

# Maternal Blood Pressure Before Pregnancy and Sex of the Baby: A Prospective Preconception Cohort Study

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## BACKGROUND

Population-level sociologic studies have suggested that adverse societal conditions may affect fetal viability in a sex-specific manner and thereby modify the ratio of male vs. female babies. This concept suggests that there may exist certain physiologic features in a woman that relate to her likelihood of delivering a boy or girl. We thus established a preconception cohort to prospectively evaluate the relationship between maternal pregravid health and sex of the baby.

## METHODS

In this analysis nested within an observational cohort study, 1,411 newly married women in Liuyang, China, underwent pregravid cardiometabolic characterization (including anthropometry and measurement of blood pressure, cholesterol, triglycerides, and glucose) at median 26.3 weeks before a singleton pregnancy, delivering at  $39.0 \pm 1.3$  weeks gestation.

## RESULTS

Systolic blood pressure before pregnancy was higher in women who delivered a boy than in those who had a girl ( $112.5 \pm 11.9$  vs.

$109.6 \pm 12.0$  mm Hg,  $P < 0.0001$ ). The prevalence of a male baby progressively increased across quintiles of pregravid systolic blood pressure ( $P < 0.0001$ ). After covariate adjustment, mean adjusted pregravid systolic blood pressure was higher in mothers of boys vs. girls ( $106.0$  vs.  $103.3$  mm Hg,  $P = 0.0015$ ). On logistic regression analysis, pregravid systolic blood pressure emerged as the only significant predictor of having a male baby (adjusted odds ratio =  $1.017$  per mm Hg, 95% confidence interval =  $1.007$ – $1.028$ ). The pregravid difference in blood pressure between mothers of boys and girls was not present during any trimester of pregnancy.

## CONCLUSION

Maternal blood pressure before pregnancy is a previously unrecognized factor that may be associated with the likelihood of delivering a boy or girl.

**Keywords:** blood pressure; fetal sex; hypertension; pregravid; prepregnancy.

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The possibility of predicting the sex of the baby in early pregnancy has long been a topic of public fascination, spawning numerous theories of maternal characteristics associated with the presence of a male or female fetus, none of which has been conclusively supported by robust scientific evidence.<sup>1</sup> Researchers have long recognized that the sex ratio at birth in human populations typically shows a slight male preponderance, the determinants of which are poorly understood.<sup>1-3</sup> Interestingly, population-level sociologic studies have suggested that this sex ratio can be modified by

adverse societal conditions, likely reflecting sex-specific differences in fetal vulnerability during gestation.<sup>4,5</sup> For example, population stressors such as natural and man-made disasters,<sup>6,7</sup> terrorist attacks,<sup>8</sup> and economic collapse<sup>9</sup> have all been reported to decrease the proportion of boys at birth, potentially due to greater spontaneous loss of male fetuses under these adverse conditions.<sup>4,5</sup> These observations raise the possibility that there may be underlying physiologic features in a woman that relate to her likelihood of sex-specific fetal loss and hence her likelihood of delivering a boy or girl.

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However, little is known about such factors in humans.<sup>10,11</sup> Thus, in this context, we established a unique preconception cohort consisting of young women who were planning to have a pregnancy in the near future and used this model to prospectively evaluate the relationship between maternal pregravid health and sex of the baby.

## METHODS

The current analysis was nested within a prospective preconception cohort study, in which women were recruited at the time of marriage in the Liuyang region of Hunan province in China. Participants underwent baseline cardiometabolic characterization at recruitment and then, whenever they subsequently became pregnant, were followed across the pregnancy up to delivery through their clinical care. Beginning in February 2009, 3,375 women were recruited into this cohort, of whom 2,382 have completed a pregnancy. Of these, 1,692 women had complete pregravid blood pressure measurements and delivery data with a singleton pregnancy. After the exclusion of 281 women who were potentially pregnant at their baseline assessment based on back-dating of the length of gestation at delivery, the study population for the current analysis consisted of 1,411 women. The study has been approved by the institutional research ethics boards of Central South University (Changsha, Hunan, China), Ottawa Hospital Research Institute (Ottawa, Canada), and Mount Sinai Hospital (Toronto, Canada), and all participants provided written informed consent.

