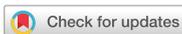


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# Cognitive and Behavioral Outcomes of School-aged Children Born Extremely Preterm: a Korean Single-center Study with Long-term Follow-up

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## ABSTRACT

**Background:** School-aged children born very preterm have been suggested to have worse cognitive and behavioral outcomes than children born full-term. Executive function (EF) is a higher level of cognitive function related to academic achievement. The present study aimed to evaluate the cognitive (including EF) and behavioral outcomes of Korean children born extremely preterm (EP) and to analyze any biological or socioeconomic risk factors for poor cognitive outcomes in this population.

**Methods:** A total of 71 infants weighing < 1,000 g at birth or born before 30 weeks of gestation (EP group) who were admitted to the neonatal intensive care unit from 2008 to 2009 were included in this study and compared with 40 term-birth controls. The Korean Wechsler Intelligence Scale for Children-Fourth Edition, Advanced Test of Attention (ATA), Stroop test, Children's Color Trails Test (CCTT), and Wisconsin Card Sorting Test (WCST) were used. Additionally, the Korean Child Behavior Checklist (K-CBCL) and Korean ADHD Rating Scale (K-ARS) were completed. Perinatal and demographic data were collected and analyzed.

**Results:** The mean full-scale intelligence quotient (FSIQ) score in the EP group was significantly lower than that of the term control group ( $89.1 \pm 18.3$  vs.  $107.1 \pm 12.7$ ;  $P < 0.001$ ). In the EP group, 26 (37%) children had an FSIQ score below 85, compared to only one child (3%) in the control group. Furthermore, the EP group showed significantly worse EF test results (ATA, Stroop test, CCTT, WCST). Except for the higher social immaturity subscore in the EP group, the K-CBCL and K-ARS scores were not different between the two groups. EP children who received laser treatment for retinopathy of prematurity (ROP) had an 8.8-fold increased risk of a low FSIQ score, and a 1-point increase in the discharge weight Z-score decreased the risk of a low FSIQ score by approximately half in this EP cohort.

**Conclusion:** This is the first Korean study to investigate the cognitive and behavioral outcomes of school-aged children born EP. In the study cohort, EP children exhibited significantly lower FSIQ scores and EF than their full-term peers, and 37% of them had cognitive problems. Nonetheless, except for social immaturity, the behavioral problems were

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### Disclosure

The authors have no potential conflicts of interest to disclose.

### Author Contributions

Conceptualization: Kim EK, Shin SH, Kim HS.  
 Data curation: Kim ES, Kim SY, Kim JH. Formal analysis: Kim ES, Kim SY, Kim JH, Kim BN, Shin MS. Investigation: Kim SY, Song IG, Jung YH, Kim JH. Methodology: Kim EK, Shin SH, Kim SY, Song IG, Jung YH, Kim JH. Software: Kim ES, Kim SY, Song IG, Jung YH, Kim JH. Validation: Kim ES, SY Kim, IG Song, YH Jung, Kim JH.

not different in EP children. Severe ROP and low discharge weight Z-score were identified as independent risk factors for low FSIQ score after adjusting for birth weight.

**Keywords:** Prematurity; Cognitive; Behavior; Executive Function; Outcomes; Children

## INTRODUCTION

The survival rate of very preterm (VP) infants (i.e., born at a gestational age of < 32 weeks) and very low birth weight (VLBW) infants (i.e., born with a birth weight of < 1,500 g) have increased since the introduction of exogenous surfactants in early 1990, and with improvements in the clinical use of mechanical ventilation.<sup>1,2</sup> With improvements in neonatal intensive care unit (NICU) care practices, major disabilities such as cerebral palsy, intellectual disability, blindness, and deafness seem to have decreased among survivors.<sup>2-4</sup> Nonetheless, VP or VLBW survivors are known to have worse cognitive and behavioral outcomes than term infants or those with normal birth weight.<sup>2-4</sup> Furthermore, some studies have suggested that the prevalence of these subtle neurodevelopmental problems has recently increased, contrary to expectations.<sup>2-4</sup> A meta-analysis conducted by Bhutta et al.<sup>2</sup> revealed that school-aged children born VP had significantly lower cognitive scores (weighted mean difference, 10.9; 95% confidence interval, 9.2–12.5) and exhibited more externalized and internalized behaviors with a twofold increased risk of attention-deficit/hyperactivity disorder (ADHD) than term-birth controls. Johnson<sup>3</sup> reviewed cognitive and behavioral outcomes after VP birth and observed a gestational age-related gradient in the intelligence quotient (IQ) and increased risk of attentional and social problems in preterm children. Studies with diagnostic criteria such as mental retardation, ADHD, and depression may include only severe cases of preterm children. Considering borderline cognitive deficits and minor behavioral problems (e.g., attention deficit), a large proportion of preterm children are at an increased risk for poor school performance.<sup>3,4</sup> Executive function (EF) is a higher level of cognitive function that develops dramatically from 2 to 5 years of age.<sup>5</sup> A meta-analysis of neurobehavioral outcomes showed poor EF, attention problems, and severe deficits in academic achievement among VP and VLBW children.<sup>4</sup> Additionally, preterm children with low EF had a higher incidence of ADHD and unpreparedness in reading and math, which lagged them behind their term peers.<sup>4,5</sup>

