Maternal Blood Pressure Rise During Pregnancy and Offspring Obesity Risk at 4 to 7 Years Old: The Jiaxing Birth Cohort

Ju-Sheng Zheng,1,2 Huijuan Liu,3 Ken K. Ong,2,4 Tao Huang,5 Yuhong Guan,3 Yuan Huang,6 Bo Yang,1 Fenglei Wang,7 and Duo Li1,7

1Institute of Nutrition & Health, Qingdao University, Qingdao 26071, China; 2Medical Research Council Epidemiology Unit, University of Cambridge School of Clinical Medicine, Cambridge CB2 0QQ, United Kingdom; 3Jiaxing Maternity and Child Health Care Hospital, Jiaxing 314051, China; 4Department of Paediatrics, University of Cambridge, Cambridge CB2 0QQ, United Kingdom; 5Saw Swee Hock School of Public Health, National University of Singapore, Singapore 117549; 6EPSRC Centre for Mathematical and Statistical Analysis of Multimodal Clinical Imaging, University of Cambridge, Cambridge CB3 0WB, United Kingdom; and 7Department of Food Science and Nutrition, Zhejiang University, Hangzhou 310058, China

Context: Maternal hypertensive disorders during pregnancy are suggested to affect obesity risk in offspring. However, little is known about the prospective association of rise in maternal blood pressure within normal range during pregnancy with this risk for obesity.

Objective: To clarify the associations of diastolic and systolic blood pressure during pregnancy among normotensive women with the risk for obesity in offspring.

Design: Prospective cohort study.

Setting: Southeast China.

Participants: Up to 2013, a total of 88,406 mother-child pairs with anthropometric measurements of offspring age 4 to 7 years were included in the present analysis.

Main Outcome Measures: Overweight/obesity risk in offspring.

Results: Among normotensive women, second- and third-trimester diastolic and systolic blood pressures were positively associated with risk for overweight/obesity in offspring: odds ratios per 10–mm Hg higher second- and third-trimester diastolic blood pressure were 1.05 (95% confidence interval (CI), 1.01 to 1.09) and 1.05 (95% CI, 1.02 to 1.10), respectively, and for systolic blood pressure were 1.08 (95% CI, 1.05 to 1.11) and 1.06 (95% CI, 1.03 to 1.09). Each 10–mm Hg greater rise in blood pressure between first and third trimesters was associated with a higher risk for offspring overweight/obesity: diastolic, 1.06 (95% CI, 1.01 to 1.10); systolic, 1.05 (95% CI, 1.02 to 1.07). Among all women (combining normotensive and hypertensive women), maternal hypertension in the second and third trimesters was associated with 49% and 14% higher risks for overweight/obesity in offspring, respectively.

Conclusions: These results suggest that rise in maternal blood pressure during pregnancy and hypertension during pregnancy, independent of maternal body size before pregnancy, are risk factors for offspring childhood obesity. (J Clin Endocrinol Metab 102: 4315–4322, 2017)

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA
This article has been published under the terms of the Creative Commons Attribution License (CC BY; http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. Copyright for this article is retained by the author(s).
Received 3 July 2017. Accepted 8 September 2017.
First Published Online 27 September 2017

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; JBC, Jiaxing Birth Cohort; OR, odds ratio; SBP, systolic blood pressure; SD, standard deviation.


Downloaded from https://academic.oup.com/jcem/article-abstract/102/11/4315/4259054 by University of Cambridge user on 07 February 2018
The prevalence of childhood obesity has increased globally during the past 2 decades, especially among developing countries, such as China. In 2010, the age-adjusted prevalence of obesity and overweight/obesity was 8.1% and 19.2%, respectively (by percentage weight-for-height standards), among Chinese children age 7 to 18 years in the Chinese National Surveys on weight-for-height standards, among Chinese children was 8.1% and 19.2%, respectively (by percentage adjusted prevalence of obesity and overweight/obesity developing countries, such as China. In 2010, the age-

Study design and participants

The Jiaxing Birth Cohort (JBC) (1999 to 2013) was initiated in 1999 based on an existing routine health monitoring system in the Jiaxing area (a middle-income area in southeast China), involving >0.3 million live mother-child pairs with extensive follow-up information of the children up to age 6 to 7 years before they started school (13). Women living at one of the seven divisions/counties in the Jiaxing area came to register at local clinics before pregnancy or at any stage of pregnancy. Thereafter, participants came to visit the local clinics regularly until the birth (16 to 28 gestational weeks: once every 4 weeks; 29 to 36 gestational weeks: once every 2 weeks; >36 gestational weeks: once per week). Up to 2013, a total of 338,413 live mother-child pairs were enrolled in the JBC study. For participants who registered in the JBC study during pregnancy, their prepregnancy anthropometric measurements were retrieved by linking to a premarriage health check database held by the Jiaxing Maternity and Child Health Care Hospital.