### Recruitment and pregravid assessment

The cost-efficient formation of a preconception cohort requires the capacity to identify women who are likely to get pregnant in the near future. The Liuyang Maternal and Infant Hospital was specifically selected for the current study because women in its catchment area typically attend a premarriage health clinic for assessment at the time of marriage registration. Thus, women who were planning to have a baby in the next 6 months were recruited from these clinics to participate in the cohort. After recruitment, participants were asked to undergo an overnight fast and then attend a baseline assessment that consisted of interviewer-administered questionnaires (regarding demographics, lifestyle, and medical history), physical examination, and the drawing of venous blood samples for biochemical analyses. At the baseline study visit, anthropometric measurements were performed by trained research staff, including weight, height, waist circumference, and calculated body mass index. Blood pressure was measured in a seated position, after 10 minutes of rest, using automated noninvasive blood pressure monitors (BpTRU). Two measurements were performed 10 minutes apart, with the average recorded.

Blood samples were drawn from the women and placed on ice immediately, transported to the laboratory within 30 minutes, and centrifuged at 3,000 rpm for 10 minutes at 4 °C. Biochemical tests were performed in the central laboratory of Central South University. Total cholesterol, high-density-lipoprotein cholesterol, triglycerides, and glucose

were measured by standard clinical biochemistry. Low-density-lipoprotein cholesterol was determined by Friedewald equation.

### Assessments during pregnancy and at delivery

Once pregnant, participants received obstetrical care through clinical services at Liuyang Maternal and Infant Hospital. Blood pressure measurements during gestation and the diagnosis of medical complications in pregnancy (gestational diabetes, pre-eclampsia) were obtained through this clinical care. Data collected at delivery included length of gestation, infant sex, birthweight, and Apgar scores.

### Statistical analyses

All analyses were conducted using SAS.9.4 (SAS Institute, Cary, NC). Univariate differences between women who delivered a boy and those who delivered a girl were assessed by 2-sample *t*-test for normally distributed continuous variables, Wilcoxon 2-sample test for skewed variables, and chi-square or fisher test for categorical variables (Table 1). Multiple linear regression models were constructed to determine whether the difference in pregravid blood pressure between the 2 groups persists after adjustment for age, education, smoking, body mass index, waist, low-density-lipoprotein cholesterol, high-density-lipoprotein cholesterol, triglycerides, and glucose.

We used the chi-square test to determine if there was a difference in the prevalence of male baby across quintiles of pregravid systolic blood pressure (quintile ranges in mm Hg: 80–99, 100–107, 108–114, 115–120, 121–171) (Figure 1a). We then constructed a multiple logistic regression model with male baby as dependent variable, with the same covariates as in the multiple linear regression models above. Based on the fitted logit response function, the predicted probability and odds for having a boy were calculated at each level of observed pregravid systolic blood pressure. LOESS method was used with local quadratic polynomials for each local regression and cubic polynomials for blending local polynomial fits (to minimize corrected akaike information criterion) to generate a spline plot of the predicted odds for having a boy vs. pregravid systolic blood pressure (Figure 1b). Multiple logistic regression analysis was performed to identify independent determinants of delivering a boy, adjusting for the same covariates as above (Table 2).

To evaluate if the pregravid difference in blood pressure between women delivering a boy and those delivering a girl persists during pregnancy (Figure 2), we plotted mean systolic blood pressure within 2 pregravid and 11 antepartum intervals (defined by weeks gestation, recognizing that participants have varying numbers of blood pressure measurements at varying weeks gestation). If a participant had >1 measurement within an interval, the average systolic blood pressure from these measurements was determined. The 2-sample *t*-test was used to compare mean systolic blood pressure in each interval between the groups.

