Effects of Interaction Between Gestational Hypertension and History of Preterm Birth on the Risk of Preterm Birth: An Analysis Based on the National Vital Statistics System Database

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Background:
Premature birth is an unsolved social and public problem. We aimed to explore the independent association and interaction effect between gestational hypertension (GH) and the history of preterm birth (HPB) on the risk of preterm birth.

Material/Methods:
A case-control study involving participants with complete birth data was conducted using the United States National Vital Statistics System in 2019. Logistic regression analysis of 3 models were performed with odds ratio (OR) and 95% confidence interval (CI). Relative excess risk of interaction (RERI), attributable proportion of interaction (AP), and synergy index (S) were used to evaluate the interaction between GH and HPB on the risk of preterm birth.

Results:
A total of 2,822,624 participants were examined, with 10.83% in the known preterm birth group and 89.17% in the control group. Following adjustments for covariates, the association between GH and HPB and preterm birth was significant with ORs of 2.604 (95% CI: 2.573-2.635) and 3.047 (95% CI: 2.997-3.097), respectively. Moreover, there was a significant interaction between GH and HPB on preterm birth risk, with an OR of 6.095 (95% CI: 5.847-6.352), RERI of 1.222 (95% CI: 0.965-1.479), AP of 0.201 (95% CI: 0.167-0.235), and S of 1.317 (95% CI: 1.250-1.387), especially in participants with maternal age 20 to 29, 30 to 34, ≥35 years, and single birth.

Conclusions:
GH and HPB might be positively associated with preterm birth, and there was an additive interaction between GH and HPB on preterm birth, indicating that obstetricians should pay more attention to prevention in this population.

Keywords: Hypertension, Pregnancy-Induced • Models, Spatial Interaction • Premature Birth

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**Background**

Preterm birth is an adverse pregnancy outcome [1]. It was the leading cause of death in children below 5 years of age in 2016, accounting for approximately 35% of the 2.5 million annual neonatal deaths globally [2,3]. Early delivery inevitably affects physical and intellectual development in fetal growth, especially increasing the risk of short-term and long-term respiratory, infectious, metabolic, and neurological morbidities and socio-emotional and cognitive challenges [4,5]. The incidence of premature birth has increased, and a certain proportion of babies are prone to premature birth even in healthy women [6]. Although the cause is considered multifactorial, the events leading to premature delivery are not entirely clear [7]. Therefore, it is crucial that we promptly learn more about preterm birth problems to provide valuable therapeutic measures.

Many factors could predispose a woman to the etiopathogenesis of preterm birth, including obstetrical and gynecological history (specifically a history of preterm birth [HPB] or cesarean section), chronic diseases, such as gestational hypertension (GH) and gestational diabetes mellitus, and pregnancy complications, such as eclampsia and infections [8,9]. In particular, GH is a unique disease that seriously endangers the health of mothers and babies during pregnancy and is one of the important causes of death of women and newborns during peri-pregnancy [10]. Women with GH have a significantly increased risk of preterm birth compared with healthy pregnant women [11]. In addition, special attention and intervention for women with HPB are also beneficial [12,13]. Studies have found that GH and HPB have been identified to be risk factors for preterm birth [14,15]. However, the effect of their interaction on preterm birth has not been widely reported.

We conducted this case-control study to identify the determinants of preterm birth and to explore the effect of the interaction between GH and HPB on the risk of preterm births based on the U.S. National Vital Statistics System (NVSS) database in the United States on preventing preterm birth in this population. We stratified for age and number of fetuses and performed subgroup analyses to explore the effect of the interaction between GH and HPB on the risk of preterm births.

**Material and Methods**

**Study Population**

In this case-control study, we used nationwide birth certificate data in the United States from the NVSS program, which is available on the official website (https://www.cdc.gov/nchs/nvss/births.htm). All states and territories in the United States were required to record basic information on birth certificates in the vital registration offices, containing the details of the mother, father, and infants. Since we analyzed the de-identified public database released by the NVSS, our study was deemed exempt from institutional review board approval.

Initially, 3 757 582 samples from 2019 were extracted from the Birth Data Files in the NVSS database. Samples with maternal age <18 (42,989), history of pre-pregnancy hypertension (61,427), and missing information on newborns (113,129) and parents (717,413) were excluded. Finally, a total of 2 822,624 eligible participants were included in this study. All participants were respectively divided into a control group (n=2,516,862) and preterm birth group (n=305,762). The screening process is presented in Figure 1.

**Figure 1.** Flowchart of selecting study participants from U.S. National Vital Statistics System 2019 database (Drawio version 13.9.9, diagrams.net).
Outcome Variable

The main outcome of interest was preterm birth, which was defined as delivery occurring before 37 weeks of gestation [9].

Explanatory Variables

GH and HPB were ascertained based on the questions on the birth certificate. GH was the elevation of blood pressure above normal for age, sex, and physiological condition and was diagnosed in pregnancy. GH included pregnancy-induced hypertension and preeclampsia [16]. HPB was defined as a mother who had history of pregnancy(ies) resulting in a live birth of less than 37 completed weeks of gestation. The information about GH and HPB status were collected from medical records directly, which were coded as “yes”, “no”, or “unknown or not stated”. In our analysis, the status of “unknown or not stated” for GH or HPB was excluded.

