

## ORIGINAL RESEARCH

# Cardiovascular Health Index Scores and Pregnancy-Induced Hypertension: An Association Study

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### ABSTRACT

**Objective** • This cohort study investigated the association between cardiovascular health index scores and pregnancy-induced hypertension (PIH).

**Methods** • A total of 1466 first-time pregnant women who delivered a single child between 2006 and 2016 were included in the study. All participants underwent a physical examination before delivery, and seven cardiovascular health indexes were collected and scored. Three groups were created based on the tri-sectional quantiles of the total score to observe whether PIH occurred among the groups. A dichotomous logistic regression analysis was carried out to investigate the relationship between cardiovascular health index scores and the occurrence of PIH.

**Results** • During the observation of 1150 subjects, 103 cases of PIH were identified, resulting in an incidence rate of 8.96%. The study found that the incidence of PIH in the three

groups was 17.5% in the first group, 6.7% in the second, and 5.8% in the third group. These rates showed a sequential decrease with statistically significant differences ( $P < .001$ ). The multifactorial regression analysis revealed that after adjusting for various factors, there was a significant inverse relationship between cardiovascular health index scores and the risk of PIH. Specifically, for every one-point increase in the seven cardiovascular health index scores, the risk of PIH decreased by 29% (OR=0.71, 95% CI 0.59-0.86).

**Conclusions** • The study found an inverse correlation between cardiovascular health index scores and PIH, with higher scores associated with lower incidences of PIH. Each cardiovascular health indicator helps to lower the risk of PIH, and optimum cardiovascular health behaviors and variables are protective factors against PIH. (*Altern Ther Health Med.* 2023;29(5):141-145).

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### INTRODUCTION

Pregnancy-induced hypertension (PIH) is a common complication of high blood pressure and can lead to serious health risks for both the mother and the baby. Numerous studies have demonstrated that common pregnancy complications, such as pregnancy-induced hypertension (PIH), can predict the risk of future chronic illnesses, including cardiovascular disease, diabetes, and breast cancer.<sup>1</sup> Based on domestic and international research, women who experience PIH are at a higher risk of developing cardiovascular disease later in life than women with uncomplicated pregnancies.<sup>2-10</sup>

The development of PIH in women may trigger a sequence of cardiovascular events. Identifying modifiable risk factors associated with PIH before conception is crucial for the effective prevention of cardiovascular disease in women.<sup>2-10</sup> Previous research has predominantly examined individual risk factors related to traditional cardiovascular risk factors and PIH.<sup>4,5</sup> Research suggests that considering seven optimal behaviors and factors related to cardiovascular health serve as more precise indicators for predicting cardiovascular disease.<sup>8-10</sup> However, the connection between cardiovascular health and the development of PIH is not fully understood. Therefore, a comprehensive approach that integrates multiple modifiable risk factors is needed to prevent the occurrence of PIH and subsequent cardiovascular disease in women. To examine this relationship, the study utilized the female Kailuan research cohort. The objective was to investigate the association between the development of PIH and the scores on the cardiovascular health indexes

## METHODS

### Study Design

This study utilized a retrospective cohort design to assess the relationship between PIH and cardiovascular health index scores in a sample of women from the Kailuan research cohort. Data on participants' cardiovascular health behaviors and factors were collected through physical examinations and self-reported questionnaires and analyzed using multifactorial regression models to control for potential confounding variables.

### Study Population and Setting

The study population for this retrospective cohort study was selected based on specific criteria. Inclusion criteria comprised of (1) female employees who had delivered a single child in Kailuan Medical Group (including Kailuan Hospital, Kailuan Fanjiazhuang Hospital, Kailuan Zhaojiazhuang Hospital, Kailuan Linxi Hospital, Kailuan Linancang Hospital, Kailuan Lujatuo Hospital, Kailuan Majiagou Hospital, Kailuan Tangjiazhuang Hospital, Kailuan Jingjiazhuang Hospital, Kailuan Qianying Hospital) between July 2006 and December 2018 and had complete delivery records, (2) women who were pregnant for the first time, (3) present or retired Kailuan Medical Group workers who underwent a health examination between July 2006 and October 2013, and (4) women who provided written consent to participate in the study. Exclusion criteria included (1) women who had pre-existing hypertension before pregnancy, (2) women who had undergone induced abortion or miscarriage, (3) women with secondary hypertension, and (4) women with incomplete study data.