**Table 1.** Characteristics of women who delivered a boy and women who delivered a girl

Pregravid assessment	Women who delivered a boy (n = 739)	Women who delivered a girl (n = 672)	P
Weeks prior to pregnancy (weeks)	24.7 (10.7, 58.7)	29.4 (10.3, 77.9)	0.07
Age (years)	24.6 ± 3.0	24.8 ± 3.1	0.36
Years of education (years)	12 (9, 12)	11 (9, 12)	0.43
Smoking (n (%))	3 (0.4)	2 (0.3)	0.73
Passive smoking exposure (n (%))	43 (5.8)	30 (4.5)	0.25
Pre-existing hypertension (%)	5 (0.7)	4 (0.6)	0.85
Pre-existing diabetes (%)	5 (0.7)	4 (0.6)	0.85
BMI (kg/m <sup>2</sup> )	20.2 ± 2.4	19.9 ± 2.3	0.09
Waist circumference (cm)	70.6 ± 7.4	70.1 ± 7.5	0.30
Systolic blood pressure (mm Hg)	112.5 ± 11.9	109.6 ± 12.0	<0.0001
Diastolic blood pressure (mm Hg)	71.7 ± 8.7	70.4 ± 8.8	0.005
Mean arterial blood pressure (mm Hg)	85.3 ± 9.2	83.4 ± 9.4	0.0002
Total cholesterol (mmol/l)	3.81 ± 1.05	3.83 ± 1.22	0.81
LDL cholesterol (mmol/l)	2.08 ± 0.78	2.11 ± 0.79	0.60
HDL cholesterol (mmol/l)	1.53 ± 0.45	1.54 ± 0.47	0.75
Triglycerides (mmol/l)	0.86 (0.61, 1.28)	0.88 (0.63, 1.26)	0.77
Glucose (mmol/l)	4.6 ± 1.1	4.6 ± 1.0	0.78
<b>At Delivery</b>			
Gestational diabetes (n (%))	21 (2.8)	13 (1.9)	0.27
Pre-eclampsia (n (%))	8 (1.1)	8 (1.2)	0.85
Length of gestation (weeks)	39.0 ± 1.3	39.1 ± 1.3	0.18
Infant birthweight (g)	3362 ± 458	3237 ± 433	<0.0001
1-minute Apgar <7 (%)	24 (3.3)	15 (2.3)	0.24

Continuous data are presented as mean ± SD (if normally distributed) or median followed by interquartile range (if skewed), and categorical variables are presented as numbers and proportions. Mean arterial blood pressure was determined as 2/3 diastolic pressure + 1/3 systolic pressure. Abbreviations: BMI, body mass index; HDL, high-density-lipoprotein; LDL, low-density-lipoprotein.