Covariates

At enrollment, participants self-reported information on the age and race of mothers and fathers. Education attainment of the mothers and fathers was assessed by the question “What is the highest level of schooling that the mother/the father will have completed at the time of delivery?” (8th grade or less, 9th through 12th grade, bachelor’s degree, master’s degree or above). The mother’s pre-pregnancy body mass index (BMI) was a measure of her body fat level based on her height and weight before pregnancy. The classification of BMI used was underweight (BMI <18.5 kg/m²), normal (18.5-24.9 kg/m²), overweight (25.0-29.9 kg/m²), obesity I (30.0-34.9 kg/m²), obesity II (35.0-39.9 kg/m²), or obesity III (≥40.0 kg/m²) [17], as determined by the National Health, Lung and Blood Institute [18]. We also examined several covariates, including weight gain during pregnancy in pounds (<11, 11-20, 21-30, 31-40, 41-98), cigarette smoking before or during pregnancy, number of fetuses, payment source for delivery, previous cesarean, pre-pregnancy diabetes, gestational diabetes, infection, eclampsia, and newborn sex. In addition, the relative excess risk of interaction (RERI), attributable proportion of interaction (AP), and synergy index (S) were used to evaluate the additive interaction between GH and HPB in association with preterm delivery and were measured by whether the estimated joint effect of 2 factors was greater than the sum of the independent effects of GH and HPB, respectively. When the confidence interval of RERI and AP contained 0 and the confidence interval of S contained 1, it suggested that there was no interaction between GH and HPB. We performed subgroup analyses by different age groups and number of fetuses to explore the interaction between GH and HPB on the risk of preterm births.

Univariate and multivariate analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). The interaction between GH and HPB on preterm delivery was performed using R version 4.20 (R Foundation for Statistical Computing, Vienna, Austria). GraphPad Prism 8 was also used to obtain the odds ratio (OR) and 95% confidence interval (CI). A P value less than 0.05 was considered statistically significant.

Results

Characteristics of the Study Population

A total of 2 822 624 samples were included in the study. Of these, the prevalence of preterm birth was 10.83%. The mean gestational age was 38.64 weeks, ranging 36.31 to 39.97 weeks. The distribution of newborn sex was relatively equal, with 48.77% female and 51.23% male. Moreover, the largest proportion of maternal and paternal demographic characteristics were 20 to 29 years of age (46.46% and 35.76%, respectively), White population (75.78% and 74.43%, respectively), method of delivery (cesarean section, forceps, spontaneous, vacuum), number of fetuses (single, multi), and sex of infant (female, male). The status of diabetes mellitus (pre-pregnancy or gestational), previous cesarean section, infection, and eclampsia were abstracted from the medical records.
Table 1. Characteristics of the study participants.

| Variables                           | Total (n=2,822,624) | Groups | Statistics | P     |
|-------------------------------------|---------------------|--------|------------|-------|
|                                     |                     | Control (n=2,516,862) | Case (n=305,762) |       |
|                                     |                     | Z=29.735 | <0.001     |       |
| Mother                             |                     |         |            |       |
| Age, years, n (%)                  |                     | Z=29.735 | <0.001     |       |
| <20                                | 78,085 (2.77)       | 68,571 (2.72) | 9,514 (3.11) |       |
| 20-29                              | 1,311,517 (46.46)   | 1,175,169 (46.69) | 136,348 (44.59) |       |
| 30-34                              | 882,267 (31.27)     | 792,704 (31.50) | 90,022 (29.44) |       |
| ≥35                                | 550,296 (19.50)     | 480,418 (19.09) | 69,878 (22.85) |       |
| Race, n (%)                        |                     |         |            |       |
| White (only)                       | 2,138,878 (75.78)   | 1,923,060 (76.41) | 215,818 (70.58) |       |
| Black (only)                       | 361,077 (12.79)     | 305,194 (12.13) | 55,883 (18.28) |       |
| ALAN (only)                        | 22,029 (0.78)       | 19,311 (0.77) | 2,718 (0.89) |       |
| Asian (only)                       | 218,888 (7.75)      | 197,191 (7.83) | 21,697 (7.10) |       |
| NHOPi (only)                       | 7,869 (0.28)        | 6,716 (0.27) | 1,153 (0.38) |       |
| More than one race                 | 73,883 (2.62)       | 65,390 (2.60) | 8,493 (2.78) |       |
| Educational attainment, n (%)      |                     |         |            | <0.001|
| 8th grade or less                  | 63,380 (2.25)       | 55,559 (2.21) | 7,821 (2.56) |       |
| 9th through 12th grade             | 836,393 (29.63)     | 732,056 (29.09) | 104,337 (34.12) |       |
| Bachelor’s degree                  | 1,498,962 (53.11)   | 1,344,370 (53.41) | 154,592 (50.56) |       |
| Master’s degree or above           | 423,889 (15.02)     | 384,877 (15.29) | 39,012 (12.76) |       |
| Pre-pregnancy BMI, kg/m², n (%)    |                     |         |            | <0.001|
| Underweight <18.5                  | 83,655 (2.96)       | 73,573 (2.92) | 10,082 (3.30) |       |
| Normal 18.5-24.9                   | 1,208,600 (42.82)   | 1,089,737 (43.30) | 118,863 (38.87) |       |
| Overweight 25.0-29.9               | 761,259 (26.97)     | 679,927 (27.01) | 81,332 (26.60) |       |
| Obesity I 30.0-34.9                | 425,406 (15.07)     | 375,000 (14.90) | 50,406 (16.49) |       |
| Obesity II 35.0-39.9               | 205,967 (7.30)      | 180,015 (7.15) | 25,952 (8.49) |       |
| Obesity III >40.0                  | 137,737 (4.88)      | 118,610 (4.71) | 19,127 (6.26) |       |
| Weight gain during pregnancy, pounds, n (%) | Z=97.035 | <0.001     |            |       |
| <11                                | 252,594 (8.95)      | 213,789 (8.49) | 38,805 (12.69) |       |
| 11-20                              | 484,997 (17.18)     | 419,376 (16.66) | 65,621 (21.46) |       |
| 21-30                              | 816,059 (28.91)     | 731,464 (29.06) | 84,595 (27.67) |       |
| 31-40                              | 700,912 (24.83)     | 638,969 (25.39) | 61,943 (20.26) |       |
| 41-98                              | 568,062 (20.13)     | 513,264 (20.39) | 54,798 (17.92) |       |
Table 1 continued. Characteristics of the study participants.

