INTRODUCTION

Over the past several decades, advances in medicine have contributed to increased survival rates for preterm (gestational age less than 37 weeks) and small for gestational age (SGA - birthweight below the 10th percentile for gestational age). The rate of preterm and SGA are increasing. Preterm and SGA are not only causes of death and illness in children under 5 years old, but also have long-term consequences throughout childhood and later life. The growth and development patterns of preterm and SGA infants are different from those of full-term infants whose weight is appropriate for their gestational age (AGA) at birth. Appropriate growth in weight, height and head circumference has a positive influence on children's cognitive development. Longitudinal, long-term follow-up studies of preterm and SGA children have mainly been conducted in high-income countries, while knowledge about the growth and development amogn preterm and SGA children is limited in low- and middle-income countries (LMIC) – where the majority of preterm and SGA infants are born.

Objectives of the study:

1. Assess physical growth of preterm and SGA children from birth to 10 years old in Thai Nguyen province.

2. Describe the cognitive development status of preterm and SGA children from birth to 10 years old.

3. Examine the relationship between physical growth of preterm and SGA children and cognitive development.

THE URGENCY OF THE SUBJECT

Preterm and SGA tend to increase. Globally, it is estimated that up to 13.4 million premature babies are born each year (accounting for 10% of all live births) and more than 23.4 million SGA babies are born (accounting for 20% of live births), mainly in LMICs. The consequences being born preterm and SGA are not only increased mortality and morbidity rates in children under 5 years old, but also related to disorders in physical growth and cognitive development later in life. These problems can be partly overcome if detected early and intervened promptly. Therefore, it is essential to study physical growth and cognitive development as well as their relationship in this group of children at all stages to improve children's health and wellbeings.

NEW CONTRIBUTIONS OF THE THESIS

- The study is designed as a longitudinal study, spanning from pre-pregnancy, pregnancy, birth, childhood and early adolescence. Data on growth and development are collected extensively across different ages

- This is the first study in Vietnam to assess the growth and development patterns of preterm and SGA children from birth throughout childhood and school age.
- The research highlightsthe relationship between physical growth and cognitive development in preterm and SGA children from prenatal stages to school age.
- The findings of this studyare valuable in monitoring and caring for the health of preterm and SGA children, thereby contributing to improving the health of Vietnamese children.

OUTLINE OF THE THESIS

The thesis is presented in 150 pages (excluding references and appendices), including the following sections: introduction (2 pages); literature review (30 pages); Research objects and methods (21 pages); research results (56 pages); discussion (37 pages); Conclusion (2 pages), and recommendations (2 page).

The thesis includes 34 tables, 15 figures, 10 diagrams. Among the 183 references, there are 14 Vietnamese references and 169 English references.

Chapter 1 : OVERVIEW

1.1 Definition of preterm and SGA

Preterm are infants with a gestational age of less than 37 weeks. Among them, very preterm are infants with a gestational age <34 weeks, late preterm are infants with a gestational age from 34 to <37 weeks.

SGA children are children whose birth weight is less than the 10th percentile. AGA children are children whose birth weight is between the 10th and 90th percentiles.

1.2. Growth of preterm and SGA children

Monitoring growth, especially for preterm and SGA children, is essential in child health care. Growth patterns of preterm and SGA children are still controversial in literature. Both preterm and SGA infants have remarkable growth rates during the neonatal period and catch up growth at different ages. In the first year of life, the lower the gestational age, the faster the growth rate and the higherability to catch up with growth. Gestational age is closely related to the rate of complications among preterm infants. As gestational age increases, complications of preterm will decreases. SGA children are often affected by fetal growth restriction, so they are often born smaller, lighter, with a lower body mass index and a smaller head circumference until age 3 years. SGA children remains shorter than their peers until they are 12 years old. The the rate of stunting in SGA children is also higher.

1.3. Developmental characteristics of preterm and SGA children

Cognitive, language, and motor development are important indicators for monitoring, evaluating, and managing preterm and SGA infants . Delayed cognitive development is the most common and severe manifestation in children with a low birth weight ≤1250g and a gestational age < 32 weeks. Results from many studies indicate that preterm infants have poorer neurodevelopmental outcomes and risk of mental retardation than full-term infants. Studies on SGA children have shown that they have a significantly lower cognitive scores compared to AGA children. Both preterm and and SGA children tend to esperience delayed speech and poorer communication skills compared to full-term children. month. These children often face challenges in receptive and expressive language, have difficulty using words, combining words, and cannot speak fluently. The rate of movement disorders in preterm and SGA infants is always higher than in the AGA group.

Currently, many different tools are used to assess children’s development worldwide.The Bayley scale evaluates the development of infants and young children (from 0 to 42 months) and the Wechsler Intelligence Scale for Children IV (WISC – IV) evaluates the development of children from 6 to 16 years old. Both of Bayley – III and WISC – IV have been standardized, validated and used in many countries, including Vietnam. Some studies used the Bayley III scale to evaluate the cognitive development of preterm children between 3 and 24 months, with follow-up assessments from 7 to 10 years, using the WISC - IV scale, and showed that these tools has the ability to predict children's language and activity, thereby determining early, appropriate and timely intervention for children.

1.4. The relationship between physical growth and cognitive development of preterm and SGA children

Although the mechanisms leading to preterm and SGA are different, they often share certain consequences. Preterm babies have incompletely developed organ structures and functions, and are easily affected by factors leading to disorders and abnormalities. SGA children are due intra-uterine growth retardation, so they are born with a smaller body size and head circumference compared to their peers. Research has shown a relationship between physical growth and neurological development; however, the degree of influence also depends on various other factors in the nurturing and developmental environment. Although catch-up growth plays a very important role in the development of preterm and SGA infants, excessive rapid growth is also a risk for later diseases, especially overweight/obesity, type 2 diabetes and heart health problems. Malnutrition in infancy and childhood is believed to have an adverse effect on cognitive development.

Chapter 2 : RESEARCH SUBJECTS AND METHODS

2.1. Study subjects: Children are those of women who participated in micronutrient supplementation trial before pregnancy, and the mothers of these children.

Inclusion criteria: Children with completed anthropometric data and have their development assessed at different stages. We divided these children into 3 groups:
- Group 1: Preterm (gestational age at birth < 37 weeks), with appropriate weight for gestational age
- Group 2: Full-term babies, birth weight lower than their gestational age (SGA group)
- Group 3: Full -term babies, appropriate weight for gestational age (AGA group)

Exclusion criteria
- Children who were both premature and SGA (n=9, sample is too small for any addiitonal analyses).
- Twins (10 pairs); children with birth defects, children who died during the follow-up period; children who relocated.