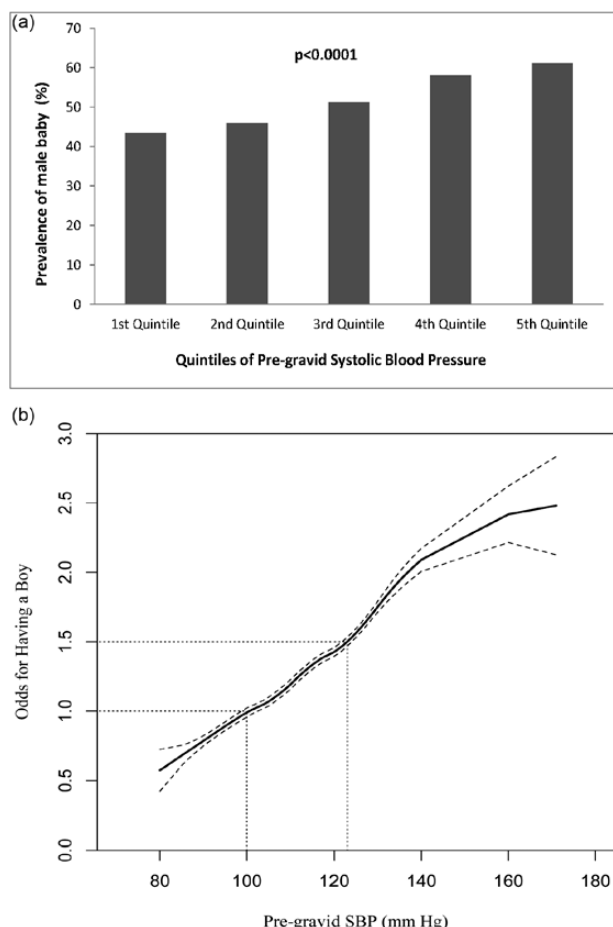
## RESULTS

The study population consisted of 1,411 women who underwent pregravid assessment at median 26.3 weeks before a singleton pregnancy. Their pregnancies resulted in the delivery of 739 boys and 672 girls at mean 39.0 ± 1.3 weeks gestation. At their baseline pregravid assessment, the women who gave birth to a boy and those who delivered a girl had no differences in age, education, smoking, body mass index, waist circumference, cholesterol, triglycerides, glucose, or pre-existing hypertension or diabetes (Table 1). Of note, however, both systolic blood pressure (112.5 ± 11.9 vs. 109.6 ± 12.0 mm Hg,  $P < 0.0001$ ) and diastolic blood pressure (71.7 ± 8.7 vs. 70.4 ± 8.8 mm Hg,  $P = 0.005$ ) were higher in the women who subsequently had a boy, as compared to those who delivered a girl.

Stratification of the study population into quintiles based on pregravid systolic blood pressure revealed a progressive increase in the prevalence of a male baby from the lowest to the highest quintile (43.4% to 46.0% to 51.2% to 58.0% to 61.2%) (Figure 1a). There was a significant difference in the prevalence of a male baby across the quintiles ( $P < 0.0001$ ). After adjustment for age, education, smoking, body mass index, waist,

low-density-lipoprotein cholesterol, high-density-lipoprotein cholesterol, triglycerides, and glucose, mean adjusted systolic blood pressure was higher in women who subsequently had a boy than in those who delivered a girl (106.0 vs. 103.3 mm Hg,  $P = 0.0015$ ). With analogous covariate adjustment, mean adjusted diastolic blood pressure was only slightly higher in those who had a boy, at borderline significance (68.9 vs. 67.8 mm Hg,  $P = 0.065$ ). It thus appears that systolic blood pressure, rather than diastolic, was more strongly linked to the sex of the neonate. Figure 1b is a spline plot showing a positive association between maternal pregravid systolic blood pressure and the odds of having a boy, after adjustment for the same baseline covariates. There was no difference in the likelihood of delivering a boy vs. a girl at maternal pregravid systolic blood pressure of 100 mm Hg. Above this threshold, there was a higher likelihood of having a boy and, below this threshold, there was a greater chance of having a girl. For example, as shown in Figure 1b, at a pregravid systolic blood pressure of 123 mm Hg, the probability of having a boy was 1.5 times greater than the probability of having a girl.

On logistic regression analysis of maternal characteristics prior to pregnancy (Table 2), systolic blood pressure



**Figure 1.** (a) The prevalence of male baby per quintile of pregravid SBP. (b) A spline plot of the association between maternal pregravid SBP and the odds (with 95% CI) of having a boy, after adjustment for age, education, smoking, BMI, waist, LDL cholesterol, HDL cholesterol, triglycerides, and glucose. Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high-density-lipoprotein; LDL, low-density-lipoprotein; SBP, systolic blood pressure.

emerged as the only significant predictor of having a male baby (adjusted odds ratio = 1.017 per mm Hg, 95% confidence interval = 1.007–1.028). Furthermore, systolic blood pressure remained the sole pregravid predictor of delivery of a male baby in a series of sensitivity analyses. The logistic regression models in these sensitivity analyses included the following conditions: (i) inclusion of passive smoke exposure in place of personal smoking, (ii) addition of diastolic blood pressure, (iii) further adjustment for time from baseline assessment to pregnancy, and (iv) exclusion of the women who had pre-existing hypertension (data not shown).

