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ORIGINAL RESEARCH

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# Neonatal sex and maternal factors associated with small-for-gestational-age neonates: A nationwide population-based study

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## Abstract

**Background and Aims:** Small-for-gestational-age (SGA) newborns have a higher risk of morbidity and mortality. Recognizing the risk factors for SGA helps raise early awareness of the issue and provides valuable insights for both healthcare providers and pregnant women. We aimed to identify determinants of SGA using population-based databases in Taiwan.

**Methods:** Data were retrieved from the National Health Insurance, Birth Reporting, and Maternal and Child Health databases for this nationwide case-control study. Live births between 20 and 44 weeks of gestation from 2005 to 2014 were enrolled and linked to their mothers to determine maternal conditions during pregnancy. For every SGA newborn, four controls matched by gestational age and birth year were randomly selected. Multivariable logistic regression was used to identify risk factors for SGA, with adjusted odds ratios (aORs) and 95% confidence intervals (CIs) accounting for potential confounders and interaction terms.

**Results:** A total of 158,405 live SGA births were identified, with 623,584 controls randomly selected. Independent risk factors for SGA included maternal age <20 years (aOR 1.68, 95% CI 1.62, 1.75); female sex in newborns (aOR 1.28, 95% CI 1.27, 1.30); socioeconomic deprivation (aOR 1.29, 95% CI 1.21, 1.38); hypertension (aOR 1.6, 95% CI 1.52, 1.67); kidney disorders (aOR 1.29, 95% CI 1.16, 1.44); thyroid disorders (aOR 1.13, 95% CI 1.09, 1.17); systemic lupus erythematosus (aOR 2.59, 95% CI 2.33, 2.89); antiphospholipid syndrome (aOR 2.08, 95% CI 1.64, 2.64); gestational hypertension (aOR 1.69, 95% CI 1.61, 1.76); pre-eclampsia (aOR 3.12, 95% CI 3.01, 3.25); and antepartum hemorrhage (aOR 1.05, 95% CI 1.03, 1.07) after adjustment for other covariates.

**Conclusions:** SGA was associated with younger maternal age, female newborns, underlying comorbidities, and obstetric conditions. Gestational hypertension

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and pre-eclampsia were significant risk factors affecting infants of both sexes and all age groups and could mask the effects of maternal age and infant sex.

KEYWORDS
live birth, neonate, newborn, risk factors, small-for-gestational-age

## 1 | INTRODUCTION

Small-for-gestational-age (SGA) can be found in both preterm and term infants and is typically assessed by comparing the actual birth weight with the expected weight at the same gestational age. SGA is typically defined as infants with birth weights below the 10th percentile for their corresponding gestational age.[1] Children born SGA may experience different patterns of physical growth.[2,3] A population-based study conducted in California demonstrated that SGA infants have a higher risk of mortality and preterm morbidity than those appropriately sized for their gestational age.[4] Another prospective cohort study in Denmark reported that SGA infants had an elevated risk of mortality due to various causes, including infection, congenital malformations, and perinatal complications, as well as heart, respiratory, and digestive diseases.[5] Moreover, SGA infants may encounter clinical issues after birth, such as metabolic syndrome, poor neurocognitive outcomes, increased healthcare costs, and a greater likelihood of developing chronic diseases, such as ischemic heart disease and chronic renal disease, later in life.[6–9]

While the prevalence of SGA infants in developed countries is approximately 10%, it can increase to approximately 20% of all live births in low- and middle-income countries.[10] Gaining a better understanding of the factors associated with SGA is crucial to facilitating early intervention and reducing adverse outcomes in both mothers and infants. The etiology of SGA is primarily a compromised nutrient supply, which may result from a combination of factors. Researchers have identified a wide range of maternal, fetal, and environmental factors, such as maternal age, smoking, hypertension, gestational diabetes, and placental insufficiency, that could contribute to the development of SGA.[11] However, the specific contribution of each factor remains controversial and may have changed over time.[12] In addition, clinical scenarios are often complex. Considering each risk factor in isolation without accounting for interaction effects between obstetric conditions and demographic factors may not be sufficient to explain the occurrence of SGA.

We aimed to determine the risk factors for SGA and investigate the interactions between obstetric conditions with maternal age and infant sex using population-based administrative databases in Taiwan. By identifying the related risk factors and high-risk populations, we hope to contribute to the development of strategies for preventing and managing SGA in infants.

**Key points**

*What's known*

- Maternal medical history of hypertension, renal disease, autoimmune diseases, and obstetric conditions, including perinatal bleeding, placental abruption, and pre-eclampsia, could be associated with small-for-gestational-age (SGA).