### Data Collection

**Epidemiological Questionnaire Design.** A uniform set of operational protocols was developed for the epidemiological questionnaires. Respondents were given a list of questions to complete as soon as possible. The information was validated through face-to-face interviews with healthcare experts who had undergone consistent training. The survey covered a range of issues, including lifestyle habits, prior history of hypertension, diabetes, and myocardial infarction, as well as familial histories of hypertension and stroke. Participants were also asked about smoking and alcohol consumption patterns, level of physical activity, quality and duration of sleep, educational background, and income status.

**Physical Examination Procedure.** Physical examinations were performed by healthcare professionals who received standardized training following established methods. The anthropometric techniques used were described in the published literature of the research group.<sup>11</sup>

**Laboratory Testing Procedure.** Blood samples were collected from the patient's elbow vein the following morning after a 12-hour fasting period. The 5 ml sample was split into two tubes. One tube, containing 1 ml of blood mixed with EDTA-K2 anticoagulant, was examined using the ABX automatic hematology analyzer (ABX MICROS 60 OT

Diagnostics, France) to perform common blood tests, such as white blood cell and platelet count. The second tube, containing 4 ml of blood, was subjected to centrifugation. After centrifugation with a radius of 12 cm, the serum component was separated and analyzed for fasting glucose, total cholesterol (TC), triglycerides, LDL-C, and HDL-C using the Hitachi 7080 Automatic Analyzer. The entire process was conducted in strict adherence to the instructions provided by the reagent manufacturer, with ongoing batch quality control measures in place. A qualified technician was assigned to execute the experimental protocol.

**Collection of Delivery Data.** Delivery data were collected from inpatient medical records. Trained healthcare staff, who had undergone uniform training per established protocols, recorded the delivery time and hospital information based on the questionnaire responses provided by the study participants. A comprehensive set of data was collected, including the age at delivery, mode and timing of delivery, pre- and post-delivery blood pressure readings, weight, height, uterine height, abdominal circumference, edema condition, fetal sex, length, weight, and survival status. In addition, laboratory tests were conducted to assess platelet count, hemoglobin level, urine protein level, and maternal and neonatal problems.

### Diagnostic Criteria Cardiovascular Health Indexes

**Health behavior.** The health behavior of study participants was assessed using four factors: (1) smoking status, with ideal defined as a non-smoker (NS), general as used to smoke and have quit (ES), and poor as a current smoker (CS); (2) body mass index (BMI), with ideal defined as BMI < 25 kg/m<sup>2</sup>, general as BMI between 25-29.9 kg/m<sup>2</sup>, and poor as BMI ≥ 30 kg/m<sup>2</sup>; (3) physical exercise, with ideal defined as ≥ 80 minutes per week, general as 0-80 minutes per week, and poor as no physical exercise; and (4) low salt diet, with ideal defined as light taste (LT), general as moderate taste (MT), and poor as high-salt diet (HSD).

**Health factors.** Three measures were used to assess health factors. (1) Total cholesterol (TC) levels were categorized as follows for non-pharmacological treatment: ideal (TC < 200 mg/dL), general (TC ranges between 200-239 mg/dL or <200 mg/dL in the case of lipid-regulating drugs intake), and poor (TC levels ≥ 240 mg/dL). (2) Blood pressure (BP) levels for non-pharmacological treatment were categorized as follows: ideal (systolic blood pressure (SBP) <120 mm Hg and diastolic blood pressure (DBP) <80 mm Hg), general (SBP ranges between 120-139 mm Hg, or DBP ranges between 80-89 mm Hg or BP <120/80 mm Hg when antihypertensive drugs are taken), and poor (SBP levels ≥ 140 mm Hg or DBP levels ≥ 90 mm Hg). (3) Fasting blood glucose (FBG) levels for non-medication treatment were categorized as follows: ideal (FBG < 100 mg/dL), general (FBG ranges between 100-125 mg/dL or <100 mg/dL in the case of hypoglycemic drugs intake), and poor (FBG levels ≥ 126 mg/dL).

