	**Mean (95% CI)**	***P***	**Mean (95% CI)**	***P***	**Mean (95% CI)**	***P***	**Mean (95% CI)**	***P***
Age, years			0.71		0.26		0.28		0.35		0.35
1st quartile (18–26)	106 (18.7%)	110.3 (108.1–112.5)		66.3 (64.7–67.9)		44.0 (42.3–45.6)		96.7 (94.8–98.7)		30.4 (29.1–31.7)	
2nd quartile (27–29)	132 (23.3%)	109.7 (107.8–111.5)		67.3 (65.8–68.7)		42.4 (41.0–43.7)		96.7 (95.0–98.4)		29.4 (28.4–30.4)	
3rd quartile (30–33)	151 (26.6%)	108.7 (106.9–110.4)		65.8 (64.5–67.1)		42.8 (41.5–44.2)		96.3 (94.7–98.0)		30.5 (29.4–31.6)	
4th quartile (34–46)	178 (31.4%)	109.5 (107.9–111.2)		67.5 (66.3–68.7)		42.1 (40.8–43.3)		98.2 (96.7–99.7)		30.7 (29.7–31.7)	
Race			<0.001		0.003		0.09		<0.001		0.33
Chinese	310 (54.7%)	108.1 (106.9–109.3)		66.0 (65.1–66.9)		42.1 (41.2–43.0)		95.9 (94.8–97.0)		29.9 (29.2–30.7)	
Malay	157 (27.7%)	112.9 (111.1–114.6)		69.0 (67.7–70.4)		43.8 (42.6–45.1)		99.9 (98.3–101.5)		30.8 (29.9–31.8)	
Indian	100 (17.6%)	108.4 (106.4–110.5)		65.7 (64.0–67.3)		42.8 (41.1–44.5)		96.3 (94.4–98.1)		30.6 (29.1–32.1)	
Education			0.006		0.001		0.80		0.002		0.72
Primary to Secondary	171 (30.3%)	110.3 (108.6–111.9)		67.5 (66.3–68.8)		42.7 (41.6–43.9)		98.1 (96.6–99.6)		30.5 (29.6–31.4)	
GCE/vocational/polytechnic	194 (34.4%)	110.9 (109.2–112.5)		67.9 (66.8–69.1)		42.9 (41.7–44.2)		98.3 (96.8–99.8)		30.4 (29.4–31.4)	
Tertiary and above	199 (35.3%)	107.5 (106.1–108.9)		65.1 (64.0–66.2)		42.4 (41.3–43.5)		95.1 (93.8–96.4)		30.0 (29.1–30.9)	
Alcohol intake			0.92		0.29		0.36		0.61		0.04
No	372 (67.6%)	109.3 (108.1–110.4)		66.4 (65.5–67.2)		42.9 (42.1–43.7)		97.1 (96.0–98.1)		30.7 (30.0–31.4)	
Yes	178 (32.4%)	109.4 (107.7–111.0)		67.2 (65.9–68.4)		42.2 (41.0–43.4)		96.6 (95.1–98.0)		29.4 (28.5–30.4)	
Smoking status			0.02		0.10		0.11		0.04		0.29
Nonsmoker	497 (88.0%)	109.0 (108.0–110.0)		66.5 (65.8–67.2)		42.5 (41.8–43.2)		96.7 (95.8–97.6)		30.2 (29.6–30.8)	
Ever-smoker	68 (12.0%)	112.5 (109.6–115.4)		68.3 (66.1–70.4)		44.2 (42.4–46.0)		99.4 (96.6–102.1)		31.1 (29.5–32.6)	
Parity			0.77		0.81		0.87		0.33		0.24