2.2. Study timeline and setting

***2.2.1. Study timeline**:* The study has been conducted from 2011 to 2023

2.2.2. Study setting

The study setting was selected from the parent study, which are 20 communes in 4 districts of Thai Nguyen province: Vo Nhai, Phu Luong, Dai Tu, Dinh Hoa

2.3. Research Methods

2.3.1. Study design : Cohort study

2.3.2. Study sample size

Sample size was calculated according to the sample size formula for cohort studies:

$$n = \frac{\left\{Z_{1-\alpha/2}\sqrt{\left[2P*(1-P*)\right)} + Z_{1-\beta}\sqrt{\left[P1(1-P1)+P2(1-P2)\right)}\right\}^2}{(P1-P2)^2}$$

n: sample size
α: type 1 error, choose α = 0.05 with 95% confidence, Z1-α/2 = 1.96.
β: type 2 error, choose β = 10%, strength = (1 – β) = 0.9, Z1-β = 1.28
P1: Incidence in the exposed group (preterm or SGA group)
P2: Incidence of disease in the unexposed group (AGA group)
P* = (P1+P2)/2: Average ratio of the 2 groups
According to Rosenberg's study, the rate of psychomotor retardation in children 9-24 months old using the Bayley child development scale in the US child development monitoring program is 13%, P2 = 0, 1362. The relative risk of preterm infants is predicted to be 2.5 times greater, P1 = 0.13* 2.5 = 0.32. P* = (P1 + P2)/2 = 0.22.

Applying the sample size calculation formula, we calculated: n = 94 for each study group. In our study, there are 147 preterm children, 180 SGA children, and 1.243 AGA children.

Sampling method:

Select communes to study

Randomly select 20 communes in 4 districts of Thai Nguyen province

Select research object

Out of a total of 1599 live births, we selected 147 premature infants, 180 full-term SGA infants and 1243 full-term, AGA infants who met the study selection criteria.

2.4. Research indicators and variables

2. 4 .1. Research Indicators

- Mother's characteristics
- Children's characteristics
- Household economic characteristics and home environment

Indicators for Objective 1:

- Average weight and weight gain velocity of preterm, SGA, and AGA infants across different stages.
- Average length/height and growth velocity in length/height of preterm, SGA, and AGA infants across different stages.
- Average head circumference and head circumference growth velocity of preterm, SGA, and AGA infants during the first two years of life.
- Average WAZ, HAZ and BMIZ of preterm, SGA, and AGA infants across different stages.
- Prevalence of underweight and stunting in preterm, SGA, and AGA infants.
- Prevalence of overweight/obesity in preterm, SGA, and AGA infants.

Indicators for Objective 2:

- Average scores and proportions of different developmental levels for cognitive development, receptive and expressive language, fine motor skills, and gross motor skills at 12 months and 24 months.
- Average scores and proportions of different levels in intellectual development domains (VCI – Verbal Comprehension Index, PRI – Perceptual Reasoning Index, WMI – Working Memory Index, PSI – Processing Speed Index, FSIQ – Full Scale Intelligence quotient) of preterm infants, SGA infants, and AGA infants at 6 years and 10 years.

Indicators for Objective 3:

- The relationship between prenatal growth (preterm status, SGA status) and the developmental status of children at 12 months and 24 months.
- The relationship between prenatal growth (preterm status, SGA status) and the development of children at 6 years and 10 years.

- The relationship between head circumference growth at 12 months and 24 months of preterm and SGA infants and their cognitive development at 10 years old.
- The relationship between physical development (HAZ, WAZ) at 2 years and 6 years of preterm and SGA infants and their cognitive development at 10 years old.
- The relationship between nutritional status (underweight and stunting) at 12 and 24 months and the cognitive development of children at 10 years old.

2.4.2. Research Variables

Maternal variables

- Mother's age at conception
- Ethnic groups: Kinh and other ethnic groups (Tay, Nung, Dao, H'Mong)
- Mother's education level:
- Mother's height
- Mother's BMI before pregnancy: BMI = Weight / Height ^{2}. Classification: Normal: BMI from 18.5 - 23 (kg/m^2), low: BMI < 18.5 kg/m^2, High: BMI > 23 kg/m^2
- Occupation
- Number of children

Child variables

- Gestational age: calculated in weeks. Gestational age is calculated by subtracting the first day of the mother’s last menstrual period from the date of delivery.
- Weight at birth: calculated in grams.
- Gender: male, female
- Length at birth: calculated in cm
- Child's age at the time of assessment: Age according to WHO conventions
- **Nutritional status:** Child feeding practices are evaluated, including breastfeeding practices and complementary feeding, using WHO criteria at the ages of 3, 6, 12, 18, and 24 months.

+ Early breastfeeding: Breastfeeding within the first hour after birth.
+ Exclusive breastfeeding: The child is only breastfed without consuming any other type of food or drink during the first 6 months after birth.
+ Meal diversity: child consumes at least 4 out of the 7 food groups (cereals, roots and tubers, legumes and nuts, dairy products, meat products, eggs, vitamin A-rich fruits and vegetables, and other fruits and vegetables).

- **Disease status at 24 months and 6 years:**

+ Acute diarrhea
+ Acute respiratory infection

Growth variables

+ Child's weight: calculated in gram.
+ Height: in cm.

+ Head circumference (HC): calculated in cm

Weight and height were converted into indicators according to INTERGROWTH-21st standards for premature infants, WHO 2006 growth standards for young children and reference growth population for children aged 5-19y. Stunting is defined as HAZ index < -2 Z-score. Underweight is defined as WAZ index <-2SD. Shortness is defined as BMIZ < -2 Z-score and overweight/obesity is defined as BMIZ > 1Z-s core. Low head circumference is defined as HCZ <-2SD Growth rate (kg/month or centimeters/month) is assessed by calculating the difference in growth between periods at birth, 3m, 6m, 12m, 18m, 2y, 6y and 10y.

Cognition variables

+ Fine motor skills, motor skills, cognitive skills, sensory language, and expressive language according to the Bayley – III scale at 12 month and 24 month.

+ VCI; PRI; WMI; PSI); FSIQ according to the WISC – IV at 6y and 10y.

Classify development levels according to standard deviation (SD).

* < -2SD (≤70 points): extremely low level
* From - 2SD to - 1 SD (71 – <85): low level
* From - 1SD to +1SD (85 – 114): average level
* > + 1SD (≥ 115): high level

- Family economic conditions at 12 months and 24 months.

-Household environmental conditions at 12 months and 24 months: Assessment of the level of support and encouragement for the child's development in the family environment (HOME inventory).

2.5. Analyze and process data: Analyze and process data according to statistical methods in biomedicine based on Stata 17.0 software with appropriate statistical tests.

2.6. Research ethics: The project was approved by the Ethics Council in Biomedical Research. Families/caregivers are explained about the purpose, rights and responsibilities when participating in the research and sign a volunteer commitment if participating in the research.