Of the 1,411 participants, 877 had blood pressure measurements recorded during pregnancy. These antepartum data ranged from 1 to 13 measurements across gestation, with 800 women having at least 5 such blood pressure measurements. In assessments at either >26 weeks pregravid or between 0 and 26 weeks prior to the pregnancy, mean systolic blood pressure was higher in those who went on to deliver a boy ( $P = 0.009$  and  $P = 0.001$ , respectively) (Figure 2). At all of the subsequent time points during the pregnancy, however, there was no difference in systolic blood pressure between women who delivered a boy and those who had a girl (Figure 2).

## DISCUSSION

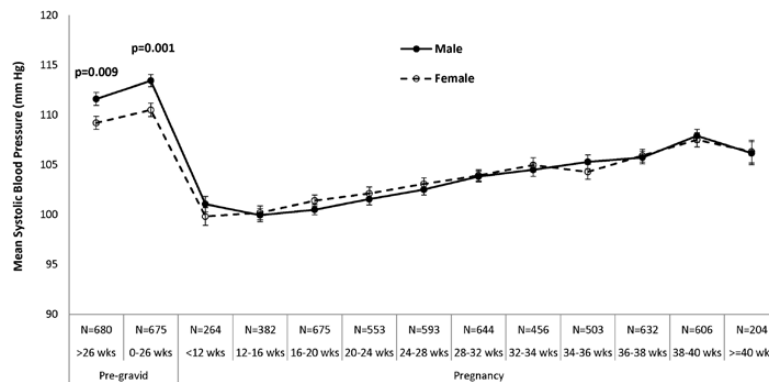
In humans, the sex of the fetus is determined by the sex chromosome of the fertilizing sperm. Although the proportion of spermatozoa carrying a Y-chromosome (yielding a male fetus) is similar to that carrying an X-chromosome (producing a female),<sup>12</sup> there is typically a slight preponderance of boys at delivery, the biologic basis for which is unclear.<sup>1,2</sup> The observation that societal stressors (disasters, terrorism, economic collapse)<sup>6–9</sup> may reduce the proportion of boys born into a population has led to the “culled cohort” theory, which posits that there is greater spontaneous loss of frail male fetuses in response to such adverse conditions.<sup>4,5</sup> In an unprecedented characterization of the longitudinal trajectory of the human sex ratio from conception to birth,

**Table 2.** Logistic regression analyses of maternal pregravid predictors of (dependent variable) delivery of a male baby, showing the unadjusted odds ratio for each pregravid predictor and the adjusted odds ratios after adjustment for all of the other pregravid predictors (fully adjusted model)

Pregravid variable	Unadjusted odds ratio	95% CI	P	Adjusted odds ratio	95% CI	P
Age (per year)	0.984	(0.951–1.018)	0.36	0.976	(0.935–1.020)	0.28
Years of education (per year)	1.006	(0.968–1.046)	0.75	1.022	(0.970–1.078)	0.41
Smoking	1.365	(0.227–8.197)	0.73	1.184	(0.161–8.715)	0.87
BMI (per kg/m <sup>2</sup> )	1.047	(0.993–1.103)	0.09	1.071	(0.991–1.157)	0.08
Waist circumference (per cm)	1.009	(0.992–1.026)	0.30	0.995	(0.971–1.019)	0.65
Systolic blood pressure (per mm Hg)	1.021	(1.012–1.030)	<0.0001	1.017	(1.007–1.028)	0.0016
LDL cholesterol (per mmol/l)	0.963	(0.838–1.106)	0.59	0.919	(0.770–1.097)	0.35
HDL cholesterol (per mmol/l)	0.962	(0.758–1.220)	0.75	1.212	(0.869–1.691)	0.26
Triglycerides (per mmol/l)	1.018	(0.865–1.199)	0.83	1.041	(0.828–1.309)	0.73
Glucose (per mmol/l)	1.015	(0.917–1.123)	0.78	0.968	(0.845–1.110)	0.64

Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high-density-lipoprotein; LDL, low-density-lipoprotein.