Nulliparous	234 (41.3%)	109.3 (107.8–110.8)		66.7 (65.7–67.7)		42.6 (41.5–43.7)		96.6 (95.3–97.9)		29.9 (29.0–30.8)	
Multiparous	333 (58.7%)	109.6 (108.4–110.8)		66.8 (65.9–67.8)		42.8 (41.9–43.6)		97.4 (96.3–98.5)		30.6 (29.9–31.3)	
Physical activity			0.21		0.02		0.55		0.01		0.42
None to light	404 (71.2%)	109.8 (108.8–110.9)		67.3 (66.5–68.1)		42.6 (41.8–43.4)		97.7 (96.7–98.7)		30.4 (29.8–31.1)	
Moderate to strenuous	163 (28.8%)	108.5 (106.9–110.2)		65.5 (64.2–66.8)		43.0 (41.7–44.3)		95.5 (94.0–97.0)		29.9 (29.0–30.9)	
Pre-pregnancy BMI, kg/m^2			<0.001		<0.001		0.02		<0.001		0.39
BMI <25.0	387 (74.1%)	107.1 (106.0–108.1)		65.0 (64.3–65.8)		42.0 (41.2–42.8)		95.0 (94.0–95.9)		29.9 (29.3–30.6)	
BMI 25.0–29.9	93 (17.8%)	113.9 (111.9–115.9)		71.0 (69.2–72.7)		42.9 (41.3–44.5)		101.5 (99.7–103.3)		30.5 (29.3–31.7)	
BMI ≥30.0	42 (8.05%)	119.9 (116.7–123.2)		74.1 (71.8–76.5)		45.8 (42.9–48.6)		105.4 (102.6–108.1)		31.2 (29.2–33.3)	
Hypertension			<0.001		<0.001		0.08		<0.001		0.08
No	537 (94.7%)	108.8 (107.9–109.8)		66.3 (65.6–67.0)		42.6 (41.9–43.2)		96.5 (95.6–97.3)		30.2 (29.6–30.7)	
Yes	30 (5.3%)	120.7 (116.8–124.6)		75.4 (72.7–78.1)		45.3 (41.7–48.9)		107.7 (104.3–111.1)		32.3 (30.1–34.6)	
Offspring characteristics											
Sex			0.13		0.03		0.85		0.27		0.27
Male	437 (53.8%)	108.8 (107.5–110.1)		66.0 (65.1–66.9)		42.8 (41.8–43.7)		96.6 (95.5–97.8)		30.6 (29.9–31.3)	
Female	375 (46.2%)	110.2 (108.9–111.5)		67.6 (66.6–68.6)		42.6 (41.6–43.6)		97.6 (96.4–98.8)		30.0 (29.2–30.8)	
Prematurity			0.05		0.007		0.92		0.03		0.92
No	507 (91.5%)	109.2 (108.2–110.2)		66.5 (65.7–67.2)		42.7 (42.0–43.5)		96.8 (95.9–97.7)		30.3 (29.8–30.9)	
Yes	47 (8.5%)	112.5 (109.3–115.7)		69.9 (67.6–72.1)		42.6 (40.4–44.9)		100.1 (96.9–103.3)		30.2 (28.4–32.1)	
Small for gestational age			0.77		0.93		0.76		0.34		0.32
No	509 (91.9%)	109.5 (108.6–110.5)		66.8 (66.0–67.5)		42.8 (42.0–43.5)		97.0 (96.1–97.9)		30.2 (29.7–30.8)	
Yes	45 (8.1%)	109.0 (106.1–112.0)		66.6 (64.4–68.8)		42.4 (39.9–44.8)		97.9 (95.1–100.7)		31.3 (29.3–33.3)	

