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從孕期到童年：母胎風險因子對兒童健康的長期影響探討

From Womb to Childhood: Evaluating the Longitudinal Effects of
Maternal and Fetal Risk Factors on Pediatric Health

蘇一字

Yi-Yu Su

指導教授：陳保中

Advisor: Professor Pau-Chung Chen

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本論文係 蘇一字 D08852004 在國立臺灣大學 環境與職業健康科學研究所 完成之博士學位論文，於民國 114 年 07 月 15 日承下列考試委員審查通過及口試及格，特此證明。

The undersigned, appointed by the Graduate Institute of Environmental and Occupational Health Science on 15 July 2025, have examined a Doctoral Dissertation entitled above presented by Yi-Yu Su D08852004 candidate, and hereby certify that it is worthy of acceptance.

口試委員 Oral examination committee:

陳保中
(指導教授 Advisor)

連中明

邱弘毅

謝武勳

鄧育良

曹仁祥

誌謝



完成這篇博士論文，對我而言不僅是學術旅程的重要里程碑，更是人生中一段深刻而充實的歷程。身為一位新生兒暨兒童急重症醫師，在臨床崗位上奔忙的同時，能夠靜下心來進行嚴謹的研究、完成博士學位，對我而言是一項極具挑戰卻也極富意義的使命。在這段漫長而堅定的旅途上，我衷心感謝許多人的支持與陪伴。

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中文摘要



背景

懷孕與出生後初期是決定兒童長期健康結果的關鍵時期。母體與胎兒的風險因子，例如高齡產婦、早產、小於胎齡兒、妊娠期體重增加及出生序等，皆可能深刻影響兒童的發育、疾病風險與死亡率。雖然相關議題在部分高收入國家已有廣泛探討，但在東亞族群中，這些因子累積性的影響與具體機制仍有待釐清。

方法

本論文整合五項以台灣全國性人口資料庫為基礎的世代研究，研究主題涵蓋：(1) 早產與小於胎齡兒的成長軌跡與幼年肥胖風險；(2) 早產與小於胎齡兒對異位性疾病（氣喘、異位性皮膚炎、過敏性鼻炎）風險的影響；(3) 母親年齡對出生預後、兒童死亡率、神經發展遲緩與過敏疾病的影響；(4) 兄弟姊妹的存在與出生序對注意力不足過動症與自閉症風險的影響；以及 (5) 妊娠期體重增加對新生兒不良預後的關聯性，並探討母親身體質量指數是否調節此關聯。我們運用多元邏輯斯迴歸與 Cox 比例風險模型，調整社經地位、都市化程度與妊娠相關因子進行分析。

結果

早產與小於胎齡兒在學齡前呈現出異於常態的生長曲線，並具有較高的肥胖風險。早產與氣喘及過敏性鼻炎風險上升相關，卻與異位性皮膚炎風險下降有關；小於胎齡兒則在足月兒中與異位性疾病風險無明顯關聯。母親年齡過低或過高皆與不良出生結果、兒童死亡率與神經發展異常風險上升有關。兄弟姊妹的存在與較低的注意力不足過動症與自閉症風險相關，但獨生子女與長子女的神經發展風險較高。過低或過高的妊娠期體重增加會增加新生兒不良預後風險，尤其在身體質量指數偏高或偏低的母親中影響更顯著。

結論

本論文結果強調孕期與新生兒期風險因子對兒童健康的長期影響，凸顯早期辨識與個別化照護的重要性。本研究有助於發展具地區適應性的公共衛生政策、妊娠與育兒指引，並可用以促進兒童健康平等與預防長期疾病負擔。

關鍵詞：

高齡產婦、早產、胎兒生長遲滯、妊娠期體重增加、神經發展障礙、異位性疾病、
出生胎序、兒童世代研究



ABSTRACT



Background

The prenatal and early postnatal periods represent critical windows during which maternal and fetal risk factors can shape lifelong health trajectories. Factors such as advanced maternal age, preterm birth, small-for-gestational-age (SGA) status, gestational weight gain (GWG), and birth order are increasingly recognized for their influence on child development, morbidity, and mortality. Despite growing global attention to these risks, their cumulative effects and population-specific implications remain underexplored in East Asian contexts.

Methods

This dissertation integrates findings from five nationwide, population-based cohort studies. We examined: (1) the longitudinal growth trajectories and early childhood obesity risk among preterm and SGA infants; (2) associations between prematurity/SGA and pediatric atopic diseases; (3) the effects of maternal age on birth outcomes, child mortality, neurodevelopmental delay, and allergic diseases; (4) the influence of sibling presence and birth order on the risk of neurodevelopmental disorders; and (5) the relationship between maternal gestational weight gain and neonatal outcomes stratified by maternal body mass index (BMI). Statistical analyses included multivariate logistic regression and Cox proportional hazards modeling, with adjustment for socioeconomic, urbanization, and obstetric confounders.

Results

Preterm and SGA infants showed distinct growth patterns and elevated obesity risk by early childhood. Prematurity was associated with higher risks of asthma and allergic rhinitis but a lower risk of atopic dermatitis. Both younger and advanced maternal age

were linked to adverse birth outcomes and increased risks of mortality, developmental delay, and allergic diseases in children. Sibling presence was protective against attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), while only children and firstborns exhibited elevated neurodevelopmental risks. Inadequate or excessive gestational weight gain was associated with increased risks of adverse neonatal outcomes, particularly among mothers at the extremes of the BMI spectrum.

Conclusion

These findings underscore the long-term health implications of maternal, fetal, and familial factors during pregnancy and early infancy. The evidence highlights the importance of precision-based prenatal care, informed reproductive counseling, and targeted pediatric surveillance. Results may inform clinical guidelines and public health strategies aimed at reducing disparities in child health rooted in early life exposures.

Keywords:

maternal age, prematurity, small for gestational age, gestational weight gain, neurodevelopmental disorders, atopic diseases, birth order, pediatric cohort study

The logo of National Taiwan University is a circular emblem. It features a central bell (Liberty Bell) with a lotus flower behind it. The text "國立台灣大學" (National Taiwan University) is written in a circle around the top, and "崇德 愛國 勵學 進德" (Chongde, Aiguo, Lixue, Jinde) is written around the bottom. The numbers "1" and "2" are placed to the right of the logo, corresponding to the two horizontal dotted lines.

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Chapter 1 Introduction



The prenatal and early postnatal periods represent critical windows for shaping the long-term health trajectories of children. During these stages of rapid development, maternal and fetal risk factors exert significant influence on birth outcomes, growth, neurodevelopment, and the emergence of chronic conditions.¹⁻³ Increasingly, evidence has emphasized the importance of early-life exposures in determining health across the life course—a concept rooted in the Developmental Origins of Health and Disease (DOHaD) hypothesis.⁴

Among various prenatal determinants, maternal age, gestational weight gain, fetal growth status, gestational age at birth, and familial structure including birth order or presence of siblings have been identified as pivotal factors that affect neonatal and pediatric health.⁵⁻⁸ While these risk factors have been extensively examined in Western populations, their cumulative and population-level effects within East Asian societies remain underexplored.

In particular, Taiwan has experienced rapid demographic and societal transitions over the past two decades—including rising maternal age, increased reliance on assisted reproductive technologies, and accelerated urbanization.^{9, 10} These shifts necessitate context-specific research to better understand how evolving maternal-fetal environments influence child health. Although prior studies in high-income countries have linked prematurity and small-for-gestational-age (SGA) status to increased risks of neurodevelopmental disorders, atopic diseases, and growth failure,¹¹ their

generalizability to Taiwanese populations remains uncertain due to contextual differences in health systems, cultural norms, and family structures.



To address these gaps, this dissertation leverages Taiwan's comprehensive population health databases to conduct a series of nationwide cohort studies examining the longitudinal effects of maternal and fetal risk factors on child health. Specifically, the research encompasses five interrelated studies:

1. Postnatal growth trajectories in preterm and SGA infants

Using longitudinal measurements, this study assesses early catch-up growth patterns and their implications for pediatric development.

2. Atopic diseases in relation to prematurity and fetal growth status

This analysis explores how early gestational conditions influence the incidence of atopic dermatitis, asthma, and allergic rhinitis during childhood.

3. Maternal age and its impact on birth outcomes and child morbidity

By stratifying maternal age groups, this research delineates how both younger and advanced maternal ages shape risks for stillbirth, mortality, congenital anomalies, and neurodevelopmental disorders.

4. Sibling structure and its association with neurodevelopmental disorders

This study investigates how birth order and sibling composition affect the likelihood of attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and developmental delay, highlighting the potential influence of familial dynamics.

5. Gestational weight gain and perinatal outcomes across maternal BMI categories

This most recent work evaluates how adherence or deviation from Institute of Medicine (IOM) recommendations for gestational weight gain influences adverse birth outcomes, with stratification by pre-pregnancy BMI, thereby offering

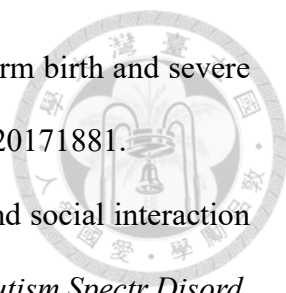
modifiable insights for clinical and public health interventions.



By integrating the results of these five studies, this dissertation offers a comprehensive evaluation of how maternal characteristics, fetal development, and family contexts jointly influence early-life health. The findings contribute important empirical evidence for clinicians, policymakers, and families seeking to optimize maternal and child health in Taiwan and comparable East Asian settings.

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Chapter 2 Long-term Effects on Growth in Preterm and SGA Infants

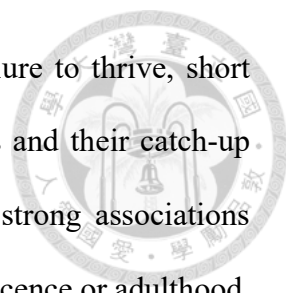


This chapter is based on the following publication:

Su, Y.-Y., Chen, P.-C. (2024). Postnatal Growth and Early Childhood Obesity in Preterm and Small-for-Gestational-Age Infants: A Nationwide Cohort Study. *Pediatric and Neonatology*, 65(2), 104–112. <https://doi.org/10.1016/j.pedneo.2024.01.005>

Introduction

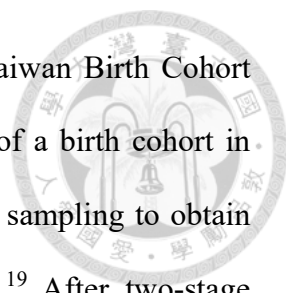
Prematurity and being born small for gestational age (SGA) are both important conditions affecting neonatal outcomes.^{1, 2} Prematurity is generally defined as a birth that occurs at a gestational age before 37 weeks, whereas SGA refers to a birth weight below the tenth percentile for a specific gestational age. With recent advancements in neonatal care, survival rates have increased for both preterm and SGA infants,^{3, 4} drawing attention to long-term morbidities such as growth problems, neurodevelopmental impairment, and metabolic disorders. The most described growth problems for preterm and SGA infants are failure to thrive and short stature,^{5, 6} the definitions of which vary in the literature but are often outlined, respectively, as a weight that is consistently below the fifth percentile and a height more than two standard deviations below the mean (less than the third percentile) in populations of the same sex and age.^{7, 8} Most preterm and SGA infants diagnosed with failure to thrive or short stature achieve catch-up growth at 1–4 years of age.⁹ However, the risks for developing childhood obesity and related comorbidities are higher even in those who catch up successfully.^{10, 11} Moreover, a proportion of them fail to catch up, causing pathological short stature and neurodevelopmental impairment through adulthood.¹²



To our knowledge, the prevalence of growth problems such as failure to thrive, short stature, and obesity among preterm or SGA infants at specific ages and their catch-up growth patterns remain uncertain. Previous studies have revealed strong associations between these populations and multiple metabolic disorders in adolescence or adulthood, including hypertension, diabetes mellitus, and cardiovascular diseases.^{13, 14} Growth hormone (GH) therapy has demonstrated beneficial effects for selected preterm or SGA infants, such as achieving normal growth and improving body composition and hyperlipidemia,^{15, 16} although the optimal follow-up program and treatment indications remain unclear. Consequently, the National Health Insurance (NHI) system in Taiwan does not currently include GH therapy for preterm or SGA infants despite promising outcomes having been reported.^{17, 18} Major obstacles to studying this specific population are the confounding factors of prematurity-related complications and small case numbers with difficulties for long-term follow-up. A well-established birth cohort may provide invaluable information about the growth patterns of this vulnerable population and help in deciding on intervention timing and strategies.

The objective of our study was to demonstrate the growth patterns and growth morbidities of premature or SGA infants in Taiwan. We compared growth patterns between term and preterm infants classed as appropriate for gestational age (AGA) or SGA until 3 years of age, evaluating their demographic data, growth-related morbidities, and catch-up growth pattern. We emphasize the importance of these long-term effects on growth in the study population, as well as calling for an appropriate tracing protocol and GH therapy suggestions in the future based on our findings.

Methods



Data were obtained from questionnaire interviews as part of the Taiwan Birth Cohort Study (TBCS). The TBCS, the first large-scale longitudinal study of a birth cohort in Taiwan, was a prospective study using multistage stratified random sampling to obtain representative samples from national birth registry data in 2005.¹⁹ After two-stage stratified random sampling, 24,200 pairs of postpartum women and newborns were initially selected as a nationally representative cohort. The postpartum women or a primary caregiver were then interviewed 6, 18, and 36 months after the deliveries using a structured questionnaire from June 2005 to December 2007, with informed consent provided by the responsible party. The sample population comprised 16,358 infants, excluding those who were lost to follow-up, post-term (born after 42 weeks' gestation), large for gestational age (birth weight over the 90th percentile for specific gestational age), part of multiple births, and those with birth defects. The TBCS collected a wide range of information on each child's health and development, including lifestyle, parenting, childcare, and social and physical environment across different developmental stages. This research involving human participants was examined and approved by the Research Ethics Committee at the National Health Research Institutes (EC1120508-E). Based on national legislation and institutional requirements, this study did not necessitate written informed consent from participants.

Each child's anthropometric data in our study were collected in follow-up surveys at 6, 18, and 36 months after the deliveries. The TBCS collected anthropometric data from two sources, the first of which was The Children's Health Booklet, which was the primary source in our study for the cohort before the age of 3 years, whereas parental reports were the primary source of data after the age of 3 years. All children in Taiwan receive seven well-child visits under the instruction of the NHI system.²⁰ Nurses recorded

anthropometric measurements in Children's Health Booklets during visits. An official letter was sent to parents before each TBCS survey reminding them to bring their child to care providers and prepare their child's anthropometric data before the following interview. TBCS interviewers were then required to carefully transcribe all anthropometric data including length/height, weight, head circumference, and measurement dates from the Children's Health Booklets.

To conduct an in-depth investigation into the changes in height, weight, and body mass index (BMI) of children at varying stages, we constructed growth curves. We acquired data at diverse time points for children at 6, 18, and 36 months through structured questionnaire interviews. Because each child had multiple measurement records, we used a linear mixed model to analyze these repetitive data. To accurately represent the nonlinear correlations among age, height, weight, and BMI, we incorporated a squared term of age in our model. In addition, we also used logistic regression to model the relevant outcomes, and adjusted for various potential confounding factors, including sex, maternal smoking during pregnancy, alcohol intake during pregnancy, maternal age during pregnancy, parents' educational background, family income, in vitro fertilization, maternal diabetes during pregnancy, gestational hypertension, preeclampsia, and breastfeeding duration exceeding 6 months. All statistical analyses were conducted based on Python 3.7.6.

Results

Demographic Characteristics and Comorbidities

The characteristic, demographic, and comorbidity factors for infants in the study group are presented in Table 2.1 Growth patterns, body composition, and metabolism reportedly

exhibit sexual dimorphism, particularly in the fetal and infantile stages^{21, 22} for both term and preterm infants. Accordingly, all analyses were conducted separately for both sexes. Infants of each sex were separated into four groups: preterm/term and SGA/AGA. Variables in the term SGA, preterm AGA, and preterm SGA groups were compared with the term AGA group as the control.

Most preterm infants in the cohort were late preterm. The highest birth weights and lengths occurred in the control groups, as expected, followed by the term SGA, preterm AGA, and preterm SGA groups for both males and females. No significant differences were observed in maternal age among the groups. Maternal and paternal educational status were lower in the term SGA and preterm AGA groups compared to the control groups of both sexes. Parental education levels were lower in the male preterm SGA group than in the female preterm SGA group. Similarly, parental income was lower in the term SGA and preterm AGA groups compared to the term AGA groups but this observation was not consistent in the preterm SGA groups. Preterm SGA infants had more maternal and pregnancy-related factors. Higher maternal smoking (14.6%) and alcohol use (14.6%) were found in male preterm SGA infants. Gestational hypertension (20.8% in males, 42.1% in females) and preeclampsia (12.5% in males, 23.7% in females) during pregnancy occurred more frequently in preterm SGA infants. In our cohort, prematurity complications were rare in all preterm infants. Approximately 20% of infants were breastfed for over 6 months, without significant differences between the groups. Female infants in the preterm SGA group were born in the highest urbanization area, whereas no striking differences were identified in the other groups.

Table 2.1 Characteristics in small for gestational age and premature infants

Male infants (n = 8469)				
Characteristics	Term AGA	Term SGA	Preterm AGA	Preterm SGA
N	7160	724	537	48
Child				
Birth gestational age	38.7 (1.1)	38.9 (1)	35 (1.7)	34.7 (2)
Birth weight (g)	3207.9 (271.1)	2617.5 (206.7)	2571.8 (420.4)	1867 (382.7)
Birth length (cm)*	50.2 (2.1)	48 (2.1)	47.3 (2.8)	43.7 (4.1)
Parents				
Mother smoking	7.2%	9.3%	8.2%	14.6%
Mother alcohol use	11.3%	11.3%	9.1%	14.6%
Mother's age	28.8 (4.8)	27.8 (4.7)	29.3 (5.1)	29.6 (6.5)
Mother education				
Junior high school or below	13.9%	15.2%	17.4%	16.7%
High school	39.5%	41.4%	40.2%	39.6%
University or above	46.6%	43.4%	42.4%	43.8%
Father education				
Junior high school or below	13.5%	14.4%	17.1%	18.8%
High school	39.2%	40.6%	40.0%	35.4%
University or above	47.3%	45.0%	42.9%	45.8%
Parents' Income				
NTD 50,000 or below	41.0%	43.0%	44.3%	45.8%
NTD 50,001 – 70,000	26.1%	27.3%	24.5%	20.8%
NTD 70,001 – 100,000	21.5%	23.2%	19.6%	16.7%
NTD 100,001 or above	11.3%	6.5%	11.6%	16.7%
Urbanization				
I	16.4%	15.9%	17.5%	14.6%
II	35.7%	36.2%	34.5%	29.2%
III	17.3%	17.5%	17.5%	18.8%
IV (rural area)	30.6%	30.4%	30.5%	37.5%
Pregnancy related variables				
IVF	1.0%	1.4%	1.3%	2.1%
Gestational diabetes	1.8%	1.4%	3.4%	2.1%
Gestational hypertension	1.3%	2.9%	2.8%	20.8%
Preeclampsia	0.4%	0.8%	1.9%	12.5%
Prematurity complications				
ROP	–	–	0.9%	0%
CLD	–	–	0.4%	0%
CP or hydrocephalus	–	–	0.2%	0%
Child variable				
Breast milk feeding > 6m	18.6%	16.9%	16.4%	16.7%
Female infants (n = 7889)				

Characteristics	Term AGA	Term SGA	Preterm AGA	Preterm SGA
N	6702	728	421	38
Child				
Birth gestational age	38.8 (1.1)	39.1 (1)	35 (1.8)	34.4 (2.5)
Birth weight (g)	3105.3 (264.4)	2538.1 (202.5)	2473.3 (423.7)	1732.1 (458.0)
Birth length (cm) [†]	49.7 (2.1)	47.4 (2.1)	46.6 (3.2)	42.6 (4.4)
Parents				
Mother smoking	7.4%	11.7%	10.9%	10.5%
Mother alcohol use	10.9%	11.8%	11.4%	10.5%
Mother's age	28.8 (4.7)	27.5 (5.1)	28.9 (5.3)	29.6 (5.6)
Mother education				
Junior high school or below	14.3%	17.1%	17.4%	7.9%
High school	39.5%	41.8%	45.8%	42.1%
University or above	46.3%	41.1%	36.8%	50.0%
Father education				
Junior high school or below	13.0%	15.6%	19.9%	13.2%
High school	39.6%	45.6%	37.6%	36.8%
University or above	47.4%	38.8%	42.6%	50.0%
Parents' Income				
NTD 50,000 or below	41.3%	49.7%	46.7%	42.1%
NTD 50,001 – 70,000	26.5%	24.1%	25.5%	28.9%
NTD 70,001 – 100,000	21.1%	18.3%	15.7%	15.8%
NTD 100,001 or above	11.1%	7.9%	12.1%	13.2%
Urbanization				
I	17.1%	16.3%	13.8%	23.7%
II	35.2%	32.3%	35.6%	36.8%
III	17.5%	19.6%	18.3%	18.4%
IV (rural area)	30.2%	31.7%	32.3%	21.1%
Pregnancy related variables				
IVF	1.0%	0.5%	1.0%	0.0%
Gestational diabetes	1.4%	1.2%	2.4%	2.6%
Gestational hypertension	1.1%	2.6%	6.4%	42.1%
Preeclampsia	0.3%	1.4%	2.4%	23.7%
Prematurity complications				
ROP	–	–	0.2%	2.6%
CLD	–	–	0.0%	0.0%
CP or hydrocephalus	–	–	0.0%	0.0%
Child variable				
Breast milk feeding > 6m	19.6%	18.3%	19.7%	23.7%

*Number of available measurements in male infants: 8169

[†]Number of available measurements in female infants: 7617

Abbreviation: IVF, in vitro fertilization; ROP, retinopathy of prematurity; CLD, chronic lung disease; CP, cerebral palsy.