Children enrolled in the JBC study visited (with their parents) the local clinics for health checks and anthropometric measurements at ages 1 to 2 months, 3 months, 6 months, 9 months, and 12 months during infancy. In the following stage, children visited the local clinics every 6 months (18, 24, 30, and 36 months) until age 36 months. Thereafter, children were asked to visit the clinics once per year before they started school (age 6 to 7 years).

Between 1999 and 2006, a total of 134,680 mother-child (singleton) pairs were enrolled in the JBC study. Mother-child pairs were excluded if they had extreme offspring birthweight (<1500 g or >5000 g; n = 85) or preterm birth (<37 gestational weeks; n = 4425), or no maternal BP record at any of the first, second, or third trimesters (n = 426). Therefore, at baseline, 129,744 mother-child pairs were included in the current study. Up to 2013, 89,185 children had follow-up information between ages 4 to 7 years (68.7% follow-up rate). For children with multiple follow-ups between 4 and 7 years of age, the later follow-up visit data were used to maximize the follow-up duration. Children were excluded if they had any missing data on anthropometric measurements (height or weight) at the follow-up visit at ages 4 to 7 years (n = 779). Finally, 88,406 mother-child pairs were included in the statistical analyses. The study protocol was approved by the ethics committee of the College of Biosystem Engineering & Food Science at Zhejiang University in China. All participants provided oral informed consent.

Measurement of maternal BP and other key variables

At each clinic visit, seated maternal BP was measured by manual BP monitors in the right arm on a single occasion after 5 to 10 minutes of resting. At each of the three trimesters, maternal pregnancy hypertension was defined as diastolic BP (DBP) ≥90 mm Hg and/or systolic blood pressure (SBP) ≥140 mm Hg. Because we could not separate different hypertensive disorders of pregnancy, such as gestational hypertension or preeclampsia (14), this definition (maternal pregnancy hypertension) represents a combination of hypertensive disorders of pregnancy. BP
measurements at the first health check (0 to 12 gestational weeks) were considered as first-trimester BP. BP measurements at a later health check between 13 and 28 gestational weeks were considered as second-trimester BP. BP measurements at a health check around 37 gestational weeks (≥29 gestational weeks) was considered as third-trimester BP.

At the first health check/recruitment of the participants, maternal demographic characteristics were collected by interview. Maternal anthropometric measurements (weight, height) were taken on site by trained nurses. Maternal BMI was based on prepregnancy (n = 43,831) or first-trimester measurements (n = 36,491).

**Offspring anthropometric assessment**

Body weight and height of the children were measured by trained nurses to the nearest 0.1 kg and 0.1 cm, respectively, at each follow-up clinic visit. Childhood overweight and obesity were defined according to the international BMI cutoff points by age and sex, as established by the International Obesity Task Force (15).

**Statistical analyses**

All statistical analyses were performed using Stata software, version 14 (Stata Corp., College Station, TX). Initially, logistic regression was used to examine the odds ratio (OR) and 95% confidence interval (CI) of offspring overweight/obesity per 10-mm Hg higher maternal DBP and SBP at first, second, and third trimesters among normotensive women in three statistical models: model 1, crude model without adjustment; model 2, adjusted for maternal age (continuous), menarcheal age (<14 years, 14 to 15 years, >15 years), education level (less than high school, high school, more than high school), occupation (farm work/house work, routine job, others), parity (primiparous or multiparous), offspring sex and offspring age at examination (continuous); and model 3, model 2 plus maternal BMI (continuous) and maternal height (continuous). We included maternal BMI and height in model 3 to examine the influence of maternal body size on the results in addition to other covariates. Sensitivity analyses were conducted under model 3 by adopting further potential confounders or inclusion criteria: model 3a used additional covariates: maternal baseline SBP at each trimester with overweight/obesity risk, or offspring birthweight, using restricted cubic spline models [four knots, according to Harrell’s recommendation (16)] among all participants, including both hypertensive and normotensive women. Four knots offer an adequate fit of the model and are a good compromise between flexibility and loss of precision caused by overfitting (16). There was no substantial difference in the shape or nonlinear association when we selected three or five knots.