*What's new*

- Interaction analysis revealed that gestational hypertension and pre-eclampsia are powerful factors with significant effects in all age groups and infants of both sexes. Meanwhile, age and sex may be risk factors for SGA only in a population without gestational hypertension or pre-eclampsia.

*What the clinical implications of this study are*

- The results imply that gestational hypertension and pre-eclampsia should be given higher priority when addressing the issue of SGA.

## 2 | METHODS

### 2.1 | Data source

The data analyzed in this study were extracted from the National Health Insurance Research Database (NHIRD), Birth Reporting Database, and Taiwan Maternal and Child Health Database (TMCHD) from 2004 to 2014. The NHIRD is the claims database of the Taiwan National Health Insurance (NHI) program, provided by the Ministry of Health and Welfare. This single-payer health insurance system was launched in 1995 and covers 99% of the Taiwanese population.[13] The NHIRD collects comprehensive information on beneficiaries, including demographic details (date of birth, sex and socioeconomic status) and medical claim records (diagnostic and procedure codes from inpatient admission and outpatient services) covered by the NHI. The

TMCHD contains the encrypted national identification numbers of children and their parents, providing parent–child linkages. This linkage was used to connect with the NHIRD, enabling the retrieval of vital medical information concerning maternal risk factors for SGA. The Birth Reporting Database provides maternal and neonatal details, such as birth weight, gestational age, Apgar scores, delivery method, and maternal age.[14] All identifiers in the data sets are encrypted by the Ministry of Health and Welfare before release to ensure privacy and confidentiality.[15] This study was approved by the Institutional Review Board (IRB) of Kaohsiung Medical University Chung-Ho Memorial Hospital (KMUHIRB-E(I)–20200440). This study was conducted in accordance with the reporting guidelines of Strengthening the Reporting of Observational Studies in Epidemiology, and Reporting of Studies Conducted Using the Observational Routinely Collected Health Data (STROBE).

## 2.2 | Study design

In this nationwide population-based case-control study, between 2005 and 2014, 2,040,966 neonates were identified from the Birth Reporting Database. After excluding multiple births, stillbirths, births at extreme gestational ages ( <20 or >45 weeks), and missing data on maternal ID, 1,949,844 live births were retained. These births were then categorized into SGA ($n$ = 158, 405) and non-SGA ($n$ = 1,791,439) groups. For every live birth categorized as SGA, four corresponding non-SGA births were matched based on the gestational age at birth and birth year. This yielded a case group of 158,405 SGA infants and a control group of 623,584 non-SGA infants (Figure 1). Subsequently, we retrospectively examined the maternal and preconception medical records, tracking back 1 year from the delivery date, to determine potential associated risk factors.

Demographic characteristics, including age, sex, socioeconomic status, comorbidities, and obstetric conditions, were incorporated as covariates. Maternal age was divided into five groups: <20, 20–29, 30–34, 35–39, and ≥40 years. Maternal comorbidities and obstetric conditions within the year preceding delivery were determined based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes in the year before delivery. These conditions included hypertension (ICD-9-CM codes 401–405, 997.91), diabetes mellitus (ICD-9-CM codes 249, 250), cardiac disorders (ICD-9-CM codes 391, 393–398, 410–416, 420–429), chronic kidney diseases (ICD-9-CM codes 403, 582, 583, 585, 586, 588, 646.2), thyroid disorders (ICD-9-CM codes 240–246), asthma