Short stature, failure to thrive, and obesity at different ages

Table 2.2 presents the crude and adjusted odds ratios (ORs) for short stature, failure to thrive, and obesity in each group at different ages compared to the term AGA control group. Short stature is defined as a body height or length lower than the third percentile for age and sex. Failure to thrive is defined as a body weight lower than the fifth percentile for age and sex. Obesity is defined as a BMI at or above the 95th percentile, which is calculated as $[\text{weight (in kg)}] \div [\text{length (in m)}]^3$. Short stature, failure to thrive, and obesity in children born prematurely is defined using corrected age (CA), which is the chronological age minus the number of weeks the infant was born before reaching 40 weeks' gestational age. After adjustment for multiple characteristic factors, the ORs for short stature and failure to thrive were significantly higher in the term and preterm SGA groups at 6 and 18 months' follow-up in both male and females ($p < 0.001$). However, no statistical differences were found for the incidence of short stature and failure to thrive at 36 months' follow-up. On the other hand, the ORs for obesity were lower in the term SGA groups at 6 and 18 months' follow-up in both male and females ($p < 0.01$), but the incidence showed no statistical differences at 36 months' follow-up compared to the control groups. Furthermore, higher ORs for obesity were noted in the preterm AGA group at 6 months' follow-up and in the preterm SGA group at 36 months' follow-up in females. The percentages of short stature, failure to thrive, and obesity at 6, 18, 36 months in all study groups are shown in Figure 2.1

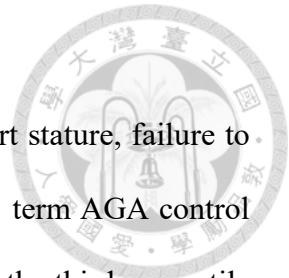




Table 2.2 Odds ratios of short stature, failure to thrive and obesity at 6, 18, 36 months in SGA and premature infants

Study group	6 months				18 months				36 months			
	Crude OR	95% C.I.	Adjusted OR*	95% C.I.	Crude OR	95% C.I.	Adjusted OR*	95% C.I.	Crude OR	95% C.I.	Adjusted OR*	95% C.I.
Male infants												
Short stature												
Term AGA	1.00	–	1.00	–	1.00	–	1.00	–	1.00	–	1.00	–
Term SGA	3.65 [†]	2.57 to 5.17	3.62 [†]	2.55 to 5.15	2.96 [†]	2.03 to 4.33	2.89 [†]	1.97 to 4.23	0.65	0.37 to 1.12	0.63	0.36 to 1.09
Preterm AGA	0.53	0.22 to 1.31	0.50	0.20 to 1.23	1.29	0.71 to 2.34	1.22	0.67 to 2.23	1.01	0.60 to 1.69	0.99	0.59 to 1.66
Preterm SGA	1.24	0.17 to 9.08	1.28	0.17 to 9.52	5.32 [‡]	1.87 to 15.10	4.98 [‡]	1.68 to 14.76	1.42	0.34 to 5.91	1.30	0.30 to 5.57
Failure to thrive												
Term AGA	1.00	–	1.00	–	1.00	–	1.00	–	1.00	–	1.00	–
Term SGA	4.94 [†]	3.76 to 6.48	4.90 [†]	3.72 to 6.44	5.18 [†]	3.90 to 6.88	5.14 [†]	3.86 to 6.84	1.07	0.82 to 1.39	1.07	0.82 to 1.40
Preterm AGA	0.52	0.24 to 1.11	0.50	0.23 to 1.07	1.56	0.96 to 2.54	1.52	0.94 to 2.48	0.43 [†]	0.28 to 0.68	0.44 [†]	0.28 to 0.69
Preterm SGA	6.67 [†]	2.95 to 15.09	6.39 ^a	2.74 to 14.89	9.18 ^a	4.19 to 20.10	9.57 ^a	4.20 to 21.79	0.71	0.22 to 2.29	0.86	0.26 to 2.80
Obesity												
Term AGA	1.00	–	1.00	–	1.00	–	1.00	–	1.00	–	1.00	–
Term SGA	0.37 [†]	0.22 to 0.63	0.37 [†]	0.22 to 0.62	0.42 [‡]	0.25 to 0.73	0.41 [‡]	0.24 to 0.71	1.24	0.91 to 1.69	1.23	0.90 to 1.69
Preterm AGA	1.55 [‡]	1.12 to 2.17	1.50 [§]	1.07 to 2.10	0.87	0.56 to 1.37	0.83	0.53 to 1.31	1.28	0.90 to 1.83	1.28	0.90 to 1.83
Preterm SGA	0.00	0.00 to inf	0.00	0.00 to inf	0.00	0.00 to inf	0.00	0.00 to inf	1.62	0.58 to 4.54	1.61	0.57 to 4.58
Female infants												
Short stature												
Term AGA	1.00	–	1.00	–	1.00	–	1.00	–	1.00	–	1.00	–
Term SGA	3.36 [†]	2.40 to 4.69	3.12 [†]	2.22 to 4.38	3.15 ^a	2.20 to 4.53	2.99 [†]	2.07 to 4.31	0.56	0.27 to 1.14	0.55	0.27 to 1.14
Preterm AGA	0.69	0.30 to 1.58	0.60	0.26 to 1.38	1.17	0.59 to 2.32	1.13	0.57 to 2.24	0.36	0.11 to 1.14	0.35	0.11 to 1.12
Preterm SGA	4.09 [§]	1.24 to 13.48	2.32	0.59 to 9.09	5.90 [†]	2.06 to 16.91	7.05 [‡]	2.20 to 22.67	1.36	0.18 to 9.96	1.34	0.16 to 11.42

Failure to thrive												
Term AGA	1.00	–	1.00	–	1.00	–	1.00	–	1.00	–	1.00	–
Term SGA	5.46 [†]	4.05 to 7.38	5.48 [†]	4.05 to 7.43	5.64 [†]	4.24 to 7.50	5.36 [†]	4.01 to 7.15	0.68	0.40 to 1.16	0.66	0.39 to 1.12
Preterm AGA	0.62	0.25 to 1.53	0.60	0.24 to 1.49	1.35	0.74 to 2.45	1.24	0.68 to 2.27	0.16 [‡]	0.04 to 0.63	0.15 [‡]	0.04 to 0.61
Preterm SGA	7.90 [†]	3.03 to 20.60	7.53 [†]	2.58 to 21.98	8.19 [†]	3.36 to 19.93	6.06 [†]	2.21 to 16.63	0.88	0.12 to 6.44	0.68	0.09 to 5.38
Obesity												
Term AGA	1.00	–	1.00	–	1.00	–	1.00	–	1.00	–	1.00	–
Term SGA	0.51 [‡]	0.33 to 0.80	0.48 [‡]	0.31 to 0.76	0.47 [‡]	0.28 to 0.79	0.43 [‡]	0.25 to 0.73	1.32 [§]	1.00 to 1.75	1.31	0.99 to 1.74
Preterm AGA	2.82 [†]	2.09 to 3.80	2.71 [†]	2.00 to 3.66	0.90	0.54 to 1.51	0.87	0.52 to 1.47	1.17	0.81 to 1.70	1.17	0.80 to 1.70
Preterm SGA	0.99	0.24 to 4.11	0.90	0.20 to 3.91	0.57	0.08 to 4.20	0.48	0.06 to 3.78	3.21 [‡]	1.41 to 7.34	2.97 [§]	1.23 to 7.18

*Adjusted for gender, maternal smoke, alcohol intake and age during pregnancy, parents' education, parents' income, in vitro fertilization, maternal gestational diabetes, gestational hypertension, preeclampsia, and breast milk feeding more than 6 months.

The number of available measurements for weight, height, and BMI of male infants are as following:

The number at 6 months of follow-up are 8320, 8267, and 8266, respectively.

The number at 18 months of follow-up are 8017, 7916, and 7911, respectively.

The number at 36 months of follow-up are all 8469.

The number of available measurements for weight, height, and BMI of female infants are as following:

The number at 6 months of follow-up are 7754, 7710, and 7706, respectively.

The number at 18 months of follow-up are 7428, 7355, and 7350, respectively.

The number at 36 months of follow-up are all 7889.

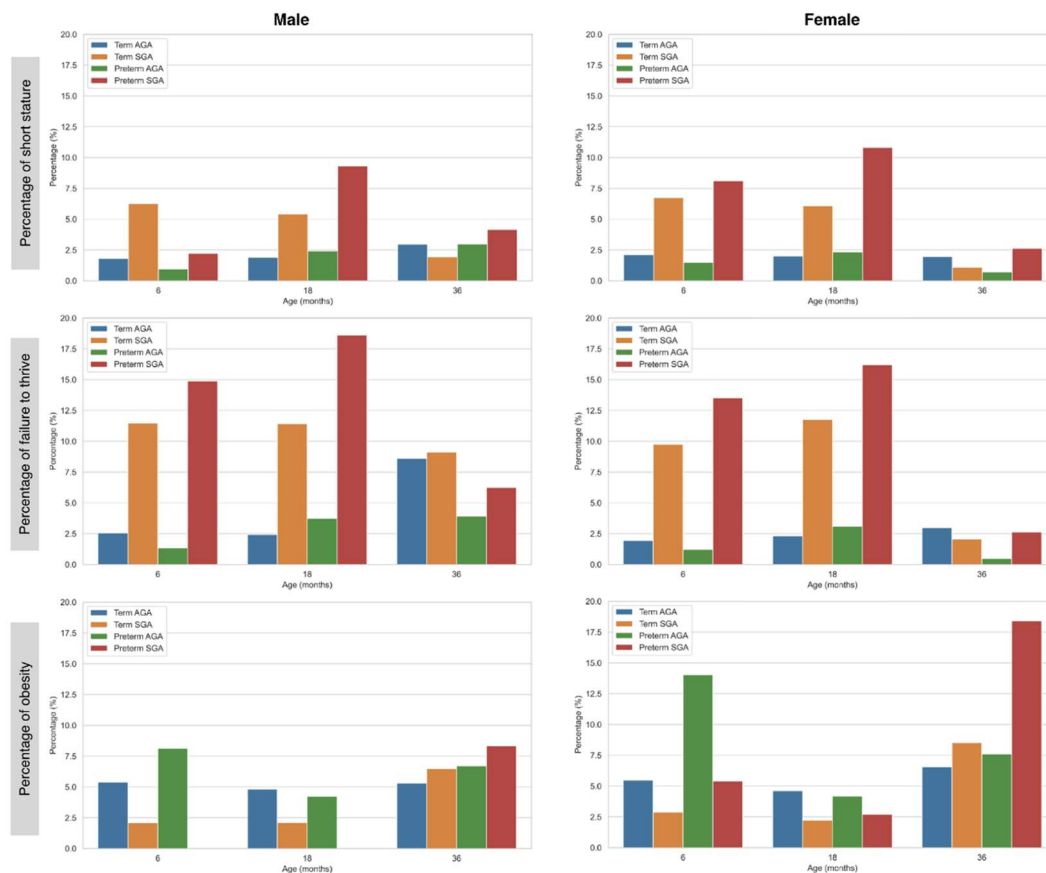
[†] $p < 0.001$

[‡] $p < 0.01$

[§] $p < 0.05$

- Short stature is defined as height $< 3^{\text{th}}$ percentile for age and sex.
- Failure to thrive is defined as body weight $< 5^{\text{th}}$ percentile for age and sex.
- Obesity is defined as body mass index (BMI) at or above the 95th percentile. BMI is calculated as [weight (in kilogram)] $\div$ [length (in m)³].
- Short stature, failure to thrive and obesity of children born prematurely is defined using corrected age, which is chronological age minus the number of weeks the infant was born before the time when the infant would have reached 40 weeks gestational age.

Figure 2.1 Percentage of short stature, failure to thrive and obesity at 6, 18, 36 months in SGA and premature infants



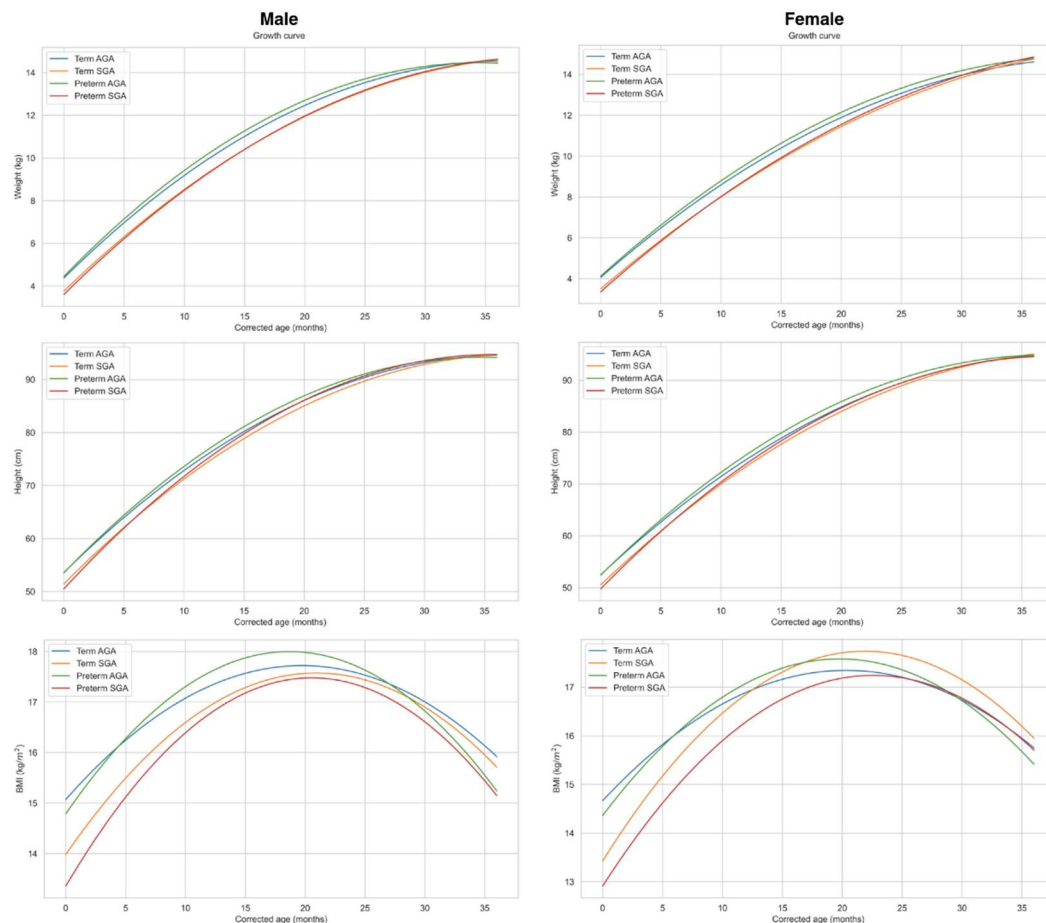
Growth curves

Figure 2.2 shows the growth curves for each study group including both sexes in the term AGA control group. Initially, weight and height were lower in the term and preterm SGA groups, as expected. The curves then became closer to the control as age increased and finally crossed over at 2 to 3 years of age, implying a catch-up pattern. Judging from the curves, preterm SGA infants had higher catch-up growth rates compared to the term SGA infants, particularly in the first year of life. Preterm AGA infants, despite having lower birth weight and length, exhibited rapid catch-up growth in the first 6

months with higher weight and height later and then maintained a steady growth rate similar to the AGA term infants during the follow-up period after the application of CA.



Figure 2.2 Growth curves of SGA and premature infants



Discussion

In our study, preterm and SGA infants generally showed catch-up growth and had no higher OR for developing short stature or failure to thrive compared to AGA term infants before 3 years of age. The findings are mostly consistent with previous research depicting the growth pattern of late preterm and SGA infants.^{5, 23} However, a knowledge

gap exists regarding the “normal” growth curves of preterm and SGA infants. Traditionally, the growth of preterm infants and nutrition needs match those of healthy fetuses, but this perspective is not supported by the evidence and is particularly difficult to achieve in very preterm or SGA infants. Not only do the environment and endocrine status differ greatly between fetal and postnatal life,²⁴ but also the application of CA in clinical practice does not accurately reflect biological age. Hence, experts have suggested using a cohort of uncomplicated preterm newborns for growth monitoring in the special population.²⁵

Although the difference was not statistically significant in the male group at 36 months’ follow-up, the preterm SGA infants in our study persistently demonstrated a higher OR for developing short stature or failure to thrive compared to preterm AGA infants. The reason for preterm SGA infants having a higher catch-up growth rate compared to term SGA infants was speculated to be the higher velocity of intrauterine growth.⁹ Nevertheless, we believe that the discrepancy in postnatal growth patterns between term and preterm infants could describe the phenomenon more precisely because the growth patterns of preterm SGA infants were close to those of the preterm AGA infants. This is comparable to the relationship between term SGA and term AGA infants according to the slope of growth curves and catch-up timing. However, this requires further

investigation to arrive at an explanation for growth patterns and velocity in preterm and SGA infants.

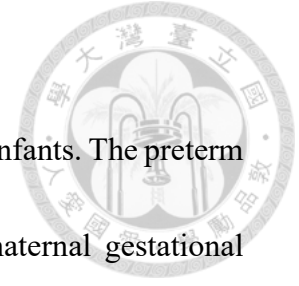


Regarding the risk of obesity, higher ORs were noted in the female infants in the preterm AGA group at 6 months' follow-up. Comparing the growth of preterm AGA infants directly to that of term AGA infants may create misleading results, particularly at early ages when overcorrections occur while applying CA. Moreover, the BMI of premature infants rises rapidly as gestational age increases in both intrauterine and postnatal life.^{26, 27} Viewing preterm AGA infants as an independent cohort at early ages may be a better approach to evaluate their growth. In our study, preterm AGA infants of both sexes had no increased risk of developing obesity at 36 months' follow-up. One explanation is that most preterm infants in our study were late preterm births and they may have had lower risk than more preterm infants. Another possibility may be the inadequate follow-up length. Maria et al. observed that preterm infants may reach a BMI nadir at 2 to 5 years of age, a so-called early adiposity rebound, compared to 5 to 7 years in term infants,²⁸ implying the most obvious BMI variation would be found at 5 to 7 years of age. The preterm SGA infants in our cohort generally had higher ORs for obesity at 36 months' follow-up, although only female infants reached statistical significance. Although the findings may have been influenced by the small sample size,

the risk of obesity was observed earlier in life compared to cohorts reported in different countries.^{9, 29} Notably, female preterm SGA infants had the highest percentage of failure to thrive at 18 months and the highest percentage of obesity at 36 months in our study.

Studies have shown that preterm and SGA infants exhibit a peculiar postnatal growth pattern with a unique composition of weight gain compared to term AGA infants.

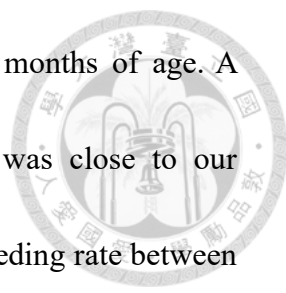
Catch-up in adipose tissue tends to be achieved earlier than in body weight and height, resulting in a body composition that is more represented by fat compared with term infants with the application of CA.³⁰ Although failure to thrive compromises neurological development, rapid growth increases the risks of obesity, dyslipidemia, hypertension, insulin resistance, and type II diabetes in later life, posing a dilemma for neonatologists.³¹ It was hypothesized that the group with the highest rate of failure to thrive was subjected to a more aggressive nutritional care policy, potentially leading to an increased risk of obesity in subsequent follow-ups. Further study is necessary to clarify the causal relationship. The optimal catch-up growth rate in preterm SGA infants is uncertain but a previous study on term SGA infants indicated that a rapid weight gain pattern in the first 2 years of life further increases the risk of obesity later in life.³² Because most infants in our study successfully caught up in weight before 3 years of age, higher risks of developing subsequent metabolic diseases and obesity were predicted based on previous investigations.^{33, 34}



Prenatal factors may also greatly affect growth in preterm and SGA infants. The preterm SGA infants in our study had a strikingly high prevalence of maternal gestational comorbidities such as gestational hypertension and preeclampsia, particularly in the case of female infants. These gestational comorbidities, which are closely related to SGA birth or intrauterine growth restriction, have also been reported to be associated with childhood and adolescent obesity independently.^{35, 36}

Parental education level and family income were not directly linked to preterm or SGA birth in our study, but the groups with lower parental education level and family income tended to present a higher prevalence of maternal smoking and alcohol use. Maternal smoking was strongly associated with preterm birth, SGA birth, or intrauterine growth restriction, whereas the effect of alcohol intake on fetal growth was probably restricted to low birth weight without increasing the risk of preterm or SGA births.^{37, 38} In addition to the direct health impact of these harmful behaviors on the population, lower educational background of caregivers and lower family income have also been reported to adversely affect the catch-up growth of preterm and SGA infants.³⁹

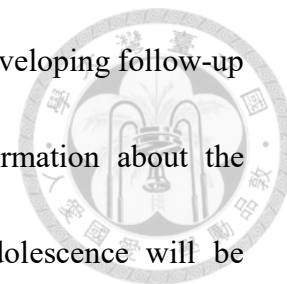
Finally, breastfeeding rates were extremely low in our cohort. Approximately 80% of



the infants in the study received exclusive formula feeding at 6 months of age. A prospective cohort study in Taiwan conducted in 2003, which was close to our enrolment time, confirmed a finding of a >50% drop in the breastfeeding rate between 1 and 3 months after delivery.⁴⁰ Even in 2000, when the World Health Organization had not yet recommended exclusive breastfeeding for the first 6 months, the average rate of any breastfeeding at 6 months among high income countries was approximately 30.7%,⁴¹ and higher than in Taiwan. Compared with exclusive formula feeding, breastfeeding exerts a protective effect against childhood obesity.⁴² Despite the limited evidence for an optimal feeding type and mode in preterm and SGA infants, studies have revealed that formula-fed infants in the population may present with faster weight gain and fat deposition, causing increased risks of developing obesity and metabolic disorders in the future.⁵ This observation may partially explain the high catch-up rate and obesity detected at early ages in our study population.

Our study has several strengths. We applied data from surveys of a nationally representative sample of 24,200 children and all anthropometric measurements were obtained at medical facilities. The results achieved high confidence levels because of the large number of participants and the measurement accuracy of health professionals. It is the first nationwide population-based study depicting the growth of SGA infants in

Taiwan, which could be used as reference for further study or for developing follow-up and intervention strategies. As the TBCS continues, more information about the population and associations with diseases in childhood and adolescence will be discovered using current data or through linkage with other reliable sources such as the NHI database.



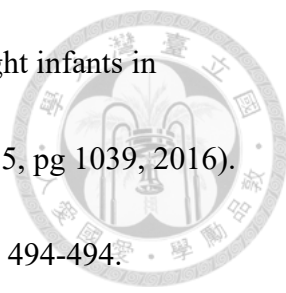
The limitations of the current study mainly lie in its cohort nature. First, infants born moderate to very preterm or with diseases requiring intensive care were not included in the study cohort despite this population having the highest risk of developing growth problems. However, our findings may serve as a reference for future research in those specific populations. Second, participants were enrolled in 2005, and their characteristics, received care, and health literacy differ greatly from those of current infants and mothers. For example, breastfeeding rates, maternal age, and in vitro fertilization are now higher in Taiwan than in the past because of social progress. Third, the follow-up length was too short to include several metabolic disorders such as hypertension, diabetes mellitus, and hyperlipidemia. An objective of our future work will be addressing the associations between the study population and these disorders, thereby facilitating proposals for follow-up protocols and interventions.

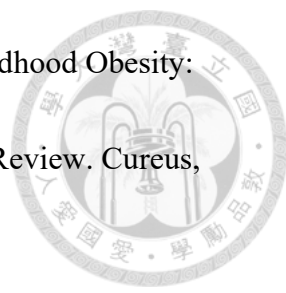
Conclusions

In conclusion, most preterm and SGA infants achieve catch-up growth before 3 years of age in Taiwan. The growth patterns of preterm and term SGA infants differ from those of preterm and term AGA infants. Preterm SGA infants are prone to higher maternal gestational comorbidities and childhood obesity, particularly in females. Pediatricians should take note of these findings and provide tailored nutritional suggestions and follow-up strategies for this population. Further research is necessary to understand the growth trajectories of preterm and SGA infants and their associations with later diseases.

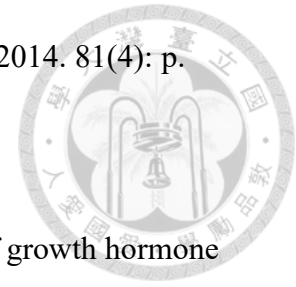
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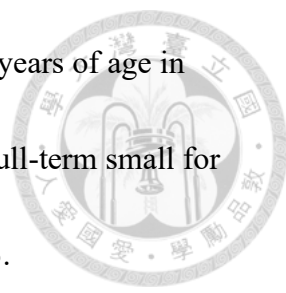
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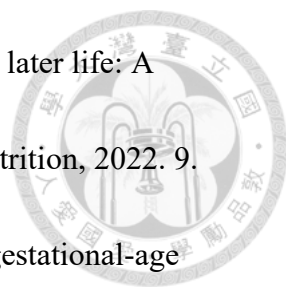
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Chapter 3 Atopic Diseases Related to Prematurity and Fetal Growth



Introduction

Atopic diseases including asthma, atopic dermatitis (AD), allergic rhinitis (AR), and food allergy, are significant chronic conditions in pediatric population and have shown increasing incidence over the past 30 to 40 years.¹ Despite their lifelong impact on patients and the substantial economic burden they place on healthcare systems, prevention strategies and treatable causes for these conditions remain unclear.² Early-life exposures, particularly during prenatal and early childhood periods when the immune system is developing, are thought to play a pivotal role in the pathogenesis of atopic diseases.³ Research in recent decades has revealed that these conditions often follow a time-based progression, beginning with AD and food allergy in infancy, followed by asthma and AR in later childhood.⁴ This phenomenon, known as the "atopic march," is likely driven by shared genetic and environmental risk factors that shape immune responses across different atopic conditions.⁵ While the mechanisms underlying this progression remain incompletely understood, certain risk factors appear to be consistently associated with multiple atopic diseases.

Among these risk factors, prematurity and small-for-gestational-age (SGA) status have

been increasingly recognized as key determinants of long-term health outcomes, including the development of atopic diseases. The Developmental Origins of Health and Disease (DOHaD) theory suggests that fetal growth patterns and early developmental exposures may predispose individuals to chronic conditions later in life.⁶ Studies indicate that preterm or SGA infants may exhibit distinct patterns of atopic disease development compared to their term or appropriate-for-gestational-age (AGA) counterparts. Notably, prematurity has been associated with an increased risk of asthma but a lower risk of AD, suggesting a differential immune trajectory in preterm infants.⁷⁻

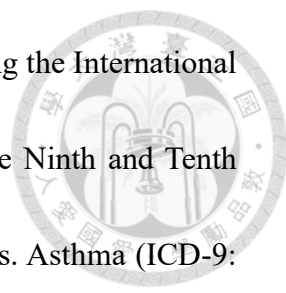
⁹ In contrast, the relationship between SGA and asthma risk remains inconsistent, with studies reporting positive, null, or even inverse associations.¹⁰⁻¹¹ These discrepancies may stem from differences in study populations, sample sizes, and definitions of atopic outcomes.

Given these uncertainties, a large-scale, longitudinal analysis is needed to better understand the relationship between prematurity, SGA status, and the development of atopic diseases. Therefore, we conducted a nationwide cohort study to estimate the association between prematurity, SGA status, and the risk of atopic diseases in the pediatric population.