BMI = indicates body mass index, CI = confidence interval, DBP = diastolic blood pressure, PP = pulse pressure, SBP = systolic blood pressure.

* Data are presented as n (column percentages) or in mean (95% confidence interval). A total of 567 women and their offspring were included in analysis, women with missing information for education (n = 3), alcohol intake (17), smoking status (n = 2), and maternal pre-pregnancy BMI (n = 45); and in offspring with missing information for prematurity and small for gestational age (n = 13) were coded as missing.

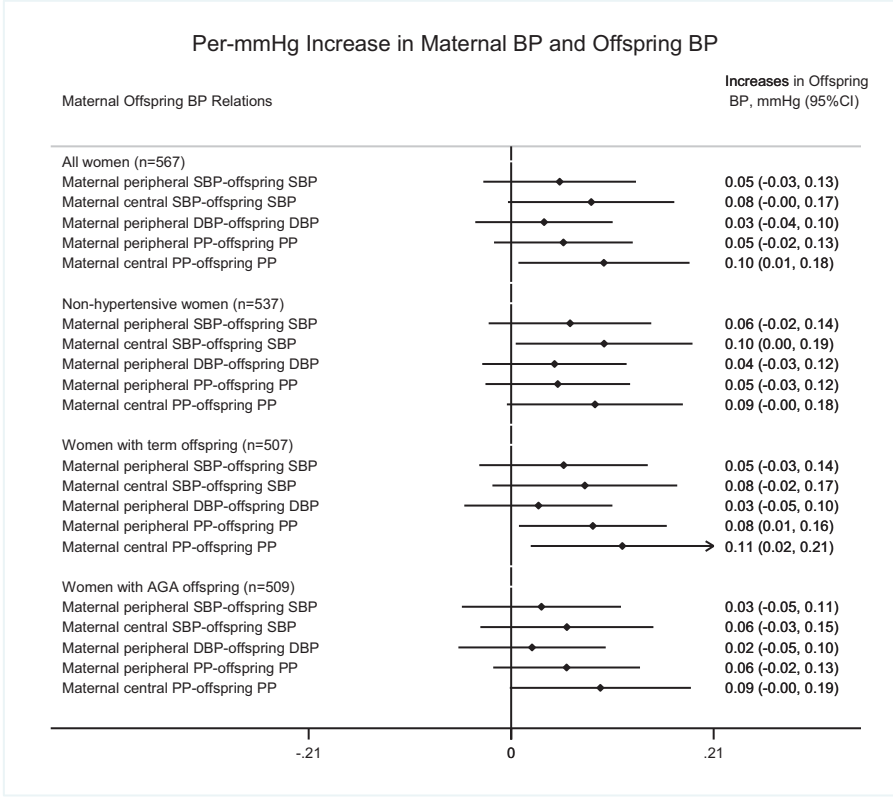

FIGURE 2. Per-mmHg increases in maternal blood pressures at 26 to 28 weeks gestation and associations with offspring blood pressures at 3 years of age.

maternal SBP and offspring PP (Table 2). Estimated increases in offspring peripheral SBP and PP were consistently greater for maternal central blood pressures than for the relations with maternal peripheral blood pressures. Findings were not significantly modified by offspring ethnicity and sex (Supplemental Tables 2–3, http://links.lww.com/MD/A505).

Having excluded women who had hypertension during pregnancy, premature, and SGA offspring, women who had normotensive pregnancies (n = 537), term (n = 507), and appropriate for gestational age (AGA; n = 509) offspring were included in the sensitivity analysis (Table 2). The maternal–offspring relations of central SBP persisted in normotensive pregnancies but were slightly attenuated in term and AGA offspring. But for central PP, the maternal–offspring relations persisted in all subgroups of analysis in women with normotensive pregnancies and those with term or AGA offspring. Other maternal–offspring blood pressure relations were qualitatively the same between the main cohort and subgroup analysis.

DISCUSSION

Previous studies have shown higher blood pressures in young children and adults whose mothers had pregnancy-related hypertension compared with offspring of mothers with normal pregnancies.[1–13] The present study builds on that knowledge by demonstrating that higher maternal central pulsatile (SBP and PP) blood pressure components in pregnancy were associated with higher blood pressures in the offspring. Importantly, the positive associations of mother–offspring blood pressures persisted in normotensive women who were free of hypertension during pregnancy and in offspring who were born term and AGA.

Positive maternal–offspring blood pressure relations have been reported previously in several studies that measured peripheral blood pressures[29,30] and maternal hypertension in nonpregnant[31,32] and pregnant women.[1–13] In the HUNT Study of Norwegians, positive correlations were reported between mother–offspring SBP ($r = 0.15$) and DBP ($r = 0.14$).[29] In a study of Dutch families with children aged 5 to 19 years, each mmHg increase in maternal peripheral SBP was associated with a 0.09 mmHg increase in offspring SBP; for DBP relation the corresponding mother–offspring increase was 0.04 mmHg.[30] Compared to these findings, we found qualitatively similar maternal–offspring blood pressure correlations in our cohort of Southeast Asian Chinese, Malay, and Indian women. In our study, each 1 mmHg increase in maternal peripheral and central SBP was associated with 0.05 and 0.08 mmHg increases in offspring SBP, although the former was not statistically significant.

In the assessment of maternal central and peripheral blood pressures relations with offspring blood pressures, we observed stronger associations in the central than peripheral blood pressures. This observation similarly has been observed in 2 separate studies in normotensive pregnant Japanese women. In these normotensive women who were free of pregnancy hypertension, central blood pressures were associated pregnancy gestation changes[33] and small for gestational age,[34] but not for peripheral blood pressures. Taken together, these findings suggest that central blood pressures may be better arterial markers than peripheral blood pressures in relation to

TABLE 2. Estimated Increases in Offspring Peripheral Blood Pressures, Per-mmHg Increase in Maternal Blood Pressures in all Women and in Subgroups of Women with Normotensive Pregnancies, Term and Appropriate for Gestational Age (AGA) Offspring*