**Cardiovascular Health Behaviors and Factors.** The Cardiovascular Health (CVH) scale evaluates cardiovascular

**Table 1.** Comparison of Baseline Information for Different Groups of Cardiovascular Health (CVH) Scores ( $\pm$ S)

|                             | First Quartile Group<br>(n = 268) | Second Quartile Group<br>(n = 552) | Third Quartile Group<br>(n = 330) | F Values | P Values |
|-----------------------------|-----------------------------------|------------------------------------|-----------------------------------|----------|----------|
| SBP Before Delivery (Mm Hg) | 120.8 $\pm$ 15.1                  | 115.52 $\pm$ 11.51 <sup>a</sup>    | 116.21 $\pm$ 13.7 <sup>a</sup>    | 10.530   | .000     |
| DBP Before Delivery (Mm Hg) | 77.78 $\pm$ 10.39                 | 74.9 $\pm$ 8.47 <sup>a</sup>       | 74.21 $\pm$ 9.54 <sup>a</sup>     | 7.613    | .001     |
| Delivery Age (Years)        | 28.73 $\pm$ 3.24                  | 28.44 $\pm$ 3.07                   | 28.65 $\pm$ 2.78                  | 1.032    | .357     |
| Gestational Week (Weeks)    | 38.32 $\pm$ 2.01                  | 38.85 $\pm$ 1.31 <sup>a</sup>      | 38.8 $\pm$ 1.55 <sup>a</sup>      | 10.755   | .000     |
| age (years)                 | 26.83 $\pm$ 3.4                   | 26.61 $\pm$ 3.14                   | 26.61 $\pm$ 2.77                  | 0.511    | .600     |
| SBP (mm Hg)                 | 115.02 $\pm$ 13.41                | 107.73 $\pm$ 10.64 <sup>a</sup>    | 103.4 $\pm$ 9.17 <sup>a,b</sup>   | 83.921   | .000     |
| DBP (mm Hg)                 | 75.66 $\pm$ 9.07                  | 71.57 $\pm$ 7.61 <sup>a</sup>      | 69 $\pm$ 6.6 <sup>a,b</sup>       | 55.648   | .000     |
| TC (mmol/l)                 | 4.95 $\pm$ 1.1                    | 4.39 $\pm$ 0.74 <sup>a</sup>       | 4.28 $\pm$ 0.61 <sup>a</sup>      | 58.762   | .000     |
| Fbg (mmol/l)                | 5.22 $\pm$ 1.34                   | 4.87 $\pm$ 1.91 <sup>a</sup>       | 4.73 $\pm$ 0.49 <sup>a</sup>      | 8.330    | .000     |
| BMI (Kg/m <sup>2</sup> )    | 25.05 $\pm$ 3.91                  | 21.73 $\pm$ 3.02 <sup>a</sup>      | 20.46 $\pm$ 2.22 <sup>ab</sup>    | 176.212  | .000     |
| UA (umol/l)                 | 274.85 $\pm$ 67.92                | 247.79 $\pm$ 63.18 <sup>a</sup>    | 255.91 $\pm$ 62.05 <sup>a</sup>   | 9.974    | .000     |
| TG (mmol/l)                 | 1.2 $\pm$ 0.75                    | 0.89 $\pm$ 0.53 <sup>a</sup>       | 0.82 $\pm$ 0.4 <sup>a</sup>       | 27.082   | .000     |
| LDL_C (mmol/l)              | 2.39 $\pm$ 0.82                   | 2.23 $\pm$ 1.2                     | 2.04 $\pm$ 0.59 <sup>ab</sup>     | 6.950    | .001     |
| HDL_C (mmol/l)              | 1.45 $\pm$ 0.39                   | 1.52 $\pm$ 0.35                    | 1.52 $\pm$ 0.4                    | 1.904    | .150     |
| HR(次/分)                     | 75.76 $\pm$ 10.6                  | 74.98 $\pm$ 9.75                   | 74.22 $\pm$ 9.44                  | 1.224    | .294     |
| WC (cm)                     | 78.2 $\pm$ 10.24                  | 72.75 $\pm$ 7.82 <sup>a</sup>      | 71.95 $\pm$ 7.09 <sup>a</sup>     | 30.121   | .000     |
| Lg (hs_Crp)                 | -0.17 $\pm$ 1.49                  | -0.63 $\pm$ 1.59 <sup>a</sup>      | -0.48 $\pm$ 1.4 <sup>a</sup>      | 4.841    | .008     |