Methods

This study utilized data from Taiwan's National Health Insurance Research Database (NHIRD), which has collected comprehensive medical records for nearly 23 million residents since 1996 and covers 99.9% of the population.¹² In 2015, the Health and Welfare Data Center (HWDC) of the Ministry of Health and Welfare (MOHW) integrated NHIRD with other health-related databases to establish the Taiwan Maternal and Child Health Database (TMCHD), providing reliable mother-child linkages for perinatal and pediatric research.¹³

The study cohort included all live births in Taiwan between January 1, 2004, and December 31, 2019. Multiple births were excluded, and infants who died during follow-up were censored from the analysis. Prematurity was defined as birth before 37 weeks of gestation, while SGA was defined as birth weight below the 10th percentile for gestational age, as assessed by healthcare providers. Infants were categorized into four groups based on gestational age and birth weight: term AGA (control group), term SGA, preterm AGA, and preterm SGA. Given the well-documented sex-related differences in growth, metabolism, and atopic disease development, all analyses were performed separately for males and females.^{14, 15}



Diagnoses of asthma, AD, AR, and food allergy were identified using the International Classification of Diseases (ICD) coding system, including both the Ninth and Tenth Revision Clinical Modification (ICD-9-CM and ICD-10-CM) codes. Asthma (ICD-9: 493, ICD-10: J45), atopic dermatitis (ICD-9: 691.8, ICD-10: L20), allergic rhinitis (ICD-9: 477, ICD-10: J30), and food allergy (ICD-9: 693.1, 995.6, ICD-10: Z91.01) were identified using their respective ICD codes. To ensure diagnostic accuracy, atopic disease diagnoses—including asthma, AD, AR, and food allergy—were confirmed based on the requirement of at least three outpatient visits or one hospital admission.

Covariates included in the analysis were demographics (sex, age), pregnancy-related factors (maternal age, pregnancy complications including gestational hypertension, preeclampsia, and premature rupture of membranes), and complications of prematurity (chronic lung disease, cerebral palsy, hydrocephalus, and necrotizing enterocolitis).

Socioeconomic status (SES) was assessed using monthly salary data from NHIRD, categorized into three income brackets: <15,840 New Taiwan Dollars (NTD), 15,841–25,000 NTD, and $\geq$ 25,001 NTD. These thresholds were selected based on Taiwan's statutory minimum wage (15,840 NTD) during the study period and an additional cutoff at 25,000 NTD to distinguish middle-income earners from higher-income groups.

Urbanization level was classified into four categories (Level I: most urbanized to Level

IV: least urbanized), based on residential characteristics including population density, educational attainment, the proportion of elderly residents, agricultural employment rates, and access to healthcare resources.¹⁶ Both socioeconomic status and urbanization level were included as covariates in logistic regression and Cox proportional hazards models to adjust for their potential confounding effects.

Descriptive analyses were performed using univariate and bivariate statistics to summarize baseline characteristics and assess initial associations. Cox proportional hazards models were employed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for all specified covariates. The Kaplan-Meier method was used to estimate the cumulative incidence for each atopic disease, and the log-rank test was applied to compare differences among groups. All statistical analyses were conducted using SAS statistical software (version 9.4; SAS Institute, Cary, NC).

Results

A total of 1,758,460 infants were included in the study, comprising 914,713 males and 843,747 females, born between 2004 and 2019. Infants who died during follow-up were censored, and multiple births were excluded. Table 3.1 presents the demographic characteristics of the study cohort. The mean gestational age for term AGA infants was

38.6 ± 1 weeks in males and 38.7 ± 1.1 weeks in females, while for term SGA infants, it was 38.8 ± 1 weeks in males and 38.9 ± 1 weeks in females, showing minimal differences from the control group. Preterm AGA infants had a mean gestational age of 34.8 ± 2 weeks in males and 34.8 ± 2.1 weeks in females, whereas preterm SGA infants were born earlier at 34.6 ± 2 weeks in males and 34.5 ± 2.1 weeks in females. Birth weight followed a similar pattern, with term AGA infants having the highest mean birth weights (3192.9 ± 272.8 g in males, 3091.1 ± 265.4 g in females) and preterm SGA infants the lowest (1851.5 ± 404 g in males, 1734.2 ± 401.1 g in females).

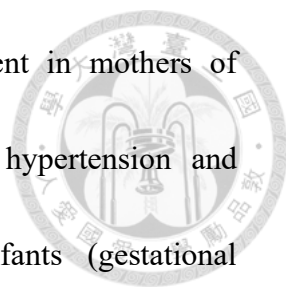
Table 3.1 Characteristics of the cohort

Characteristics	Term AGA	Term SGA	Preterm AGA	Preterm SGA
Male				
n	764369	81599	61104	7641
Birth gestational age (weeks)	38.6 (1)	38.8 (1)	34.8 (2)	34.6 (2)
Birth body weight (grams)	3192.9 (272.8)	2602.2 (206.5)	2524.1 (462.1)	1851.5 (404)
Pregnancy related variables				
Maternal age	30.1 (4.7)	29.3 (5)	30.4 (5.2)	30.7 (5.3)
Diabetes	5771 (0.76%)	516 (0.63%)	995 (1.63%)	169 (2.21%)
Hypertension	3546 (0.46%)	1006 (1.23%)	1093 (1.79%)	773 (10.12%)
Premature rupture of membranes	8698 (1.14%)	897 (1.1%)	4679 (7.66%)	587 (7.68%)
Preeclampsia or eclampsia	1353 (0.18%)	535 (0.66%)	862 (1.41%)	973 (12.73%)
Cesarean section	251752 (32.94%)	22491 (27.56%)	25348 (41.48%)	4205 (55.03%)
Prematurity complications[†]				
All	2222 (0.29%)	474 (0.58%)	1897 (3.1%)	412 (5.39%)
Other variables				
Urbanization level				
I (highest)	218909 (28.64%)	21930 (26.88%)	16389 (26.82%)	2092 (27.38%)

II	251231 (32.87%)	26653 (32.66%)	19953 (32.65%)	2342 (30.65%)
III	144135 (18.86%)	15549 (19.06%)	11672 (19.1%)	1496 (19.58%)
IV (lowest)	150094 (19.64%)	17467 (21.41%)	13090 (21.42%)	1711 (22.39%)
Socioeconomic status				
<15840	95779 (12.53%)	13270 (16.26%)	9746 (15.95%)	1346 (17.62%)
15841-25000	319467 (41.79%)	34334 (42.08%)	25641 (41.96%)	3040 (39.79%)
>=25001	349123 (45.67%)	33995 (41.66%)	25717 (42.09%)	3255 (42.60%)
Female				
n	712395	78864	46731	5757
Birth gestational age (weeks)	38.7 (1.1)	38.9 (1)	34.8 (2.1)	34.5 (2.1)
Birth body weight (grams)	3091.1 (265.4)	2524.8 (199)	2424.5 (468)	1734.2 (401.1)
Pregnancy related variables				
Maternal age	30.1 (4.7)	29.3 (4.9)	30.4 (5.2)	30.9 (5.3)
Diabetes	4925 (0.69%)	446 (0.57%)	812 (1.74%)	120 (2.08%)
Hypertension	3441 (0.48%)	884 (1.12%)	1147 (2.45%)	704 (12.23%)
Premature rupture of membranes	7873 (1.11%)	805 (1.02%)	3740 (8%)	354 (6.15%)
Preeclampsia or eclampsia	1391 (0.2%)	575 (0.73%)	915 (1.96%)	918 (15.95%)
Cesarean section	226426 (31.78%)	20723 (26.28%)	20152 (43.12%)	3482 (60.48%)
Prematurity complications [†]				
All	1478 (0.2%)	356 (0.45%)	1350 (2.89%)	288 (5%)
Other variables				
Urbanization level				
I (highest)	204526 (28.71%)	21414 (27.15%)	12635 (27.04%)	1570 (27.27%)
II	234141 (32.87%)	25716 (32.61%)	15060 (32.23%)	1834 (31.86%)
III	134177 (18.83%)	14921 (18.92%)	8947 (19.15%)	1073 (18.64%)
IV (lowest)	139551 (19.59%)	16813 (21.32%)	10089 (21.59%)	1280 (22.23%)
Socioeconomic status				
<15840	89488 (12.56%)	12480 (15.82%)	7969 (17.05%)	1051 (18.26%)
15841-25000	296481 (41.62%)	33444 (42.41%)	19385 (41.48%)	2277 (39.55%)
>=25001	326426 (45.82%)	32940 (41.77%)	19377 (41.46%)	2429 (42.19%)

[†] Prematurity complications encompassed chronic lung disease, cerebral palsy, hydrocephalus, and necrotizing enterocolitis

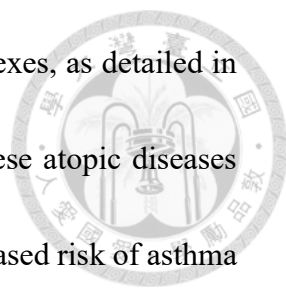
Maternal characteristics varied across groups. Mean maternal age at delivery was



similar, but pregnancy-related complications were more prevalent in mothers of preterm infants compared to term AGA controls. Gestational hypertension and preeclampsia were particularly elevated in preterm SGA infants (gestational hypertension: 10.12% in males, 12.23% in females; preeclampsia: 12.73% in males, 15.95% in females), compared to term AGA controls (0.46% in males, 0.48% in females for hypertension; 0.18% in males, 0.2% in females for preeclampsia). Although term SGA infants also had a higher incidence of pregnancy complications than controls, the differences were less pronounced. Cesarean section rates were higher in preterm infants, particularly those born SGA.

Neonatal complications associated with prematurity were most frequent in preterm SGA infants, who had the highest rates of chronic lung disease, cerebral palsy, hydrocephalus, and necrotizing enterocolitis (5.39% in males, 5% in females), followed by preterm AGA infants (3.1% in males, 2.89% in females), term SGA infants (0.58% in males, 0.45% in females), and term AGA controls (0.29% in males, 0.2% in females). Additionally, preterm and SGA infants were more likely to reside in highly urbanized areas and have lower socioeconomic status compared to term AGA infants.

Atopic Diseases and Risk Associations



The incidence of asthma, AD, and AR differed across groups and sexes, as detailed in Tables 3.2 and 3.3. Males had higher overall incidence rates of these atopic diseases than females. Prematurity was significantly associated with an increased risk of asthma (HR: 1.19, 95% CI: 1.17–1.21 in males; HR: 1.17, 95% CI: 1.15–1.20 in females) and AR (HR: 1.03, 95% CI: 1.01–1.04 in males; HR: 1.03, 95% CI: 1.02–1.05 in females). In contrast, prematurity was associated with a lower risk of AD (HR: 0.94, 95% CI: 0.92–0.97 in males; HR: 0.95, 95% CI: 0.93–0.98 in females) among AGA infants. Similar patterns were observed in preterm SGA infants, who exhibited increased risks of asthma (HR: 1.17, 95% CI: 1.13–1.22 in males; HR: 1.21, 95% CI: 1.16–1.28 in females) and AR (HR: 1.07, 95% CI: 1.03–1.10 in males; HR: 1.06, 95% CI: 1.02–1.11 in females), but a reduced risk of AD (HR: 0.92, 95% CI: 0.86–0.98 in males; HR: 0.95, 95% CI: 0.88–1.03 in females).

Table 3.2 Allergic diseases in male infants across each group

	Incidence (per 10 ⁵)	95%CI	Crude HR	95%CI	Adjusted HR [†]	95%CI
Asthma						
Term AGA	3287.8	3274.4 to 3301.1	1.00	-	1.00	-
Term SGA	3274	3233.3 to 3314.7	0.99	0.98 to 1.01	1.01	0.99 to 1.02
Preterm AGA	3947.7	3894.9 to 4000.5	1.20	1.18 to 1.22	1.19	1.17 to 1.21
Preterm SGA	3994.2	3843 to 4145.5	1.20	1.15 to 1.24	1.16	1.12 to 1.21
Atopic dermatitis						
Term AGA	1251.8	1244.1 to 1259.5	1.00	-	1.00	-
Term SGA	1180.9	1158 to 1203.8	0.95	0.93 to 0.96	0.98	0.96 to 1.00
Preterm AGA	1173.4	1147.1 to 1199.8	0.94	0.92 to 0.96	0.94	0.92 to 0.97
Preterm SGA	1159.7	1085.3 to 1234.2	0.92	0.86 to 0.98	0.92	0.86 to 0.98
Allergic rhinitis						
Term AGA	5971.9	5952.7 to 5991.1	1.00	-	1.00	-
Term SGA	5780.3	5722.9 to 5837.7	0.97	0.96 to 0.98	0.99	0.98 to 1.00
Preterm AGA	6144.3	6075 to 6213.5	1.03	1.02 to 1.04	1.03	1.01 to 1.04
Preterm SGA	6492.7	6289 to 6696.4	1.08	1.05 to 1.12	1.06	1.02 to 1.09
Food allergy						
Term AGA	5.9	5.4 to 6.4	1.00	-	1.00	-
Term SGA	7.2	5.5 to 8.9	1.21	0.94 to 1.56	1.18	0.91 to 1.51
Preterm AGA	5.7	4 to 7.5	0.98	0.71 to 1.34	0.94	0.68 to 1.30
Preterm SGA	6.8	1.4 to 12.3	1.15	0.51 to 2.56	0.95	0.41 to 2.21

† Adjusted for age, gender, pregnancy related variables, prematurity complications and other variables mentioned in Table I

Table 3.3 Allergic diseases in female infants across each group

	Incidence (per 10 ⁵)	95%CI	Crude HR	95%CI	Adjusted HR [†]	95%CI
Asthma						
Term AGA	2466.2	2454.5 to 2477.8	1.00	-	1.00	-
Term SGA	2485.6	2450.4 to 2520.7	1.01	0.99 to 1.02	1.02	1.00 to 1.03
Preterm AGA	2938.9	2888.5 to 2989.4	1.19	1.17 to 1.21	1.17	1.15 to 1.20
Preterm SGA	3134.4	2984.4 to 3284.4	1.25	1.19 to 1.31	1.20	1.14 to 1.26
Atopic dermatitis						
Term AGA	1101	1093.6 to 1108.5	1.00	-	1.00	-
Term SGA	1051.4	1029.6 to 1073.3	0.96	0.94 to 0.98	0.99	0.96 to 1.01
Preterm AGA	1042.2	1014 to 1070.4	0.95	0.92 to 0.98	0.95	0.93 to 0.98
Preterm SGA	1084.3	1001.4 to 1167.2	0.98	0.90 to 1.05	0.95	0.88 to 1.03
Allergic rhinitis						
Term AGA	4577.2	4560.4 to 4594	1.00	-	1.00	-
Term SGA	4510.1	4460.2 to 4560	0.98	0.97 to 1.00	1.00	0.99 to 1.02
Preterm AGA	4751.4	4684.3 to 4818.6	1.04	1.03 to 1.06	1.03	1.02 to 1.05
Preterm SGA	5006.1	4807.7 to 5204.5	1.09	1.05 to 1.13	1.05	1.01 to 1.09
Food allergy						
Term AGA	4.5	4 to 4.9	1.00	-	1.00	-
Term SGA	6.1	4.5 to 7.7	1.37	1.04 to 1.82	1.33	1.01 to 1.77
Preterm AGA	5.7	3.7 to 7.7	1.28	0.89 to 1.85	1.10	0.75 to 1.61
Preterm SGA	4.5	0.9 to 13.3	1.01	0.32 to 3.15	0.73	0.22 to 2.36

[†] Adjusted for age, gender, pregnancy related variables, prematurity complications and other variables

mentioned in Table I

SGA status in term infants was not associated with increased atopic disease risk. However, in preterm infants, SGA showed a slight but non-significant increase in AR risk compared

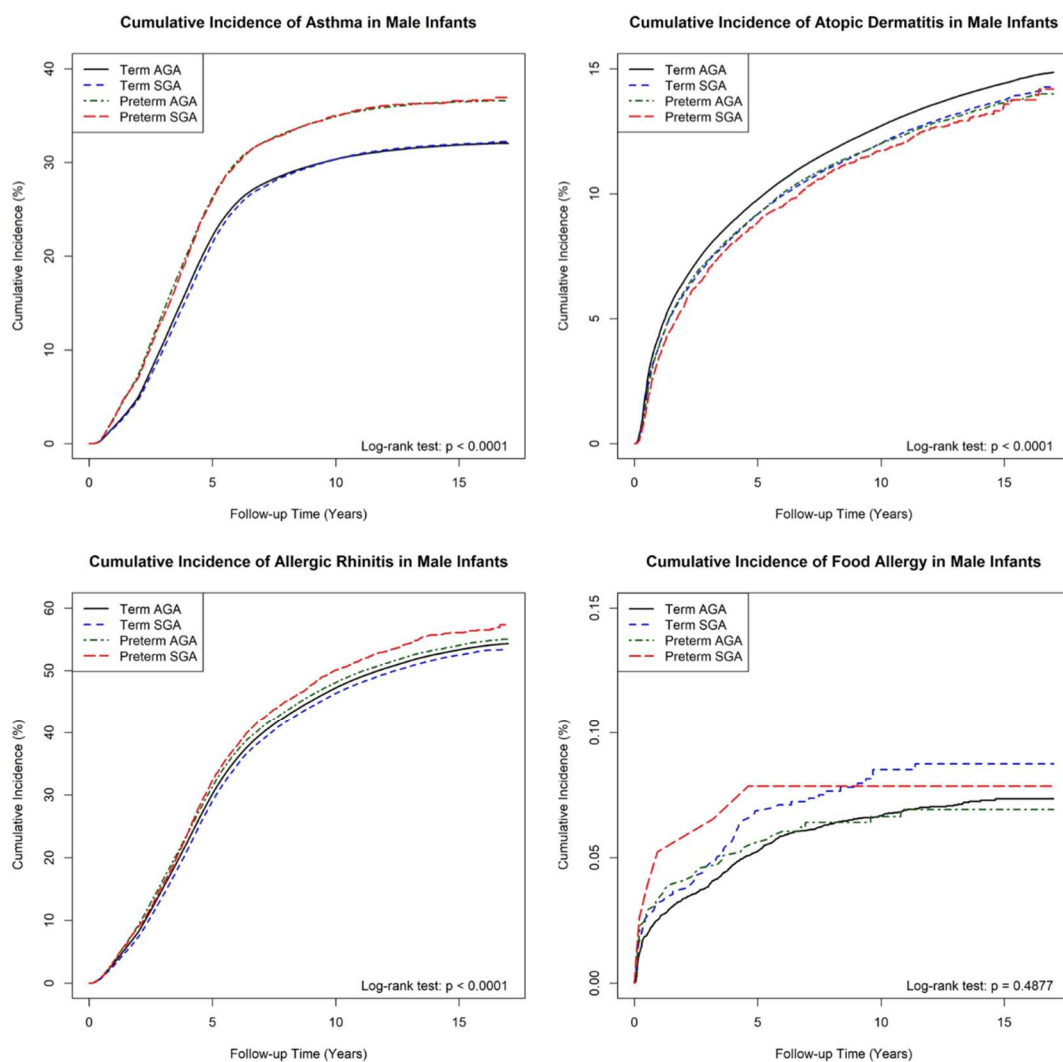
to preterm AGA infants. Neither prematurity nor SGA was linked to food allergy development during follow-up.



Cumulative Incidence of Atopic Diseases

Figures 3.1 and 3.2 present the cumulative incidence curves for atopic diseases across study groups. AD was primarily diagnosed before two years of age, as indicated by the steepest rise in cumulative incidence early in life. Term AGA infants consistently had the highest cumulative incidence of AD throughout the follow-up period.

Figure 3.1 Cumulative incidence of each atopic disease in male infants



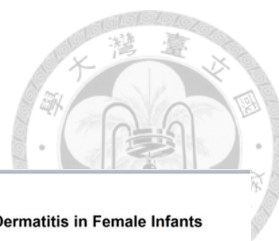
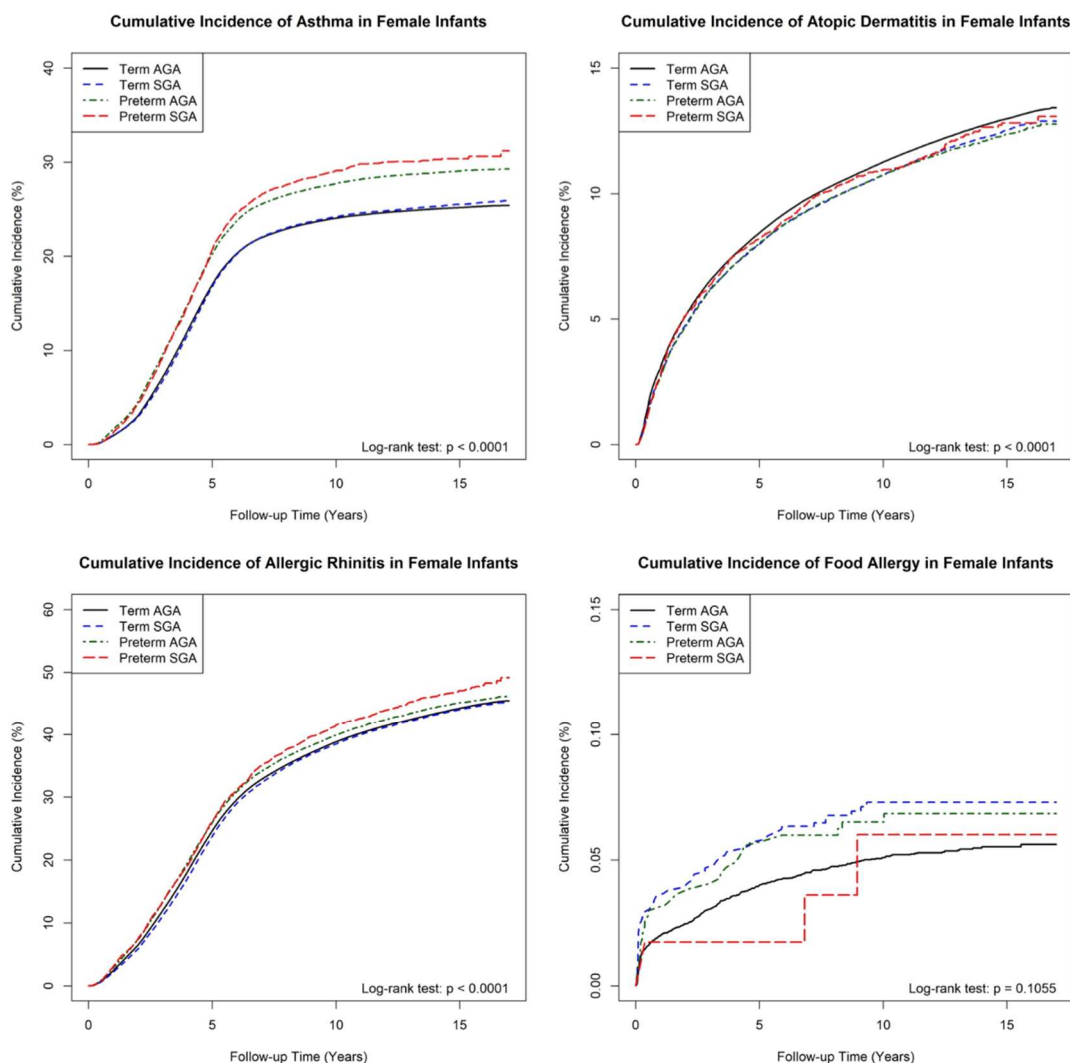


Figure 3.2 Cumulative incidence of each atopic disease in female infants



Asthma diagnoses peaked between two and five years of age, after which the cumulative incidence curve flattened. Preterm infants had a higher cumulative incidence of asthma than term infants, with the largest gap emerging after age five. Among preterm infants, preterm SGA had the highest cumulative incidence of asthma, followed by preterm AGA, term SGA, and term AGA controls. The incidence of AR followed a similar trend, with most diagnoses occurring between two and five years of age. Preterm infants had higher

cumulative incidence of AR than term AGA controls, with preterm SGA infants showing the highest risk. For food allergy, the highest cumulative incidence was observed in term SGA infants, though the small number of cases suggests that this finding should be interpreted with caution.