Chapter 3 : RESULTS

3.1. General characteristics of research subjects

Table 3.1. Characteristics of children born preterm, SGA and AGA

Characteristic, mean ±SD	AGA	Preterm	SGA	p
Gestational age (weeks)	39.5 ±1.3	34.9 ±1.7	40.5 ±1.7	<0.001
Female (%)	50.0	44.2	48.3	0.39
Child feeding				
Breastfeed early	52.4	38.0	57.0	0.002
Breastfeed exclusively	58.9	56.3	62.7	0.53
Dietary diversity at 1y	69.5	64.8	75.4	0.79
Child morbidity 2y				
ARI	48,1	50,8	57,2	0,094
Acute diarrhea	5,5	7,9	7,0	0,47
Child morbidity 6y				
ARI	29.2	28.5	40.8	0.012
Acute diarrhea	0.7	2.,4	3.3	0.009

Comment: SGA children have the lowest average weight and length at birth (2570.9 grams and 47.0 cm), followed by preterm (2874.4 grams and 48.7 cm), p< 0.001. The average gestational age was 34.9; 39.5 and 40.5 weeks of amniotic fluid for preterm, AGA and SGA infants, respectively (p<0.001). There were no differences in gender among the child groups.

Table 3.2. Genaral characteristics of preterm infants by degree of prematurity

Characteristic	28-<32 weeks	32-<34 weeks	34-<37 weeks	p
n(%)	11(7,5)	22(15,0)	114(77,5)	<0,001
GA, Mean ±SD	30,7 ± 0,6	33,0 ± 0,6	35,7 ± 0,8	<0,001
Female, %	54,5	50,0	42,1	0,61
Weight (kg) Mean ±SD	2554,5 ± 573,9	2616,8 ± 518,2	2956,5 ± 404,7	<0,001
Length (cm) Mean ±SD	47,9 ± 2,4	48,4 ± 2,7	48,7 ± 2,9	0,75

Comment: Preterm infants in the study group are primarily late preterm (gestational age 34 - < 37 weeks), accounting for the highest percentage at 77.5%, with an average gestational age of 35.7 weeks

3.2. Physical growth characteristics of preterm, SGA and AGA children in the first 10y of life

Table 3.3. Characteristics of growth and weight of preterm, SGA, AGA children

Weight (kg), mean (SD)	AGA	Preterm	SGA	P
At birth	3.18 ± 0.35	2.91 ± 0.44	2.60 ± 0.30	<0.001
3m	5.25 ± 0.68	5.08 ± 0.75	4.79 ± 0.70	<0.001
6m	7.75 ± 0.93	7.79 ± 0.92	7.11 ± 0.81	<0.001
12m	8.88 ± 1.02	8.76 ± 0.98	8.16 ± 0.96	<0.001
18m	9.73 ± 1.05	9.60 ± 0.98	8.99 ± 0.96	<0.001
24m	10.90 ± 1.15	10.63 ± 1.08	10.09 ± 1.06	<0.001
6y	18.96 ± 3.15	18.87 ± 2.87	17.79 ± 3.53	<0.001
10y	30.55 ± 7.51	31.26 ± 7.09	28.32 ± 7.30	<0.001

Comment: SGA children have the lowest birth weight and the weight growth of this group of children continues to be lower than AGA and preterm children at allstages. Compared with the AGA group, preterm had lower birth weights and at 3m (2.91 kg vs. 3.18 kg and 5.08 kg vs. 5.25 kg). But from 6m onwards, the weight growth of preterm is equivalent to that of AGA.

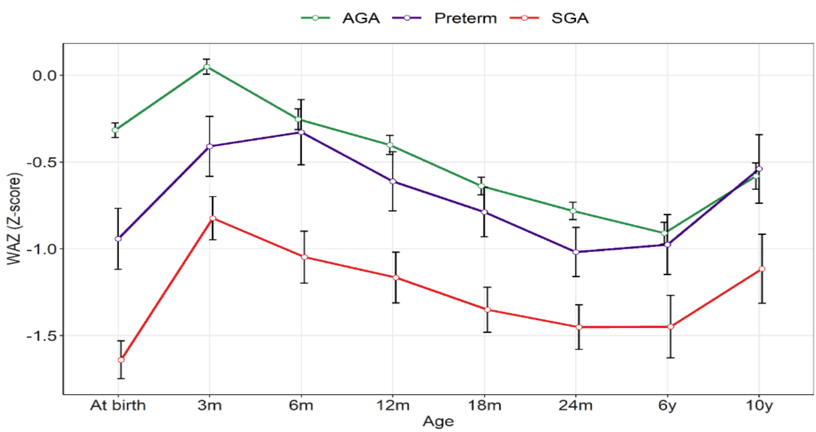


Figure 3.1. Growth characteristics according to WAZ in preterm, SGA and AGA children

Comment: The average WAZ value of SGA children is lower than that of AGA children and premature children through all stages. In contrast, preterm children catch up with growth through the WAZ at 6 months, the period 12 –

24m tends to decrease lower but reaches the same level as full-term children at 6y and 10y.

Table 3.4. Length/height growth of premature infants, SGA infants and AGA infants through stages

Length/height, cm, mean ±SD	AGA	Preterm	SGA	P
At birth	49.26 ±2.83	48.67±2.87	47.03 ±3.12	<0.001
3m	57.47 ±2.52	56.89±2.76	56.23 ±2.60	<0.001
6m	67.29 ±2.55	66.93±2.63	65.68 ±2.38	<0.001
12m	72.88 ±2.6	72.51±2.75	71.12 ±2.72	<0.001
18m	77.66 ±2.67	77.16±2.37	75.82 ±2.48	<0.001
24m	83.16 ±3.07	82.59±2.99	81.25 ±3.09	<0.001
6y	113.82 ±5.15	113.46±4.76	112.20 ±5.85	0.001
10y	135.47 ±6.81	135.88±6.43	133.43±6.61	<0.001

Comment: Growth in length/height of SGA children is always lower than that of AGA children and preterm children through all stages. Children born preterm in the first 6m have a shorter length than children born AGA, but after that the length of preterm is always similar to AGA.