Interaction between different pregnancy BP and different maternal/infant characteristics (maternal age, BMI, menarcheal age, and offspring sex) on risk for offspring overweight/obesity was examined by adding relevant interaction terms to model 3. We further examined potential mediation by birthweight, and the proportion (% of total effect) mediated by birthweight using the method proposed by Kenny (17). The binary_mediation command in Stata was used to estimate the mediation effect for our dichotomous outcome (overweight/obesity compared with normal weight), and bias-corrected 95% CI was calculated via bootstrapping with 500 replications (18). A two-tailed P value < 0.05 was considered to indicate a statistically significant difference.

**Results**

**Population characteristics**

The mean maternal age at birth of offspring was 25 years [standard deviation (SD), 3.7] and mean maternal BMI was 20.5 kg/m² (SD, 2.6). Mean maternal DBP increased from 68.4 to 69.1 to 75.3 mm Hg in the first, second, and third trimesters, respectively; similarly, SBP increased from 105.9 to 108.7 to 115.2 mm Hg (Supplemental Fig. 1). Mean gestational age at BP measurement in the first, second, and third trimesters was 9.3 weeks (SD, 2.8), 26.4 weeks (SD, 1.8), and 38.7 weeks (SD, 1.1), respectively. Among the children who were followed up at age 4 to 7 years [mean age, 5.9 years (SD, 0.7)], 9.1% were overweight (6.6%) or obese (2.5%). The proportion of children who were overweight/obese was higher among mothers who had younger age, higher BMI, earlier menarcheal age, higher education levels, a routine job, a first pregnancy, or caesarean delivery and in male offspring (Table 1).

**Maternal BP during pregnancy and offspring overweight/obesity at childhood**

Among normotensive women, apparent positive associations between first-trimester BP and risk for overweight/obesity in offspring were attenuated on adjustment for mother’s BMI and height (model 3). By contrast, second- and third-trimester maternal DBP and SBP were positively associated with risk for offspring overweight/obesity: third-trimester DBP: OR per 10-mm Hg increase, 1.05 (95% CI, 1.01 to 1.10); third-trimester SBP: OR, 1.06 (95% CI, 1.03 to 1.09) in adjusted models (model 3) (Fig. 1, Table 2). Similarly, maternal hypertension in first trimester was not associated with offspring risk for overweight/obesity, whereas hypertension in the second (OR, 1.49; 95% CI, 1.18 to 1.89) and third (OR,
1.14; 95% CI, 1.05 to 1.25) trimesters was associated with higher risk for offspring overweight/obesity (Fig. 2). Across both normotensive and hypertensive women, the associations between maternal BP and offspring overweight/obesity risk appeared to be largely linear or J-shaped (Supplemental Fig. 2). In sensitivity analyses, excluding women without prepregnancy BMI slightly attenuated the association only with third-trimester DBP (Supplemental Table 1). No interaction was observed between DBP and SBP with any maternal characteristic.

Changes in DBP and SBP from the first to the third trimester among normotensive women were positively associated with risk for offspring overweight/obesity: DBP: OR per 10 mm Hg rise: 1.06 (95% CI, 1.02 to 1.10); SBP: OR, 1.05 (95% CI, 1.02 to 1.07) (Fig. 3). Across adjacent trimesters, BP changes
from the second to the third trimesters were positively associated with risk for offspring overweight/obesity, but surprisingly, no association was seen with BP change from the first to the second trimester. In sensitivity analyses, results were similar in the larger sample that included hypertensive women (Supplemental Fig. 3).

Potential mediation by birthweight

Among normotensive women, in adjusted models, first-trimester DBP and SBP were inversely associated with birthweight. By contrast, second- and third-trimester SBP (Supplemental Fig. 4) and change in SBP between the first and third trimesters were positively associated with birthweight (Supplemental Fig. 5). Conversely, maternal hypertension at each of the three trimesters was associated with lower birthweight (Supplemental Fig. 6).