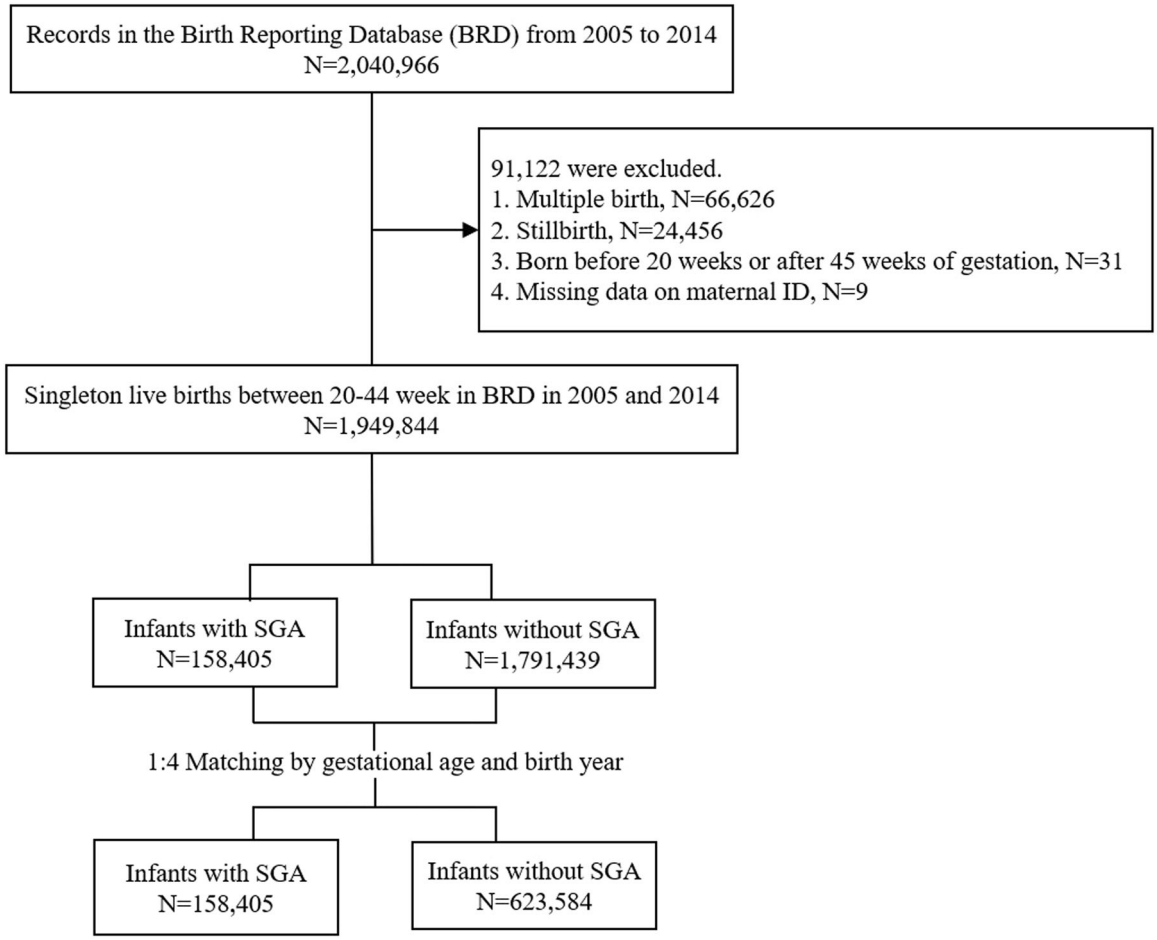


**FIGURE 1** Flow chart illustrating the enrolment of small-for-gestational-age live births and the control group from 2005 to 2014.

(ICD-9-CM code 493), systemic lupus erythematosus (SLE, ICD-9-CM code 710.0), antiphospholipid syndrome (APS, ICD-9-CM code 795.79), anemia (ICD-9-CM codes 648.2, 285.0), gestational hypertension (GHTN, ICD-9-CM codes 642.0–642.3, 642.9), gestational diabetes mellitus (GDM, ICD-9-CM codes 648.0, 648.8), pre-eclampsia (ICD-9-CM codes 642.4–642.7), antepartum hemorrhage (ICD-9-CM code 641), and prenatal infection (ICD-9-CM code 647). GDM was recognized by ICD-9-CM codes 648.0 (Diabetes mellitus complicating pregnancy, childbirth, or the puerperium) and 648.8 (Abnormal glucose tolerance of mother complicating pregnancy, childbirth, or the puerperium). Underlying type 1 and type 2 diabetes were separately identified using ICD-9-CM codes 250 and 249, respectively.

## 2.3 | Outcomes

The primary outcome was SGA, which was defined as the birth weight of a live birth below the 10th percentile for the corresponding gestational age, stratified by sex.

## 2.4 | Statistical analysis

To minimize the effect of discrepancies in gestational age and year of delivery, we performed exact matching with a 1:4 ratio based on these criteria. Hence, for every live birth categorized as SGA, four corresponding non-SGA births were matched based on gestational age at birth and year of delivery. Demographic characteristics are presented as counts (percentages) for categorical variables and as means (standard deviations) for continuous variables. Differences in the distributions of covariates between the case and control groups were examined using Pearson's $\chi^2$ test and paired $t$ test for categorical and continuous variables, respectively. The tests were two-tailed, with $p < 0.05$ considered statistically significant. Stepwise selection was performed to retain significant confounders in the conditional logistic regression model and evaluate their impact on the primary outcome.[16] We further evaluated the interactive effects of obstetric conditions with age or sex on the risk of SGA by assessing the statistical significance of the interaction terms in the regression model. All analyses were performed using the statistical software SAS version 9.4 (SAS Institute).