| Variables | Total (n=2,822,624) | Groups | Statistics | P    |
|-----------|---------------------|--------|------------|------|
|           |                     | Control (n=2,516,862) | Case (n=305,762) |       |      |
| Cigarette smoking before pregnancy, n (%) |                     |         | χ²=1519.916 | <0.001 |
| No        | 2,641,622 (93.59)   | 2,360,454 (93.79) | 281,168 (91.96) |       |      |
| Yes       | 181,002 (6.41)      | 156,408 (6.21)    | 24,594 (8.04)   |       |      |
| Cigarette smoking during pregnancy, n (%) |                     |         | χ²=14762.66 | <0.001 |
| No        | 2,678,657 (94.90)   | 2,402,448 (95.45) | 276,209 (90.33) |       |      |
| Yes       | 143,967 (5.10)      | 114,414 (4.55)    | 29,553 (9.67)   |       |      |
| Pre-pregnancy diabetes, n (%) |                     |         | χ²=4083.661 | <0.001 |
| No        | 2,800,127 (99.20)   | 2,499,769 (99.32) | 300,358 (98.23) |       |      |
| Yes       | 2,2497 (0.80)       | 17,093 (6.88)     | 5,404 (1.77)    |       |      |
| Gestational diabetes, n (%) |                     |         | χ²=2381.176 | <0.001 |
| No        | 2,627,430 (93.08)   | 2,349,277 (93.34) | 278,153 (90.97) |       |      |
| Yes       | 195,194 (6.92)      | 167,585 (6.66)    | 27,609 (9.03)   |       |      |
| GH, n (%) |                     |         | χ²=35482.04 | <0.001 |
| No        | 2,598,570 (92.06)   | 2,343,667 (93.12) | 254,903 (83.37) |       |      |
| Yes       | 224,054 (7.94)      | 173,195 (6.88)    | 50,859 (16.63)  |       |      |
| Previous cesarean, n (%) |                     |         | χ²=2323.624 | <0.001 |
| No        | 2,387,472 (84.58)   | 2,137,937 (84.94) | 249,535 (81.61) |       |      |
| Yes       | 435,152 (15.42)     | 378,925 (15.06)   | 56,227 (18.39)  |       |      |
| HPB, n (%) |                     |         | χ²=29512.78 | <0.001 |
| No        | 2,730,558 (96.74)   | 2,450,703 (97.37) | 279,855 (91.53) |       |      |
| Yes       | 92,066 (3.26)       | 66,159 (2.63)     | 25,907 (8.47)   |       |      |
| Payment source for delivery, n (%) |                     |         | χ²=5663.578 | <0.001 |
| Medicaid  | 995,105 (35.25)     | 868,767 (34.52)   | 126,338 (41.32) |       |      |
| Private insurance | 1,612,435 (57.13) | 1,453,712 (57.76) | 158,723 (51.91) |       |      |
| Self-pay  | 112,534 (3.99)      | 102,521 (4.07)    | 10,013 (3.27)   |       |      |
| Other     | 102,550 (3.63)      | 91,862 (3.65)     | 10,688 (3.50)   |       |      |
| Method of delivery, n (%) |                     |         | χ²=42464.18 | <0.001 |
| Cesarean  | 888,811 (31.49)     | 742,763 (29.51)   | 146,048 (47.77) |       |      |
| Forceps   | 14,777 (0.52)       | 13,611 (0.54)     | 1,166 (0.38)    |       |      |
| Spontaneous | 1,845,156 (65.37)  | 1,691,156 (67.19) | 154,000 (50.37) |       |      |
| Vacuum    | 73,880 (2.62)       | 69,332 (2.75)     | 4,548 (1.49)    |       |      |
Table 1 continued. Characteristics of the study participants.

| Variables                        | Total (n=2,822,624) | Control (n=2,516,862) | Case (n=305,762) | Statistics | P     |
|----------------------------------|---------------------|-----------------------|------------------|------------|-------|
| Number of fetus, n (%)           |                     |                       |                  |            |       |
| Single                           | 2,730,417 (96.73)   | 2,477,439 (98.43)     | 252,978 (82.74)  | χ²=212579.9 | <0.001|
| Multi                            | 92,207 (3.27)       | 39,423 (1.57)         | 52,784 (17.26)   |            |       |
| Infection, n (%)                 |                     |                       |                  |            |       |
| No                               | 2,767,788 (98.06)   | 2,469,685 (98.13)     | 298,103 (97.50)  | χ²=568.855  | <0.001|
| Yes                              | 54,836 (1.94)       | 47,177 (1.87)         | 7,659 (2.50)     |            |       |
| Eclampsia, n (%)                 |                     |                       |                  | χ²=4985.065 | <0.001|
| No                               | 2,815,422 (98.74)   | 2,512,300 (98.92)     | 303,122 (99.14)  |            |       |
| Yes                              | 7,202 (0.26)        | 4,562 (0.18)          | 2,640 (0.86)     |            |       |