**Figure 2.** Time from baseline assessment to pregnancy was missing in 56 women. For each interval, the lower bound is inclusive and the upper bound is exclusive. Comparison of mean systolic blood pressure at the following points in time between women who delivered a boy and those who delivered a girl: >26 weeks pregravid, 0–26 weeks pregravid, <12 weeks gestation, 12–16 weeks gestation, 16–20 weeks gestation, 20–24 weeks gestation, 24–28 weeks gestation, 28–32 weeks gestation, 32–34 weeks gestation, 34–36 weeks gestation, 36–38 weeks gestation, 38–40 weeks gestation, and >40 weeks gestation.

Orzack *et al.* recently reported that the sex ratio actually varies across gestation.<sup>13</sup> Specifically, the sex ratio is balanced at conception followed by male-biased fetal mortality in the first 2 weeks of gestation, female-biased mortality over the next 4 months, and then balanced mortality thereafter until greater loss of males in the last 5 weeks of gestation.<sup>13</sup> Overall, they found that total female mortality exceeds total male mortality *in utero*.<sup>13</sup> It thus appears that sex-biased fetal loss is likely a determinant of the proportion of boys and girls born in a population. Maternal physiologic characteristics that potentially may relate to such loss, however, have been unclear.

In this context, there has previously been interest in maternal diet as a possible determinant.<sup>3,11</sup> Evolutionary biologists have hypothesized that female mammals are able to modify the sex ratio of the offspring in response to their maternal condition such that healthy and well-nourished mammals are more likely to give birth to sons.<sup>14</sup> In experimental studies, female mice receiving a high-fat/low-carbohydrate diet have been shown to produce more sons, whereas those receiving a low-fat/high-carbohydrate diet have more female offspring.<sup>3,11</sup> However, studies to date have not yielded consistent findings to support an effect of maternal diet on neonatal sex in humans.<sup>15–19</sup> In a study of 740 women, higher preconceptional energy intake (on retrospective recall) was associated with a greater incidence of boys,<sup>15</sup> although the statistical validity of this finding has been questioned.<sup>16</sup> Similarly, conflicting findings have been reported on the respective effects of both famine and war on the population sex ratio.<sup>17–21</sup> At present, the impact, if any, of maternal diet on neonatal sex in humans thus remains unclear.

One of the limiting factors in previous human studies has been the reliance on retrospective study designs. In this context, the preconception cohort design of the current study provided the unique opportunity to systematically evaluate maternal cardiometabolic status in a prospective manner shortly before pregnancy. In doing so, this analysis has revealed that directly measured pregravid systolic blood pressure differs between women who go on to deliver a boy and those who have a girl. The robustness of this novel finding is highlighted in 3 ways. First, the difference in blood

pressure was sizable (almost 3 mm Hg) both before and after covariate adjustment. Second, on a series of logistic regression analyses, pregravid systolic blood pressure consistently emerged as the only significant predictor of the sex of the baby, with no other maternal characteristics nearing any such association. Third, the pregravid difference in systolic blood pressure between future mothers of boys and girls was readily apparent prior to gestation but was not evident at any time during pregnancy (Figure 2). Taken together, these data specifically implicate maternal blood pressure prior to the pregnancy as a predictor of the sex of the neonate.