		Offspring Blood Pressure Outcomes, mmHg					
		Peripheral SBP		Peripheral DBP		Peripheral PP	
Maternal Blood Pressures, mmHg	N	ß (95% CI)	*P*	ß (95% CI)	*P*	β (95% CI)	*P*
Peripheral SBP							
All women	567	0.05 (−0.03 to 0.13)	0.21	−0.02 (−0.07 to 0.04)	0.52	0.07 (0.01 to 0.13)	0.02
Women with normotensive pregnancies	537	0.06 (−0.02 to 0.14)	0.16	−0.01 (−0.06 to 0.05)	0.86	0.07 (0.01 to 0.13)	0.03
Women with term offspring	507	0.05 (−0.03 to 0.14)	0.22	−0.03 (−0.09 to 0.03)	0.29	0.09 (0.02 to 0.15)	0.007
Women with GUSTO AGA offspring	509	0.03 (−0.05 to 0.11)	0.45	−0.03 (−0.09 to 0.02)	0.24	0.07 (0.01 to 0.13)	0.03
Women with Intergrowth AGA offspring	528	0.04 (−0.04 to 0.12)	0.30	−0.03 (−0.08 to 0.03)	0.30	0.07 (0.01 to 0.13)	0.02
Peripheral DBP							
All women	567	0.09 (−0.01 to 0.20)	0.09	0.03 (−0.04 to 0.10)	0.35	0.06 (−0.02 to 0.13)	0.14
Women with normotensive pregnancies	537	0.10 (−0.01 to 0.21)	0.07	0.04 (−0.03 to 0.12)	0.24	0.06 (−0.02 to 0.14)	0.15
Women with term offspring	507	0.08 (−0.04 to 0.19)	0.18	0.03 (−0.05 to 0.10)	0.47	0.05 (−0.03 to 0.13)	0.24
Women with GUSTO AGA offspring	509	0.07 (−0.04 to 0.18)	0.19	0.02 (−0.05 to 0.10)	0.58	0.05 (−0.03 to 0.13)	0.22
Women with Intergrowth AGA offspring	528	0.09 (−0.01 to 0.20)	0.09	0.03 (−0.04 to 0.10)	0.44	0.06 (−0.01 to 0.14)	0.11
Peripheral PP							
All women	567	0.00 (−0.10 to 0.09)	0.96	−0.06 (−0.12 to 0.01)	0.09	0.05 (−0.02 to 0.13)	0.14
Women with normotensive pregnancies	537	0.00 (−0.10 to 0.10)	0.98	−0.05 (−0.12 to 0.02)	0.19	0.05 (−0.03 to 0.12)	0.21
Women with term offspring	507	0.01 (−0.09 to 0.12)	0.82	−0.07 (−0.14 to 0.00)	0.05	0.08 (0.01 to 0.16)	0.03
Women with GUSTO AGA offspring	509	−0.02 (−0.12 to 0.09)	0.76	−0.07 (−0.14 to 0.00)	0.05	0.06 (−0.02 to 0.13)	0.14
Women with Intergrowth AGA offspring	528	−0.02 (−0.11 to 0.08)	0.76	−0.07 (−0.14 to 0.00)	0.04	0.05 (−0.02 to 0.13)	0.14
Central SBP							
All women	567	0.08 (0.00 to 0.17)	0.06	0.00 (−0.06 to 0.05)	0.88	0.09 (0.02 to 0.15)	0.006
Women with normotensive pregnancies	537	0.10 (0.00 to 0.19)	0.04	0.01 (−0.05 to 0.07)	0.76	0.09 (0.02 to 0.15)	0.01
Women with term offspring	507	0.08 (−0.02 to 0.17)	0.12	−0.02 (−0.08 to 0.04)	0.55	0.10 (0.03 to 0.16)	0.006
Women with GUSTO AGA offspring	509	0.06 (−0.03 to 0.15)	0.21	−0.02 (−0.09 to 0.04)	0.47	0.08 (0.01 to 0.15)	0.02
Women with Intergrowth AGA offspring	528	0.07 (−0.01 to 0.16)	0.09	−0.02 (−0.08 to 0.04)	0.60	0.09 (0.03 to 0.16)	0.006
Central PP							
All women	567	0.04 (−0.08 to 0.16)	0.50	−0.05 (−0.14 to 0.03)	0.19	0.10 (0.01 to 0.18)	0.03
Women with normotensive pregnancies	537	0.05 (−0.08 to 0.17)	0.46	−0.04 (−0.12 to 0.05)	0.36	0.09 (0.00 to 0.18)	0.06
Women with term offspring	507	0.04 (−0.09 to 0.17)	0.55	−0.07 (−0.16 to 0.01)	0.10	0.11 (0.02 to 0.21)	0.02
Women with GUSTO AGA offspring	509	0.02 (−0.11 to 0.14)	0.80	−0.08 (−0.16 to 0.01)	0.09	0.09 (0.00 to 0.19)	0.05
Women with Intergrowth AGA offspring	528	0.02 (−0.10 to 0.15)	0.70	−0.07 (−0.16 to 0.01)	0.10	0.09 (0.00 to 0.19)	0.04