Discussion

Prematurity and Atopic Diseases

In this study, prematurity was associated with an increased risk of asthma and AR in childhood but a decreased risk of AD. These findings align with results from other nationwide databases and systematic reviews, which demonstrate a stronger association between prematurity and atopic diseases as gestational age decreases.^{8, 17-19} Although the mechanisms underlying prematurity-associated asthma are beyond the scope of this study, multiple contributing factors have been proposed. These include underdeveloped airways, increased antibiotic exposure, heightened susceptibility to viral infections, reduced breastfeeding rates, and an altered gut microbiota.²⁰ Conversely, the association between prematurity and a lower risk of AD may be linked to increased skin permeability in preterm infants, early antigen exposure in the neonatal intensive care unit, and differences in skin microbiota composition.¹⁹

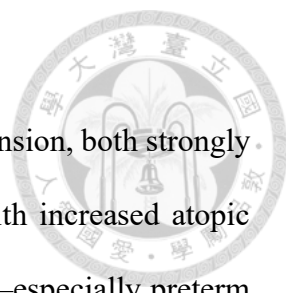
The relationship between prematurity and AR remains controversial in the literature. Some studies suggest that prematurity increases AR risk during childhood but may become a protective factor in adulthood.^{21, 22} One possible explanation for these inconsistencies is the varying follow-up durations across studies. Atopic diseases often manifest at different stages of childhood, with environmental exposures and immune maturation playing a role in disease development. Over time, medical interventions such

as vaccination, inhalers, allergy medications, and immunotherapy, as well as evolving environmental exposures, may modify disease risk. Additionally, asthma and AR share common inflammatory pathways, as evidenced by eosinophilic infiltration in the bronchial mucosa of AR patients, even in the absence of asthma.²³ The "one airway, one disease" concept further supports the close relationship between these two conditions, reinforcing the importance of simultaneous evaluation and treatment.²⁴

SGA and Atopic Diseases

SGA status showed no significant association with atopic diseases in term infants, and only a weak, non-significant association with AR in preterm infants. Prior studies examining fetal growth restriction and atopic diseases have reported conflicting results. For example, a large cohort study from Denmark, Sweden, and Finland found that SGA was associated with a slightly increased risk of asthma-related hospitalization in term infants, whereas a UK-based cohort linked prenatal growth faltering to atopic eczema development in infancy.^{10, 25} However, these associations were modest despite large sample sizes and were inconsistent with findings from other research.²⁶

One potential reason for these discrepancies is the heterogeneous nature of SGA. Fetal growth restriction can manifest as asymmetrical intrauterine growth restriction (IUGR)—often caused by extrinsic factors such as placental insufficiency—or symmetrical IUGR, which may result from intrinsic factors such as chromosomal abnormalities or early intrauterine infections. These varying etiologies may influence immune development differently, complicating the relationship between SGA and atopic diseases. Additionally, IUGR infants are frequently born prematurely, often before SGA status can be fully assessed, which may further obscure associations.²⁷



Maternal complications such as preeclampsia and gestational hypertension, both strongly linked to fetal growth restriction,^{28, 29} have also been associated with increased atopic disease risk in offspring.^{30, 31} In this study, mothers of SGA infants—especially preterm SGA infants—had higher rates of preeclampsia and gestational hypertension, which may have influenced disease risk despite statistical adjustments. Furthermore, maternal atopic history, a key hereditary risk factor for atopic diseases, is often associated with increased risks of both prematurity and fetal growth restriction.³² This interplay between maternal health, fetal growth, and atopic disease risk suggests that SGA alone may not be a sufficient marker for developmental exposures influencing atopic disease outcomes.

Strengths and Limitations

This study has several strengths. It is the first nationwide cohort study in Taiwan to examine the relationship between preterm birth, SGA status, and atopic diseases, leveraging data from a highly representative healthcare system. The large sample size enhances statistical power, and the robust linkage between maternal and child health records enables a comprehensive analysis of perinatal risk factors. The findings provide valuable insights into early-life risk factors for atopic diseases, supporting the development of prevention and screening strategies.

However, certain limitations should be acknowledged. First, some potential confounders, including the severity of SGA, maternal atopic history, and specific environmental exposures, were not available in the dataset, which may have influenced the observed associations. Second, the database does not account for participants' mobility or activity patterns, limiting our ability to assess actual environmental exposures beyond

urbanization level. Lastly, while the study covers the full pediatric period, follow-up duration may still be insufficient to fully capture long-term disease progression. As children grow older, additional exposures and lifestyle factors may modify the influence of perinatal risk factors on atopic diseases.

Conclusion

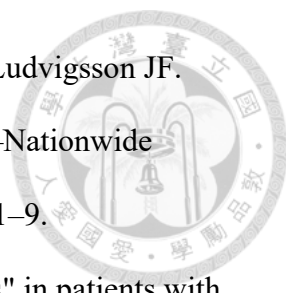
This study suggests that prematurity is associated with an increased risk of asthma and AR and a reduced risk of AD in Taiwanese children. These findings highlight the need for integrated prevention and early screening strategies tailored to preterm infants. In contrast, SGA was not significantly associated with atopic diseases in term infants, though it may modestly increase the risk of AR in preterm infants. Future research should explore alternative fetal growth indicators, such as the Ponderal Index, to better understand the complex interplay between fetal growth and immune system development. Further investigations are needed to elucidate underlying mechanisms and establish causal relationships between perinatal factors and atopic disease risk.

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Chapter 4 Maternal Age and Pediatric Outcomes



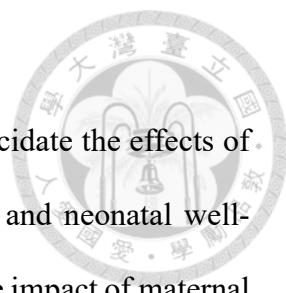
This chapter is based on the following publication:

Su, Y.-Y., Chen, P.-C. (2024). Revisiting Maternal Age and Child Health: A Nationwide Birth Cohort Study in Taiwan. *Journal of the Formosan Medical Association* (in press).
<https://doi.org/10.1016/j.jfma.2024.03.001>

Introduction

Delayed childbearing has emerged as a significant global trend in recent decades, driven by personal choices, cultural values, medical advancements, and economic factors. On the other hand, the global fertility rate has also declined, more than halving over the past 70 years.¹ These factors have increased maternal age and advanced age pregnancies. Advanced maternal age impacts offspring's health, including birth outcomes, development, cognition, behavior, and morbidities.^{2,3} However, advanced maternal age also implies higher parental educational attainment and family income, which have positive impacts on children's health from a socioeconomic perspective.⁴ The effects of maternal age on child health represent a unique interaction between congenital biological factors and acquired environmental influences.

Despite extensive research in Europe, the causes, trends, and long-term consequences of rising maternal age in Taiwan remain relatively unexplored. This is notable given that Taiwan exhibits one of the steepest increases in maternal age globally.⁵ According to demographic data from 2019 by the Ministry of the Interior in Taiwan, the average age of Taiwanese females having their first child is around 31 years old, with 23% of them being over 35 years old. This is 2.4 times higher compared to 10 years earlier, when only 9.4% of first-time mothers were over 35 years old in 2009.⁶

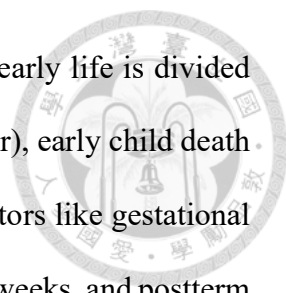


Our study aimed to conduct a nationwide cohort investigation to elucidate the effects of maternal age on offspring health. Given the emphasis on maternal and neonatal well-being for better childhood and adult health, it is crucial to consider the impact of maternal age. We hypothesize that maternal age has a prolonged impact on various aspects of children's health.

Methods

Research data was obtained from Taiwan's National Health Insurance Research Database (NHIRD). The database, with records from nearly 23 million residents since 1996, covers 99.9% of Taiwan's population.⁷ The Health and Welfare Data Center (HWDC) of Taiwan's Ministry of Health and Welfare (MOHW) merged the NHIRD with other health-related databases in 2015, establishing the Taiwan Maternal and Child Health Database (TMCHD).⁸ This integration provides reliable and accurate links between mothers and children. Our cohort included infants born between January 1, 2004, and December 31, 2014. These data were linked to the NHIRD and Death Registration Database for follow-up through 2020, ensuring a minimum follow-up duration of six years for each participant. The follow-up period ensures that the cohort captures the critical age range for diagnosing neurodevelopmental disorders, such as ADHD, which is typically between 7 and 16 years.⁹ The infants were then divided into six groups based on maternal age at birth: <20 years old, 20-24 years old, 25-29 years old, 30-34 years old, 35-40 years old, and ≥ 40 years old. Stillbirth was included as an outcome but excluded from further post-delivery analyses.

Outcome Variables



Stillbirth is defined as fetal death at 20 weeks or later. Mortality in early life is divided into neonatal death (within 28 days), infant death (28 days to one year), early child death (1-4 years), and child death (5-17 years). Birth outcomes include factors like gestational age, birth body weight, and multiple births. Preterm birth is before 37 weeks, and postterm birth is after 42 weeks of gestation. Small for gestational age (below 10th percentile) and large for gestational age (above 90th percentile) were defined by birth weight.¹⁰ Congenital anomalies at birth are reported from the national birth registration database. Neurodevelopmental disorders include cerebral palsy (ICD-9: 343, ICD-10: G80), developmental delay (ICD-9: 783.42, ICD-10: R62.0), autism (ICD-9: 299, ICD-10: F84), and ADHD (ICD-9: 314, ICD-10: F90). Atopic diseases include atopic dermatitis (ICD-9: 691.8, ICD-10: L20), asthma (ICD-9: 493, ICD-10: J45), and allergic rhinitis (ICD-9: 477, ICD-10: J30).

Confounding Variables

Outcomes were adjusted for covariates including age, gender, maternal and pregnancy-related variables, socioeconomic status, and urbanization level. Maternal and pregnancy-related variables were derived from birth registration data coded from hospital delivery reports. These variables included diabetes, hypertension, premature rupture of membranes, preeclampsia or eclampsia, and Cesarean section in the current birth. Socioeconomic status was assessed using monthly insurance salary data reported in the National Health Insurance database. Salary was grouped into three categories: <15,840, 15,841–25,000, and $\geq$ 25,001 New Taiwan Dollars (NTD). These groupings were based on Taiwan's statutory minimum wage during the study period (15,840 NTD) and an additional threshold at 25,000 NTD to distinguish middle-income earners from higher-income groups. These categories were included as covariates in the models to reflect

economic differences among participants and align with established income stratification practices in studies utilizing the National Health Insurance Research Database (NHIRD). Urbanization level was categorized into four groups (Level I: highest, Level IV: lowest) based on residential characteristics. These categories were determined by factors such as population density, education levels, the percentage of elderly residents, the proportion of agricultural employment, and the availability of healthcare resources.¹¹

Statistical Analysis

To evaluate the effect of maternal age at birth on stillbirth, we used logistic models to calculate odds ratios (ORs) and their 95% confidence intervals (CIs), adjusting for various potential confounding factors, including gender, maternal and pregnancy-related variables (such as diabetes, hypertension, premature rupture of membranes, preeclampsia or eclampsia, and Cesarean section), socioeconomic status, and urbanization level. To evaluate the other post-delivery outcomes, we excluded the stillbirths and then employed Cox proportional hazards models to calculate hazard ratios (HRs) and their 95% confidence intervals (CIs), considering the same potential confounding factors as in the logistic models. All statistical analyses were conducted using SAS statistical software (version 9.4; SAS Institute, Cary, NC). We used cubic splines to model maternal age relationships with outcomes in R 4.3.3.

The study adhered to confidentiality guidelines, with ethics approval granted. Data analysis was conducted anonymously, and the Research Ethics Committee of the National Health Research Institutes (No: EC1120508-E) waived the requirement for informed consent. All procedures were carried out in compliance with the pertinent guidelines and regulations.



Results

A total of 2,068,672 infants, comprising 1,078,039 males and 990,633 females, were included in the study. Table 4.1 summarizes stillbirth rates, mortality, birth outcomes, neurodevelopmental disorders, and atopic diseases by maternal age. Table 4.2 lists confounding factors: sex, pregnancy-related variables, urbanization level, and socioeconomic status. The cohort's sex ratio was 1.09, with no significant differences across maternal age groups. Older mothers had higher risks of pregnancy complications and more Cesarean sections. Similarly, urbanization level and socioeconomic status were positively related to maternal age, indicating that mothers of more advanced age tended to live in highly urbanized regions with better economic capability.

Table 4.1 Summary statistics for outcome variables by maternal age at the time of birth

Variables	Maternal age at birth (years old)						
	Total	<20	20-24	25-29	30-34	35-39	≥40
Total n	2068672 (100%)	31657 (1.53%)	222687 (10.76%)	636226 (30.76%)	793641 (38.36%)	330720 (15.99%)	53741 (2.60%)
Stillbirth (0 day)	23494 (1.14%)	836 (2.64%)	2316 (1.04%)	5737 (0.9%)	8195 (1.03%)	5021 (1.52%)	1389 (2.58%)
Total n (excluding stillbirths)	2045178 (100%)	30821 (1.51%)	220371 (10.78%)	630489 (30.83%)	785446 (38.4%)	325699 (15.93%)	52352 (2.56%)
Mortality (excluding stillbirths)							
Neonatal death >0 - <28 days	3409 (0.17%)	87 (0.28%)	350 (0.16%)	888 (0.14%)	1237 (0.16%)	679 (0.21%)	168 (0.32%)
Infant death 28-364 days	3467 (0.17%)	173 (0.56%)	589 (0.27%)	992 (0.16%)	1124 (0.14%)	496 (0.15%)	93 (0.18%)
Early child death 1-4 years	2144 (0.10%)	97 (0.31%)	379 (0.17%)	675 (0.11%)	637 (0.08%)	288 (0.09%)	68 (0.13%)
Child death 5-17 years	1594 (0.08%)	56 (0.18%)	253 (0.11%)	535 (0.08%)	501 (0.06%)	208 (0.06%)	41 (0.08%)
Birth outcomes (excluding stillbirths)							
Birth gestational age (weeks)	38.3 (1.7)	38.2 (2)	38.4 (1.7)	38.4 (1.6)	38.3 (1.7)	38.1 (1.9)	37.8 (2)
Birth body weight (gm)	3071.9 (462.1)	2940.2 (454)	3031.4 (436.3)	3073.1 (439.2)	3083.5 (462.5)	3081.1 (503.0)	3075.1 (539.8)

Multiple births	61658 (3.01%)	340 (1.1%)	3638 (1.65%)	13943 (2.21%)	26540 (3.38%)	15037 (4.62%)	2160 (4.13%)
Preterm	183413 (8.97%)	3536 (11.47%)	17720 (8.04%)	48918 (7.76%)	69700 (8.87%)	36379 (11.17%)	7160 (13.68%)
Postterm	2965 (0.14%)	126 (0.41%)	519 (0.24%)	1024 (0.16%)	876 (0.11%)	354 (0.11%)	66 (0.13%)
Small for gestational age	202608 (9.91%)	5000 (16.22%)	27787 (12.61%)	64324 (10.2%)	72191 (9.19%)	28685 (8.81%)	4621 (8.83%)
Large for gestational age	165512 (8.09%)	1205 (3.91%)	12283 (5.57%)	44454 (7.05%)	66163 (8.42%)	34525 (10.60%)	6882 (13.15%)
Congenital anomalies at birth	159875 (7.82%)	2125 (6.89%)	14528 (6.59%)	45745 (7.26%)	64992 (8.27%)	27673 (8.50%)	4812 (9.19%)
Neurodevelopmental disorders (excluding stillbirths)							
Cerebral palsy	6404 (0.31%)	170 (0.55%)	716 (0.32%)	1797 (0.29%)	2349 (0.3%)	1149 (0.35%)	223 (0.43%)
Developmental delay	252064 (12.32%)	3799 (12.33%)	24598 (11.16%)	73196 (11.61%)	99288 (12.64%)	43623 (13.39%)	7560 (14.44%)
Autism	30229 (1.48%)	337 (1.09%)	2270 (1.03%)	7772 (1.23%)	12303 (1.57%)	6254 (1.92%)	1293 (2.47%)
ADHD	143854 (7.03%)	2860 (9.28%)	17353 (7.87%)	45099 (7.15%)	52287 (6.66%)	22274 (6.84%)	3981 (7.60%)
Atopic diseases (excluding stillbirths)							
Atopic dermatitis	251385 (12.29%)	2350 (7.62%)	21009 (9.53%)	74875 (11.88%)	103364 (13.16%)	43138 (13.24%)	6649 (12.70%)
Asthma	563980 (27.58%)	6775 (21.98%)	57729 (26.2%)	180319 (28.6%)	219573 (27.96%)	86370 (26.52%)	13214 (25.24%)
Allergic rhinitis	902118 (44.11%)	10070 (32.67%)	87840 (39.86%)	284223 (45.08%)	355202 (45.22%)	142411 (43.72%)	22372 (42.73%)

Table 4.2 Summary statistics for confounding variables by maternal age at the time of birth

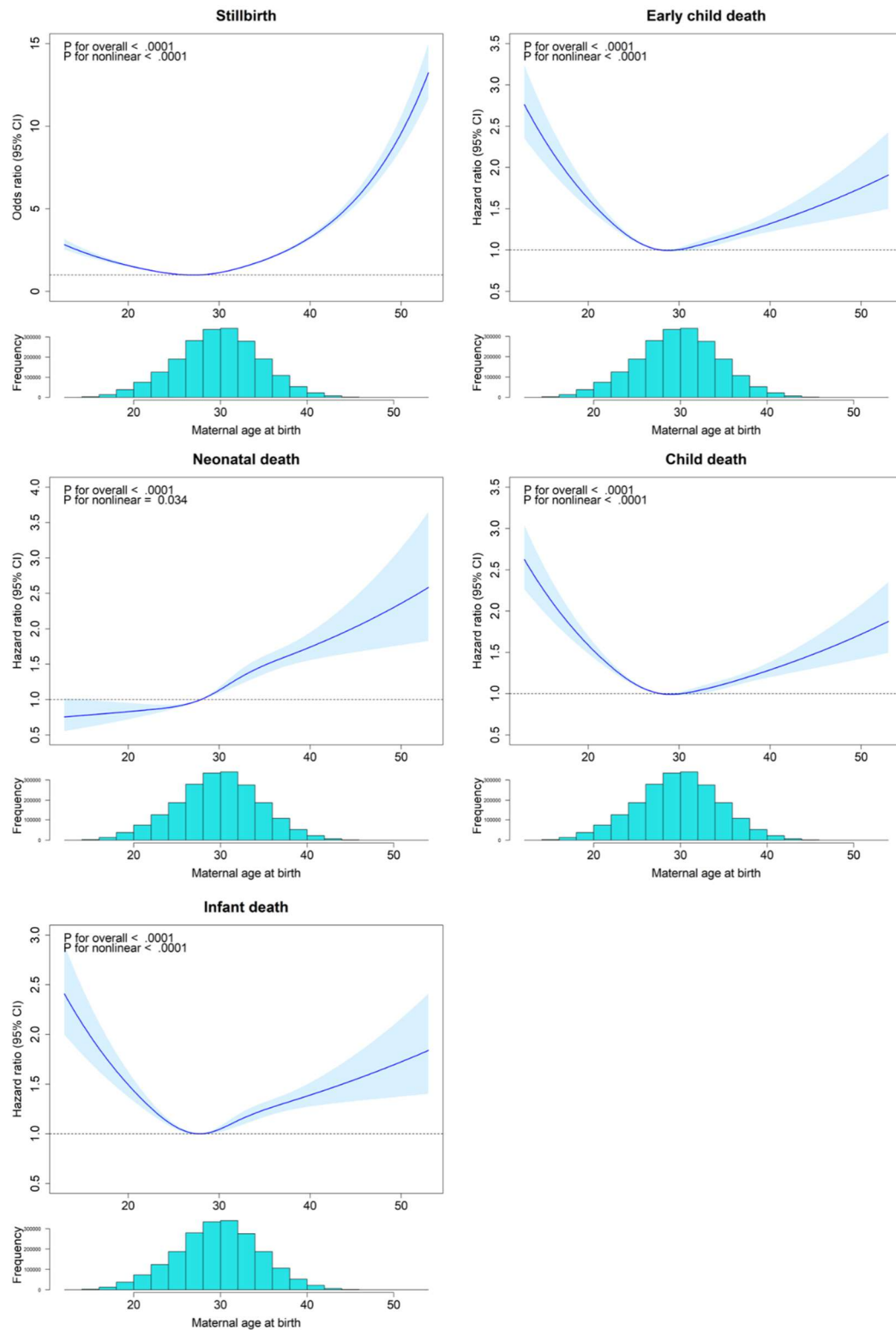
Variables	Maternal age at birth (years old)						
	Total	<20	20-24	25-29	30-34	35-39	≥40
N	2068672 (100%)	31657 (1.53%)	222687 (10.76%)	636226 (30.76%)	793641 (38.36%)	330720 (15.99%)	53741 (2.60%)
Sex							
Male	1078039 (52.11%)	16537 (52.24%)	115611 (51.92%)	331243 (52.06%)	413549 (52.11%)	172999 (52.31%)	28100 (52.29%)
Female	990633 (47.89%)	15120 (47.76%)	107076 (48.08%)	304983 (47.94%)	380092 (47.89%)	157721 (47.69%)	25641 (47.71%)
Parity							
Primipara	1237681 (59.83%)	27023 (85.36%)	153917 (69.12%)	411851 (64.73%)	445770 (56.17%)	167318 (50.59%)	31802 (59.18%)
Multipara	830991 (40.17%)	4634 (14.64%)	68770 (30.88%)	224375 (35.27%)	347871 (43.83%)	163402 (49.41%)	21939 (40.82%)
Maternal and pregnancy-related variables							
Diabetes	20823 (1.01%)	34 (0.11%)	545 (0.24%)	3267 (0.51%)	8395 (1.06%)	6706 (2.03%)	1876 (3.49%)
Hypertension	16764 (0.81%)	154 (0.49%)	1102 (0.49%)	3691 (0.58%)	6172 (0.78%)	4324 (1.31%)	1321 (2.46%)
Premature rupture of membranes	34979 (1.69%)	448 (1.42%)	2993 (1.34%)	9827 (1.54%)	14326 (1.81%)	6264 (1.89%)	1121 (2.09%)
Preeclampsia or eclampsia	10422 (0.5%)	96 (0.3%)	644 (0.29%)	2257 (0.35%)	4000 (0.5%)	2704 (0.82%)	721 (1.34%)
Cesarean section	738452 (35.7%)	5904 (18.65%)	56546 (25.39%)	199414 (31.34%)	293443 (36.97%)	152981 (46.26%)	30164 (56.13%)
Other variables							
Urbanization							
I	555293 (26.84%)	4361 (13.78%)	38385 (17.24%)	151348 (23.79%)	234700 (29.57%)	108599 (32.84%)	17900 (33.31%)
II	649722 (31.41%)	7665 (24.21%)	63855 (28.67%)	199894 (31.42%)	256411 (32.31%)	105156 (31.80%)	16741 (31.15%)
III	376001 (18.18%)	6111 (19.3%)	46916 (21.07%)	127662 (20.07%)	137332 (17.3%)	50411 (15.24%)	7569 (14.08%)
IV	487656 (23.57%)	13520 (42.71%)	73531 (33.02%)	157322 (24.73%)	165198 (20.82%)	66554 (20.12%)	11531 (21.46%)
Socioeconomic status							
<15840	371728 (17.97%)	16750 (52.91%)	71755 (32.22%)	109889 (17.27%)	109512 (13.8%)	52469 (15.87%)	11353 (21.13%)
15841-25000	813822 (39.34%)	12338 (38.97%)	111977 (50.28%)	290859 (45.72%)	273767 (34.5%)	106631 (32.24%)	18250 (33.96%)
≥25001	883122 (42.69%)	2569 (8.12%)	38955 (17.49%)	235478 (37.01%)	410362 (51.71%)	171620 (51.89%)	24138 (44.92%)

Stillbirths and Mortality

Stillbirth rates were highest in mothers under 20, decreased with age, but rose again after 30. Neonatal and infantile mortality demonstrated a similar relationship with maternal age at birth. Likewise, child mortality at ages one to four years and five to seventeen years decreased as maternal age increased, but rebounded when maternal age exceeded 35 years. Although still apparent, the difference in offspring mortality between each maternal age group at birth appears to diminish as the child's age increases.

Figure 4.1 shows the association between maternal age, control variables, and mortality, adjusted for confounders. These data reveal a reverse J-shaped relationship between maternal age and child mortality at different ages. Similarly, stillbirth rates also display a J-shaped relationship with maternal age. However, an exception is observed for neonatal mortality, which exhibits a positive correlation with increasing maternal age, indicating that young maternal age (<20 years) alone has less impact on neonatal death.