Across both normotensive and hypertensive women, the associations between second- and third-trimester DBP and SBP and offspring birthweight were nonlinear (Supplemental Fig. 7). In mediation analyses among normotensive women, birthweight explained 24.2%, 9.2%, and 5.9% of the associations between second-trimester SBP, third-trimester SBP, and change in SBP from first to third trimesters with risk for offspring overweight/obesity, respectively (Supplemental Table 2).

Discussion

In this large prospective cohort study, we found that higher second- and third-trimester (but not first-trimester) DBP and SBP among normotensive women were positively associated with risk for offspring overweight/obesity. In addition, changes in DBP and SBP between the first and the third trimesters were positively associated with risk for offspring overweight/obesity among normotensive women. These associations were independent of maternal body size and were only partially mediated by higher offspring birthweight. Maternal hypertension in the second and third trimesters (but not the first trimester) was also positively associated with risk for offspring overweight/obesity yet was associated with lower offspring birthweight.

To the best of our knowledge, only a few studies have examined the prospective association of maternal hypertensive status with risk for offspring overweight/obesity (7, 8). In the Avon Longitudinal Study of Parents and Children study in the United Kingdom, gestational hypertension, compared with normotension, was

<table>
<thead>
<tr>
<th>Exposure</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>1.03 (0.99, 1.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP</td>
<td>1.02 (1.00, 1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Second trimester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>1.05 (1.01, 1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP</td>
<td>1.08 (1.05, 1.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Third trimester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>1.05 (1.01, 1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP</td>
<td>1.06 (1.03, 1.09)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The analyses were based on women without hypertension at each corresponding trimester. Model 1: crude model without adjustment. Model 2: adjusted for maternal characteristics (age, menarcheal age, education level, occupation, parity status, and corresponding DBP or SBP at previous trimesters), offspring sex, and age at examination. Model 3: model 2 plus maternal BMI and height.
associated with a 41% (OR, 1.41; 95% CI, 1.02 to 1.95) higher relative risk for offspring obesity at age 9 years (7). In addition, a recent meta-analysis and systematic review suggested that hypertensive disorders of pregnancy were associated with higher adult offspring BMI and risk for overweight/obesity (8).

Results from our present study confirm those previous reports (7, 8), and add evidence that maternal second- and third-trimester BP are positively associated with risk for offspring overweight/obesity in women without hypertension. The apparent positive association of first-trimester BP with childhood overweight/obesity was explained by confounding due to larger maternal size. In particular, change in BP during pregnancy, especially between the second and third trimesters, was positively associated with offspring adiposity risk. Taken together, our findings suggest that monitoring and control of the BP rise from middle to late pregnancy might be important, not only for pregnancy outcomes but also for the prevention of childhood obesity.

There is accumulating evidence that high maternal BP or hypertensive disorders of pregnancy are associated with offspring BP (7, 8, 19–21). Epidemiologic studies unequivocally support the positive association between body weight and BP and between obesity and hypertension (22). It was hypothesized that adiposity is along the causal pathway of maternal gestational hypertensive disorders with high BP in offspring (7). This speculation needs confirmation in future studies.

The potential effects of pregnancy hypertensive disorders and normal range BP during pregnancy on higher risk for offspring obesity may involve quite different mechanisms. Hypertensive disorders of pregnancy are well-known causes of intrauterine growth restriction (5, 23, 24), and DBP > 90 mm Hg (a threshold commonly used to define hypertensive disorders) is inversely associated with birthweight (9). Higher third-trimester umbilical artery vascular resistance, a parameter reflecting the placental dysfunction (25, 26), has been associated with slower fetal growth and a smaller size at birth but higher childhood BMI (27). The mechanism linking intrauterine growth restriction with later adiposity may include change in fetal adipose tissue morphology and metabolism, altered pathway regulating appetite, and modification of hormone and epigenome in fetus (28). Therefore, we postulated that hypertensive disorders during pregnancy may promote childhood overweight/obesity through its effect on intrauterine growth restriction.