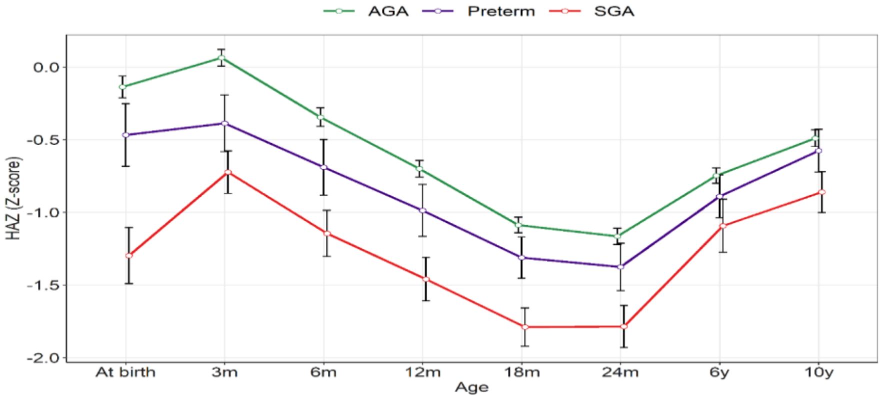


Figure 3. 2 . Growth characteristics according to HAZ of preterm, SGA and AGA children

Comment: There was no significant difference in HAZ between the 3 study groups. Compared with the AGA children, preterm children had a lower HAZ at 2y of age, then HAZ gradually increased and tended to catch up at 6-10y of age. Meanwhile, the SGA children had a lower HAZ than the AGA children through all stages.

Table 3.5. Characteristics of head circumference growth of children born preterm, SGA and AGA infants over time

HC (cm) Mean ±SD	AGA	Preterm	SGA	P
At birth	32.71 ±2.43	32.40±3.36	30.87 ±2.43	<0.001
3m	39.21 ±1.70	39.11±1.72	38.70 ±1.55	0.002
6m	42.41 ±1.49	42.42±1.73	41.86 ±1.65	<0.001
12m	44.71 ±1.44	44.65±1.29	43.94 ±1.41	<0.001
18m	45.76 ±1.47	45.84±1.29	45.15 ±1.46	<0.001
24m	46.61±1.49	46.63±1.29	45.86 ±1.38	<0.001

Comment: SGA children always have lower head circumference than preterm and AGA children from birth to 24 months (p<0.001). Preterm have a lower head circumference than AGA children in the first 12m of life, and at 18m and 24m. Preterm have a higher head circumference than AGA children (p<0.001).

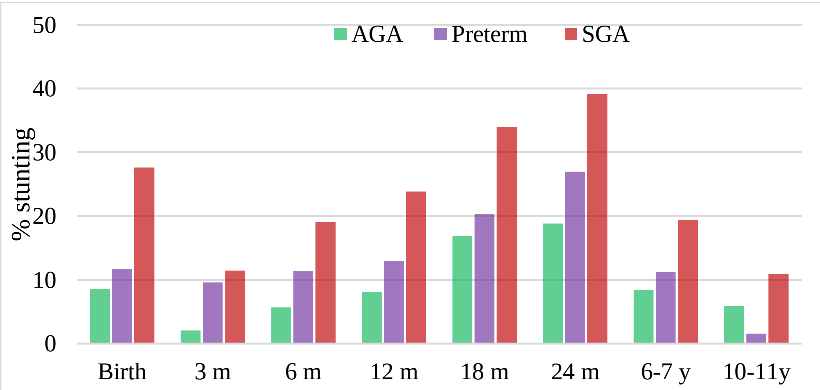


Figure 3.3. Stunting in children born preterm, SGA and AGA over time

Comment: SGA children always have the highest stunting rate at all stages. This rate in preterm children is higher than that of AGA children at birth until age 6, then lower than that of AGA children at age 10.

3.3. Characteristics of cognitive development of preterm and SGA children from birth to 10 years of age

Table 3.6. Cognitive, language and motor scores of preterm, SGA and AGA children at 12 and 24 months of age

	AGA	Preterm	SGA	P
At 12m *mean ± SD*				
Cognition	112.2 ± 10.2	113.7 ±10.6	111.2 ± 11.0	0.15
Receptive language	103.2 ± 12.3	103.4 ±13.0	102.0 ± 12.6	0.56
Expressive language	92.8 ± 10.4	93.1 ± 9.5	91.0 ± 10.5	0.15
Fine motor	106.0 ± 12.1	105.8 ±12.2	106.0 ± 13.2	0.98
Gross motor	**98.9 ± 11.7**	**98.5 ± 12.3**	**95.7 ± 11.6**	**0.012**
At 24m *mean ± SD*				
Cognition	99.8 ± 9.9	99.0 ± 9.3	98.3 ± 10.6	0.17
Receptive language	102.8 ± 10.8	102.8 ±10.7	101.3 ± 10.6	0.27
Expressive language	101.4 ± 9.8	102.3 ± 9.2	100.4 ± 10.4	0.28
Fine motor	**108.4 ± 13.1**	**105.9 ±11.1**	**106.5 ± 13.1**	**0.044**
Gross motor	101.9 ± 11.3	101.7 ±10.6	101.7 ± 11.2	0.98

Comment: At 12m, SGA children had the lowest gross motor score (95.7 points), followed by preterm (98.5 points), AGA children had the highest gross motor score (95.7 points). This difference is statistically significant with $p < 0.05$. At 24m, preterm had the lowest fine motor score (105.9 points), followed by SGA children (106.5 points), and the highest was AGA children (108.4 points). This difference is significant at $p < 0.05$.

Table 3.7. Developmental scores of preterm, SGA and AGA children at 6y, 10y

	AGA	Preterm	SGA	P
At 6y*, mean ± SD*				
VCI	82.0±12.6	81.4±11.4	79.7±12.4	0.12
PRI	93.6±14.3	92.9±15.1	90.1±14.9	0.025
WMI	101.9±11.7	99.8±12.6	101.3±9.3	0.15
PSI	89.7 ±12.3	87.9±11.6	87.5±12.4	0.064
FSIQ	88.7 ±12.3	87.2±11.4	85.8±11.9	0.18
At 10y*, mean ± SD*				
VCI	90.5±14.1	88.2±14.3	86.8±14.2	0.003
PRI	93.0±12.8	89.9±12.9	89.4±13.5	<0.001
WMI	103.1±15.7	101.0±15.4	100.4±15.4	0.055
PSI	93.2±11.7	89.6 ±10.1	91.0±11.6	<0.001
FSIQ	92.9 ±13.5	89.4±12.5	89.0±13.5	<0.001

AGA: appropriate weight for gestational age, SGA: small for gestational age, VCI: verbal comprehension index, PRI: Perceptual thinking, WMI: working memory, PSI: Speed processing, FSIQ: General Intelligence

Comment: At 6 y, there are differences in the PRI, PSI and FSIQ scores of the 3 groups of children. SGA children had the lowest development scores of the 3 groups in the areas of PRI (90.1 points), PSI (87.5 points) and FSIQ (85.8 points), followed by preterm children PRI (92.9 points, PSI (89.7 points) and FSIQ (88.7 points). There are no differences in VCI and WMI scores of the 3 groups of children at this stage. At 10y, there are differences in scores in all 5 assessment areas: VCI, PRI, WMI, PSI and FSIQ of 3 groups of children.