<sup>a</sup> $P < .05$  when compared with the first group<sup>b</sup> $P < .05$  when compared with the second group

**Abbreviations:** Age, age; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; FBG, fasting blood glucose; BMI, body mass index; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HR, resting heart rate; WC, waist circumference; UA, uric acid; hs-Crp, high-sensitivity C-reactive protein.

health behaviors and factors, and is derived from the CVH Score, a composite scoring system developed by Mark D. Huffman.<sup>12</sup> The CVH Score assigns points to seven items, with poor assigned 0 points, general assigned 1 point, and ideal assigned 2 points. The possible score range for the CVH Score is 0–14 points.

### Diagnostic Criteria for PIH

The diagnostic criteria for PIH was based on the Chinese Guidelines for the Prevention and Control of Hypertension (2005 Revision) characterized as follows: After 20 weeks of pregnancy, a pregnant woman is considered to have PIH if her blood pressure is  $\geq 140/90$  mm Hg (1 mm Hg = 0.133 kPa), or if it has increased by  $\geq 25/15$  mm Hg compared to her pre-pregnancy or early pregnancy baseline, with measurements taken at least twice during a 6-hour interval.

### Statistical Analysis

Data from four physical tests were recorded by terminals at each hospital that conducted physical examinations and transmitted across a network to create an Oracle 10.2 g database on a computer server. SPSS 13.0 was used to perform statistical analyses. Analysis of variance was employed to compare the variances between groups, and continuous variables were presented as mean  $\pm$  standard deviation. Categorical variables were evaluated using the chi-square test and reported as n (%). Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the variables that impacted PIH. The significance threshold was set at  $P < .05$  (two-tailed test).

## RESULTS

### Comparison of General Conditions of the Study Population

A total of 1466 females who became pregnant for the first time and gave birth to a single child between 2006 and 2016 after undergoing a physical examination in 2006–2007 were included in this study. The pre-delivery physical examination data of each woman was used as baseline data, and 316 cases with missing data on any of the seven cardiovascular health (CVH) indicators were excluded. In the statistical analysis, a total of 1,150 cases were examined. The study population had a mean age of  $26.7 \pm 3.1$  years at physical examination, a mean age of  $28.6 \pm 3.0$  years at delivery, and a mean interval of  $1.82 \pm 0.69$  years between physical examination and delivery.

The study evaluated seven indicators of CVH, which were scored as ideal (score = 2), general (score = 1), or poor (score = 0). The sum of these scores provided a total score ranging from 0 to 14. The study subjects were classified into three groups based on their total score using tri-sectional quantiles: the first group had a total score of  $\leq 9$ , the second group had a total score of 10 to 11, and the third group had a total score of  $\geq 12$ .

The baseline data obtained during physical examination revealed that the second and third-quartile groups had significantly lower SBP, DBP, TC, BMI, uric acid, waist circumference, and high-sensitivity C-reactive protein levels compared to the first-quartile group ( $P < .05$ ). Pre-delivery data analysis showed that the second and third quartile groups had lower SBP and DBP compared to the first quartile group ( $P < .05$ ), and their gestational weeks were significantly longer ( $P < .05$ ). For additional information, please refer to Table 1.

**Table 2.** Comparison of The Incidence of PIH In Different Groups of CVH Scores

|      | First<br>Quartile Group<br>(Cases/%) | Second<br>Quartile Group<br>(Cases/%) | Third<br>Quartile Group<br>(Cases/%) |
|------|--------------------------------------|---------------------------------------|--------------------------------------|
| NPIH | 221/82.5%                            | 515/93.3%                             | 311/94.2%                            |
| PIH  | 47/17.5%                             | 37/6.7%                               | 19/5.8%                              |