Fig. 4.1 Exposure–response relationship between maternal age and mortality

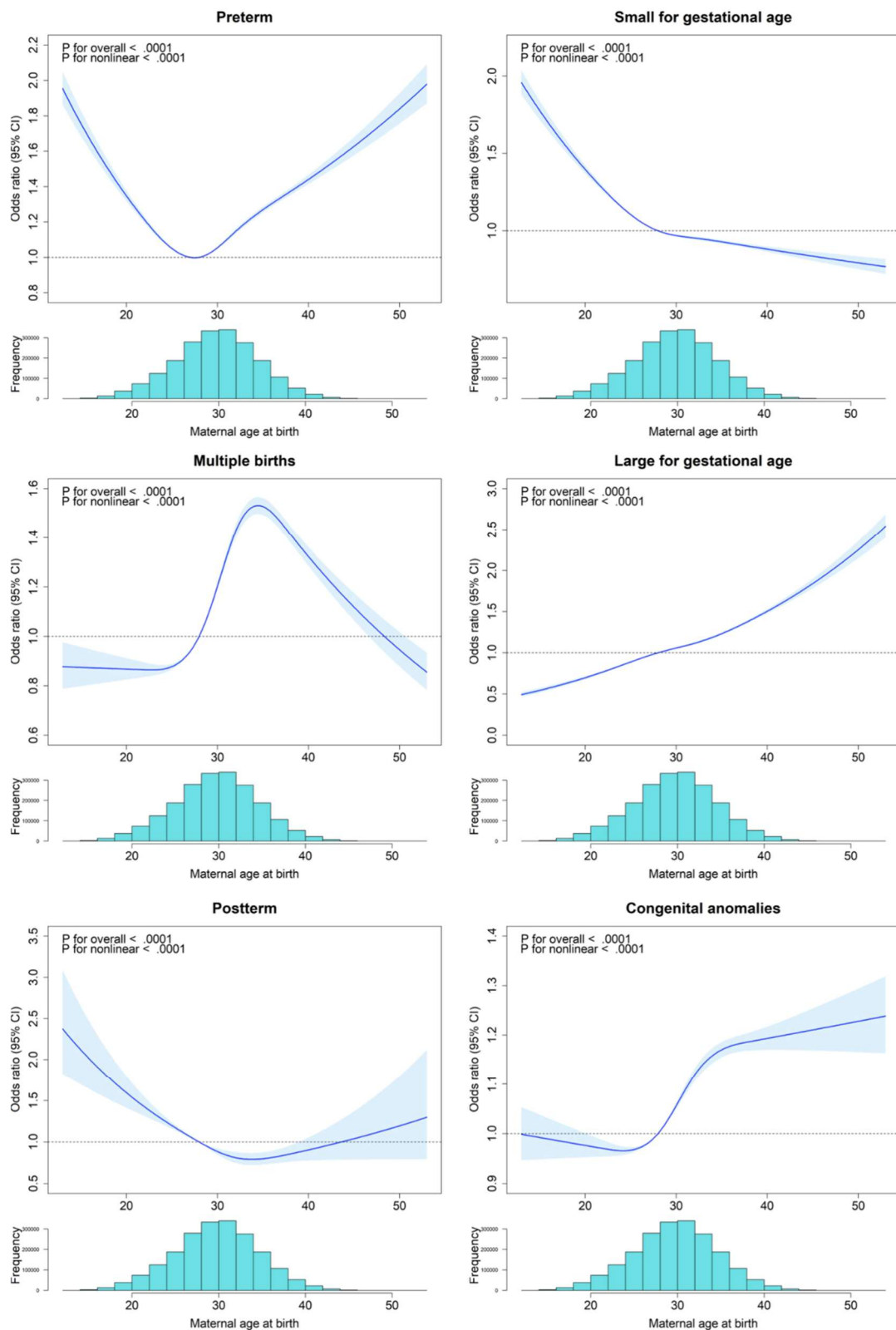


Birth Outcomes

Regarding birth outcomes, as maternal age increased, gestational age exhibited a decrease, while birth weight demonstrated an increase. Consequently, the risks of prematurity and being large for gestational age (LGA) were elevated, whereas the risks of post-term births and being small for gestational age (SGA) diminished with advancing maternal age at birth. It is noted that the incidence of preterm births increases as maternal age decreases among mothers below 25 years of age, compared to mothers aged 25-29 years, even though the mean gestational age at birth is consistently negatively related to maternal age. Multiple births and congenital anomalies increased with maternal age, except for higher congenital anomaly risks in mothers under 20.

The association between maternal age, control variables, and birth outcomes is presented in Figure 4.2 After adjusting for confounding factors, a reverse J-shaped relationship is observed between maternal age and the risks of preterm birth and post-term birth. Furthermore, maternal age exhibits a positive correlation with the risk of being LGA and a negative correlation with the risk of being SGA, even after accounting for confounding factors. The association between young maternal age and the risks of multiple births and congenital anomalies disappeared after adjusting for control variables, while advanced maternal age continued to show significant associations.

Fig. 4.2 Exposure–response relationship between maternal age and birth outcomes



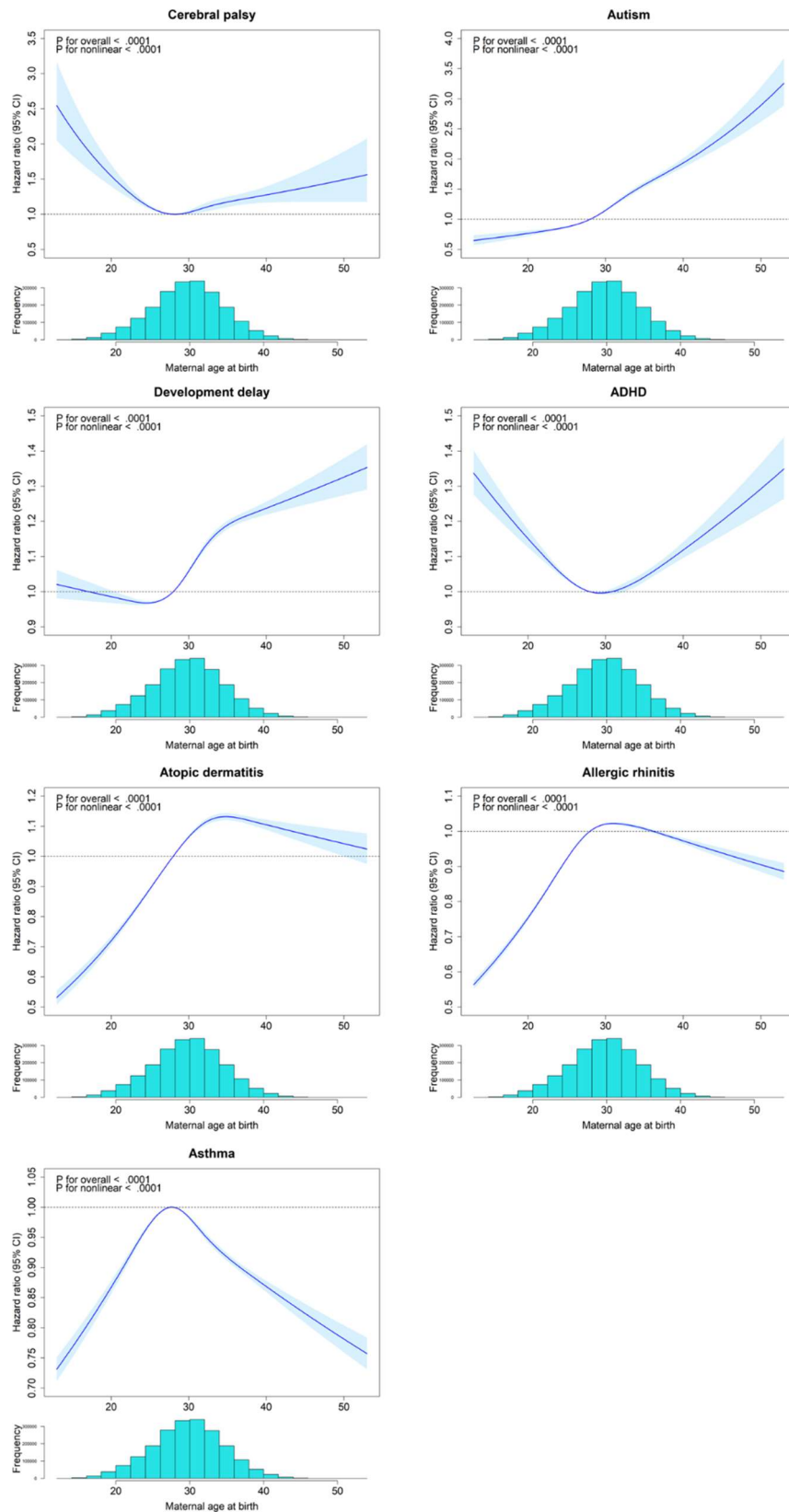
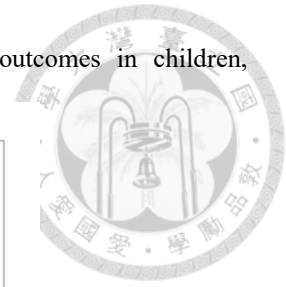
Neurodevelopmental Disorders

Neurodevelopmental disorders, including developmental delay, cerebral palsy, autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD), exhibited varying associations with maternal age, each with different nadirs. Children born to mothers in their 20s had the lowest risks for developmental delay, cerebral palsy, and ASD, while the risk of ADHD was lowest in children born to mothers aged 30-34 years. Figure 4.3 shows a reverse J-shaped association between maternal age and risks of developmental delay, cerebral palsy, and ADHD. However, the risk of ASD exhibited a positive correlation with increasing maternal age.

Atopic Diseases

Atopic dermatitis (AD), asthma, and allergic rhinitis (AR) increased with maternal age but diminished after 30. Figure 4.3 reveals an inverted U-shaped association between atopic disease incidence and maternal age after adjustment.

Fig. 4.3 Exposure–response relationships between maternal age and health outcomes in children, illustrating neurodevelopmental outcomes and atopic diseases



Discussion

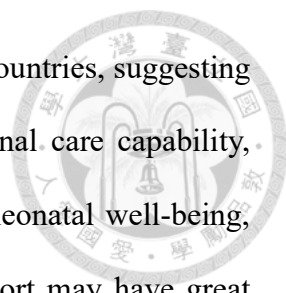
Sex Ratio and Maternal Age

The cohort's sex ratio was approximately 1.09, with no significant differences across maternal age groups. The decline in son preference in Taiwan since 1990 makes sex-selective abortion unlikely.^{12,13} While the relationship between maternal age and sex ratio at birth is debated, our findings align with studies suggesting environmental factors play a more significant role than maternal condition.¹⁴

Stillbirth and Neonatal Mortality

Advanced and young maternal age are linked to stillbirths and neonatal death in various cohort studies.¹⁵ In our study, while young maternal age did not increase the risk of neonatal death after adjusting for covariates, the risks for stillbirth and mortality in children of other ages remained associated with young maternal age. The lack of a reverse J-shaped pattern in neonatal mortality can be attributed to two primary factors. First, the limited number of neonatal deaths in the young maternal age group (<20 years old) reduces the ability to establish a reverse J-shaped association after adjusting for confounding variables. Second, young maternal age is associated with higher rates of pregnancy termination, often driven by limited socioeconomic resources. This results in a shift in mortality to earlier gestational periods, transitioning from neonatal deaths to stillbirths. Similar patterns have been observed in other population-based cohorts, where factors such as birth defects, pregnancy terminations, and clinical practices significantly influenced perinatal mortality trends.¹⁶ This suggests a complex interplay of biological and environmental factors. In low- and middle-income countries, factors like maternal education and lack of postnatal care significantly impact neonatal mortality, independent of maternal age.¹⁷ Additionally, regional variation in the relationship between young





maternal age and neonatal mortality has been observed in different countries, suggesting differences in environmental risk factors. We speculate that maternal care capability, reflected by socioeconomic status and urbanization, is crucial for neonatal well-being, independent of maternal age. Adequate prenatal and perinatal support may have great potential in improving outcomes in neonates of both young and advanced age mothers.

Long-term Impact of Maternal Age

Young and advanced maternal age had prolonged effects on child mortality. Literature has demonstrated that maternal and socioeconomic factors are equally and highly impactful on child mortality.¹⁸ Evidence on long-term maternal age impact on child health varies across countries. Some studies suggest children of older mothers have advantages in nutrition and education, which may persist into adulthood.¹⁹ Some believe that the benefits of being born to an advanced-age mother are significant, provided the child survives the more adverse perinatal outcomes. Conversely, our results indicate maternal age effects persist into adulthood, impacting long-term mortality. This finding is supported by a survey of elderly individuals the United States,²⁰ which found that offspring born to mothers younger than 25 or older than 35 have worse outcomes in mortality, self-rated health, height, and obesity compared to those born to mothers aged 25–34.

The use of in vitro fertilization (IVF) is more common among older mothers and raises questions about its potential influence on child health outcomes.²¹ Due to the nature of our data, we could not evaluate the direct effects of IVF in this study. However, evidence from a large-scale Japanese cohort suggests that IVF conception is not associated with adverse long-term health or developmental outcomes.²² Further research is needed to

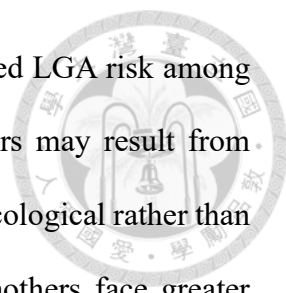
explore specific IVF protocols and their implications for child health.



Birth Outcomes and Maternal Age

Both young and advanced maternal ages are associated with preterm birth risks, as supported by other studies.²³ Interestingly, as maternal age increased over time, a report from the United States found that the incidence of preterm births decreased from 2007 to 2014. On the contrary, during our study period from 2004 to 2014, the incidence of preterm births in Taiwan showed an increase.²⁴ It is plausible to conclude that the overall decline in preterm births, attributable to a reduction in births among younger mothers, was counterbalanced by an increase in births among mothers of advanced age. The trend of delayed childbearing ultimately resulted in elevated preterm birth risks.²⁵ We believe that the risks for preterm birth will continue to rise globally as the effect of increased maternal age gradually outweighs advancements in medical and public health policies.

Advanced maternal age is also linked to higher birth weights, reducing SGA risks but increasing LGA risks, consistent with studies from Nordic countries.²⁶ However, it is worth noting that evidence shows the risks for low birth weight increased in advanced age mothers after adjusting for parity, which is also positively related to birth body weight.²⁷ In our study, the risks for LGA were independently associated with advanced maternal age after adjusting for variables, including parity. Based on our results, Low birth weight and LGA risks are likely to rise in Taiwan as maternal age increases. The observed linear relationship between maternal age and birth weight outcomes (SGA and LGA), rather than a J-curve, likely stems from several factors. First, the positive association between maternal age and birth weight reported in the literature plateaus around ages 30–40.²⁸ Second, despite adjustments for gestational diabetes, unmeasured



maternal metabolic or lifestyle factors may contribute to the increased LGA risk among advanced-age mothers. Third, higher SGA risks in younger mothers may result from incomplete physical growth and relative malnutrition, linked to gynecological rather than chronological age.²⁹ In resource-constrained settings, adolescent mothers face greater nutritional demands, impacting fetal growth. While our study cannot establish causality, these factors provide plausible explanations for the observed trends. The risk of multiple births was positively related to maternal age. Although beyond the scope of our study, evidence suggests that advanced maternal age may not be an additional risk factor for neonatal outcomes in twins, whereas twin pregnancies are associated with increased risk for most adverse perinatal outcomes.³⁰ Together with advanced maternal age, the risks for multiple births may also have an additive effect on the increased incidence of Cesarean sections.

Our findings on congenital anomalies align with previous research showing increased risks in advanced age mothers, with limited impact in younger mothers. Although not identified in our study, some literature suggests major congenital anomalies decrease with maternal age, indicating an "all-or-none" phenomenon.³¹

Neurodevelopmental Disorders and Maternal Age

The association between maternal age and neurodevelopmental disorders in children varies depending on different races, regions, developmental aspects, and specific disorders being targeted. Our results are in line with previous literature. For example, advanced maternal age is associated with an increased risk of developing ASD and ADHD.³² Conversely, young maternal age is closely associated with ADHD but has been found to have no influence on ASD risks in some cohorts.³³ These results should be

interpreted carefully, as both ASD and ADHD are strongly affected by genetic and environmental factors. High familial risk populations show a reverse relationship between maternal age and ASD compared to general population samples.³⁴ Additionally, the genetic relationship between ADHD and reproductive traits may explain why young mothers have higher ADHD risk offspring.³⁵

Nonetheless, a reverse J-shaped relationship between maternal age and children's neurodevelopmental wellness is well accepted, as reflected in the risks for cerebral palsy and developmental delay. This relationship can be largely explained by the increased risks for preterm birth and adverse birth outcomes in advanced age mothers, as well as antenatal factors in young maternal age.

Survivorship bias is a potential concern when evaluating long-term neurodevelopmental outcomes like cerebral palsy and developmental delay. In our study, only stillbirths were excluded, while all live births were included, inherently accounting for early mortality. The significantly higher prevalence of developmental delay—over tenfold compared to mortality—minimizes the likelihood of bias in our findings. Additionally, the reverse J-shaped relationship observed between maternal age and cerebral palsy incidence, along with similar trends between maternal age and mortality across different child age groups, supports the robustness of our results. The Cox proportional hazards model, used in this study, is a statistical tool commonly applied in survival analysis and helps account for survivorship bias by focusing on time-to-event data. It is particularly effective when handling censored data, such as cases where individuals have not yet experienced the event of interest by the end of the study. This methodological approach further strengthens the reliability of our findings. However, we acknowledge that some residual bias may still

exist and encourage further studies to explore this in greater depth.



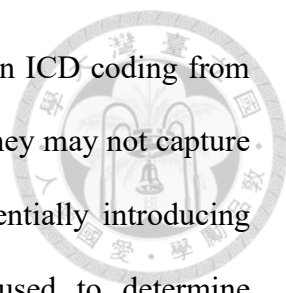
Atopic Diseases and Maternal Age

Increasing maternal age appeared to lower the risks of developing atopic diseases in offspring in our cohort. The "developmental origins of health and disease" (DOHaD) hypothesis suggests that maternal age, as an early developmental exposure, may influence the risks of developing chronic illnesses like atopic diseases later in life. However, studies in this area have demonstrated controversial results. Systemic review and meta-analysis regarding maternal risks factors in AD reported perinatal events and family history being the major determining risk factors.³⁶ We infer that, given the multifactorial nature of atopic diseases, genetic and environmental factors, along with perinatal events, contribute more to the development of these diseases. The role of maternal age cannot adequately explain the risk and remains uncertain. This underscores the need for an evidence synthesis of published studies on the topic.

Strengths and Limitations

This is the first nationwide cohort study in Taiwan to analyze the health impacts on children by maternal age, with high confidence due to the large participant number covered by the NHI. While focused on Taiwan, the findings may offer valuable insights for other East Asian populations and warrant further study. This research can aid in the development of public health strategies to better support the health of mothers and their children. The association between health outcomes and other factors related to maternal age, such as parity, Cesarean section, and ART, could be further explored.

The main limitation of this study is the nature of the database, which prevents establishing



causal relationships. Additionally, disease definitions relied solely on ICD coding from health insurance claims. While these codes are routinely validated, they may not capture the full clinical spectrum of diseases or distinguish subtypes, potentially introducing misclassification bias. The location of household registration, used to determine urbanization levels, may not always reflect the participants' actual place of residence, which could lead to misclassification of related exposures. Another limitation is that the data did not consider mobility and time-activity patterns, which partially reflect environmental exposure. Although we surveyed mortality and long-term disease effects, the optimal follow-up length remains unknown. Lastly, the association between diseases and maternal age could be diluted by other exposures.

Conclusions

We believe that as maternal age increases, socioeconomic resources may fail to counterbalance the negative effects of physiological decline. This imbalance can lead to various unfavorable long-term health outcomes in offspring. The complexities in these relationships underscore the need for further exploration to clarify contributing factors and pathways. Understanding the interplay between maternal age, socioeconomic status, and health outcomes is crucial for effective intervention development.

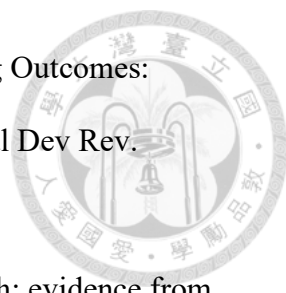
To address these issues, public health systems must support advanced age mothers and their children with comprehensive care, tailored education, and targeted interventions. Our study underscores the need for continued research to unravel the complexities of how maternal age influences long-term health outcomes in offspring, particularly in Taiwan. By doing so, we can inform and refine public health strategies to support families more effectively, ensuring healthier futures for children born to mothers of advanced age.

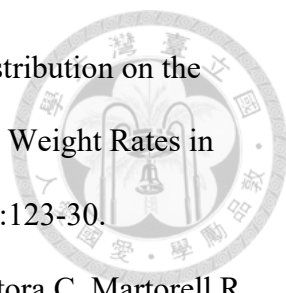


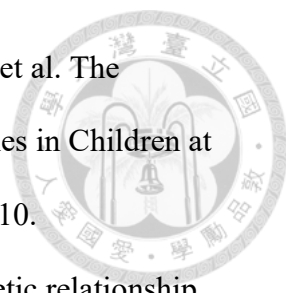
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Chapter 5 Birth Order and Neurodevelopmental Disorders



Introduction

Autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and cerebral palsy (CP) are significant neurodevelopmental disorders in children, characterized by complex etiologies and long-term impacts on healthcare systems and families. Emerging research suggests that siblings of children with neurodevelopmental disorders, such as CP, may face higher risks of related morbidities and early mortality, potentially due to shared genetic or environmental factors.¹ Furthermore, sibling dynamics, such as birth order and family size, may shape neurodevelopmental outcomes. Firstborn children might encounter unique challenges due to shifts in parental attention, potentially increasing vulnerability to ADHD, while later-born children have been associated with lower adaptive functioning and intelligence scores.^{2,3} With declining birth rates and smaller family sizes globally and in Taiwan, investigating the impact of birth order and sibling presence on neurodevelopmental outcomes is increasingly relevant.⁴

Both ADHD and ASD exhibit strong genetic influences. Meta-analysis of 37 twin studies estimates the heritability of ADHD and related traits, such as inattentiveness and hyperactivity, to be approximately 74%.⁵ Similarly, ASD twin studies report heritability estimates ranging from 40% to 80%, with variation depending on population and study design.⁶ Despite the predominant role of genetics, environmental factors, such as family structure and sibling dynamics, also contribute significantly to the development and expression of these disorders. For example, environmental factors account for 10% to 40% of the variance in ADHD twin studies, and social interaction outcomes in individuals

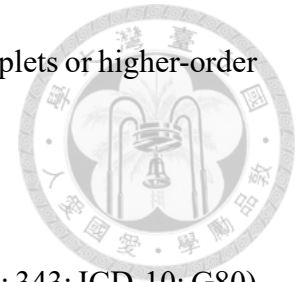
with ASD can be positively influenced by sibling relationships.^{7, 8} These modifiable environmental factors are particularly important from a public health perspective, as they may provide opportunities for targeted interventions. However, few studies have investigated the relevance of birth order to ADHD or ASD, and whether single children face higher or lower risks compared to children in larger families remains largely unexplored. Investigating these gaps is critical to inform strategies aimed at mitigating risks associated with sibling dynamics and improving outcomes for children and their families.

This study aims to investigate the effects of sibling factors, including birth order and sibling dynamics, on childhood neurodevelopmental disorders. Utilizing a large, nationally representative cohort from Taiwan's Birth Registration Database, we analyzed these associations while accounting for potential confounding factors. This research seeks to address gaps in the existing literature and provide insights into the influence of sibling dynamics on neurodevelopmental outcomes, contributing to a better understanding of these complex conditions.

Methods

We utilized Taiwan's Birth Registration Database, including all live births from January 1, 2004, to December 31, 2014, linked to the National Health Insurance Research Database (NHIRD) and Death Registration Database for follow-up through 2020. The NHIRD is a comprehensive database that has collected medical records for nearly 23 million Taiwanese residents since 1996, covering approximately 99.9% of the population.⁹ Participants were categorized into four groups by sibling status and birth order: single child, first-born sibling, second-born sibling, and third-or-later-born sibling.

For consistency, twins were classified as second-born siblings, and triplets or higher-order multiples were classified as third-born siblings.



Neurodevelopmental disorders included in this study were CP (ICD-9: 343; ICD-10: G80), developmental delay (ICD-9: 783.42; ICD-10: R62.0), ASD (ICD-9: 299; ICD-10: F84), and ADHD (ICD-9: 314; ICD-10: F90). Birth outcomes, considered as confounding variables, included gestational age and birth weight. Preterm birth was defined as delivery before 37 completed weeks of gestation, and small-for-gestational-age was defined as a birth weight below the 10th percentile for gestational age.¹⁰ Socioeconomic status was evaluated using monthly salary data from the National Health Insurance database, categorized into three income brackets: less than 15,840 New Taiwan Dollars (NTD), 15,841–25,000 NTD, and 25,001 NTD or more. These thresholds were chosen based on Taiwan's statutory minimum wage during the study period (15,840 NTD) and an additional cutoff of 25,000 NTD to differentiate middle-income earners from higher-income groups. Urbanization levels were classified into four categories (Level I: most urbanized, Level IV: least urbanized), reflecting residential characteristics such as population density, educational attainment, the proportion of elderly residents, agricultural employment rates, and access to healthcare resources.¹¹

We employed the Kaplan-Meier method to estimate the cumulative incidence of neurodevelopmental disorders across groups and used the log-rank test to compare differences in disease risk between groups. Cox proportional hazards models were then used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs), adjusting for potential confounders, including maternal age, child gender, preterm status, small for gestational age, monthly insurance salary, and urbanization level. Subgroup analyses

were conducted to evaluate the robustness of the observed associations and to explore potential influences of multiple births, genetic factors, and specific confounders. These subgroups included singletons, with multiple births excluded to minimize potential biases, singletons from families without two or more siblings sharing the same disorder to reduce shared genetic effects, and stratifications based on gender, maternal age, preterm versus full-term status, monthly insurance salary, and urbanization level. All statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute, Cary, NC).