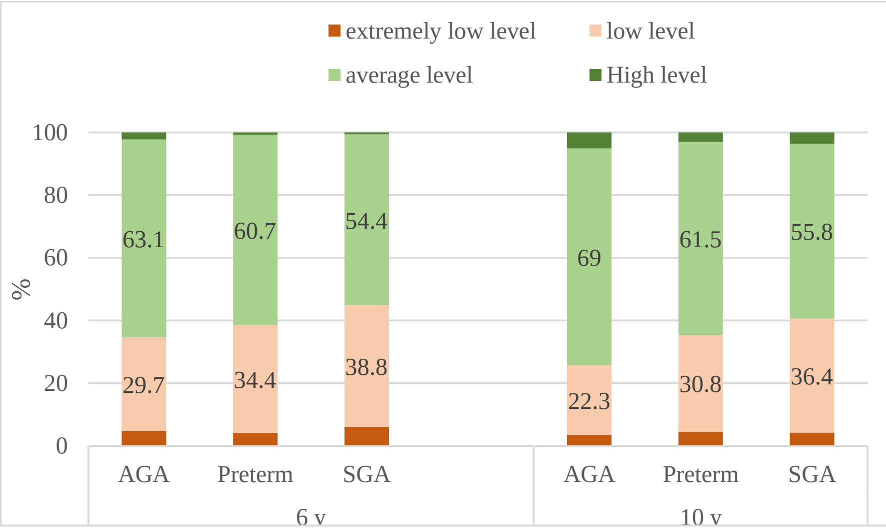


Figure 3.4 . Percentage of development levels of preterm, SGA and AGA children at 6 and 10y

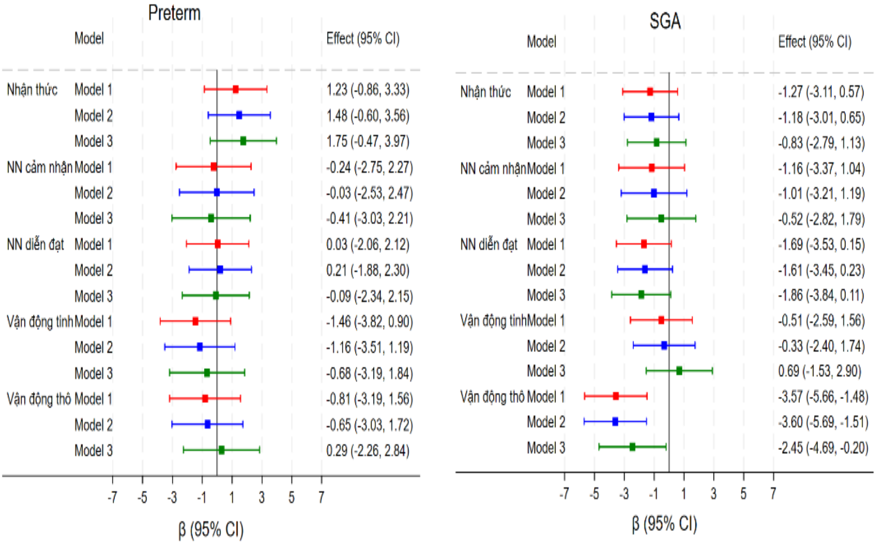
Comment:

- At 6y, the proportion of children with FSIQ scores at the average level in the group of AGA, preterm and SGA children is 63.1%, 60.7% and 54.4%, respectively. SGA children had the highest percentage of low FSIQ scores at 38.8%, followed by preterm children (34.4%), and AGA children (29.7%). However, this difference was not statistically significant (p=0.21).

At 10y, the classification of development levels of child groups at this stage is more clearly different than at age 6. The rate of low FSIQ scores in SGA children is the highest (36.4%), followed by preterm (39.8%), and AGA children have the lowest rate (22.3%). This difference was statistically significant (p=0.003)

3.4. The relationship between physical growth and cognition among preterm and SGA children

3.4.1. The relationship between preterm or SGA and child's cognition in the first 10 years of life



All estimates are from multivariable logistic regression adjusted for confounders including child (sex, age), mother (age, education,) and environment family. AGA: appropriate for gestational age, AOR: adjusted odds ratio, CI: confidence interval, Preterm: premature, SGA: small for gestational age.

Figure 3.5. The relationship between preterm or SGA and child development at 12m

Comment: Compared to AGA children, SGA children had gross motor scores 3.6 points lower, 95%CI (-5.66, -1.48) and sensory language scores 1.7 points lower, 95 %CI (-3.53, 0.15). After controlling for confounding factors in the multivariate model, SGA children had gross motor scores 2.45 points lower, 95%CI (-4.69, -0.20). There is no relationship between premature or SGA children and their cognitive, expressive language and fine motor development at 12 months.

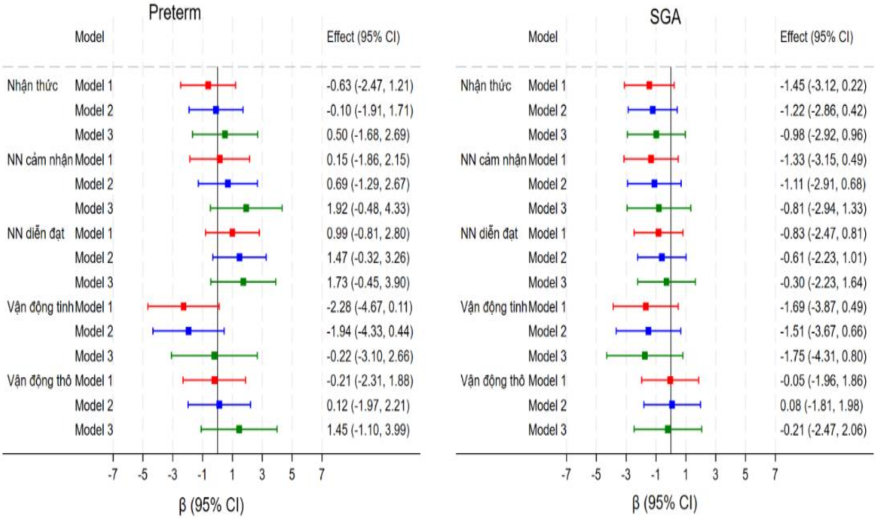


Figure 3.6. The relationship between preterm or SGA and child's cognition at 24m

Comment: At 24 months, SGA children had lower cognitive scores compared to AGA children in most areas; however, this difference was not statistically significant. There was no association between preterm birth and the child's development at 24 months.