**Father**

| Age, years, n (%) | Z=17.017 | <0.001 |
|-------------------|----------|--------|
| <20               | 37,392   (1.32)   | 32,781  (1.30)   | 4,611  (1.51)   |
| 20-29             | 1,009,237 (35.76) | 901,235 (35.81) | 108,002 (35.32) |
| 30-34             | 857,856 (30.39)   | 771,392 (30.65)  | 86,464 (28.28)  |
| ≥35               | 918,139 (32.53)   | 811,454 (32.24)  | 106,685 (34.89) |

| Race, n (%)        | χ²=8641.218 | <0.001 |
|--------------------|-------------|--------|
| White (only)       | 2,101,009 (74.43) | 1,888,540 (75.03) | 212,559 (69.52) |
| Black (only)       | 422,565 (14.97)   | 359,840 (14.30)   | 62,725 (20.51)  |
| ALAN (only)        | 21,355 (0.76)     | 18,670 (0.74)     | 2,685 (0.88)    |
| Asian (only)       | 196,853 (6.97)    | 178,077 (7.08)    | 18,776 (6.14)   |
| NHOPI (only)       | 8,812 (0.31)      | 7,597 (0.30)      | 1,215 (0.40)    |
| More than one race | 72,030 (2.55)     | 64,228 (2.55)     | 7,802 (2.55)    |

| Educational attainment, n (%) | Z=-70.653 | <0.001 |
|------------------------------|-----------|--------|
| 8th grade or less            | 77,081 (2.73)   | 67,646 (2.69)   | 9,435 (3.09)    |
| 9th through 12th grade       | 1,057,070 (37.45) | 926,248 (36.80) | 130,822 (42.79) |
| Bachelor's degree            | 1,345,735 (47.68) | 1,210,266 (48.09) | 135,469 (44.31) |
| Master's degree or above     | 342,738 (12.14)   | 312,702 (12.42)  | 30,036 (9.82)   |

**Newborn**

| Sex of infant, n (%)          | χ²=565.388 | <0.001 |
|------------------------------|------------|--------|
| Female                       | 1,376,712 (48.77) | 1,233,785 (49.02) | 142,927 (46.74) |
| Male                         | 1,445,912 (51.23) | 1,283,077 (50.98) | 162,835 (53.26) |

ALAN – American Indian or Alaska Native; NHOPI – Native Hawaiian or Pacific Islander; GH – gestational hypertension; HPB – history of preterm birth.
Comparation of Preterm Birth and Control Group

The included variables were significantly different between the preterm birth group and non-preterm birth group (Table 1). The proportion of cigarette smoking before or during pregnancy (8.04% and 9.67%, respectively, \( P < 0.001 \)), pre-pregnancy or gestational diabetes (1.77% and 9.03%, respectively, \( P < 0.001 \)), previous cesarean section (18.39%, \( P < 0.001 \)), infection (2.50%, \( P < 0.001 \)), HPB (8.47%, \( P < 0.001 \)), and GH (16.63%, \( P < 0.001 \)) in the preterm delivery group were higher than in those without preterm delivery. Moreover, the distribution of age, race, pre-pregnancy BMI, weight gain during pregnancy, method of delivery, number of fetus, payment source for delivery, previous cesarean, pre-pregnancy diabetes, gestational diabetes, infection, eclampsia, sex of infant.

Independent Association of GH and HPB on Preterm Birth

Table 2 demonstrates that there was a positive independent association of GH and HPB with preterm delivery. Compared with parous women who did not have GH and HPB, the ORs

| Variables | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|
| GH | OR 95% CI | \( P \) | OR 95% CI | \( P \) | OR 95% CI | \( P \) | Standardized coefficient |
| No | Ref | Ref | Ref | Ref | Ref | Ref | |
| Yes | 2.700 2.672-2.729 | <0.001 | 2.635 2.607-2.664 | <0.001 | 2.604 2.573-2.635 | <0.001 | 0.143 |
| HPB | | | | | | | |
| No | Ref | Ref | Ref | Ref | Ref | Ref | |
| Yes | 3.431 3.380-3.482 | <0.001 | 3.104 3.057-3.151 | <0.001 | 3.047 2.997-3.097 | <0.001 | 0.109 |

Table 2. Logistic regression analyses of the influence of gestational hypertension and history of preterm birth on preterm birth.

| GH | HPB | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| No | No | Ref | Ref | Ref | Ref | Ref | Ref | Ref | Ref |
| Yes | No | 3.523 3.467-3.581 | <0.001 | 3.277 3.224-3.331 | <0.001 | 3.199 3.143-3.255 | <0.001 |
| Yes | Yes | 6.638 6.388-6.897 | <0.001 | 6.117 5.885-6.358 | <0.001 | 6.095 5.847-6.352 | <0.001 |
| RERI | 1.389 (1.129-1.649) | 1.143 (0.900-1.385) | 1.222 (0.965-1.479) |
| AP | 0.209 (0.178-0.241) | 0.187 (0.154-0.219) | 0.201 (0.167-0.235) |
| S | 1.327 (1.266-1.391) | 1.287 (1.226-1.351) | 1.317 (1.250-1.387) |