AGA = appropriate for gestational age, CI = confidence interval, DBP = diastolic blood pressure, GUSTO = Growing Up in Singapore Towards healthy Outcomes, PP = pulse pressure, SBP = systolic blood pressure.

* Normotensive women referred to women without chronic or gestational hypertension or preeclampsia. Term offspring referred to offspring being born at 37 weeks gestation or later and AGA referred to offspring who were at the 10th percentile or greater for gestational age adjusted birth weight by GUSTO cohort and the Intergrowth study cut-offs. All analysis were performed using multiple linear regressions with adjustments for maternal age, education level, parity, smoking status, alcohol consumption and physical activity during pregnancy, pre-pregnancy BMI; and offspring sex, ethnicity, BMI, and height at 3 years of age.

pregnancy outcomes. However, evidence for the stronger role of central blood pressures compared with peripheral blood pressures was demonstrated only in nonpregnant populations[17] as the literature in pregnant women is scarce. Therefore, further studies examining maternal blood pressures during pregnancy incorporating both central and peripheral measures are needed.

The positive association of mother and offspring blood pressures, as early as 3-years old in the present cohort, suggests that the higher blood pressures in offspring of women with higher pregnancy blood pressures occur early in life. And, as blood pressure tracks in life,[35] the higher blood pressure in the offspring of women with higher pregnancy blood pressure is also likely to persist in life. This has been demonstrated in studies that examined maternal hypertension in pregnant[1–13] and nonpregnant women[31,32] in relation to blood pressures in offspring aged between 5 and 30 years of age.

The higher early childhood SBP and PP may impact on cardiovascular health in later life. Evidence from long-term follow-up studies of children and young adults indicates that childhood SBP is a predictor of arterial stiffness in adulthood[36] and higher incidence of hypertension in young adults with higher blood pressure and parental hypertension.[32] Although this raises the possibility that optimal blood pressure compliance through antenatal monitoring and primary health prevention strategies could have long-term benefits for offspring health, this hypothesis needs to be further addressed in long-term cohort studies and randomized trials.

Overall, the positive maternal–offspring blood pressures relations in the present study are consistent with earlier studies that the blood pressure phenotype clusters in family.[12,13,30–32] The independent associations between maternal–offspring blood pressures may be explained by several mechanisms. First, in-utero exposure to higher maternal blood pressures may lead

to higher blood pressures and vascular dysfunction in the offspring. In a sibling study by Jayet et al,[37] higher pulmonary artery pressure and smaller flow-mediated dilations in sibling exposed to preeclampsia compared with the sibling unexposed to preeclampsia. And in other studies of offspring of maternal preeclampsia,[26,37,38] In-utero exposure to preeclampsia or maternal hypertension has been associated with altered renin angiotensin and sympathetic nervous systems, oxidative stress and impaired cardio-vascular structure, and function in the offspring. These observations, collectively, support the intrauterine effect of maternal hypertension during pregnancy on offspring' vascular function in later life and is in line with fetal programming hypothesis.[26,38]

Second, the positive maternal–offspring SBP and PP relations may also be contributed by genetic factors[15] as SBP and PP, being markers for arterial stiffness, are heritable conditions.[39–41] Findings from the Framingham Study offspring cohort of 817 pedigrees suggest that measures of central arterial stiffness located at distinct locations within the genome were heritable and may modulate different hemodynamic components.[41] Other evidence from familial studies have also supported a genetic explanation,[29,31,32] based on the independent and addictive effects of maternal and paternal hypertension observed on blood pressures in the offspring.

Third, a mechanism involving nongenetic factors, such as salt intake,[23,42] may be shared across the maternal–offspring pairs. Findings from animal studies suggest that maternal salt intake has been found to be associated with altered fetal kidney development and function; and these could have set the offspring to higher blood pressures early in life.[43] However, based on 2 recent reports from the Avon Longitudinal Study of Parents and Children, the observation that higher blood pressures in the offspring of women with preeclampsia persisted even after accounting for salt intake,[4,5] suggesting that salt intake may only partially mediate the relations between maternal hypertension and blood pressures in the offspring.