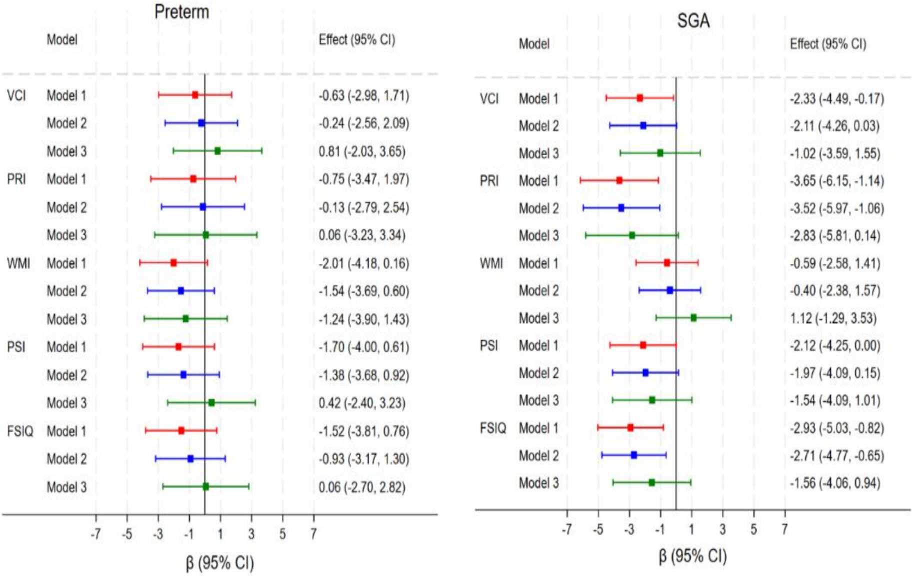


Figure 3.7. The relationship between preterm or SGA and child cognition at 6y

Comment: At 6 years of age, compared to AGA children, SGA children had lower VCI scores by 2.33 points (95% CI: -4.49; -0.17), lower PRI scores by 3.65 points (95% CI: -6.15; -1.14), lower PSI scores by 2.12 points (95% CI: -4.25; 0.00), and lower FSIQ scores by 2.93 points (95% CI: -4.77; -0.65) (Model 1). For preterm children, compared to AGA children, the differences in development at 6 years of age across the domains were not significant.

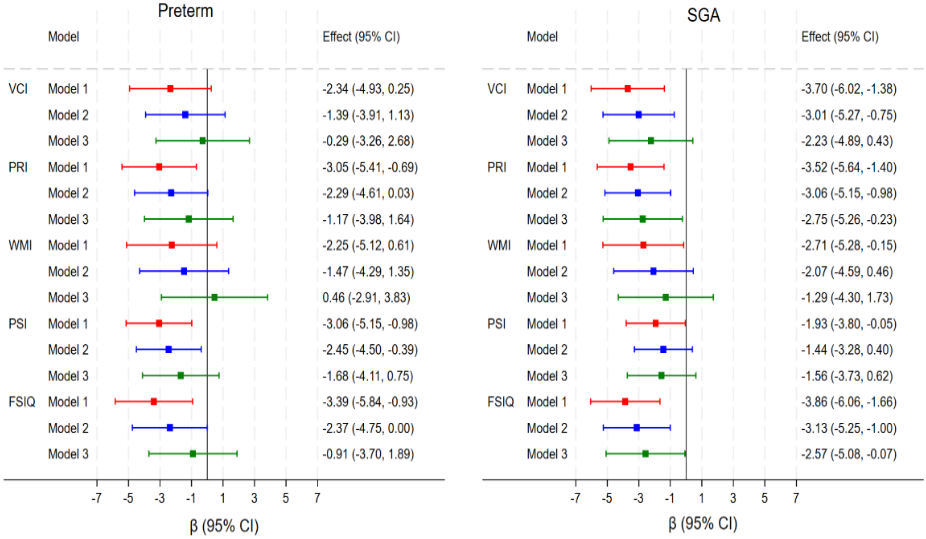


Figure 3.8. The relationship between preterm or SGA and child cognition at 10y

Comment: At 10 years of age, compared to AGA children, SGA children had lower development scores across all domains: -3.7 points in VCI, -3.5 points in PRI, -2.7 points in WMI, -1.9 points in PSI, and -3.9 points in FSIQ (Model 1). Compared to AGA children, preterm children had lower PRI scores by 3.05 points, lower PSI scores by 3.06 points, and lower FSIQ scores by 3.39 points.

3.4.2. The relationship between physical growth and child development in the first 10 years of life

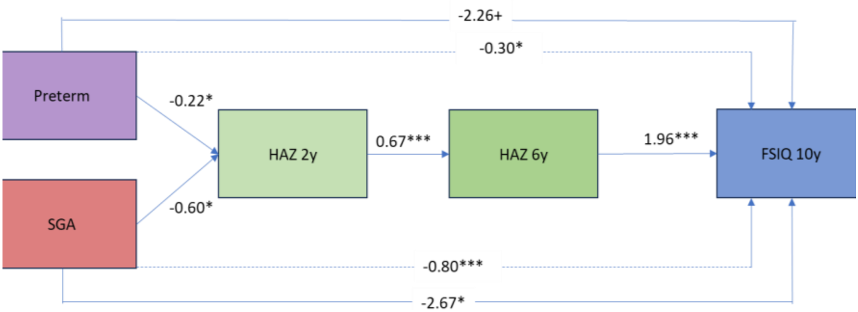


Diagram 3.1. The relationship between height growth and FSIQ score at age 10 in preterm and SGA children

Comment:

- Preterm has a direct impact on the child's FSIQ score at 10 years old (reduced by 2.26 points). Preterm also indirectly affects a child's FSIQ score through affecting physical growth . Compared with full-term children, premature children have a height-for-age index HAZ at 2years old that is 0.22 SD lower. A decrease of 0.22 HAZ at age 2 had an indirect effect on FSIQ scores at age 10 (a decrease of 0.3 points). The total direct and indirect effect from preterm birth on FSIQ is 2.56 points. SGA status has a direct impact on the child's FSIQ score (reduced by 2.67 points) . SGA also indirectly affects children's FSIQ scores directly through its influence on Physical growth: SGA reduces HAZ by 0.6 SD at age 2 years. A decrease of 0.60 HAZ at age 2 had an indirect effect on FSIQ scores at age 10 (a decrease of 0.8 points). The total direct and indirect effect from SGA to FSIQ is 3.47 points.