Table 3. Logistic regression analyses of the effects of the interaction between gestational hypertension and history of preterm birth on preterm birth.
for preterm birth were increased in the those who had GH (OR: 2.700, 95% CI: 2.672-2.729) and HPB (OR: 3.431, 95% CI: 3.380-3.482) in the unadjusted model. In Model 2, mothers with GH (OR: 2.635, 95% CI: 2.607-2.664) and HPB (OR: 1.342, 95% CI: 3.057-3.151) were linked with an increased risk of preterm birth compared with parous women who did not have GH and HPB. Moreover, both GH and HPB were associated with an increased prevalence rate of preterm birth in the fully adjusted Model 3 (adjusted OR: 2.604, [95% CI: 2.573-2.635] of GH, adjusted OR: 3.047, [95% CI: 2.997-3.097] of HPB). GH was more associated with preterm birth than was HPB (0.143 vs 0.109) (Table 2).

Interaction Between GH and HPB on Preterm Birth

The ORs of preterm birth were higher in mothers with GH and HPB than in mothers who did not have GH and HPB (Table 3), with OR of 6.095 (95% CI: 5.847-6.352), \( P < 0.001 \). Figure 2

Figure 2. Odds ratio (OR) values in the interaction between gestational hypertension and history of preterm birth. (A) Model 1: univariate analysis. (B) Model 2: adjusted for age, race, and educational attainment of mother and father. (C) Model 3: adjusted for age, race, and educational attainment regarding father and mother, pre-pregnancy body mass index, weight gain during pregnancy, cigarette smoking before and during pregnancy, method of delivery, number of fetus, payment source for delivery, previous cesarean, pre-pregnancy diabetes, gestational diabetes, infection, eclampsia, sex of infant (GraphPad PRISM version 8.0.1, GraphPad Software, Inc).
shows the ORs and standard deviation visualization results of the interaction terms in the 3 models. The results of 3 models in Table 3 show that there was a significant synergistic effect of GH and HPB on preterm birth. In Model 3, the adjusted value of RERI was 1.222 (95% CI: 0.965-1.479), AP was 0.201 (95% CI: 0.167-0.235), and S was 1.317 (95% CI: 1.250-1.387). Among them, the value of AP was 0.201 after adjusting for the variables, indicating that 20.1% of preterm birth cases were caused by the interaction between GH and HPB in the sample of this study. In addition, Figure 3 shows there was an additive effect of the interaction between GH and HPB on preterm birth. In the participants with HPB, GH was significantly associated with the risk of preterm birth (OR: 1.933, 95% CI: 1.848-2.022), and in the participants with GH, HPB was significantly associated with the risk of preterm birth (OR: 2.301, 95% CI: 2.203-2.403) (Table 4).

Interaction Between GH and HPB on Preterm Birth in Different Ages and Number of Fetuses

As shown in Table 5, in Model 3, the significant synergistic effect of GH and HPB on preterm birth among pregnant women aged 20 to 29 years, with an adjusted value of RERI of 1.431 (95% CI: 0.993-1.870), AP of 0.226 (95% CI: 0.172-0.281), and S
Table 4. Logistic regression analyses of the influence of GH on preterm birth in the participants with HPB, and the influence of HPB on preterm birth in the participants with GH.

|          | Model 1        | Model 2        | Model 3        |
|----------|----------------|----------------|----------------|
|          | OR (95% CI)    | P              | OR (95% CI)    | P              | OR (95% CI)    | P              |
| Non-HPB  |                |                |                |
| GH       | 2.726 (2.696-2.756) | <0.001         | 2.704 (2.674-2.735) | <0.001         | 2.663 (2.631-2.696) | <0.001         |
| HPB      |                |                |                |
| GH       | 2.436 (2.341-2.534) | <0.001         | 2.272 (2.183-2.365) | <0.001         | 2.301 (2.203-2.403) | <0.001         |
| Non-GH   |                |                |                |
| GH       | 3.523 (3.467-3.581) | <0.001         | 3.272 (3.219-3.326) | <0.001         | 3.187 (3.132-3.244) | <0.001         |

OR – odds ratio; CI – confidence interval; GH – gestational hypertension; HPB – history of preterm birth.

**Model 1**: univariate analysis; **Model 2**: the variables including age, race, and educational attainment of mother and father were corrected; **Model 3**: adjusted variables included age, race, and educational attainment regarding father and mother, pre-pregnancy BMI, weight gain during pregnancy, cigarette smoking before and during pregnancy, method of delivery, number of fetus, payment source for delivery, previous cesarean, pre-pregnancy diabetes, gestational diabetes, infection, eclampsia, sex of infant.