# 3 | RESULTS

A total of 623,584 non-SGA controls were matched to 158,405 infants with birth weights below the 10th percentile for their gestational age. The demographic characteristics of both groups are summarized in Table 1. In the SGA group, there was a higher proportion of female newborns, younger mothers, individuals with socioeconomic deprivation, and maternal comorbidities, such as hypertension, cardiac disorders, chronic kidney diseases, thyroid disorders, SLE, APS, GHTN, pre-eclampsia, and antepartum hemorrhage. In contrast, the proportions of mothers with diabetes mellitus and anemia were lower in the SGA group. There were no significant between-group differences in the prevalence of asthma and prenatal infections.

The impact of each of these covariates was estimated using conditional logistic regression and is presented in Table 2. Following the stepwise selection process, certain factors were associated with

**TABLE 1** Neonatal sex and maternal characteristics of infants with or without SGA.

| Characteristic | SGA ($n$ = 158,405) | Non-SGA ($n$ = 623,584) | $p$ Value[a] |
|---|---|---|---|
| Neonatal sex, $n$ (%) | | | <0.001 |
| Male | 73,987 (46.7) | 329,866 (52.9) | |
| Female | 84,418 (53.3) | 293,717 (47.1) | |
| Maternal age (years), Mean (SD) | 29.7 (5.1) | 30.4 (4.8) | <0.001 |
| Maternal age (years), $n$ (%) | | | |
| <20 | 3779 (2.4) | 7846 (1.3) | <0.001 |
| 20–29 | 71,630 (45.2) | 250,624 (40.2) | |
| 30–34 | 56,744 (35.8) | 243,828 (39.1) | |
| 35–39 | 22,475 (14.2) | 104,211 (16.7) | |
| ≥40 | 3777 (2.4) | 17,075 (2.7) | |
| Socioeconomic deprivation, $n$ (%) | 1346 (0.9) | 3519 (0.6) | <0.001 |
| Comorbidities, $n$ (%) | | | |
| Hypertension | 3770 (2.4) | 6178 (1.0) | <0.001 |
| Diabetes mellitus | 3237 (2.0) | 15,366 (2.5) | <0.001 |
| Cardiac disorders | 2904 (1.8) | 10,437 (1.7) | <0.001 |
| Chronic kidney diseases | 525 (0.3) | 1221 (0.2) | <0.001 |
| Thyroid disorders | 4764 (3.0) | 16,838 (2.7) | <0.001 |
| Asthma | 2283 (1.4) | 8848 (1.4) | 0.50 |
| Anemia | 4755 (3.0) | 21,245 (3.4) | <0.001 |
| SLE | 617 (0.4) | 874 (0.1) | <0.001 |
| APS | 120 (0.08) | 201 (0.03) | <0.001 |
| Obstetric condition, $n$ (%) | | | |
| Gestational hypertension | 4189 (2.6) | 6979 (1.1) | <0.001 |
| Gestational diabetes mellitus | 15,377 (9.7) | 70,179 (11.3) | <0.001 |
| Pre-eclampsia | 6032 (3.8) | 6871 (1.1) | <0.001 |
| Antepartum hemorrhage | 14,813 (9.4) | 56,446 (9.1) | <0.001 |
| Prenatal infection | 2297 (1.5) | 9112 (1.5) | 0.74 |

Abbreviations: APS, antiphospholipid syndrome; SGA, small-for-gestational-age; SLE, systemic lupus erythematosus.

[a]$p$ Value was obtained using a paired $t$ test for continuous variables and Pearson's chi-square test for categorical variables.