**Note:** Chi-square  $\chi^2 = 31.779$ ; *P* value: *P* < .001

**Abbreviations:** NPIH, Non-proteinuric hypertension; PIH, Proteinuric hypertension.

**Table 3.** Regression Analysis Affecting the Occurrence of PIH

| Model     | Predictor Variables   | B      | S.E.  | Wald  | <i>P</i> value | OR Values | 95% CI    |
|-----------|-----------------------|--------|-------|-------|----------------|-----------|-----------|
| Model One | First Quartile Group  |        |       |       |                | 1         |           |
|           | Second Quartile Group | -1.085 | 0.234 | 21.50 | <.001          | 0.34      | 0.21-0.53 |
|           | Third Quartile Group  | -1.247 | 0.286 | 19.06 | <.001          | 0.29      | 0.16-0.50 |
| Model Two | First Quartile Group  |        |       |       |                | 1         |           |
|           | Second Quartile Group | -0.993 | 0.329 | 9.13  | .003           | 0.37      | 0.19-0.71 |
|           | Third Quartile Group  | -1.347 | 0.398 | 11.46 | .001           | 0.26      | 0.12-0.57 |
|           | Delivery age          | 0.091  | 0.039 | 5.53  | .019           | 1.10      | 1.02-1.18 |

**Abbreviations:** B, regression coefficient; S.E., standard error; Wald, Wald statistic; OR values, odds ratios; 95% CI, 95% confidence interval.

**Table 4.** Regression analysis affecting the occurrence of PIH (score after removing one indicator)

| Indicator  | B      | S.E.  | Wald  | <i>P</i> value | OR values | 95% CI    |
|--|--------|-------|-------|----------------|-----------|-----------|
| CVH scores for 7 items                                   | -0.338 | 0.095 | 12.65 | <.001          | 0.71      | 0.59-0.86 |
| CVH scores for 6 items after removal of blood pressure   | -0.294 | 0.103 | 8.15  | .004           | 0.75      | 0.61-0.91 |
| CVH score for 6 items after removing blood glucose       | -0.339 | 0.100 | 11.61 | .001           | 0.71      | 0.59-0.87 |
| CVH score for 6 items after removal of cholesterol       | -0.384 | 0.102 | 14.21 | <.001          | 0.68      | 0.56-0.83 |
| CVH score for 6 items after removal of body mass index   | -0.343 | 0.108 | 10.16 | .001           | 0.71      | 0.57-0.88 |
| CVH score for 6 items after removal of smoking behavior  | -0.414 | 0.114 | 13.29 | <.001          | 0.66      | 0.53-0.83 |
| CVH score for 6 items after removal of dietary habits    | -0.318 | 0.100 | 10.07 | .002           | 0.73      | 0.6-0.89  |
| CVH score for 6 items after removal of physical activity | -0.340 | 0.100 | 11.60 | .001           | 0.71      | 0.59-0.87 |

**Abbreviations:** B, regression coefficient; S.E., standard error; Wald, Wald statistic; OR values, odds ratios; 95% CI, 95% confidence interval.

### Comparison of PIH Incidence

Out of 1150 subjects observed, 103 cases of PIH were diagnosed, representing an incidence of 8.96%. The study found that the incidence of PIH decreased sequentially in the first, second, and third groups, with rates of 17.5%, 6.7%, and 5.8%, respectively, and statistically significant differences (*P* < .001). More information can be found in Table 2.

### Regression Analysis of Factors Affecting PIH Occurrence

Dichotomous logistic regression analysis was used with the frequency of PIH as the dependent variable. According to

the univariate analysis of Model One, individuals in the second and third quartile groups had a lower risk of PIH than those in the first quartile group. The corresponding odds ratios (OR) and their 95% confidence intervals (CI) were 0.34 (0.21-0.53) and 0.29 (0.16-0.50), respectively. Model Two was further adjusted for possible influences related to delivery age, the time between physical examination and delivery, TG, UA, LDL-C, HDL-C, waist circumference, high-sensitivity C-reactive protein, and resting heart rate. According to the univariate analysis of Model Two, the second and third quartile groups had a decreased risk of PIH compared to the first quartile group, with ORs and 95% CIs of 0.37 (0.19-0.71) and 0.26 (0.12-0.57), respectively. In addition, the risk of PIH increased with delivery age. Specifically, the risk of PIH increased by 10% for every year increase in delivery age, with an OR of 1.10 and a 95% CI of 1.02-1.18. Detailed results can be found in Table 3.