Table 5. Logistic regression analyses of the interaction between GH and HPB on preterm birth in different ages and number of fetus.

| Maternal age | GH | HPB | Model 1 | Model 2 | Model 3 | Interaction for Model 3 |
|--------------|----|-----|---------|---------|---------|-------------------------|
| <20 Years    |                |       |         |         |         |                         |
| No           | No            | Ref  |         |         |         |                         |
| No           | Yes           | 3.980| 3.374-4.695 | <0.001 | 3.903| 3.307-4.607 | <0.001         | 3.246| 2.716-3.879 | <0.001 | RERI (95% CI) | 1.739 | (-1.749-5.227) | AP (95% CI) | 0.274 | (-0.130-0.679) | S (95% CI) | 1.484 | (0.763-2.883) |
| Yes          | No            | 2.176| 2.043-2.317 | <0.001 | 2.172| 2.039-2.314 | <0.001         | 2.349| 2.195-2.514 | <0.001 | RERI (95% CI) | 1.431 | (0.993-1.870) | AP (95% CI) | 0.226 | (0.172-0.281) | S (95% CI) | 1.368 | (1.257-1.448) |
| Yes          | Yes           | 7.044| 4.275-11.608| <0.001 | 6.691| 4.054-11.045| <0.001         | 6.334| 3.676-10.916| <0.001 | RERI (95% CI) | 1.396 | (0.925-1.866) | AP (95% CI) | 0.219 | (0.161-0.278) | S (95% CI) | 1.352 | (1.236-1.478) |

Maternal age 20-29

| Maternal age | GH | HPB | Model 1 | Model 2 | Model 3 | Interaction for Model 3 |
|--------------|----|-----|---------|---------|---------|-------------------------|
| No           | No            | Ref  |         |         |         |                         |
| No           | Yes           | 3.656| 3.565-3.748 | <0.001 | 3.429| 3.343-3.516 | <0.001         | 3.262| 3.175-3.352 | <0.001 | RERI (95% CI) | 1.431 | (0.993-1.870) | AP (95% CI) | 0.226 | (0.172-0.281) | S (95% CI) | 1.368 | (1.257-1.448) |
| Yes          | No            | 2.562| 2.519-2.605 | <0.001 | 2.569| 2.527-2.613 | <0.001         | 2.631| 2.584-2.680 | <0.001 | RERI (95% CI) | 1.396 | (0.925-1.866) | AP (95% CI) | 0.219 | (0.161-0.278) | S (95% CI) | 1.352 | (1.236-1.478) |
| Yes          | Yes           | 6.629| 6.222-7.062 | <0.001 | 6.261| 5.874-6.673 | <0.001         | 6.325| 5.908-6.772 | <0.001 | RERI (95% CI) | 1.396 | (0.925-1.866) | AP (95% CI) | 0.219 | (0.161-0.278) | S (95% CI) | 1.352 | (1.236-1.478) |

Maternal age 30-34

| Maternal age | GH | HPB | Model 1 | Model 2 | Model 3 | Interaction for Model 3 |
|--------------|----|-----|---------|---------|---------|-------------------------|
| No           | No            | Ref  |         |         |         |                         |
| No           | Yes           | 3.624| 3.522-3.730 | <0.001 | 3.357| 3.261-3.456 | <0.001         | 3.295| 3.193-3.400 | <0.001 | RERI (95% CI) | 1.396 | (0.925-1.866) | AP (95% CI) | 0.219 | (0.161-0.278) | S (95% CI) | 1.352 | (1.236-1.478) |
| Yes          | No            | 2.844| 2.786-2.904 | <0.001 | 2.806| 2.749-2.865 | <0.001         | 2.675| 2.615-2.737 | <0.001 | RERI (95% CI) | 1.396 | (0.925-1.866) | AP (95% CI) | 0.219 | (0.161-0.278) | S (95% CI) | 1.352 | (1.236-1.478) |
| Yes          | Yes           | 7.061| 6.605-7.548 | <0.001 | 6.522| 6.098-6.976 | <0.001         | 6.366| 5.921-6.844 | <0.001 | RERI (95% CI) | 1.396 | (0.925-1.866) | AP (95% CI) | 0.219 | (0.161-0.278) | S (95% CI) | 1.352 | (1.236-1.478) |
Table 5 continued. Logistic regression analyses of the interaction between GH and HPB on preterm birth in different ages and number of fetus.