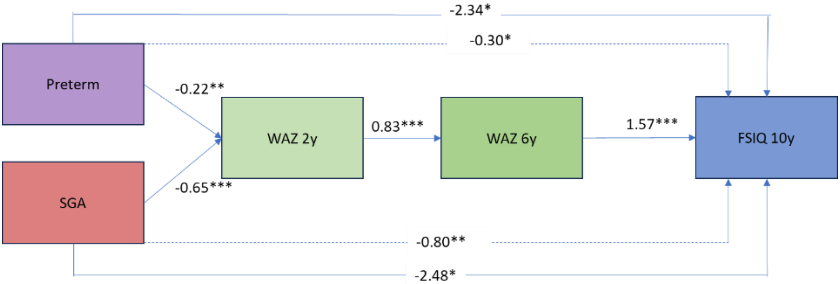


Diagram 3.2. The relationship between weight growth and FSIQ score at age 10 in preterm and SGA children

Comment: In the linear structural model, preterm birth directly reduces FSIQ by 2.34 points. At the same time, preterm birth also indirectly affects FSIQ through its influence on weight. Compared to AGA children, preterm children have a WAZ score at age 2 that is 0.22 SD lower. Since WAZ at age 2 is closely related to WAZ at age 6 (0.83 points), and WAZ at age 6 is closely related to FSIQ score at age 10 (1.57 points), the indirect effect through WAZ on FSIQ is a reduction of 0.3 points. The total effect, both direct (-2.34 points) and indirect (-0.3 points), of preterm birth on FSIQ is -2.64 points. The total effect, both direct (-2.48 points) and indirect (-0.8 points), of SGA on FSIQ is -2.56 points.

3.4.3. Relationship of nutritional status at 12 months and 24 months with child development at 10 years old

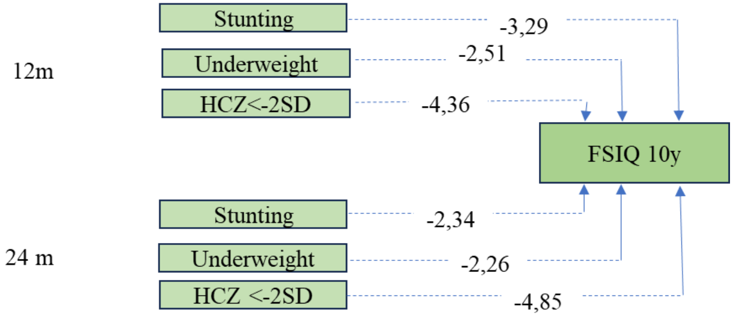


Diagram 3.3. Relationship of nutritional status at 12 months and 24 months with child development at 10y

Comment: At 12 months, compared to children who are not malnourished, stunted children have 3.29 points lower FSIQ score at age 10. Underweight children scored 2.51 points lower, and children with small head circumference scores 4.36 points lower. At 24 months, compared to children without malnutrition, stunted children had FSIQ scores 2.34 points lower, underweight children 2.26 points lower, and children with small head circumference 4.85 points lower.

Chapter 4 : DISCUSSION

In a cohort study lasting more than 10 years, conducted in Thai Nguyen province. This is the first study in Vietnam on two subjects: preterm and SGA children. At the end of this research period, we obtained meaningful results about the growth and development patterns of Vietnamese children.

4.1. General characteristics of research subjects

SGA and preterm had significantly lower mean birth weight and length ($p < 0.001$) than the AGA group**.** Mean gestational age was 34.9, 39.5, and 40.5 weeks for preterm, AGA, and SGA infants, respectively. The average birth weight of full-term, premature, and SGA infants is 3183 grams, 2874 grams, and 2570 grams, respectively. In the preterm group, the majority were classified as late preterm births (77.5% between 34 and <37 weeks), while the remaining 22.5% were preterm births with a gestational age <34 weeks. The distribution ratio of gestational age and birth weight is also consistent with previous domestic studies, as well as studies around the world and is also equivalent to WHO statistics. The rate of early breastfeeding was lowest in the group of premature infants ($p < 0.05$). This can be explained by the fact that preterm have incomplete sucking and swallowing reflexes and may have difficulty breastfeeding in the first days after birth, so the rate of early breastfeeding in these babies is lower than that of AGA.

4.2. Growth characteristics of children born preterrm and children born and SGA in the first 10 years

In this study, we found that preterm infants gain weight rapidly in the first 6 months. At birth, compared to the full-term AGA group, preterm infants were lighter and shorter (weight and length were 3.2 kg versus 2.9 kg and 49.3 cm versus 48.7 cm, respectively). By 3 months of age, preterm infants are still lighter and shorter than AGA babies (5.1 kg vs. 5.3 kg and 48.7 cm vs.57.5 cm), but then especially after 6 months of age preterm infants have similar weight and length measurements as full-term AGA infants. In contrast, SGA children always had lower weight, length, WAZ, HAZ and BMIZ index than the AGA group in all stages although the difference gradually decreased over time.

Our findings of rapid postnatal growth during the first 6 months of life in preterm infants are consistent with previous studies, although the extent of catch-up growth is different. We also know that rapid growth during the third trimester of pregnancy is greater than at any time in postnatal life, and that premature infants born during this period of accelerated growth can continue to growth. Furthermore, the group of preterm infants in the study group were mainly late premature infants (77.5% of infants had a gestational age of 34 - 37 weeks). This is a group that is less likely to suffer from serious diseases during the neonatal period. have the ability to develop better after birth. In our study, SGA children caught up growth late and had short stature in school. This is also consistent with studies on growth outcomes of SGA children. Our study results are consistent with some previous studies suggesting that SGA children have a late growth catch-up, which usually occurs in the last years of childhood. The slow growth and short stature of SGA children is explained by the fact that this group of children is often associated with growth retardation in utero; it is hypothesized that these children have a relative resistance factor. with some growth hormones such as GH, IGF-I and Insulin or defective with IGF-I receptor mediators, this is the basis for changes in the endocrine program.

4.3. Developmental characteristics of preterm and SGA children

Our research results show that in the first 2 years of life, there are no significant differences in cognitive, language and motor development of premature children, SGA children and AGA children. Because the study assessed early time points, at 12 and 24 months of age, differences in the developmental areas of the child groups were not clearly seen. This is also consistent with studies that suggest that the developmental differences between premature and SGA children compared to full-term AGA children become clearer as the children grow older. Therefore, longer studies are needed to clearly see the differences in the development patterns of groups of children.

The findings of our study highlight the long-term influence of birth phenotype (premature birth or low birth weight for gestational age) on children's cognition in school. SGA children had lower developmental scores than AGA children in various developmental domains at both ages 6 and 10 years.

This difference becomes more apparent as children get older. For the group of premature children, we also observed that this group of children had lower development scores than AGA children, but this association was no longer significant in multivariate analysis models that controlled for confounding factors. Our research results also highlight the role of child rearing, mother's education level and household environment in the cognitive development of these groups of children. Among the controlled variables, mother's education level and family environment showed positive associations with children's cognition and academic achievement at age 10 years. Compared with children born to mothers with low levels of education, children whose mothers had college or graduate degrees scored 6-11 points higher in various cognitive domains and total scores. FSIQ is 6.12 points higher. Similarly, the family environment emerges as a fundamental factor in children's cognition. Children living in a good environment have FSIQ scores 4.6 points higher.