The mechanism by which pregravid blood pressure may relate to neonatal sex is unclear. In this regard, the apparent specificity of the blood pressure difference between mothers of sons and daughters to the pregravid state (i.e., the absence of this difference during gestation) potentially may implicate fetal sex-specific attrition in early pregnancy. Of note, the aforementioned study by Orzack *et al.* reported male-biased fetal mortality in the first 2 weeks of gestation followed by female-biased mortality over the next 4 months.<sup>13</sup> Moreover, there are differences in early placentation depending on the sex of the fetus, as apparent in sex-specific gradients in placental biomarkers.<sup>22</sup> Given that changes in maternal vascular function are needed in early pregnancy to accommodate the increased blood flow required by the fetoplacental unit,<sup>23</sup> maternal blood pressure potentially may be relevant to early placentation in a sex-specific manner. While sex-specific attrition may indeed be the mechanistic basis underlying the current findings, it should be noted that our data cannot differentiate between a lesser capacity of the female fetus to tolerate higher systolic pressures or an inability of the male fetus to tolerate lower pressures. Further research will thus be needed to evaluate the potential sex-specific implications of maternal pregravid blood pressure on the physiology of the fetus. In addition, as shown in Figure 2, women who delivered a boy may have had a larger early pregnancy drop in systolic blood pressure from their pregravid measurement than did those who delivered a girl. It is possible that this difference may reflect a fetal sex-specific effect on maternal vascular adaptation to pregnancy. Evaluation of

the relationship between fetal sex and maternal vascular adaptation is thus needed.

A limitation of this study is the absence of data on the use of antihypertensive medications by the participants. However, only 9 women had a history of hypertension at baseline and the findings were unchanged upon their exclusion. Another limitation is the absence of data on spontaneous miscarriages, the fetal sex ratio of which at specific weeks of gestation would be of great interest. In addition, the study population largely consisted of young, healthy normal weight women such that the generalizability of the findings to older, less healthy women with higher body weight remains to be determined. Moreover, the study was conducted only in Chinese women and hence replication of the findings should be sought in other populations. Nevertheless, as described in the Methods section, the choice of Liuyang as the location of this study was critical in enabling the cost-effective formation of a preconception cohort of young women who were likely to have a pregnancy in the near future. This preconception cohort has provided a unique model that made it possible to identify the relationship between pregravid maternal blood pressure and sex of the baby.

Our findings hold both clinical and research implications. Clinically, the identification of a pregravid systolic blood pressure threshold in this population above which the probability of having a boy may be enhanced or below which one may be more likely to deliver a girl raises the possibility of blood pressure modification prior to pregnancy for the purpose of influencing one's likelihood of having a child of a particular sex. While the feasibility of such action remains to be established, this possibility could be particularly problematic and potentially dangerous in populations which may favor the birth of one sex over the other. From a research perspective, the current findings suggest that maternal blood pressure warrants study for sex-specific effects on fetal physiology and viability. The insight so derived potentially may help to elucidate mechanistic determinants of the sex ratio after conception. Finally, a declining proportion of male births in industrialized countries (United States, Canada, Denmark, Netherlands) over the past several decades has been queried as a possible sentinel health indicator.<sup>24</sup> Our findings suggest that growing societal emphasis on healthy lifestyles and a resultant beneficial impact on blood pressure in young women (a trend that has been documented globally over the past 30 years)<sup>25</sup> may warrant consideration as a potential contributor in this regard.

In summary, maternal pregravid systolic blood pressure is a previously unrecognized factor associated with the likelihood of having a boy or girl in a subsequent pregnancy. Higher systolic blood pressure before pregnancy is a robust independent predictor of delivering a male baby. Furthermore, this relationship reveals a threshold for maternal pregravid systolic blood pressure above/below which the probability of delivering a boy/girl, respectively, may be favored. This novel insight suggests the existence of fetal sex-specific effects of maternal blood pressure that may hold implications for both reproductive planning and our understanding of the fundamental mechanisms underlying the sex ratio in humans.

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## DISCLOSURE

The authors declared no conflict of interest.

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