The findings of this study should be interpreted in consideration of its strengths and limitations. Strengths of this study include the prospectively measured maternal and offspring blood pressures, performed according to a standard protocol by trained research personnel and the ability to measure and account for various maternal and offspring factors in our analysis. However, there are several limitations to our study. First, 333 (28.7%) women from the original 1162 women in the GUSTO base cohort were excluded from the present study follow-up due to incomplete or poor maternal recording of radial pulse wave form. Of the remaining 829 (71.3%) women that were followed up, 262 were also excluded due to missing offspring blood pressure information at the GUSTO 3rd year study visit. However, our findings are unlikely to be affected by selection bias as maternal blood pressures were similar in those who were included and excluded from analysis. Second, as maternal blood pressures were measured only once during pregnancy, we were unable to examine the blood pressure changes during pregnancy in relation to blood pressures in the offspring. The equipment used in the present study for the measurement of maternal and offspring blood pressures has yet to be validated in pregnant women and young children. However, the estimation of maternal central blood pressures using n-point moving average has been validated in 2 adult studies with excellent correlation with invasively measured central blood pressures (r ranging from 0.89 to 0.99).[21,44] Our effect estimates may be affected by residual confounding, for example, from self-reported measures of maternal pre-pregnancy BMI and from lack of adjustment for maternal dietary intake (like salt).[45,46] Lastly, the nonsignificant findings from our main analysis and tests for effect modifications may be constrained by the lack of power. Further studies, with adequate sampling of ethnic specific groups, are needed to explore the overall and potential ethnic differences in the maternal–offspring blood pressure relations in Asian women.

In conclusion, the pulsatile central maternal blood pressures during pregnancy may be important determinants of offspring blood pressures. As the maternal–offspring blood pressure persists even in in normotensive pregnancies and in term and AGA offspring, ensuring optimal blood pressure compliance during pregnancy could have long-term implications for cardiovascular health in the offspring.

ACKNOWLEDGMENTS

*The authors thank the GUSTO study group includes Pratibha Agarwal, Arijit Biswas, Choon Looi Bong, Birit FP Broekman, Shirong Cai, Jerry Kok Yen Chan, Yiong Huak Chan, Cornelia Yin Ing Chee, Helen Y. H Chen, Yin Bun Cheung, Audrey Chia, Amutha Chinnadurai, Chai Kiat Chng, Mary Foong-Fong Chong, Yap-Seng Chong, Shang Chee Chong, Mei Chien Chua, Chun Ming Ding, Eric Andrew Finkelstein, Doris Fok, Marielle V. Fortier, Peter D. Gluckman, Keith M. Godfrey, Anne Eng Neo Goh, Yam Thiam Daniel Goh, Joshua J. Gooley, Wee Meng Han, Mark Hanson, Christiani Jeyakumar Henry, Joanna D. Holbrook, Chin-Ying Hsu, Hazel Inskip, Jeevesh Kapur, Kenneth Kwek, Ivy Yee-Man Lau, Bee Wah Lee, Yung Seng Lee, Ngee Lek, Sok Bee Lim, Yen-Ling Low, Iliana Magiati, Lourdes Mary Daniel, Michael Meaney, Cheryl Ngo, Krishnamoorthy Naiduvaje, Wei Wei Pang, Anqi Qiu, Boon Long Quah, Victor Samuel Rajadurai, Mary Rauff, Salome A. Rebello, Jenny L. Richmond, Anne Rifkin-Graboi, Seang-Mei Saw, Lynette Pei-Chi Shek, Allan Sheppard, Borys Shuter, Leher Singh, Shu-E Soh, Walter Stunkel, Lin Lin Su, Kok Hian Tan, Oon Hoe Teoh, Mya Thway Tint, Hugo P S van Bever, Rob M. van Dam, Inez Bik Yun Wong, P. C. Wong, Fabian Yap, George Seow Heong Yeo. The authors also thank the support from the Translational Clinical Research (TCR) Flagship Program on Developmental Pathways to Metabolic Disease funded by the National Research Foundation (NRF) and administered by the National Medical Research Council (NMRC), Singapore (NMRC/TCR/004-NUS/2008); additional funding provided by the Singapore Institute for Clinical Sciences and A*STAR and National Institute for Health Research through the NIHR Southampton Biomedical Research Centre.*

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