**TABLE 2** Estimated effects of neonatal sex and maternal factors on small-for-gestational-age.

| Variable | Crude OR (95% CI) | *p* Value | Adjusted OR[a] (95% CI) | *p* Value[b] |
|---|---|---|---|---|
| Neonatal sex, female | 1.28 (1.27, 1.30) | <0.0001 | 1.28 (1.27, 1.30) | <0.001 |
| Maternal age | | | | |
| <20 | 1.69 (1.62, 1.76) | <0.0001 | 1.68 (1.62, 1.75) | <0.001 |
| 20–29 | 1.00 | | 1.00 | |
| 30–34 | 0.81 (0.80, 0.82) | <0.0001 | 0.80 (0.79, 0.81) | <0.001 |
| 35–39 | 0.75 (0.73, 0.76) | <0.0001 | 0.73 (0.72, 0.74) | <0.001 |
| ≥40 | 0.76 (0.74, 0.79) | <0.0001 | 0.72 (0.69, 0.75) | <0.001 |
| Socioeconomic deprivation | 1.51 (1.42, 1.61) | <0.0001 | 1.29 (1.21, 1.38) | <0.001 |
| Comorbidities | | | | |
| Hypertension | 2.49 (2.38, 2.59) | <0.0001 | 1.60 (1.52, 1.67) | <0.001 |
| Diabetes mellitus | 0.83 (0.80, 0.86) | <0.0001 | 0.80 (0.76, 0.83) | <0.001 |
| Heart disorders | 1.10 (1.05, 1.14) | <0.0001 | | |
| Chronic kidney diseases | 1.70 (1.53, 1.88) | <0.0001 | 1.29 (1.16, 1.44) | <0.001 |
| Thyroid disorders | 1.12 (1.08, 1.16) | <0.0001 | 1.13 (1.09, 1.17) | <0.001 |
| Asthma | 1.02 (0.97, 1.06) | 0.5220 | | |
| Anemia | 0.88 (0.85, 0.91) | <0.0001 | 0.85 (0.82, 0.87) | <0.001 |
| Systemic lupus erythematosus | 2.81 (2.53, 3.11) | <0.0001 | 2.59 (2.33, 2.89) | <0.001 |
| Antiphospholipid syndrome | 2.37 (1.89, 2.97) | <0.0001 | 2.08 (1.64, 2.64) | <0.001 |
| Obstetrical conditions | | | | |
| Gestational hypertension | 2.43 (2.33, 2.52) | <0.0001 | 1.69 (1.61, 1.76) | <0.001 |
| Gestational diabetes mellitus | 0.85 (0.83, 0.86) | <0.0001 | 0.85 (0.84, 0.87) | <0.001 |
| Pre-eclampsia | 3.72 (3.59, 3.85) | <0.0001 | 3.12 (3.01, 3.25) | <0.001 |
| Antepartum hemorrhage | 1.04 (1.02, 1.06) | 0.0002 | 1.05 (1.03, 1.07) | <0.001 |
| Prenatal infection | 0.99 (0.95, 1.04) | 0.7522 | | |

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Adjustment for other confounders selected through the stepwise procedure.

[b]*p* Value was obtained using Pearson's chi-square test.

increased odds of SGA after accounting for potential confounders. These included female sex in newborns (adjusted odds ratio [aOR] 1.28, 95% confidence interval [CI] 1.27, 1.30); maternal age <20 years (aOR 1.68, 95% CI 1.62, 1.75) compared with 20–29 years; socioeconomic deprivation (aOR 1.29. 95% CI 1.21, 1.38); various maternal comorbidities, such as hypertension (aOR 1.60, 95% CI 1.52, 1.67), chronic kidney disease (aOR 1.29, 95% CI 1.16, 1.44), thyroid disorders (aOR 1.13, 95% CI 1.09, 1.17), SLE (aOR 2.59, 95% CI 2.33, 2.89), APS (aOR 2.08, 95% CI 1.64, 2.64); and obstetric conditions, such as GHTN (aOR 1.69, 95% CI 1.61, 1.76), pre-eclampsia (aOR 3.12, 95% CI 3.01, 3.25), and antepartum hemorrhage (aOR 1.05, 95% CI 1.03, 1.07). In contrast, infants born to mothers aged 30–34, 35–39, and ≥40 years (aOR 0.80, 95% CI 0.79, 0.81; aOR 0.73, 95% CI 0.72, 0.74; aOR 0.72, 95% CI 0.69, 0.75; respectively, compared with those born to mothers aged 20–29 years), as well as those with diabetes mellitus (aOR 0.80, 95% CI 0.76, 0.83); anemia (aOR 0.85, 95% CI 0.82, 0.87); and GDM (aOR 0.85, 95% CI 0.84, 0.87), exhibited lower odds of SGA after accounting for other confounders.

The interaction terms were added to the stepwise selection process to rebuild the model. The estimated effects are demonstrated in Table 3. Among the obstetric factors, the interactive effects of GHTN and pre-eclampsia with sex were statistically significant ($p < 0.001$). For male infants, the aORs associated with GHTN and pre-eclampsia were 1.85

**TABLE 3** The estimated effects of gestational hypertension and pre-eclampsia on SGA stratified by maternal age groups and neonatal sex.

| | SGA, *n* (%) | Non-SGA, *n* (%) | aOR (95% CI)[a] |
|---|---|---|---|
| Male | | | |
| Gestational hypertension | 2059 (2.86) | 3602 (1.11) | 1.85 (1.72, 1.99) |
| Pre-eclampsia | 2899 (4.02) | 3495 (1.07) | 3.32 (3.10, 3.55) |
| Female | | | |
| Gestational hypertension | 2085 (2.53) | 3301 (1.14) | 1.64 (1.52, 1.77) |
| Pre-eclampsia | 3069 (3.72) | 3311 (1.14) | 2.95 (2.76, 3.15) |
| 20–29 | | | |
| Gestational hypertension | 1259 (1.76) | 2113 (0.84) | 1.52 (1.39, 1.68) |
| Pre-eclampsia | 1775 (2.48) | 2118 (0.85) | 2.67 (2.44, 2.92) |
| 30–34 | | | |
| Gestational hypertension | 1569 (2.77) | 2637 (1.08) | 1.72 (1.57, 1.88) |
| Pre-eclampsia | 2356 (4.15) | 2565 (1.05) | 3.30 (3.03, 3.59) |
| ≥35 | | | |
| Gestational hypertension | 1316 (5.01) | 2153 (1.78) | 1.85 (1.62, 2.12) |
| Pre-eclampsia | 1837 (7.00) | 2123 (1.75) | 3.18 (2.82, 3.60) |