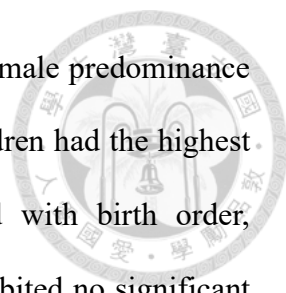
The study was approved by the National Health Research Institutes' Ethics Committee. Data analysis was performed anonymously, and the requirement for informed consent was waived. All procedures adhered to ethical guidelines and regulations.

The data supporting the findings of this study were obtained from the National Health Insurance Research Database, maintained by the Bureau of National Health Insurance, Department of Health. Due to licensing restrictions, these data are not publicly available. However, data may be made available upon reasonable request and with permission from the National Health Research Institutes. The datasets used and analyzed in this study are available from the corresponding author upon reasonable request.

Results

Descriptive Statistics

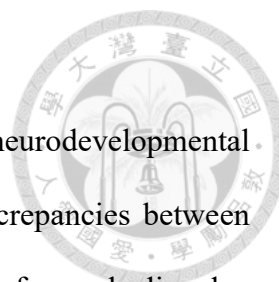
A total of 2,045,178 children were included in the study, with descriptive statistics summarized in Table 5.1. Among children with siblings, the risk of CP increased with birth order, while ASD and ADHD were most prevalent in first-born siblings and decreased with later birth order. Single children, serving as the control group, exhibited



higher risks of ASD and ADHD compared to those with siblings. A male predominance was observed across all groups (overall sex ratio: 1.09). Single children had the highest male-to-female ratio (1.20), while male predominance increased with birth order, reaching 1.16 in third-or-later-born siblings. First-born siblings exhibited no significant sex preference (1.01). Advanced maternal age (≥ 35 years) was most frequent among single children and increased with birth order among siblings. First-born siblings had the longest gestational age, followed by single children, second-born, and third-or-later-born siblings. Birth weight declined with increasing birth order, with single children having the highest average and third-or-later-born siblings the lowest. Differences in gestational age and birth weight were minimal and likely not clinically significant. Prematurity risks increased with birth order, while small-for-gestational-age risk showed no consistent trend. Higher birth order was associated with lower family income and rural residence.

Table 5.1 Summary statistics for outcome variables and confounding variables by number of siblings and birth order

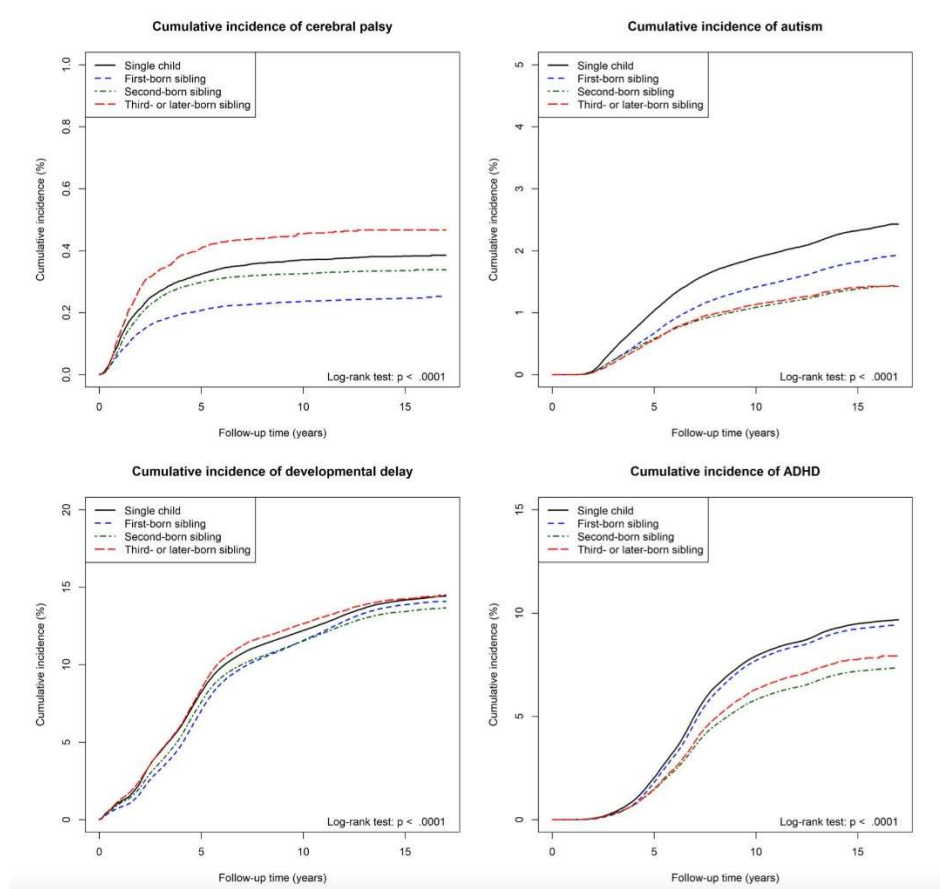
Variables	Number of Siblings and Birth Order				
	Total	Single Child	First-born Sibling	Second-born Sibling	Third- or later-born Sibling
Total n	2045178 (100%)	463544 (22.7%)	725077 (35.5%)	729300 (35.7%)	127257 (6.2%)
Neurodevelopmental disorders					
Cerebral palsy	6404 (0.3%)	1724 (0.4%)	1725 (0.2%)	2385 (0.3%)	570 (0.5%)
Developmental delay	252064 (12.3%)	59918 (12.9%)	88849 (12.3%)	87296 (12.0%)	16001 (12.6%)
Autism	30229 (1.5%)	9414 (2.0%)	11035 (1.5%)	8359 (1.2%)	1421 (1.1%)
ADHD	143855 (7.0%)	37614 (8.1%)	56241 (7.8%)	42514 (5.8%)	7486 (5.9%)
Gender					
Male	1065666 (52.1%)	252447 (54.5%)	364783 (50.3%)	380146 (52.1%)	68290 (53.7%)
Female	979512 (47.9%)	211097 (45.5%)	360294 (49.7%)	349154 (47.9%)	58967 (46.3%)
Maternal age (years old)					
<20	30820 (1.5%)	6793 (1.5%)	19291 (2.7%)	4313 (0.6%)	423 (0.3%)
20-24	220370 (10.8%)	40516 (8.7%)	110027 (15.2%)	59297 (8.1%)	10530 (8.3%)
25-29	630489 (30.8%)	112073 (24.2%)	288416 (39.8%)	196216 (26.9%)	33784 (26.6%)
30-34	785448 (38.4%)	170551 (36.8%)	255059 (35.2%)	310213 (42.5%)	49625 (39.0%)
≥35	378051 (18.5%)	133611 (28.8%)	52284 (7.2%)	159261 (21.8%)	32895 (25.9%)
Birth outcomes					
Birth gestational age	38.3 (1.7)	38.3 (1.7)	38.6 (1.6)	38.0 (1.8)	37.7 (2.1)
Birth body weight	3071.9 (462.1)	3090.6 (462.5)	3083.5 (421.5)	3064.6 (480.5)	2980.4 (553.1)
Preterm	183410 (9.0%)	38350 (8.3%)	43253 (6.0%)	78911 (10.8%)	22896 (18.0%)
Small for gestational age	202609 (9.9%)	46966 (10.1%)	79659 (11.0%)	62044 (8.5%)	13940 (11.0%)
Socioeconomic status					
Monthly insurance salary (New Taiwan dollars)					
<15840	365945 (17.9%)	97962 (21.1%)	120852 (16.7%)	114356 (15.7%)	32775 (25.8%)
15841-25000	803389 (39.3%)	175842 (37.9%)	276025 (38.1%)	295916 (40.6%)	55606 (43.7%)
≥25001	875844 (42.8%)	189740 (40.9%)	328200 (45.3%)	319028 (43.7%)	38876 (30.6%)
Urbanization					
I	548176 (26.8%)	136981 (29.6%)	196711 (27.1%)	189657 (26.0%)	24827 (19.5%)
II	642616 (31.4%)	145770 (31.5%)	231119 (31.9%)	229599 (31.5%)	36128 (28.4%)
III	372190 (18.2%)	80825 (17.4%)	133012 (18.3%)	134266 (18.4%)	24087 (18.9%)
IV	482196 (23.6%)	99968 (21.6%)	164235 (22.7%)	175778 (24.1%)	42215 (33.2%)



Cumulative Incidence by Birth Order and Sibling Status

Figure 5.1 illustrates the cumulative incidences of childhood neurodevelopmental disorders stratified by the number of siblings and birth order. Discrepancies between groups became most pronounced after the mean age of diagnosis for each disorder. Specifically, these differences were evident after 16 months for CP, 5 years for ASD, and 7 years for ADHD.¹²⁻¹⁴ The consistent discrepancy across all ages for developmental delay highlights its unique risk profile compared to other disorders. These findings underscore the influence of birth order and sibling status on the timing and magnitude of neurodevelopmental risks.

Figure 5.1 Cumulative incidence of childhood neurodevelopmental disorders by sibling status and birth order

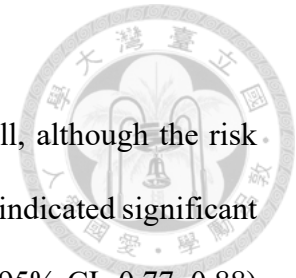


Adjusted Analyses

The adjusted analyses are presented in Table 5.2, revealing a consistent reduction in neurodevelopmental disorder risks among children with siblings compared to single children. However, nuanced differences were observed based on sibling birth order.

Table 5.2 The relationship between number of siblings and birth order, maternal age, confounding variables and childhood neurodevelopmental disorders

Control variables	Neurodevelopment disorders			
	Cerebral palsy	Developmental delay	Autism	ADHD
Number of siblings and birth order				
Single child	Reference	Reference	Reference	Reference
First-born sibling	0.71 (0.66 to 0.76)	1.04 (1.03 to 1.05)	0.95 (0.92 to 0.97)	1.05 (1.03 to 1.06)
Second-born sibling	0.83 (0.77 to 0.88)	0.95 (0.94 to 0.96)	0.61 (0.60 to 0.63)	0.77 (0.75 to 0.78)
Third- or later-born sibling	0.89 (0.80 to 0.98)	0.97 (0.96 to 0.99)	0.60 (0.57 to 0.64)	0.79 (0.77 to 0.81)
Maternal age (years old)				
<20	1.64 (1.40 to 1.93)	1.01 (0.98 to 1.04)	0.79 (0.71 to 0.88)	1.17 (1.13 to 1.21)
20-24	1.10 (1.01 to 1.20)	0.94 (0.93 to 0.95)	0.81 (0.77 to 0.85)	1.05 (1.03 to 1.07)
25-29	Reference	Reference	Reference	Reference
30-34	0.99 (0.93 to 1.05)	1.13 (1.12 to 1.14)	1.34 (1.30 to 1.38)	1.00 (0.99 to 1.02)
≥35	1.04 (0.97 to 1.12)	1.22 (1.21 to 1.24)	1.73 (1.67 to 1.78)	1.08 (1.07 to 1.10)
Gender				
Male	1.24 (1.18 to 1.30)	1.80 (1.79 to 1.82)	4.30 (4.17 to 4.43)	3.19 (3.15 to 3.23)
Birth outcomes				
Preterm	6.71 (6.36 to 7.08)	1.60 (1.58 to 1.62)	1.40 (1.35 to 1.45)	1.32 (1.29 to 1.34)
Small for gestational age	2.02 (1.90 to 2.15)	1.41 (1.39 to 1.43)	1.22 (1.18 to 1.27)	1.24 (1.22 to 1.26)
Socioeconomic status				
Monthly insurance salary (New Taiwan dollars)				
<15840	1.08 (1.00 to 1.16)	1.08 (1.06 to 1.09)	1.13 (1.09 to 1.16)	1.29 (1.27 to 1.31)
15841-25000	0.99 (0.93 to 1.04)	0.99 (0.98 to 1.00)	0.89 (0.86 to 0.91)	1.07 (1.06 to 1.08)
≥25001	Reference	Reference	Reference	Reference
Urbanization				
I	Reference	Reference	Reference	Reference
II	0.95 (0.89 to 1.01)	0.88 (0.88 to 0.89)	0.89 (0.86 to 0.91)	0.87 (0.86 to 0.88)
III	1.04 (0.97 to 1.12)	0.85 (0.84 to 0.86)	0.79 (0.77 to 0.82)	0.77 (0.76 to 0.79)
IV	0.98 (0.91 to 1.05)	0.81 (0.80 to 0.82)	0.71 (0.69 to 0.74)	0.68 (0.67 to 0.69)



Regarding CP, children with siblings exhibited reduced risks overall, although the risk showed a slight increase with higher birth order. Hazard ratios (HRs) indicated significant reductions: 0.71 (95% CI: 0.66–0.76) for first-born siblings, 0.83 (95% CI: 0.77–0.88) for second-born siblings, and 0.89 (95% CI: 0.80–0.98) for those born third or later.

ASD followed a similar trend of lower risks among children with siblings. First-born siblings had the highest risk among those with siblings (HR: 0.95, 95% CI: 0.92–0.97), but the risk decreased substantially for second-born siblings (HR: 0.61, 95% CI: 0.60–0.63) and remained low for third-or-later-born siblings (HR: 0.60, 95% CI: 0.57–0.64).

ADHD presented a different pattern. While first-born siblings had a slightly elevated risk compared to single children (HR: 1.05, 95% CI: 1.03–1.06), the risk was notably lower in second-born siblings (HR: 0.77, 95% CI: 0.75–0.78) and third-or-later-born siblings (HR: 0.79, 95% CI: 0.77–0.81).

For developmental delay, the birth order effect was less pronounced compared to the other disorders. First-born siblings exhibited a marginally increased risk relative to single children (HR: 1.04, 95% CI: 1.03–1.05), whereas second-born siblings had reduced risks (HR: 0.95, 95% CI: 0.94–0.96), with third-or-later-born siblings showing a further slight reduction (HR: 0.97, 95% CI: 0.96–0.99).

Subgroup Analyses

Subgroup analysis results are presented in Table 5.3. Excluding multiple births and cases where two or more siblings shared the same disorder, singletons with siblings consistently

demonstrated lower risks for CP, ASD, ADHD, and developmental delay compared to single children.

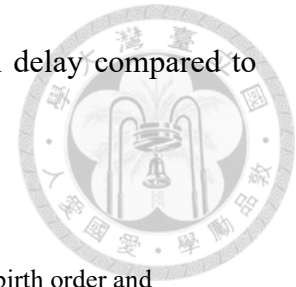


Table 5.3 Subgroup analyses for the relationship between number of siblings and birth order and childhood neurodevelopmental disorders

Number of siblings and birth order	Neurodevelopment disorders			
	Cerebral palsy	Developmental delay	Autism	ADHD
Singletons (excluding multiple births)				
Single child	Reference	Reference	Reference	Reference
First-born sibling	0.72 (0.67 to 0.77)	1.04 (1.03 to 1.05)	0.94 (0.92 to 0.97)	1.05 (1.03 to 1.06)
Second-born sibling	0.84 (0.79 to 0.90)	0.95 (0.94 to 0.96)	0.61 (0.59 to 0.63)	0.76 (0.75 to 0.77)
Third- or later-born sibling	0.91 (0.81 to 1.02)	0.99 (0.97 to 1.01)	0.61 (0.58 to 0.65)	0.80 (0.78 to 0.83)
Singletons (excluding multiple births and two or more siblings with the same disorder)				
Single child	Reference	Reference	Reference	Reference
First-born sibling	0.71 (0.66 to 0.76)	0.83 (0.82 to 0.84)	0.88 (0.85 to 0.90)	0.91 (0.89 to 0.92)
Second-born sibling	0.83 (0.78 to 0.89)	0.71 (0.70 to 0.71)	0.55 (0.53 to 0.56)	0.60 (0.59 to 0.61)
Third- or later-born sibling	0.87 (0.77 to 0.97)	0.63 (0.62 to 0.65)	0.53 (0.49 to 0.56)	0.56 (0.54 to 0.58)
Male				
Single child	Reference	Reference	Reference	Reference
First-born sibling	0.72 (0.66 to 0.79)	1.04 (1.03 to 1.05)	0.96 (0.93 to 0.99)	1.04 (1.02 to 1.06)
Second-born sibling	0.82 (0.76 to 0.90)	0.91 (0.90 to 0.92)	0.60 (0.58 to 0.62)	0.75 (0.74 to 0.76)
Third- or later-born sibling	0.83 (0.73 to 0.95)	0.92 (0.90 to 0.94)	0.57 (0.54 to 0.61)	0.76 (0.74 to 0.78)
Female				
Single child	Reference	Reference	Reference	Reference
First-born sibling	0.69 (0.62 to 0.77)	1.05 (1.03 to 1.07)	0.88 (0.82 to 0.95)	1.08 (1.05 to 1.11)
Second-born sibling	0.83 (0.75 to 0.92)	1.03 (1.01 to 1.05)	0.69 (0.64 to 0.74)	0.82 (0.79 to 0.84)
Third- or later-born sibling	0.97 (0.83 to 1.12)	1.09 (1.06 to 1.12)	0.74 (0.65 to 0.85)	0.89 (0.84 to 0.94)
Maternal age < 30 years old				
Single child	Reference	Reference	Reference	Reference
First-born sibling	0.75 (0.68 to 0.84)	1.02 (1.00 to 1.03)	0.84 (0.80 to 0.89)	1.03 (1.01 to 1.05)
Second-born sibling	0.87 (0.78 to 0.98)	0.97 (0.95 to 0.98)	0.57 (0.53 to 0.60)	0.78 (0.76 to 0.80)
Third- or later-born sibling	1.01 (0.86 to 1.19)	1.10 (1.07 to 1.13)	0.68 (0.61 to 0.75)	0.87 (0.84 to 0.91)
Maternal age ≥ 30 years old				
Single child	Reference	Reference	Reference	Reference
First-born sibling	0.68 (0.62 to 0.75)	1.05 (1.03 to 1.06)	0.93 (0.90 to 0.96)	1.06 (1.04 to 1.08)
Second-born sibling	0.79 (0.73 to 0.85)	0.94 (0.92 to 0.95)	0.62 (0.60 to 0.64)	0.75 (0.74 to 0.76)

Third- or later-born sibling	0.80 (0.70 to 0.91)	0.91 (0.89 to 0.93)	0.56 (0.53 to 0.60)	0.73 (0.70 to 0.75)
Preterm				
Single child	Reference	Reference	Reference	Reference
First-born sibling	0.66 (0.59 to 0.75)	0.96 (0.93 to 0.99)	1.02 (0.93 to 1.11)	1.04 (1.00 to 1.09)
Second-born sibling	0.87 (0.78 to 0.96)	0.90 (0.87 to 0.92)	0.66 (0.60 to 0.72)	0.78 (0.74 to 0.81)
Third- or later-born sibling	0.84 (0.73 to 0.97)	0.92 (0.88 to 0.95)	0.62 (0.54 to 0.71)	0.77 (0.72 to 0.82)
Full term				
Single child	Reference	Reference	Reference	Reference
First-born sibling	0.73 (0.67 to 0.79)	1.05 (1.04 to 1.06)	0.94 (0.91 to 0.97)	1.05 (1.03 to 1.06)
Second-born sibling	0.80 (0.73 to 0.87)	0.96 (0.95 to 0.97)	0.61 (0.59 to 0.63)	0.76 (0.75 to 0.78)
Third- or later-born sibling	0.96 (0.83 to 1.10)	0.98 (0.96 to 1.00)	0.60 (0.56 to 0.64)	0.79 (0.77 to 0.81)
Monthly insurance salary < 25000 New Taiwan dollars				
Single child	Reference	Reference	Reference	Reference
First-born sibling	0.71 (0.65 to 0.78)	1.04 (1.03 to 1.06)	0.94 (0.91 to 0.98)	1.04 (1.02 to 1.06)
Second-born sibling	0.86 (0.79 to 0.94)	0.98 (0.96 to 0.99)	0.64 (0.62 to 0.67)	0.78 (0.77 to 0.79)
Third- or later-born sibling	0.98 (0.87 to 1.11)	1.04 (1.02 to 1.07)	0.67 (0.63 to 0.72)	0.84 (0.81 to 0.86)
Monthly insurance salary ≥ 25001 New Taiwan dollars				
Single child	Reference	Reference	Reference	Reference
First-born sibling	0.69 (0.62 to 0.77)	1.03 (1.01 to 1.05)	0.93 (0.89 to 0.97)	1.04 (1.02 to 1.06)
Second-born sibling	0.76 (0.69 to 0.85)	0.90 (0.89 to 0.92)	0.57 (0.55 to 0.60)	0.73 (0.71 to 0.75)
Third- or later-born sibling	0.71 (0.59 to 0.85)	0.84 (0.81 to 0.87)	0.48 (0.43 to 0.53)	0.68 (0.64 to 0.71)
Urbanization I & II				
Single child	Reference	Reference	Reference	Reference
First-born sibling	0.70 (0.64 to 0.76)	1.04 (1.03 to 1.06)	0.94 (0.90 to 0.97)	1.04 (1.02 to 1.06)
Second-born sibling	0.81 (0.74 to 0.88)	0.94 (0.93 to 0.95)	0.61 (0.58 to 0.63)	0.76 (0.74 to 0.77)
Third- or later-born sibling	0.84 (0.73 to 0.97)	0.93 (0.91 to 0.95)	0.59 (0.54 to 0.64)	0.75 (0.73 to 0.78)
Urbanization III & IV				
Single child	Reference	Reference	Reference	Reference
First-born sibling	0.72 (0.65 to 0.80)	1.04 (1.02 to 1.05)	0.95 (0.91 to 1.00)	1.06 (1.03 to 1.08)
Second-born sibling	0.84 (0.76 to 0.93)	0.96 (0.94 to 0.97)	0.62 (0.59 to 0.65)	0.77 (0.76 to 0.79)
Third- or later-born sibling	0.93 (0.81 to 1.08)	1.01 (0.98 to 1.03)	0.60 (0.55 to 0.66)	0.81 (0.78 to 0.84)

*Adjusted for gender, maternal age, preterm, small for gestational age, monthly insurance salary, and urbanization except the subgrouping variable

Notably, the subgroup excluding families with multiple siblings sharing the same disorder further reduced the likelihood of shared genetic influences, strengthening the hypothesis

that the observed trends are driven by birth order and environmental factors. Stratified analyses also highlighted differences by gender, maternal age, preterm versus full-term status, monthly insurance salary, and urbanization level. For instance, the protective effects of having siblings were more pronounced in boys for ASD and ADHD, whereas socioeconomic factors, such as lower family income and rural residence, attenuated these effects across all disorders.

These findings suggest that the trends observed are not solely attributable to family history or genetic predisposition, but rather reflect the interplay between sibling dynamics and modifiable environmental factors.

Discussion

Sex Ratio and Maternal Age

The sex ratio and maternal age patterns in our cohort reflect societal dynamics and family preferences in Taiwan. Single children showed an elevated sex ratio of 1.20, reflecting stronger male preference compared to children with siblings. Despite declining son preference since the 1990s, linked to reduced sex-selective abortions and increased female education, this trend persists among single children, likely due to the higher proportion of advanced maternal age mothers in this group, reflecting smaller family size preferences.¹⁵ Similarly, increasing male preference with higher birth order may result from the interplay of older maternal age and lower socioeconomic status in larger families, suggesting traditional preferences persist in specific demographics. Further exploration of these societal and familial influences is needed.

Birth Outcomes

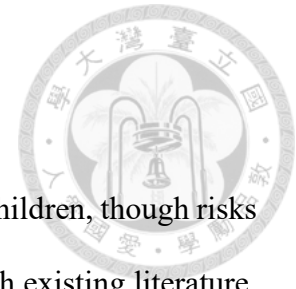
Birth outcomes reflected maternal age, birth order, and socioeconomic factors. Gestational age was longest in first-born siblings, while prematurity risks increased with higher birth order, likely due to advanced maternal age—a known risk factor for preterm birth. The association of birth order with prematurity remains unclear, with inconsistent findings across studies.^{16, 17}

Birth weight decreased with higher birth order, likely due to the opposing effects of parity and maternal age. While parity tends to increase birth weight, advanced and young maternal ages are associated with lower birth weights, especially in larger families.^{18,19} Consequently, no clear relationship between birth order and small-for-gestational-age risk was observed.