High birthweight is also a well-known risk factor for of childhood obesity (29). Therefore, we postulated that among normotensive women, higher birthweight might mediate the positive association between maternal SBP and childhood overweight/obesity. However, the relationship between maternal BP and offspring birthweight is complex. Our findings that first-trimester BP was inversely associated with birthweight are consistent with a recent genetic Mendelian randomization study indicating a causal fetal growth-restricting effect of maternal SBP (30). First-trimester BP may be more strongly correlated with prepregnancy BP and common genetic determinants of nonpregnancy BP than mid-pregnancy to late pregnancy BP. In contrast to first-trimester BP and hypertensive disorders, normal range maternal BP during mid-pregnancy to late pregnancy is associated not with
intrauterine growth restriction but with higher offspring birthweight. Our findings are supported by a previous large study of 210,814 mother-infant pairs: Maternal DBP after 34 weeks’ gestation (but not earlier in pregnancy) showed an inverted U-shaped relation with birthweight and perinatal survival, with a maximum birthweight at a DBP of ~80 mm Hg (9).

The mechanism behind the positive association between normal-range BP and higher birth weight is unclear. In the absence of placental vasculature resistance, increasing maternal BP may be advantageous for placental blood flow and fetal growth. However, late pregnancy DBP >80 mm Hg appears to be disadvantageous for both short- and long-term health outcomes. That previous study did not have data on SBP (8). We found that second-trimester SBP was positively associated with birthweight, even at above-normal range SBP, and birthweight mediated 24% of the effect of the second-trimester SBP on childhood overweight/obesity in our analysis. These results suggested that higher maternal second-trimester SBP affected risk for offspring overweight/obesity, partly through increasing birthweight of the children.

The strengths of this study include its large sample size, prospective design, and high follow-up rate. In addition, the JBC study has repeated BP measurements at different stages of pregnancy, and both maternal and offspring demographic characteristics and lifestyle are well documented at each visit by trained nurses or doctors. Furthermore, the results of the current study are robust, as suggested by a variety of sensitivity analyses.

The study has several limitations. First, maternal BP data are based on a single measurement at each visit. Second, we were unable to distinguish between gestational hypertension and preeclampsia due to lack of information on urine protein. However, our primary aim was to examine BP among normotensive women, with pregnancy hypertension as a secondary exposure. Third, the JBC study is based on a single region in southeast China and may not necessarily be more broadly representative, although many of our findings are consistent with those seen in other populations. Fourth, due to the heterogeneity of gestational weeks for the weight measurement among different participants. Fifth, both birthweight and postnatal weight gain might potentially mediate the association between maternal BP and offspring obesity. However, because of limited availability of postnatal weight data up to 4 years, the mediation analysis focused only on birthweight. Finally, there may be other potential confounders in this observational study.

In conclusion, among normotensive women, greater gestational rises in DBP and SBP were associated with higher risk for offspring childhood overweight/obesity. This association was partially mediated by higher offspring birthweight. These findings provide insights into the biologic mechanisms linking to childhood obesity. The 5% to 8% increment in the odds of childhood overweight/obesity corresponding to the higher maternal BP in the second or third trimester might have important public health implications for the prevention of childhood obesity, given the increasing prevalence of childhood obesity in the past decades in China. These findings also added to the rationale to monitor and limit the BP rise in mid-pregnancy to late pregnancy.

Acknowledgments

We thank all the participants involved in the Jiaxing Birth Cohort and all the staff working on the project.

Financial Support: This work is supported by the National Basic Research Program of China (973 Program: 2015CB553604), by the National Natural Science Foundation of China (81273054), and by the Ph.D. Programs Foundation of Ministry of Education of China (2012011110107). J.-S.Z. is supported by the Marie Sklodowska-Curie Fellowships (701708, RG82205, SJAI/051). K.K.O. is supported by the Medical Research Council (Unit Programme number MC_UU_12015/2). The funders have no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions: The authors’ responsibilities were as follows: J.-S.Z., H.L., Y.G., and D.L. contributed to the research design. J.-S.Z., K.K.O., and D.L. wrote the paper, and J.-S.Z. performed the statistical analysis for the manuscript. T.H., Y.H., and F.W. contributed to the interpretation and revision of the report. All authors contributed toward critical review of the manuscript during the writing process. All authors approved the final version of the report.

Current Affiliation: B. Yang’s current affiliation is School of Public Health, Wenzhou Medical University, Wenzhou 325035, China.

Correspondence and Reprint Requests: Duo Li, PhD, Institute of Nutrition & Health, Qingdao University, 308 Ningxia Road, Qingdao 266071, China. E-mail: duoli@qdu.edu.cn.

Disclosure Summary: The authors have nothing to disclose.

References