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; SGA, small-for-gestational-age.

[a]Adjustment for confounders selected through the stepwise procedure.

(95% CI 1.72, 1.99) and 3.32 (95% CI 3.10,3.55), respectively, which were higher than those for female infants (aORs 1.64 [95% CI 1.52, 1.77] and 2.95 [95% CI 2.76, 3.15], respectively). The interactions of GHTN and pre-eclampsia with age were also significant ($p < 0.001$). As maternal age increased, the aORs exhibited an upward trend. When stratified by age groups, both GHTN and pre-eclampsia were linked to higher odds of SGA in infants born to women aged 20–29 years (aOR 1.52, 95% CI 1.39, 1.68 for GHTN; aOR 2.67, 95% CI 2.44, 2.92 for pre-eclampsia). A similar increased likelihood of SGA was observed in infants born to women aged 30–34 years (aOR 1.72, 95% CI 1.57, 1.88 for GHTN; aOR 3.30, 95% CI 3.03, 3.59 for pre-eclampsia) and those born to women aged ≥35 years (aOR 1.85, 95% CI 1.62, 2.12 for GHTN; aOR 3.18, 95% CI 2.82, 3.60 for pre-eclampsia) after adjustment for other covariates. The results indicate that as the maternal age increases, there is a notable increase in the risk for GHTN.

We further examined the impact of obstetric conditions on the incidence of SGA, stratified by demographic factors, as shown in Table 4. Notably, significant effects of infant sex and maternal age were only observed among infants born to women without pregnancy-induced hypertensive disorders, such as GHTN or pre-eclampsia; however, for infants born to women with such conditions, this significant effect diminished. Female infants were associated with higher odds of SGA (aOR 1.29, 95% CI 1.27, 1.30) compared to males, after accounting for other covariates only in those born to women without GTHN or pre-eclampsia. Similarly, maternal age 30–34 (aOR 0.80, 95% CI 0.79, 0.81) and ≥35 (aOR 0.72, 95% CI 0.71,0.73) years were associated with reduced odds of SGA compared to maternal age 20–29 years, but solely in infants born to women without GHTN or pre-eclampsia. The results revealed that obstetric conditions exerted a stronger influence on SGA than demographic factors.

## 4 | DISCUSSION

### 4.1 | Main findings

This population-based case-control study identified several risk factors associated with SGA, including female sex in infants, younger maternal age, socioeconomic deprivation, maternal hypertension, chronic kidney disease, thyroid disorders, SLE, APS, GHTN, pre-eclampsia, and antepartum hemorrhage. Diabetes mellitus, anemia, and GDM were associated with lower odds of developing SGA. Our findings further revealed significant interactions between pregnancy-induced hypertensive disorders, sex of the newborn, and maternal age. For infants born to women with GHTN or pre-eclampsia, maternal age and female sex in newborns showed no significant impact on SGA, thereby indicating the greater impact of obstetric conditions on the incidence of SGA compared to the effect of demographic factors.

### 4.2 | Strengths and limitations

A major strength of this study is its population-based design. Based on the NHIRD, this study collected data on almost all live SGA births in the country. The results incorporate the demographic characteristics and risk factors for the entire SGA population, which minimized the possibility of sampling error. Another strength is that we defined SGA based on domestic population birth weights. This avoids misdiagnoses due to discrepancies associated with race and ethnicity. Covariates were included using a stepwise selection procedure, which aided in removing collinear variables that could undermine and mask the effects of the independent variables.[17]

However, several limitations should be noted when interpreting the results of this study. First, defining SGA can be challenging because of the difficulty in accurately assessing gestational age. In general, gestational age is calculated according to the date of the last menstrual period, which could be affected by recall bias or factors, such as irregular menstrual cycles or vaginal bleeding. Second, the inherent limitations of observational studies should not be disregarded. Although we included most confounders, there could be some unmeasured confounding effects from factors, such as

**TABLE 4** The estimated effects of infant sex and maternal age on SGA stratified by gestational hypertension and pre-eclampsia.