Single children had the highest proportion of mothers with advanced maternal age, reflecting delayed childbearing in higher socioeconomic families. In contrast, maternal age increased with birth order among siblings, compounding prematurity and low birth weight risks in larger families. Lower monthly insurance salaries and rural residence in these families further highlight the need for tailored antenatal care, especially as delayed childbearing trends continue globally.

Neurodevelopmental Disorders

Our study consistently demonstrated reduced neurodevelopmental disorder risks among children with siblings compared to single children, suggesting a protective effect of sibling presence. This trend was observed across CP, ASD, ADHD, and developmental delay, though the relationship between birth order and these disorders varied, reflecting the complexity of sibling dynamics and family environments.



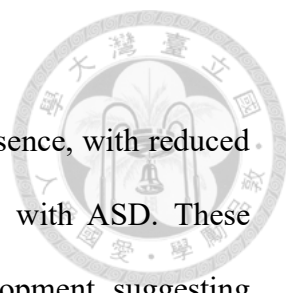
Cerebral palsy

Children with siblings exhibited lower CP risks compared to single children, though risks increased slightly with birth order. These findings align partially with existing literature. For instance, while studies in developed countries found no consistent link between birth order and CP, research from South India suggested reduced CP incidence in higher-order births due to improved obstetric and perinatal care practices.^{20, 21} Our findings suggest that maternal age, socioeconomic conditions, and caregiving burden likely contribute to these patterns. Single children, often born to older mothers, may face heightened perinatal risks, while families with children with CP may opt against additional births. Among siblings, increased maternal age and poorer socioeconomic conditions in larger families likely drive the slight increase in CP risks with birth order.

Subgroup analyses excluding multiple births and siblings with CP indicated that twin and genetic effects were not primary drivers of these trends, emphasizing the multifactorial nature of CP risk. Future research should explore targeted interventions for families with advanced maternal age or limited socioeconomic resources.

Autism spectrum disorder

Children with siblings had lower ASD risks compared to single children, with risks decreasing progressively as birth order increased. First-born siblings exhibited the highest risk, aligning with studies identifying earlier birth order as an independent ASD risk factor.²² A potential explanation is the role of theory of mind (ToM) development. Sibling interactions, characterized by spontaneity, cooperation, and competition, may uniquely facilitate ToM development, mitigating ASD symptoms.^{23, 24}



Our subgroup analyses supported the protective effect of sibling presence, with reduced risks persisting even after excluding multiple births and siblings with ASD. These findings highlight the importance of family dynamics in ASD development, suggesting that older siblings play a pivotal role in fostering social and cognitive development. Further research should investigate the interplay between genetic predispositions, sibling dynamics, and developmental milestones.

Attention Deficit Hyperactivity Disorder

ADHD exhibited a nuanced relationship with sibling dynamics. First-born siblings had slightly elevated risks, while later-born siblings demonstrated significantly reduced risks. These findings align with recent studies suggesting higher ADHD risks in firstborn children, potentially due to developmental challenges and heightened parental vigilance.^{25, 26} This elevated risk may stem from unique developmental challenges faced by firstborn children, including fewer parental resources, greater responsibilities, and heightened parental vigilance toward potential physical or psychological abnormalities. Such factors could contribute to a diagnostic bias, amplifying ADHD diagnoses in firstborns.

Evidence underscores the critical role of parenting and family environment in shaping ADHD outcomes.²⁷ Supportive environments mitigate symptoms, while adverse conditions exacerbate them. Like ASD, ADHD involves deficits in ToM, suggesting that sibling interactions may promote social and cognitive skills, reducing ADHD symptoms.²⁸ These findings underscore the need for further exploration of familial and environmental factors in ADHD risk and management.



Developmental delay

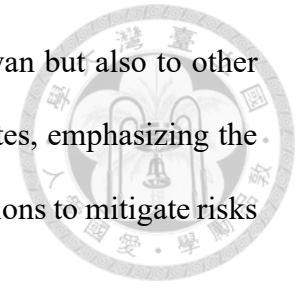
The birth order effect on developmental delay was less pronounced than for other neurodevelopmental disorders. Later-born siblings exhibited progressively reduced risks, suggesting that sibling interactions may facilitate neurodevelopment.²⁹ While the resource dilution model posits that larger families provide fewer resources per child, evidence suggests that positive sibling interactions may counteract this effect.³⁰

Our subgroup analyses revealed that socioeconomic status significantly modulates these dynamics. In lower-income families, developmental delay risks were higher in children with siblings, consistent with the resource dilution model. Conversely, in higher-income, urban families, sibling presence was associated with a protective effect. These findings emphasize the interplay between sibling dynamics, socioeconomic resources, and developmental outcomes. Targeted interventions for families in low-income settings are essential to mitigate developmental risks.

Strengths and Limitations

This study leverages a nationally representative cohort in Taiwan to examine the impacts of birth order and family structure on multiple neurodevelopmental disorders. The NHIRD's extensive coverage ensures comprehensive participant inclusion and minimizes selection bias, while the large sample size enhances statistical power and allows detailed subgroup analyses. By addressing a research area with mixed prior evidence, this study provides valuable insights into how birth order influences neurodevelopmental outcomes. Furthermore, it highlights the importance of identifying high-risk groups, such as single-child families and families with advanced maternal age, to guide screening and

intervention strategies. These findings are relevant not only to Taiwan but also to other regions experiencing increasing maternal age and declining birth rates, emphasizing the need for tailored public health policies and family-centered interventions to mitigate risks in vulnerable populations.

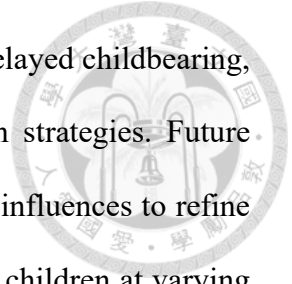


The primary limitation of this study is its reliance on observational data from administrative health databases, which precludes the establishment of causal relationships. While the ICD coding system used to define neurodevelopmental disorders is routinely validated, it may not capture the full clinical spectrum of diseases or distinguish subtypes, potentially introducing misclassification bias. This limitation may affect the generalizability of the findings to specific subgroups of these disorders. Additionally, the use of household registration data to classify urbanization levels may not always reflect the participants' actual place of residence, potentially misclassifying environmental exposures. The study also lacked data on mobility and time-activity patterns, which could influence environmental exposure assessments and contribute to residual confounding. Addressing these gaps in future studies could further refine our understanding of the complex interplay between family structure, birth order, and neurodevelopmental outcomes.

Conclusions

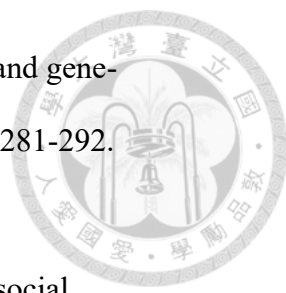
Our study highlights the interplay between sibling dynamics, birth order, and neurodevelopmental disorder risks, emphasizing how family structure influences child development. Protective effects of having siblings were evident but varied by birth order, maternal age, and socioeconomic factors. Single children and families with advanced maternal age exhibited higher risks, underscoring the need to support vulnerable groups.

These findings align with global trends of declining birth rates and delayed childbearing, emphasizing the importance of tailored screening and intervention strategies. Future research should investigate causal mechanisms and broader societal influences to refine public health policies, ensuring equitable developmental support for children at varying neurodevelopmental risks.



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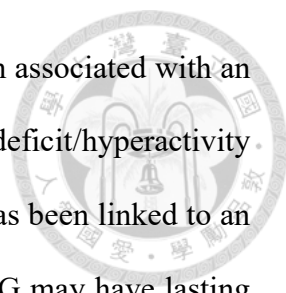
Chapter 6 Gestational Weight Gain and Perinatal Outcomes



Introduction

Gestational weight gain (GWG), defined as the amount of weight gained during pregnancy, is closely linked to both maternal and offspring health.¹ While GWG is recognised as a critical modifiable factor in perinatal outcomes, the definition of optimal GWG remains a topic of ongoing debate. Recommendations for GWG were first issued by the Institute of Medicine (IOM) in 1990, defining target ranges based on pre-pregnancy body mass index (BMI), a key predictor of birthweight. These guidelines were later updated in 2009 to include twin pregnancies, though they remained limited in scope and did not incorporate factors such as gestational diabetes mellitus (GDM).² Criticisms of both versions centered on their reliance on low-quality evidence and limited generalisability. In 2013, the American College of Obstetricians and Gynaecologists (ACOG) called for revisions, particularly for women with obesity, based on a growing body of research.³ Collectively, these developments demonstrate the absence of a universally optimal GWG standard and highlight the need for individualised recommendations that reflect maternal characteristics such as BMI, comorbidities, ethnicity, and age.

Various offspring health outcomes have been linked to GWG. In terms of perinatal outcomes, GWG below the IOM guidelines has been associated with increased risks of small for gestational age (SGA) and preterm birth, while GWG exceeding the guidelines has been related to large for gestational age (LGA), macrosomia, and higher rates of caesarean delivery.⁴ Beyond the perinatal period, abnormal GWG has also been

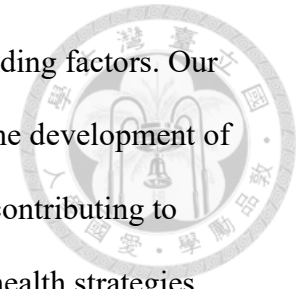


implicated in adverse long-term outcomes. Excessive GWG has been associated with an elevated risk of neurodevelopmental disorders such as attention-deficit/hyperactivity disorder and autism spectrum disorder, whereas insufficient GWG has been linked to an increased risk of intellectual disability.⁵ Additionally, excessive GWG may have lasting metabolic effects on offspring, including higher body weight, increased abdominal adiposity, and adverse lipid profiles.⁶ Despite the growing body of literature supporting these associations, recent evidence suggests that lowering—or even removing—the lower limit of GWG recommendations for pregnant women with obesity may lead to improved offspring outcomes.⁷ A study conducted in China found that using a locally developed guideline by the Chinese Nutrition Society produced comparable outcomes to those based on IOM recommendations,⁸ emphasising the potential benefits of tailoring GWG targets to specific populations.

In Taiwan, clinical practitioners commonly follow the GWG recommendations issued by the Health Promotion Administration (HPA), which are largely based on the IOM guidelines. However, significant differences exist between Asian and American women in terms of race, body weight, height, and perinatal risk profiles. These discrepancies raise concerns about the appropriateness of directly applying Western-based guidelines to Asian populations. A recent study conducted at a single medical centre in Taiwan further highlighted the need to revise GWG recommendations by incorporating the physiological characteristics and clinical data of the local population.⁹

This study aims to investigate the relationship between maternal GWG and pregnancy outcomes across different maternal pre-pregnancy BMI categories. Utilising data from the Taiwan Birth Cohort Study (TBCS), a large and nationally representative dataset,

we analysed these associations while adjusting for potential confounding factors. Our goal is to generate reliable, population-specific evidence to inform the development of optimal GWG recommendations for Taiwanese women, ultimately contributing to improved maternal and child health through evidence-based public health strategies.



Methods

Cohort Selection

This study used data from the TBCS, a nationally representative dataset maintained by the Health and Welfare Data Science Centre (HWDC) under the Ministry of Health and Welfare (MOHW), Taiwan. The TBCS target population was drawn from all 206,465 livebirths in Taiwan in 2005 using a two-stage stratified random sampling approach, applying the probability proportional to size method. A total of 24,200 mother–infant pairs were initially selected for follow-up.

Longitudinal follow-up surveys were conducted at multiple time points, including when the children were aged 6 months, 18 months, 3 years, 5.5 years, 7 years, 8 years, 9 years, 12 years, and 13 years.¹⁰ At the 6-month follow-up, 21,248 participants completed a structured face-to-face interview, yielding a response rate of 87.8%. Interviews were conducted by trained interviewers and included data on demographic characteristics, maternal health status, and pregnancy-related variables. For this analysis, only full-term singleton births were included. Preterm births (<37 weeks' gestation), post-term births (>42 weeks), and multiple births were excluded. After applying these criteria, eligible mother–infant pairs were retained for analysis.

Exposure

GWG was calculated from self-reported maternal height, pre-pregnancy weight, and delivery weight, obtained during the 6-month postpartum survey. Adequacy of GWG was assessed according to the 2009 IOM guidelines, as cited in the MOHW publication *Proper Gestational Weight Management for Maternal and Infant Health*.¹¹ These guidelines provide recommended GWG ranges based on pre-pregnancy BMI categories.

Although the 2009 IOM revision adopted World Health Organization (WHO) BMI classifications, Taiwan applies a different system. Therefore, this study used the BMI categorisation defined by the MOHW: underweight ($<18.5 \text{ kg/m}^2$), normal weight ($18.5\text{--}23.9 \text{ kg/m}^2$), overweight ($24.0\text{--}26.9 \text{ kg/m}^2$), and obese ($\geq 27.0 \text{ kg/m}^2$).¹²

Outcomes

The primary outcomes examined were high birthweight, LBW, LGA, and SGA. High birthweight was defined as $\geq 4,000$ grams, and LBW as $< 2,500$ grams. LGA referred to infants whose birthweight exceeded the 90th percentile for gestational age, and SGA referred to those below the 10th percentile. Maternal complications assessed included GDM, gestational hypertension, preeclampsia, and premature rupture of membranes.

Statistical Analysis

Participants were stratified into four BMI categories based on the MOHW classification. Multivariable logistic regression models were constructed to evaluate the association between GWG and each pregnancy outcome, estimating odds ratios (ORs) and 95% confidence intervals (CIs). Models were stratified by pre-pregnancy BMI and adjusted for potential confounders, including maternal age, infant sex, parity, maternal education,

and urbanisation level. Maternal age was categorised into five groups: <25, 25–29, 30–34, 35–39, and ≥ 40 years. Infant sex was recorded as male or female. Parity was defined as primiparous or multiparous. Educational attainment was grouped into three levels: middle school or below, high school, and university or above, reflecting differences in socioeconomic status and health literacy. Urbanisation level of residence was classified as urban, suburban, or rural to capture regional variation in access to healthcare and resources. All statistical analyses were conducted using Python, version 3.11.7.

Results

A total of 18,970 full-term singleton mother–infant pairs met the eligibility criteria and were included in the final analysis. Pregnancy outcomes and complications were examined across maternal pre-pregnancy BMI categories to evaluate the associations between maternal weight status and perinatal health.

Pregnancy Outcomes and Maternal Complications

As shown in Table 6.1, pregnancy outcomes and complications differed substantially by pre-pregnancy BMI. GWG was inversely associated with maternal BMI: underweight and normal weight mothers gained an average of 14.5 kg, compared with 13.3 kg and 12.6 kg in overweight and obese groups, respectively. In contrast, birth weight increased with higher maternal BMI, rising from 3062.7 g among underweight women to 3250.8 g in the obese group. The prevalence of high birthweight and LGA infants was greater among overweight and obese mothers, while LBW and SGA infants were more common in the underweight group.

Pregnancy complications also exhibited BMI-related trends. GDM, gestational hypertension, and preeclampsia were more frequently observed among overweight and obese women, while these complications were comparatively rare in underweight mothers. The incidence of premature rupture of membranes remained relatively stable across BMI categories.

Table 6.1 Pregnancy outcomes and complications across pre-pregnancy BMI categories

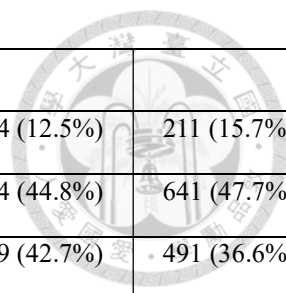
Pregnancy outcomes and complications	Pre-pregnancy BMI categories (kg/m ²)				
	Total	≤18.4	18.5–23.9	24.0–26.9	≥27.0
	Mean (SD) /N (%)	Mean (SD) /N (%)	Mean (SD) /N (%)	Mean (SD) /N (%)	Mean (SD) /N (%)
Total Number	18970	3534	12456	1637	1343
Gestational weight gain (kg)	13.7 (5.2)	14.5 (4.8)	14.5 (4.9)	13.3 (5.4)	12.6 (5.7)
Birth weight (g)	3193.6 (389.0)	3062.7 (358.4)	3177.7 (368.2)	3283.1 (395.8)	3250.8 (433.5)
High birth weight	425 (3.2%)	32 (0.9%)	245 (2.0%)	76 (4.6%)	72 (5.4%)
Low birth weight	502 (2.8%)	156 (4.4%)	277 (2.2%)	27 (1.6%)	42 (3.1%)
Large for gestational age	1719 (11.6%)	148 (4.2%)	1064 (8.5%)	289 (17.7%)	218 (16.2%)
Small for gestational age	1646 (8.3%)	473 (13.4%)	1000 (8.0%)	78 (4.8%)	95 (7.1%)
Gestational diabetes	413 (3.0%)	35 (1.0%)	245 (2.0%)	58 (3.5%)	75 (5.6%)
Gestational hypertension	316 (3.0%)	20 (0.6%)	143 (1.1%)	74 (4.5%)	79 (5.9%)
Preeclampsia	109 (0.9%)	7 (0.2%)	59 (0.5%)	20 (1.2%)	23 (1.7%)
Premature rupture of membrane	2362 (12.2%)	422 (11.9%)	1579 (12.7%)	203 (12.4%)	158 (11.8%)

Maternal characteristics

Table 6.2 presents maternal characteristics stratified by pre-pregnancy BMI. Maternal age showed a non-linear distribution across BMI groups. The proportion of women aged ≥ 35 years was lowest in the underweight group (15.7%) and highest in the overweight group (28.6%), followed by the obese (26.7%) and normal weight (23.9%) groups. Younger maternal age (< 25 years) was most prevalent among underweight women (34.6%) and declined with increasing BMI, reaching 20.0% in the normal weight group, 16.4% in the overweight group, and 20.3% in the obese group.

Table 6.2 Maternal Characteristics across pre-pregnancy BMI categories

Maternal Characteristics	Pre-pregnancy BMI categories (kg/m ²)				
	Total	≤ 18.4	18.5–23.9	24.0–26.9	≥ 27.0
	N (%)	N (%)	N (%)	N (%)	N (%)
Total Number	18970	3534	12456	1637	1343
Maternal age (years old)					
<25	4256 (22.4%)	1223 (34.6%)	2491 (20.0%)	269 (16.4%)	273 (20.3%)
25-29	5600 (29.5%)	1125 (31.8%)	3629 (29.1%)	476 (29.1%)	370 (27.6%)
30-34	4744 (25.0%)	631 (17.9%)	3348 (26.9%)	423 (25.8%)	342 (25.5%)
35-39	1634 (8.6%)	182 (5.1%)	1126 (9.0%)	189 (11.5%)	137 (10.2%)
≥ 40	2736 (14.4%)	373 (10.6%)	1862 (14.9%)	280 (17.1%)	221 (16.5%)
Infant sex					
Male	9888 (52.1%)	1793 (50.7%)	6566 (52.7%)	835 (51.0%)	694 (51.7%)
Female	9082 (47.9%)	1741 (49.3%)	5890 (47.3%)	802 (49.0%)	649 (48.3%)
Parity					
Primipara	9812 (51.7%)	2209 (62.5%)	6438 (51.7%)	611 (37.3%)	554 (41.3%)
Multipara	9158 (48.3%)	1325 (37.5%)	6018 (48.3%)	1026 (62.7%)	789 (58.7%)



Maternal education					
Middle school and below	2723 (14.4%)	638 (18.1%)	1670 (13.4%)	204 (12.5%)	211 (15.7%)
High school	7531 (39.7%)	1492 (42.2%)	4664 (37.4%)	734 (44.8%)	641 (47.7%)
University and above	8716 (45.9%)	1404 (39.7%)	6122 (49.1%)	699 (42.7%)	491 (36.6%)
Urbanization					
Urban	9099 (48.0%)	1695 (48.0%)	6085 (48.9%)	711 (43.4%)	608 (45.3%)
Suburban	5235 (27.6%)	957 (27.1%)	3429 (27.5%)	451 (27.6%)	398 (29.6%)
Rural	4636 (24.4%)	882 (25.0%)	2942 (23.6%)	475 (29.0%)	337 (25.1%)

The overall sex ratio in the cohort was approximately 1.09, slightly favouring male infants, with no notable variation across BMI groups. Primiparity was more common among underweight and normal weight mothers, reported in 62.5% and 51.7%, respectively, compared with 37.3% and 41.3% among overweight and obese women.

Maternal educational attainment also varied by BMI. University-level education was most prevalent in the normal weight group (49.1%) and less frequent in the underweight (39.7%), overweight (42.7%), and obese (36.6%) groups. A modest trend was noted in residential distribution, with overweight and obese mothers more likely to reside in rural areas than those with lower BMI.

BMI-Stratified Associations of Gestational Weight Gain and Perinatal Outcomes

Figure 6.1 shows scatter plots of GWG and birthweight by pre-pregnancy BMI category. A generally positive association between GWG and birthweight was observed across all BMI groups, although the strength of the association appeared weaker and more dispersed among overweight and obese mothers. In underweight and normal weight groups, birthweight increased gradually with GWG, particularly within the 10–

20 kg range. Among overweight and obese women, this relationship was less linear and more variable. Across all BMI categories, extreme GWG values were associated with wider variability in birthweight, encompassing both low and high extremes. This pattern was most evident in the underweight and obese groups.

Figure 6.1 Relationship between gestational weight gain and birth body weight stratified by pre-pregnancy BMI categories

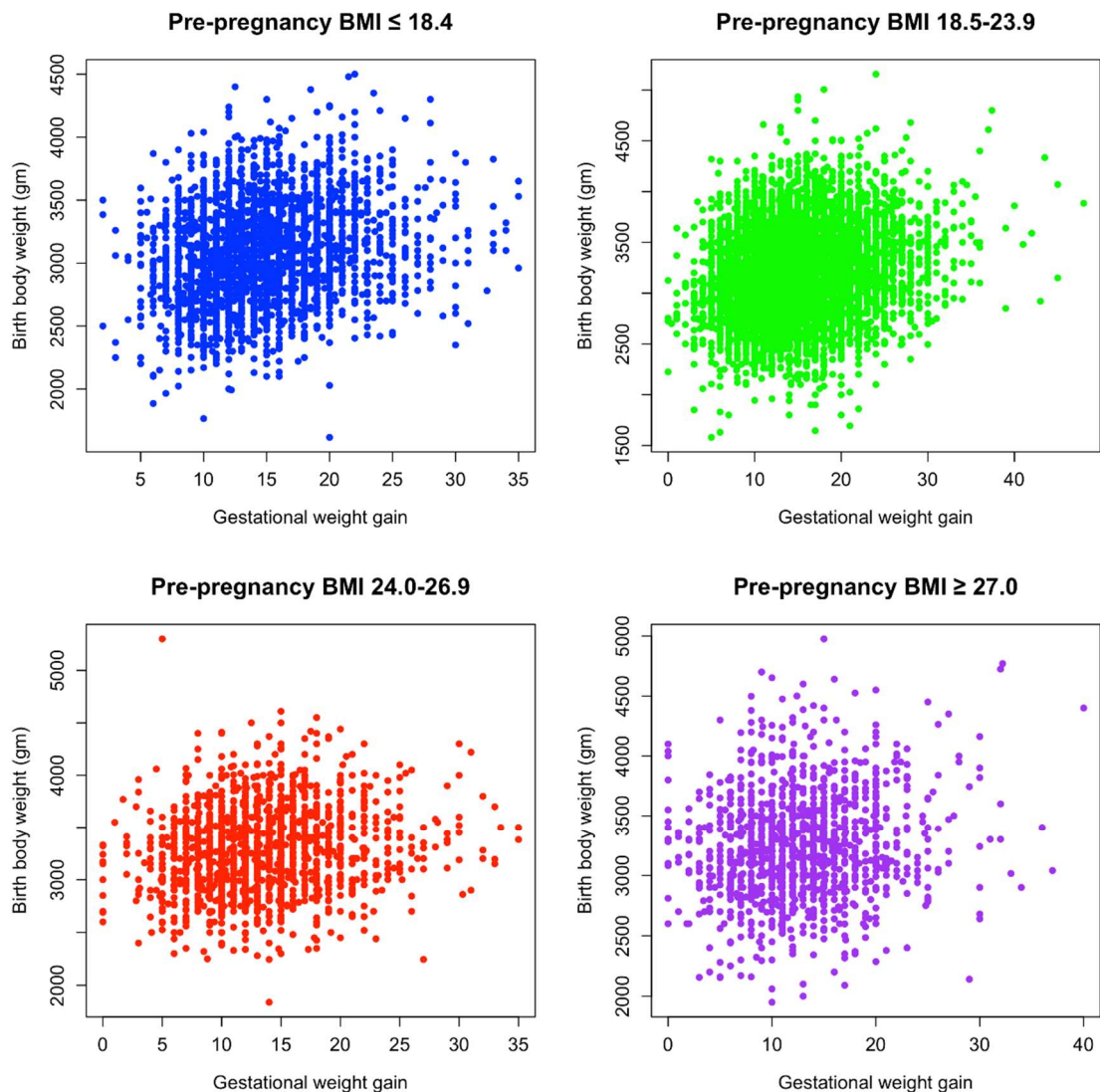


Figure 6.2 illustrates the BMI-specific associations between GWG and adverse neonatal outcomes. Across all BMI groups, greater GWG was linked to an increased likelihood

of high birthweight and LGA, especially among underweight, normal weight, and obese women. This association appeared less pronounced in the overweight group. Conversely, risks of LBW and SGA were higher at the lower end of the GWG spectrum, particularly in the underweight and normal weight groups, with a milder effect observed in overweight and obese mothers.