After controlling for potential confounding factors, a multivariable regression analysis revealed that the risk of pregnancy-induced hypertension (PIH) decreased by 29% for every unit increase in the seven-point Cardiovascular Health (CVH) Index score (OR = 0.71, 95% CI 0.59-0.86). To further investigate the impact of individual CVH components on the development of PIH, each of the six remaining CVH components was analyzed after removing one at a time. The results indicated that each component was independently associated with a decreased risk of PIH, refer to Table 4 for further details.

### DISCUSSION

Women have long been known to have a higher mortality rate from cardiovascular disease compared to men.<sup>14-17</sup> However, since the beginning of the 20th century, national and international research on heart disease in women has increased. The gender gap in heart disease survival has narrowed due to further improvements in treatment.<sup>18-19</sup> PIH is a disease specific to women that may initiate female cardiovascular disease.<sup>19</sup> Available data suggest that the prevalence of PIH ranges from 6% to 10% in American and European populations and approximately 9% in China.<sup>12-18</sup> The present study aimed to investigate the association between cardiovascular health and the risk of PIH. In the present study, the prevalence of PIH was found to be 8.8%, which is consistent with other domestic and international studies.<sup>5-10</sup>

Previous studies on the association between indicators before delivery and PIH often focused on a single indicator, such as weight.<sup>12-19</sup> In contrast, this study analyzed the combined effect of seven indicators and found that a higher



score on the ideal health indicator was associated with a lower incidence of PIH. The findings from the multifactorial logistic regression analysis conducted in this study indicate that, after adjusting for confounding variables, the likelihood of experiencing pregnancy-induced hypertension (PIH) was reduced by 63% and 74% in the second and third-quartile groups, respectively, compared to the first quartile group. Moreover, for each unit increase in the composite score measuring cardiovascular health across seven indicators, the risk of developing PIH decreases by 29%. Conversely, the risk of PIH increases by 10% for every additional year in maternal age at delivery. After isolating each cardiovascular health (CVH) factor, the cumulative scores of the remaining six CVH were recalculated, providing a better assessment of individual CVH on the development of PIH.

The results of the multifactorial regression analysis indicated that the risk of PIH decreased by 25%, 29%, 32%, 29%, 34%, 27%, and 29%, respectively, for each 1-point increase in the total cardiovascular health index score as each factor was sequentially removed: blood pressure, blood glucose, cholesterol, body mass index, smoking, dietary habits, and physical activity. These findings demonstrate that each CVH indicator contributes to reducing the risk of PIH. Interestingly, the relationship between ideal CVH indicators and PIH risk weakened when individual CVH indicators were removed from the model. These findings suggest that effective pre-pregnancy preventive measures, such as a comprehensive approach that includes quitting smoking, weight loss, increased physical activity, and adherence to a low-sodium diet, may be more beneficial for achieving optimal vascular health before pregnancy, rather than targeting individual behavioral factors. It is hypothesized that focusing on pre-pregnancy lifestyle management could reduce the incidence of PIH and the risk of fatal perinatal complications and future cardiovascular disease in women, as all four health factors (physical activity, salt habit, body weight, and smoking) are modifiable.

## Study Limitations

The present study is subject to several limitations that should be acknowledged. Firstly, the study was conducted at a single site with a relatively small sample size, which may limit the generalizability of the findings to other populations. Secondly, the study lacked a sufficient number of individuals diagnosed with PIH, making it challenging to analyze pre-eclampsia (PE) (hypertension with proteinuria) in precisely defined subgroups. A larger sample size is required to understand better the association between hypertension and proteinuria in PE subtypes. Thirdly, social relationships and psychological factors were not included in the study's statistical analysis, thus precluding an evaluation of their association with PIH. Therefore, future studies should explore the potential relationship between improving cardiovascular health indicators before pregnancy and reducing the incidence of PIH.

## CONCLUSION

This study found that a higher composite score measuring cardiovascular health across seven indicators was associated with a decreased risk of developing PIH while increasing maternal age at delivery was associated with an increased risk of PIH. Each of the CVH indicators contributed to reducing the risk of PIH. The study also suggests that pre-pregnancy lifestyle management may be a more effective approach to achieving optimal vascular health before pregnancy, rather than adjusting individual behavioral factors. The study highlights the importance of pre-pregnancy cardiovascular health and lifestyle management in reducing the risk of PIH and improving maternal and fetal outcomes.

## CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

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