| | SGA, *n* (%) | Non-SGA, *n* (%) | aOR (95% CI)[a] | *p* Value[b] |
|---|---|---|---|---|
| Gestational hypertension | | | | |
| Male | 2059 (49.69) | 3602 (52.18) | 1 | |
| Female | 2085 (50.31) | 3301 (47.82) | 0.79 (0.55, 1.12) | 0.19 |
| 20–29 | 1259 (30.38) | 2113 (30.61) | 1 | |
| 30–34 | 1569 (37.86) | 2637 (38.20) | 1.14 (0.75, 1.73) | 0.54 |
| ≥35 | 1316 (31.76) | 2153 (31.19) | 1.37 (0.90, 2.08) | 0.15 |
| No gestational hypertension | | | | |
| Male | 70,017 (46.53) | 322,079 (52.90) | 1 | |
| Female | 80,465 (53.47) | 286,755 (47.10) | 1.29 (1.27, 1.30) | <0.001 |
| 20–29 | 70,371 (46.76) | 248,511 (40.82) | 1 | |
| 30–34 | 55,175 (36.67) | 241,191 (39.62) | 0.80 (0.79, 0.81) | <0.001 |
| ≥35 | 24,936 (16.57) | 119,133 (19.57) | 0.72 (0.71, 0.73) | <0.001 |
| Pre-eclampsia | | | | |
| Male | 2899 (48.58) | 3495 (51.35) | 1 | |
| Female | 3069 (51.42) | 3311 (48.65) | 1.12 (0.89,1.40) | 0.35 |
| 20–29 | 1775 (29.74) | 2118 (31.12) | 1 | |
| 30–34 | 2356 (39.48) | 2565 (37.69) | 1.23 (0.93, 1.64) | 0.15 |
| ≥35 | 1837 (30.78) | 2123 (31.19) | 1.03 (0.78, 1.38) | 0.82 |
| No pre-eclampsia | | | | |
| Male | 69,177 (46.53) | 322,186 (52.91) | 1 | |
| Female | 79,481 (53.47) | 286,745 (47.09) | 1.29 (1.27, 1.30) | <0.001 |
| 20–29 | 69,855 (46.99) | 248,506 (40.81) | 1 | |
| 30–34 | 54,388 (36.59) | 241,263 (39.62) | 0.80 (0.79, 0.81) | <0.001 |
| ≥35 | 24,415 (16.42) | 119,163 (19.57) | 0.72 (0.71, 0.73) | <0.001 |

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; SGA, small-for-gestational-age.

[a]Adjustment for confounders selected through the stepwise procedure.

[b]*p* Value was obtained using Pearson's chi-square test.

maternal lifestyle or nutritional status. Abnormal placenta could be another unmeasured confounder. Further study might be required to evaluate the influence of these unmeasured covariates. Third, coding accuracy could be a concern as the possibility of incorrect ICD-9 coding cannot be ruled out. Nevertheless, most codes are reviewed and validated by auditors to ensure the accuracy of claims. Several validation studies conducted to assess the accuracy of diagnosis codes in the NHIRD have demonstrated modest to high sensitivity and positive predictive values for these codes.[13] In addition, a literature review of 50 published validation studies of diagnosis codes and related algorithms for a wide range of health outcomes in Taiwan reported positive predictive values ranging from 80% to 99%.[18] Individuals with incomplete or aberrant data were excluded from the study. From 2005 to 2014, 2,040,966 eligible cases were identified. Of these, nine cases with missing maternal ID data were excluded. Finally, the results may not be generalized to other countries with different races and ethnicities, but they are representative of real-world data covering most of the population in Taiwan.

## 4.3 | Interpretation

The data extracted from the NHIRD revealed that 8.12% (158,405/1,949,844) of live births had birth weights lower than the 10th percentile of the gestational age in Taiwan. This prevalence is comparable to that in other developed countries.[19–21] After matching for gestational age and birth year, significant differences in demographic characteristics were observed between the SGA and control groups, including neonatal sex, maternal age, socioeconomic deprivation, hypertension, diabetes mellitus, heart disorders, chronic kidney disorders, anemia, SLE, APS, GHTN, GDM, pre-eclampsia, and antepartum hemorrhage.