Figure 6.2 Associations Between Gestational Weight Gain and Neonatal Outcomes Stratified by Pre-pregnancy BMI

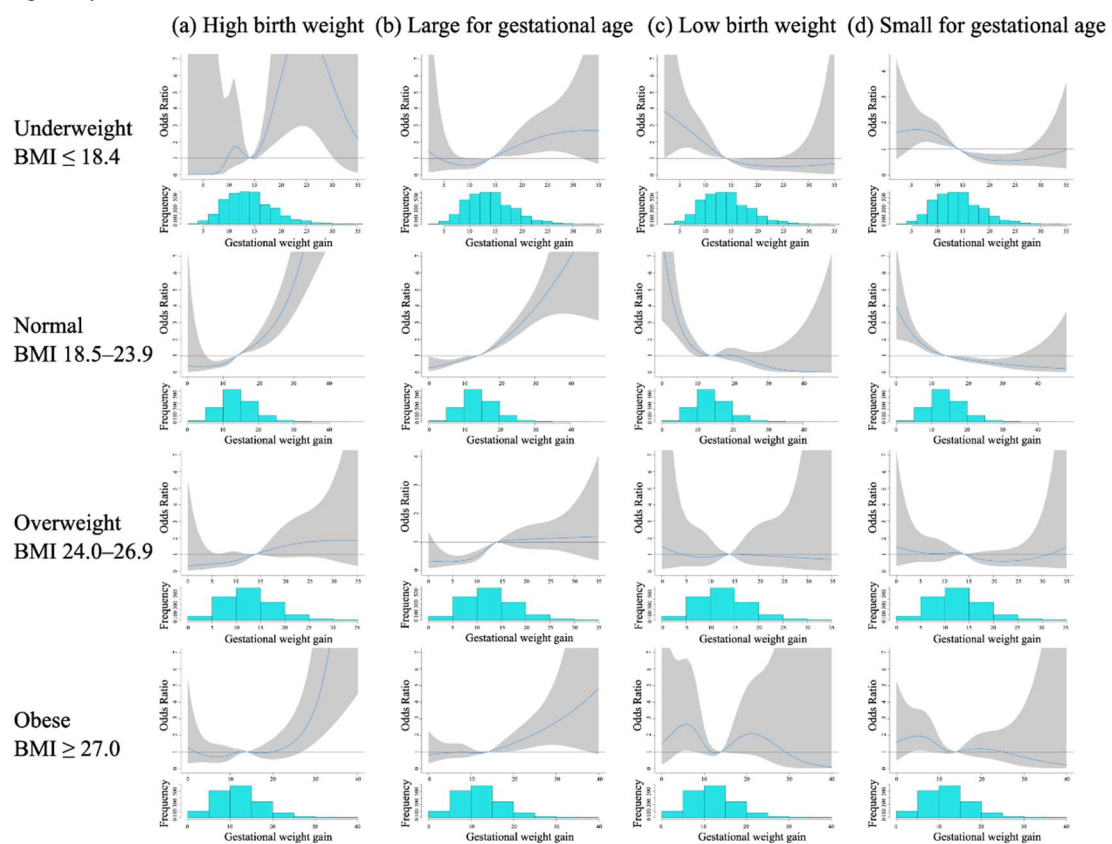
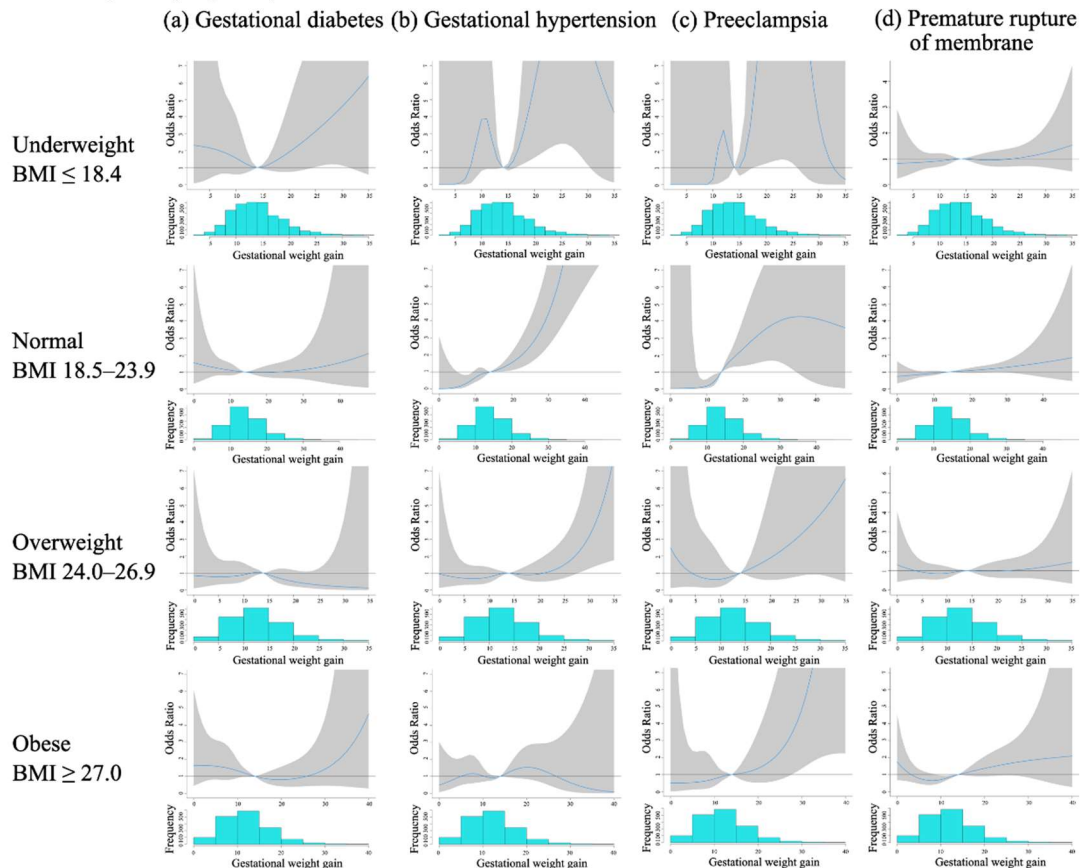


Figure 6.3 shows trends in maternal complications by GWG and BMI category. The probability of GDM, gestational hypertension, and preeclampsia increased with higher GWG in all BMI groups, with a more gradual and consistent rise in underweight and normal weight women. Among overweight and obese mothers, complication rates remained relatively steady until GWG exceeded approximately 15 kg, after which the

risk rose more sharply. The incidence of premature rupture of membranes remained stable across the GWG range, with only a slight upward trend at higher GWG levels in all groups.

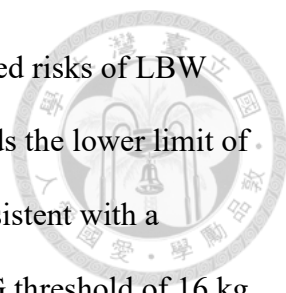


Figure 6.3 Associations Between Gestational Weight Gain and Maternal Pregnancy Complications Stratified by Pre-pregnancy BMI



Discussion

Our findings are consistent with previous literature indicating that GWG is closely associated with pregnancy outcomes and support the use of a BMI-stratified approach in guiding GWG recommendations.¹³ However, existing guidelines, such as those issued by the IOM, may not be universally applicable, especially for women at the extremes of the BMI spectrum.^{14, 15} In our study, underweight mothers exhibited increased risks of

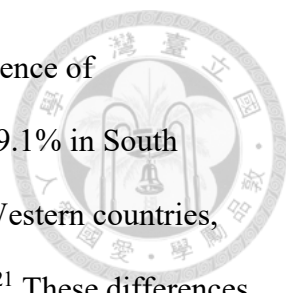


GDM, gestational hypertension, and preeclampsia, along with elevated risks of LBW and SGA infants when GWG fell below 14 kg. This threshold exceeds the lower limit of the IOM-recommended range of 12.5–18 kg. These findings are consistent with a separate nationwide cohort study in Taiwan, which identified a GWG threshold of 16 kg associated with increased LBW risk.¹⁶ In contrast, among overweight and obese mothers, the risks of GDM, hypertensive disorders, and adverse fetal growth outcomes such as high birthweight and LGA remained relatively low until GWG exceeded 15 kg. This is notably higher than the IOM upper limits of 7–11.5 kg for overweight and 5–9 kg for obese women.

These results have important implications for clinical care and public health policy. They emphasise the need for region-specific GWG guidelines that account for local BMI distributions. Given the variation in maternal body composition and perinatal risk across settings, adjusting GWG targets based on population characteristics may help optimise outcomes. This perspective is supported by a recent meta-analysis involving over one million women from diverse ethnic and geographic backgrounds, which concluded that applying population-specific BMI classifications is essential when implementing IOM recommendations in non-Western contexts.¹⁷

Maternal Demographics and Population-Specific Considerations

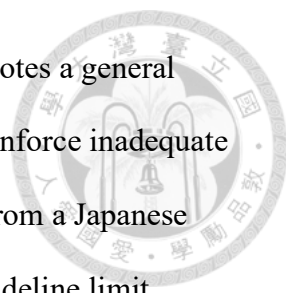
In our cohort, 18.6% of mothers were classified as underweight based on the BMI criteria defined by the MOHW. This proportion exceeded the combined percentage of those classified as overweight (8.6%) and obese (7.1%). The MOHW classification aligns closely with the WHO definition, with the main difference being a lower obesity threshold of BMI ≥ 27 , compared to 30.¹² The BMI distribution observed in Taiwan



resembles that of other East Asian countries. For example, the prevalence of underweight women, using WHO criteria, was 16.3% in Japan and 19.1% in South Korea.^{18, 19} In contrast, markedly lower rates have been reported in Western countries, such as 5% in the United Kingdom and 3.4% in the United States.^{20, 21} These differences may reflect variations in diet and cultural norms, including a stronger societal emphasis on thinness in East Asia.^{22, 23} Although achieving a healthy BMI is widely recognised as a cornerstone of preconception care, public health efforts in many high-income countries have disproportionately focused on overweight and obesity. Underweight status, despite being more prevalent in Asian populations such as ours, has received comparatively little attention. This is a critical gap, as improving maternal nutritional status prior to conception has been associated with improved perinatal outcomes.^{24, 25}

We also observed that mothers with higher educational attainment were more likely to have a normal BMI. Prior research has shown that the relationship between education and obesity varies by context—being positive in many low-income countries but reversed in high-income settings.²⁶ In Taiwan, as in other rapidly developing Asian nations, shifts toward energy-dense but nutrient-poor diets and more sedentary lifestyles have contributed to a growing burden of overweight and obesity.^{27, 28} Our findings highlight the importance of improving educational attainment and implementing public health strategies to raise awareness of healthy BMI before pregnancy. Enhanced health literacy could encourage better nutritional practices and lifestyle behaviours, leading to improved outcomes for both mothers and infants.

Finally, based on our findings, the current GWG recommendation of 12.5–18 kg for underweight women issued by Taiwan’s HPA may be insufficient or at least



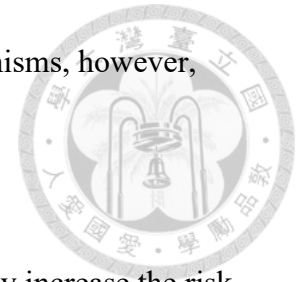
suboptimal. Notably, the HPA's maternal health handbook still promotes a general GWG target of 10–14 kg for all women, which may inadvertently reinforce inadequate goals for underweight mothers.²⁹ This concern aligns with findings from a Japanese study in which women who targeted weight gain below the upper guideline limit achieved lower GWG but saw no improvement in outcomes.³⁰ These findings demonstrate the need for healthcare providers and policymakers to consider more tailored GWG guidance. Interventions should include personalised dietary counselling before and during pregnancy, alongside a revision of GWG targets that better reflect regional and cultural contexts.

Differential Effects of GWG Across BMI Categories

Our findings revealed a positive correlation between GWG and birthweight across all BMI categories, with a stronger and more linear association observed in the underweight and normal weight groups. A similar trend was evident for adverse neonatal outcomes, including LBW and SGA. This suggests that mothers with non-obese BMI may be more susceptible to insufficient GWG, resulting in elevated risks of suboptimal fetal growth. These patterns are consistent with previous studies in Asian populations.^{19, 31}

Although lower BMI is generally viewed as protective against pregnancy complications, underweight mothers in our cohort showed stronger associations between inadequate GWG and risks of GDM, gestational hypertension, and preeclampsia.³² In contrast, these associations were relatively modest among mothers with normal, overweight, or obese BMI. This paradox may reflect compensatory or accelerated placental development in undernourished pregnancies, reinforcing the importance of achieving

adequate preconception BMI.^{33, 34} The underlying biological mechanisms, however, remain to be elucidated.

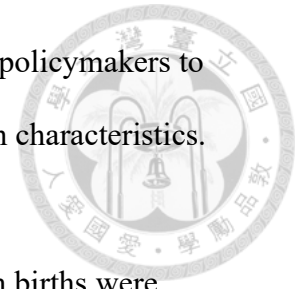


Among overweight and obese women, higher GWG did not markedly increase the risk of GDM or gestational hypertension. Nonetheless, preeclampsia remained consistently associated with excessive GWG across all BMI strata. This threshold effect may stem from the elevated baseline risk of these complications in women with higher BMI, alongside increased clinical vigilance during pregnancy.^{35, 36} Nonetheless, GWG remains a critical modifiable factor in mitigating these adverse outcomes, and current GWG recommendations for overweight and obese mothers appear to be applicable within this population.

Strengths and Limitations

This study has several notable strengths. First, it leveraged a large, nationally representative sample from the TBCS. While gestational weight gain (GWG) data were collected via maternal questionnaires and may be subject to recall bias, infant anthropometric measurements were obtained by healthcare professionals in medical facilities, ensuring higher accuracy and reliability for outcome measures. Second, this is the first population-based study in Taiwan to comprehensively examine the relationship between GWG and multiple pregnancy outcomes across pre-pregnancy BMI categories. These results provide a solid foundation for future research and the development of targeted follow-up or intervention strategies. As the TBCS continues to track participants into adolescence, the dataset offers valuable opportunities to investigate long-term outcomes through linkage with other data sources, including the National Health Insurance (NHI) database, which contains comprehensive health service

utilisation records. Third, the study provides important evidence for policymakers to develop GWG recommendations better aligned with local population characteristics.



However, several limitations should be acknowledged. First, preterm births were excluded from the analysis, despite preterm delivery being a key adverse outcome associated with inadequate GWG. While this limits the generalisability of the findings to preterm populations, the results remain relevant for informing future studies focused on this subgroup. Second, participants were enrolled in 2005, and maternal characteristics, health literacy, and care patterns have since evolved—particularly with rising maternal age and increased use of assisted reproductive technologies in Taiwan. Third, the cross-sectional design precludes conclusions regarding long-term child health outcomes. Future work should aim to address these gaps by evaluating the association between maternal GWG and childhood disorders, with the goal of informing appropriate early interventions and follow-up strategies.

Conclusion

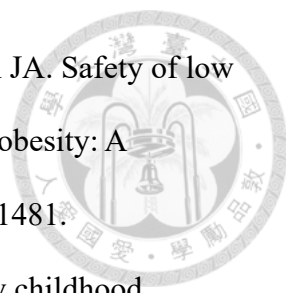
This nationwide study demonstrates that the impact of GWG on pregnancy outcomes varies significantly across maternal BMI categories. Underweight women, often considered lower risk, showed greater vulnerability to adverse outcomes when GWG was insufficient. In contrast, overweight and obese women appeared more resilient to moderate weight gain, with the exception of a consistently elevated risk of preeclampsia. These findings highlight the limitations of applying universal GWG guidelines and point to the need for recommendations that consider regional BMI patterns and changing maternal health profiles. As the TBCS continues to yield

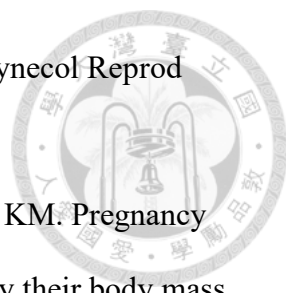
longitudinal data, future research should further examine the long-term effects of GWG on offspring health to inform more targeted public health strategies.

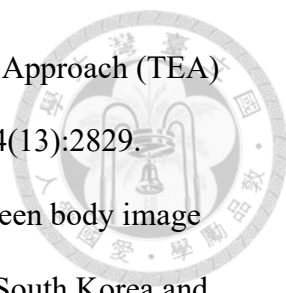


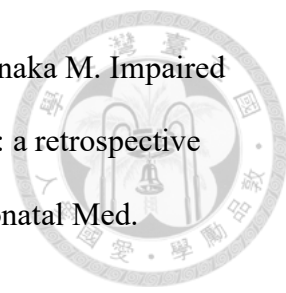
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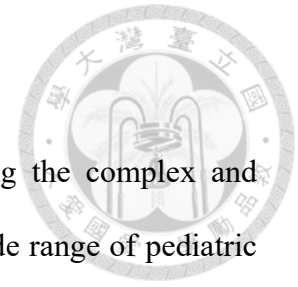
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Chapter 7 Conclusion



This dissertation presents five population-based studies examining the complex and interconnected influences of maternal and fetal risk factors on a wide range of pediatric health outcomes. Collectively, these findings highlight the critical importance of prenatal and early postnatal environments in shaping long-term trajectories in physical growth, immune function, and neurodevelopmental integrity.

The first study found that while many preterm and small-for-gestational-age (SGA) infants exhibit catch-up growth by early childhood, certain subgroups, particularly preterm SGA girls, remain at heightened risk for early-onset obesity. These findings suggest that such children require continued surveillance and individualized nutritional strategies beyond infancy to reduce long-term metabolic risks.

The second study revealed distinct patterns in the development of atopic diseases. Premature birth was associated with increased risks of asthma and allergic rhinitis, but a reduced likelihood of atopic dermatitis. In contrast, SGA status alone did not demonstrate consistent associations. These observations indicate that early growth patterns and perinatal exposures may influence immune programming through divergent biological pathways.

The third investigation identified maternal age as a significant factor influencing multiple dimensions of child health. Both adolescent and advanced maternal age were associated with higher risks of adverse birth outcomes, infant mortality, developmental delays, and allergic disorders. These associations reflect not only biological vulnerabilities but also

socioeconomic and healthcare disparities linked to maternal age.



The fourth study examined how family structure may shape neurodevelopment. Children with siblings exhibited lower risks of neurodevelopmental disorders, including attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), compared to firstborn or only children. These findings suggest that early social environments may play a meaningful role in the development of cognitive and behavioral regulation.

The final study evaluated gestational weight gain (GWG) in relation to maternal body mass index (BMI) and pregnancy outcomes. Deviation from Institute of Medicine (IOM) guidelines was associated with higher risks of adverse neonatal outcomes, particularly when underweight mothers gained too little or overweight mothers gained excessively. These findings reinforce the need for locally relevant, BMI-specific guidance throughout pregnancy.

In sum, these five studies provide comprehensive evidence that both biological and social factors encountered in early life exert lasting effects on child health and development. The findings support the formulation of evidence-based clinical and public health strategies that address risk at multiple levels, from the individual to the population.

Limitations and Considerations

Several limitations should be acknowledged when interpreting the findings of this dissertation. First, the retrospective nature of the analyses—drawing from pre-existing datasets—precludes definitive conclusions about causality. While longitudinal associations were identified, further prospective cohort studies and mechanistic

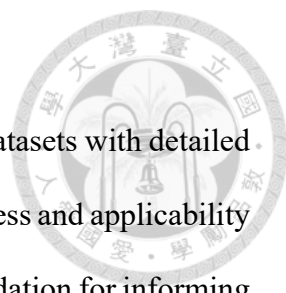
investigations are required to validate potential causal pathways and uncover underlying biological mechanisms.



Second, this research relied primarily on administrative databases, including the National Health Insurance Research Database (NHIRD) and the Taiwan Birth Certificate Registry, supplemented by parental-reported questionnaire data in the Taiwan Birth Cohort Study (TBCS). These data sources are subject to recall bias, misclassification, and diagnostic variability, especially for conditions like atopic diseases and neurodevelopmental disorders that may evolve over time or be differentially diagnosed across clinical settings. Future work incorporating multiple data sources—such as clinical registries, school-based assessments, or direct evaluations—may help mitigate these biases.

Third, the study populations were born between 2004 and 2012, which may limit generalizability to current birth cohorts. In Taiwan, demographic and obstetric profiles have shifted markedly in recent years, with increasing maternal age, declining birth rates, rising use of assisted reproductive technologies (ART), and higher rates of cesarean deliveries. These changes may influence perinatal outcomes and child health trajectories. Continued surveillance using updated cohorts and time-trend analyses will be essential to assess the evolving impacts of these demographic shifts.

Fourth, although the NHIRD provides substantial geographic coverage, residential address information may not accurately reflect actual living environments due to frequent household registration inconsistencies and population mobility. However, in Taiwan, residential movement tends to occur from rural to urban areas, suggesting that any misclassification is likely non-differential and may bias results toward the null.



Despite these limitations, the use of large, nationally representative datasets with detailed birth, maternal, and health outcome information enhances the robustness and applicability of our findings. The insights generated herein provide a valuable foundation for informing maternal-child health strategies and public health policies both within Taiwan and in similar East Asian contexts.

Implications and Future Research

Implications

The findings of this dissertation highlight several actionable implications for public health policy, clinical practice, and maternal-child health programs in Taiwan.

First, preterm and SGA infants represent a vulnerable population at elevated risk for suboptimal growth trajectories, metabolic disturbances, and early-onset obesity. Current surveillance systems and clinical interventions in Taiwan remain insufficient. There is a pressing need to establish standardized postnatal growth monitoring protocols that incorporate anthropometric assessments, nutritional counseling, body composition tracking, and timely referral for growth hormone therapy where indicated.

Second, given the elevated risk of atopic diseases among children born preterm or SGA, early-life environmental modifications—such as guidance on home allergen exposure and nutritional practices—could be integrated into pediatric preventive care. Routine screening and anticipatory guidance for allergic conditions during infancy may facilitate timely diagnosis and improve long-term outcomes.

Third, maternal age emerged as a consistent determinant of multiple adverse outcomes, including perinatal complications, neurodevelopmental disorders, and allergic diseases. With a steadily rising maternal age trend in Taiwan, it is imperative to enhance educational outreach and support systems for older expectant mothers, while concurrently investing in pediatric follow-up services that proactively address the needs of these higher-risk offspring.

Fourth, this research confirms the importance of birth order and sibling composition in shaping neurodevelopmental risks. As Taiwan faces declining fertility rates and a growing proportion of only children, national policies should prioritize early screening and intervention programs for neurodevelopmental disorders, especially for children lacking sibling interactions, which may be protective in social and cognitive development.

Fifth, the study of GWG suggests that current international guidelines may not fully align with local epidemiologic patterns. Particularly, underweight women before pregnancy may benefit from targeted preconception counseling to achieve optimal weight, and customized GWG recommendations should be developed based on population-specific data. Establishing such standards would support both clinicians and expectant mothers in minimizing adverse birth outcomes.

Future Research

Building on the current work, several future research directions are warranted to deepen our understanding and strengthen intervention strategies:

- Lifecourse tracking of growth and metabolic health: Longitudinal studies leveraging both the NHIRD and the TBCS can examine how early-life adversity in

preterm and SGA infants translates into metabolic syndrome, obesity, and cardiovascular risk into adolescence and adulthood.

- Intervention trials targeting allergy prevention in infancy: Conducting structured dietary and environmental counseling interventions in the first year of life for preterm and SGA infants, followed by long-term monitoring, could elucidate whether such programs reduce the incidence or severity of atopic diseases.
- Etiological exploration in offspring of older mothers: Prospective cohort studies investigating potential mediators—such as placental function, epigenetic modifications, or psychosocial stress—may inform tailored screening and early intervention approaches for high-risk dyads involving advanced maternal age.
- Family context and neurodevelopmental trajectories: Future work should track the family structure, parenting styles, and socioeconomic context of children with neurodevelopmental disorders to identify modifiable risk factors and develop family-based or school-based therapeutic models.
- Localized GWG education and outcome assessment: Interventional studies offering preconception and prenatal counseling based on locally derived GWG guidelines may clarify the efficacy of such strategies in improving pregnancy outcomes, particularly in underweight or overweight women planning pregnancies.