Like previous studies, our study shows that SGA children consistently score lower than AGA children in many different cognitive domains. This is consistent with previous studies that have demonstrated the long-term impact of early life factors on children's cognitive development.

In infants born SGA, it is hypothesized that prolonged IGF-1 deficiency due to intrauterine malnutrition may have long-term effects on brain structure and differentiation, possibly affecting affects learning and memory. In addition, some other studies show that increased Glucocorticoid levels during childhood trauma can have adverse effects on brain development. Or lesions of the basal ganglia may explain difficulties with executive function in SGA children. The impact of low birth weight for gestational age on cognitive ability becomes more pronounced as the child grows older and may be due to many different factors, including the influence of biological and environmental factors. school of life. Biologically, the effects of being born SGA may accumulate over time, exacerbating cognitive deficits as children face increasing cognitive demands with age. As cognitive tasks become more complex, any underlying deficits in brain function may become apparent.

Although premature infants initially had lower cognitive scores than AGA infants, this association became nonsignificant when adjusted for maternal factors, household environment, and feeding habits. child care. The findings of our study contrast with previous studies suggesting that there are significant differences between premature and full-term infants in cognitive or academic outcomes. This difference may be due to the characteristics of the study population. Unlike other studies that focus mainly on the group of very preterm infants (with gestational age <34 weeks), our study population focuses on the group of late preterm infants (78% with gestational age ≥ 34 weeks).

4.4. The relationship between physical growth and cognitive development of pretern and SGA children during the first 10 years of life

Our research results show that vulnerable newborns (born prematurely or with low birth weight for gestational age) have lower height-for-age than normal children. The slow growth in height at 2 years old is related to the increase in height at 6y. It is also the poor growth in height of these groups of children that has a negative impact on children's development scores at 10y in all areas of assessment. Human growth and development is a continuous process throughout life, and the period beyond the first 1000 days of life is also important for optimizing an individual's potential. The consequences of poor nutrition at age 2 continue to affect children's cognitive development. Our study results are also consistent with previous studies suggesting that stunting is related to poor cognitive development in children. Kosy and colleagues showed that stunted children at 2 years old, 5 years old and 9 years old had IQ scores 4.6 points lower than children who had never been stunted. Children who were stunted at age 2 but recovered later had IQ scores 5.8 points lower than children who had never been stunted.

CONCLUSIONS

Based on the results of the study on physical growth, cognitive development, and the relationship between physical growth and cognitive development of preterm and SGA children during the first 10 years of life in Thai Nguyen, we present the following conclusions:

1. The physical growth of preterm children is only slower than that of full-term AGA children during the first 3 months after birth, whereas SGA children consistently exhibit slower physical growth at various stages throughout the first 10y of life

- SGA children have slower growth in weight, height, and head circumference compared to AGA children at all time points, while preterm children grow rapidly, reaching their fastest growth rate at 6 months of age.

- The WAZ, HAZ, and BMIZ indices of SGA children are lower than those of AGA children. Preterm children catch up with AGA children in the WAZ index at 6 months, 6y, and 10y. The BMIZ index of preterm children fluctuates but is higher than that of AGA children at 6 months, 6y, and 10y.

- The rate of malnutroition is highest in the SGA group. Preterm children have a higher rate of stunting compared to AGA children from 0 to 6y, but this rate is lower by age 10.

- SGA children are 3.13 times more likely to be underweight than AGA children at 2 years old, 2.2 times more likely at 6 years old, and 1.9 times more likely at 10y.

- SGA children are 2.7 times more likely stunting compared to AGA children at 2 years old and 2.5 times more likely at 6y.

2. Children born preterm and children born SGA exhibit poorer cognitive development, and this tendency becomes more pronounced as they grow during the first ten years of life.

- In the first two years of life, the cognitive development of premature infants and SGA children is comparable.

- By age six, SGA children have the lowest developmental scores in the areas of PRI (90.1), PSI (87.5), and FSIQ (85.8). Premature infants have scores in the areas of PRI (92.9), PSI (87.9), and FSIQ (87.2).

- At age ten, SGA children score the lowest in the areas of VCI (86.8), PRI (89.4), WMI (100.4), and FSIQ (89.0). Premature infants have the lowest score in the area of PSI (89.6).

- The rates of low and extremely low FSIQ developmental levels in SGA children are 44.9% and 40.6%, respectively, at ages six and ten, while the corresponding rates for preterm children are 38.5% and 35.4%.

3. Physical growth is significantly related to the cognitive development of children born and children born SGA.

- The growth of children during the fetal period, reflected by the conditions of being premature and SGA, is associated with their cognitive development at ages six and ten. At 6y, SGA children score lower than AGA children in the areas of VCI (2.33 points), PRI (3.65 points), PSI (2.12 points), and total FSIQ (2.93 points). Preterm children also have lower developmental scores compared to AGA children in all areas, although this difference is not statistically significant. At 10y, SGA children score lower than AGA children in all developmental indices, particularly with an FSIQ score lower by 3.86 points. Premature infants also have an FSIQ score lower by 3.39 points compared to AGA children.

- Postnatal physical growth is also related to the cognitive development of children. At 12 months, stunted growth results in a decrease of 2.61 points in PRI, 4.95 points in WMI, 2.07 points in PSI, and 3.29 points in FSIQ; being underweight results in a decrease of 3.55 points. At 24 months, stunted growth leads to a decrease of 1.82 points in VCI, 1.93 points in PRI, 2.42 points in WMI, 1.54 points in PSI, and 2.34 points in FSIQ. Poor head circumference growth at 12 months results in a decrease of 3.65 points in VCI, 4.26 points in PRI, 2.91 points in WMI, 2.65 points in PSI, and 4.36 points in FSIQ at age ten. Poor head circumference growth at 24 months leads to a decrease of 4.59 points in VCI, 3.42 points in PRI, 3.49 points in WMI, 3.61 points in PSI, and 4.85 points in FSIQ.
- Prematurity and SGA have a direct and indirect impact on the development of children at age ten in all areas: FSIQ, VCI, PRI, WMI, and PSI, through weight and height growth. The total impact from prematurity on FSIQ, including both direct (-2.34 points) and indirect (-0.3 points) effects, is -2.64 points. The total impact from SGA on FSIQ, including both direct (-2.48 points) and indirect (-0.8 points) effects, is -2.56 points.

RECOMMENDATIONS

- Enhance monitoring, management, and prenatal care to reduce the rates of prematurity and SGA.
- Developing special educational programs to support the learning of premature and SGA children is necessary
- Guidance and support should be provided to families with premature infants on how to care for and nurture their children.
- Organize training programs for healthcare staff, teachers, and the community on how to identify and support premature and SGA children.
- There is a need for larger-scale studies with broader scope and longer duration on the growth and development patterns of premature and SGA children.