The initial univariate analysis revealed that pre-eclampsia was the strongest risk factor for SGA, followed by SLE, hypertension, GHTN, and APS. Maternal asthma and prenatal infections were not significantly associated with SGA. This result is consistent with those of previous studies.[22–24] After adjusting for other confounders using multivariable analysis, pre-eclampsia and hypertension remained the leading risk factors for SGA. Hypertensive disorders can contribute to pathological changes in the placenta,[25] which can result in adverse outcomes, including intrauterine growth restriction.[26,27] Panaitescu et al. reported that chronic hypertension, with or without pre-eclampsia, was independently associated with increased risk of SGA.[28,29] pre-eclampsia during the early stages of pregnancy is associated with poor placentation and dysfunctional spiral artery remodeling,[30] which can be complicated by intrauterine fetal growth restriction.[31]

Autoimmune diseases can influence placental perfusion and restrict fetal growth by disturbing placentation, which leads to poor vascularization, thereby affecting the blood supply.[32,33] SLE was shown to be associated with an increased risk of preterm births, low birth weights, and SGA infants in a large prospective study in Japan.[34] An umbrella review conducted in 2024 reported higher odds of low birth weight babies in women with SLE or systemic sclerosis.[35] Consistent with previous studies, we found that both SLE and APS were independently associated with higher odds of SGA.

Underlying maternal diseases, including thyroid disorders and chronic kidney disease, were also associated with SGA. Thyroid hormones play an important role in metabolism and normal development. While a systematic review in 2020 reported that maternal subclinical hypothyroidism may be associated with SGA infants,[36] other studies have demonstrated that both hyper- and hypothyroidism could be risk factors for SGA and other perinatal complications.[37,38] McCowan et al. described chronic kidney disease as a maternal risk factor in SGA infants.[39] Other factors, such as chronic hypertension, APS, pre-eclampsia, and GHTN, were confirmed in our study.

Furthermore, demographic characteristics, including younger maternal age and socioeconomic deprivation, were related to higher odds of being born SGA in our model. A scoping review concluded that younger maternal age, low socioeconomic status, primiparity, hypertensive disorders during pregnancy, and anemia are risk factors for developing intrauterine growth restriction.[40] A secondary analysis of a prospective, population-based pregnancy cohort in rural Nepal found that greater wealth and male fetal sex were protective factors against SGA.[41]

Anemia was not identified as a risk factor for SGA infants in the present study. A systematic review concluded that anemia could only be a risk factor for SGA infants in the first trimester.[42] Another review revealed that moderate-to-severe anemia, but not mild anemia, was associated with SGA.[43] While the incidence of severe anemia or anemia occurring in the first trimester could be relatively low, unmeasured factors, such as iron supplementation, might mask the effects of anemia on SGA.

Since the relationship between neonatal sex, maternal factors, and the occurrence of SGA could be complex and indirect, we introduced interaction terms into the model to clarify the potential effect modifications. The sex-specific adjusted OR of SGA in association with pregnancy-induced hypertensive disorders, such as GHTN or pre-eclampsia, was higher in male infants than in female infants. The influences of neonatal sex and maternal age were significant only in the population without GHTN or pre-eclampsia. This may imply that obstetric conditions should be given higher priority when addressing the issue of SGA. The clinical implications of our findings require further clarification in future studies. The clinicians might be inclined to manage and ensure that GHTN, pre-eclampsia, chronic kidney disease, thyroid disorders, SLE, and APS are well-controlled, while also aggressively monitoring fetal weight.

## 5 | CONCLUSION

Several factors were independently associated with higher odds of infants being born SGA, including female sex of infants, younger maternal age, socioeconomic deprivation, hypertension, chronic kidney disease, thyroid disorders, SLE, APS, GHTN, pre-eclampsia, and antepartum hemorrhage. Infants born to older mothers and those with mothers with comorbidities, such as diabetes mellitus, anemia, and GDM, were less likely to be born SGA. In addition, GHTN and pre-eclampsia were associated with higher odds of SGA across neonatal sexes and among different maternal age groups. However, neonatal sex and maternal age were only significantly associated with SGA in infants born to mothers without GHTN or pre-eclampsia. Therefore, the management of GHTN and pre-eclampsia should be a priority in the prevention of SGA births.

### AUTHOR CONTRIBUTIONS

**Pei-Han Fu**: Conceptualization; funding acquisition; investigation; writing—original draft; writing—review and editing. **Chia-Hung Yu**: Conceptualization; funding acquisition; investigation; writing—original draft; writing—review and editing. **Hao-Wei Chung**: Investigation; resources; writing—review and editing. **Pei-Hua Wu**: Data curation; formal analysis; methodology; software; visualization; writing—review and editing. **Chiao-Yun Huang**: Data curation; formal analysis; methodology; software; visualization; writing—review and editing. **Fu-Wen Liang**: Conceptualization; funding acquisition; methodology; project administration; supervision; validation; visualization; writing—review and editing.

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### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Collaboration Center of Health Information Application, but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the Ministry of Health and Welfare.

## TRANSPARENCY STATEMENT

The lead author Fu-Wen Liang affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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