| GH       | HPB      | Model 1 | OR  | 95% CI   | P   | Model 2 | OR  | 95% CI   | P   | Model 3 | OR  | 95% CI   | P   | Interaction for Model 3 |
|----------|----------|---------|-----|----------|-----|---------|-----|----------|-----|---------|-----|----------|-----|--------------------------|
| Maternal age ≥35 |         |         |     |          |     |         |     |          |     |         |     |          |     |                          |
| No       | No       | Ref     |     |          |     |         |     |          |     |         |     |          |     |                          |
| No       | Yes      | 3.143   | 3.044-3.245 | <0.001 | 3.004 | 2.908-3.102 | <0.001 | 3.042 | 2.939-3.149 | <0.001 | RERI (95% CI) | 0.717 | 0.289-1.146 |
| Yes      | No       | 2.987   | 2.918-3.057 | <0.001 | 2.925 | 2.857-2.994 | <0.001 | 2.729 | 2.660-2.800 | <0.001 | AP (95% CI) | 0.131 | 0.062-0.199 |
| Yes      | Yes      | 5.988   | 5.581-6.425 | <0.001 | 5.618 | 5.234-6.031 | <0.001 | 5.489 | 5.087-5.921 | <0.001 | S (95% CI) | 1.315 | 1.248-1.386 |
| Single birth |         |         |     |          |     |         |     |          |     |         |     |          |     |                          |
| No       | No       | Ref     |     |          |     |         |     |          |     |         |     |          |     |                          |
| No       | Yes      | 3.648   | 3.586-3.712 | <0.001 | 3.378 | 3.319-3.437 | <0.001 | 3.224 | 3.167-3.283 | <0.001 | RERI (95% CI) | 1.242 | 0.972-1.509 |
| Yes      | No       | 2.681   | 2.648-2.713 | <0.001 | 2.660 | 2.627-2.692 | <0.001 | 2.713 | 2.678-2.748 | <0.001 | AP (95% CI) | 0.201 | 0.166-0.236 |
| Yes      | Yes      | 6.783   | 6.513-7.064 | <0.001 | 6.236 | 5.985-6.497 | <0.001 | 6.179 | 5.922-6.447 | <0.001 | S (95% CI) | 1.315 | 1.248-1.386 |
| Multiple births |         |         |     |          |     |         |     |          |     |         |     |          |     |                          |
| No       | No       | Ref     |     |          |     |         |     |          |     |         |     |          |     |                          |
| No       | Yes      | 2.773   | 2.575-2.987 | <0.001 | 3.378 | 3.319-3.437 | <0.001 | 3.224 | 3.167-3.283 | <0.001 | RERI (95% CI) | 0.708 | 0.121-1.537 |
| Yes      | No       | 1.935   | 1.859-2.014 | <0.001 | 2.66 | 2.627-2.692 | <0.001 | 2.141 | 2.054-2.232 | <0.001 | AP (95% CI) | 0.155 | 0.000-0.311 |
| Yes      | Yes      | 3.956   | 3.323-4.708 | <0.001 | 6.236 | 5.985-6.497 | <0.001 | 5.554 | 5.816-5.433 | <0.001 | S (95% CI) | 1.249 | 0.985-1.584 |

OR – odds ratio; CI – confidence interval; Ref – reference; GH – gestational hypertension; HPB – history of preterm birth; RERI – relative excess risk of interaction; AP – attributable proportion of interaction; S – synergy index.

Model 1: univariate analysis; Model 2: the variables including age, race, and educational attainment of mother and father were corrected; Model 3: adjusted variables included age, race, and educational attainment regarding father and mother, pre-pregnancy BMI, weight gain during pregnancy, cigarette smoking before and during pregnancy, method of delivery, number of fetus, payment source for delivery, previous cesarean, pre-pregnancy diabetes, gestational diabetes, infection, eclampsia, sex of infant.

of 1.368 (95% CI: 1.257-1.448); in women aged 30 to 34 years, with an adjusted value of RERI of 1.396 (95% CI: 0.925-1.866), AP of 0.219 (95% CI: 0.161-0.278), and S of 1.352 (95% CI: 1.236-1.478); and in women aged 35 and older, with an adjusted value of RERI of 0.717 (95% CI: 0.289-1.146), AP of 0.131 (95% CI: 0.062-0.199), and S of 1.190 (95% CI: 1.080-1.311).

In Model 3, the significant synergistic effect of GH and HPB on preterm birth existed in the participants producing singleton pregnancies with the adjusted value of RERI of 1.242 (95% CI: 0.972-1.509), AP of 0.201 (95% CI: 0.166-0.236), and S of 1.315 (95% CI: 1.248-1.386) (Table 5). There was no interaction in pregnant women younger than 20 years of age and in those who had multiple births.

Discussion

Premature birth is a serious obstetric outcome with profound effects on babies, parents, and the entire community. It is one of the most important unresolved perinatal and public health issues. In the present study, using birth data from the NVSS dataset, 2 822 624 participants were included for...
analyzing the association between GH and HPB on the risk of preterm birth. The results indicated that GH and HPB increased the risk of preterm birth after adjustment for various potential confounding variables. Additionally, it also suggested a synergistic interaction between GH and HPB on preterm birth. The synergistic interaction was present in groups of pregnant women aged 20 to 29, 30 to 34, and ≥35 years and in participants who gave birth to singleton pregnancies. These results are significant for guiding research on determinants, better identifying at-risk populations, and implementing prevention strategies, and facilitating preterm birth surveillance.

GH is a well-established risk factor for preterm birth. We observed a significant positive association between GH and preterm birth in the whole study population. In previous studies, GH significantly increased the risk of preterm birth, with an OR of 1.8 in the Ottawa and Kingston Birth Cohort from 2002 to 2009 [19]. A meta-analysis of 9 studies revealed that GH was still the main factor in the risk of preterm birth, although the determinants of preterm birth were multifactorial in the population of Ethiopia [20], which was in line with the report from the United Kingdom [21]. Studies from China also indicated that GH was a significant risk factor for preterm birth and the risk of preterm delivery was higher among women with GH [7, 10]. These findings were consistent with our results. This suggests the relationship between GH and preterm birth is likely to hold widely for pregnancy.

Furthermore, several studies also revealed HPB was the major risk factor for preterm birth in a current pregnancy [10, 14, 22, 23], which was consistent with our results that HPB was significantly positively associated with preterm birth in the adjusted model. A study conducted in Kenya of preterm infants showed that HPB was associated with premature birth [22]. A 12-month retrospective population-based study conducted using registry data from the PEARL-Peristat Study examined 15,865 singleton live births, and HPB (OR: 7.23, 95% CI: 4.44-11.77) was identified as an independent predictor in univariate and multivariate analyses (P<0.001) [14]. In a secondary analysis study of data for 2149 women, a history of previous preterm birth independently and significantly increased the odds of preterm birth overall (OR: 2.13, 95% CI: 1.19-3.80) [23]. Meanwhile, maternal HPB was commonly reported to confer a 1.5-fold to 2-fold increased risk in subsequent pregnancies [24]. However, Ernest et al showed that there was no significant association between HPB and preterm labor in a 1:2 unmatched case-control study, but they emphasized that the indications of previous and current premature birth were very important [25].

The mechanism of the association between GH and preterm birth could be the systemic arteriole spasm caused by GH, significantly reduced blood concentration and blood volume, decreased placental bed blood perfusion, and acute atherosclerosis, making pregnant women prone to placental abruptio and premature delivery [8]. In addition, HPB as one of the risk factors for preterm birth may be related to the genetic susceptibility to preterm birth [26]. However, the biological cause of approximately half of spontaneous preterm births was unknown [27]. In particular, HPB has an induced obstetric indication, and when the mother has not experienced the same or different obstetric indications, then the current preterm birth is unpredictable. In general, when the HPB is spontaneous, then the chance of preterm birth is currently higher. This is a consistent finding that HPB and recurrent preterm births are closely related to current preterm births, especially natural delivery [28].

In the present study, it is worth noting that there was a significant synergistic interaction between GH and HPB on preterm birth. On the one hand, a well-functioning placenta plays a crucial role in normal pregnancy. Intrauterine growth restriction caused by lower placental perfusion is responsible for the association between GH and the increased risk of preterm birth, which is currently affected by genetic factors or long-term pathophysiology [29]. GH can be reported to be associated with placental dysfunction due to inflammation [30]. Ghidini and Salafia evaluated the placental histology in women with previous preterm birth and found that women had more acute or even chronic inflammation (ie, bacterial vaginosis) compared with those who did not have HPB [30]. Intrauterine inflammation leads to deficits in the capacity of the placenta to maintain bioenergetic and metabolic stability during pregnancy, ultimately resulting in preterm birth [31]. On the other hand, both GH and HPB are genetically susceptible. Several studies have established preliminary evidence supporting a genetic influence on preterm birth [32]. Women who were born prematurely themselves, have a family history of preterm birth, and have a preterm birth experience are at increased risk of preterm birth [22, 23, 33, 34]. In addition, the related research showed that GH has a certain family heredity [35]. Therefore, when HPB and GH appear at the same time, they may form a more critical combination than HPB or GH as risk factors alone, increasing the risk of preterm birth. In the present study, HPB could increase the risk of preterm birth in women with GH, and GH could increase the risk of preterm birth in women with HPB; that is, the 2 had an interaction effect on the occurrence of preterm birth. Currently, the mechanisms are unclear, but GH and HPB have a common cause in placental insufficiency or heredity, or both. Nonetheless, further investigation is warranted to elucidate the underlying mechanisms for the intriguing interaction between GH and HPB on premature delivery among women.

In the subgroup analyses, a significant synergistic interaction between GH and HPB on preterm birth was found in pregnant women aged 20 to 29, 30 to 34, and ≥35 years of age, suggesting that these 3 age groups had a large effect on the risk of preterm birth. The mechanism of the association between GH and HPB on the risk of preterm birth was further explored in the present study, HPB could increase the risk of preterm birth in women with GH, and GH could increase the risk of preterm birth in women with HPB; that is, the 2 had an interaction effect on the occurrence of preterm birth. Currently, the mechanisms are unclear, but GH and HPB have a common cause in placental insufficiency or heredity, or both. Nonetheless, further investigation is warranted to elucidate the underlying mechanisms for the intriguing interaction between GH and HPB on premature delivery among women.
preterm birth upon dual exposure (GH and HPB). In addition, our results showed that synergistic interaction was present in the population with singleton births but not in the population with multiple births. Studies have shown that the prognosis of multiple births is worse than that of single births, and the risk of preterm birth increases with the increase of multiple births [36]. These results suggest that clinicians should focus on GH and HPB in singleton pregnant women aged 20 to 35 and over 35 years and intervene in time for possible preterm birth.

The strengths of this study were as follows. First, to the best of our knowledge, this is the first study to explore GH and HPB and their possible synergistic interaction on premature birth. Second, the use of adequate sample size from the NVSS database, including 2,822,624 eligible participants with delivery information about mothers and their neonates, was used in this study. Third, 3 indexes were conducted to evaluate the interaction in the current study considering wide ranges of potential confounding factors. The study also had several limitations. First, there was no clear clinical subtype in the NVSS database indicating that preterm labor was spontaneous, medically induced, or premature rupture of membranes. Therefore, we could not assess the interaction between GH and HPB on preterm birth based on these clinical subtypes. Second, the study was done retrospectively, which implied potential information bias due to the study design; therefore, the findings should be prudently interpreted. Third, the results did not indicate causation but rather correlation between the risk factors (GH and HPB) and premature delivery. Prospective studies are needed to further investigate the mechanisms underlying GH and HPB on the risk of preterm birth.

Conclusions

Our results indicated that GH and HPB were associated with an increased risk of preterm delivery, and there was a synergistic interaction. Pre-pregnancy counseling and prenatal care should focus on mothers with GH and HPB in a timely manner. The control of high blood pressure is especially important to maintain fetal blood flow. Improving the quality of medical care for pregnant women can reduce risk factors for preterm birth.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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