Data on the school-age cognitive outcomes of infants born extremely preterm (EP, born before 30 weeks of gestation) or VP have mostly been obtained from studies conducted in Western countries.<sup>6</sup> Even with notable improvements in the survival rates of EP or VP infants in Korea,<sup>7</sup> their long-term neurocognitive outcomes remain unknown. Hence, the present study aimed 1) to evaluate the cognitive (including EF) and behavioral outcomes of school-aged children born preterm in Korea and 2) to analyze risk factors for poor cognitive outcomes in these children.

## METHODS

### Study design

This follow-up study included surviving extremely low birth weight (ELBW; born with a birth weight of < 1,000 g) or preterm infants born before 30 weeks of gestation (defined as EP infants in this study), who were admitted to the NICU at Seoul National University

Children's Hospital (SNUCH) from January 2008 to December 2009. Tests were intended to be performed at 7–8 years of age. Additionally, controls born term with birth weight over 2.5 kg who had neither major congenital anomalies nor history of psychiatric diagnoses were recruited via an in-hospital announcement. The enrollment ratio was planned as 2:1 (EP group:control group). The minimum number for the EP and the control groups were calculated as 53 and 26, respectively, with an anticipated IQ in the control group of  $100 \pm 15$ ; an IQ mean weighted difference, 10;  $\alpha$ , 0.05;  $\beta$ , 0.2; power, 0.8; and an enrollment ratio 2:1.

### Perinatal data

Perinatal factors in preterm children were prospectively reviewed. Common complications of prematurity, including respiratory distress syndrome, use of multiple surfactants, pharmacological or surgical treatment of patent ductus arteriosus, intraventricular hemorrhage (IVH; grade 3 or 4),<sup>8</sup> periventricular leukomalacia (PVL), necrotizing enterocolitis ( $\geq$  stage 2),<sup>9</sup> bronchopulmonary dysplasia,<sup>10</sup> laser treatment of retinopathy of prematurity (ROP), and culture proven sepsis, were compared among EP infants.

### Demographic data

Sociodemographic data, including the marital status of the mother, maternal and paternal education, family structure, number of siblings, parental occupation, and family income, were collected during the tests.

### Outcome measures

Psychologists who were unaware of the perinatal findings or post-discharge details assessed the children.

### Cognitive test

General intellectual ability was evaluated using the Korean Wechsler Intelligence Scale for Children-Fourth Edition.<sup>11</sup> The Full-Scale IQ (FSIQ) was used to assess general intelligence, and the index scores of its four subdomains were evaluated for more specific cognitive information. The Verbal Comprehension Index was used as a measure of knowledge of word meanings and verbal reasoning abilities; the Perceptual Reasoning Index, as a measure of visuoconstructional skills and visual reasoning abilities; the Working Memory Index, as a measure of immediate and working memory; and the Processing Speed Index, as a measure of speed and accuracy of information processing. Each index score was standardized by age, with a mean of 100 and a standard deviation (SD) of 15. The test results of children with severe neurologic deficits (moderate-to-severe cerebral palsy,  $n = 5$ ; bilateral deafness with cochlear implant,  $n = 1$ ) were included in the study.

### EF neuropsychological tests

#### *Advanced Test of Attention (ATA)*

The ATA is a computerized cognitive test that measures sustained and selective attention and impulsivity in children.<sup>12</sup> The ATA comprises a visual attention test and an auditory attention test. The following four major variables are used: omission errors (failure to respond to targets), which serve as a measure of inattention; commission errors (erroneously responding to non-targets), which are considered a measure of impulsivity; response time for correct responses; and the SD of these response times (response time variability), which is regarded as a measure of attention consistency. A high T-score indicates inattention or impulsivity, whereas a T-score exceeding 65 (over 1.5 SD) is considered to be the “ADHD” range.

### *Stroop Color-Word Test*

The Stroop test measures the inhibitory control of prepotent behavior and consists of three kinds of card sessions: word, color, and incongruent color-word.<sup>13</sup> Each of 100 cards contains a stimulus, and the children must read them aloud as quickly as possible. The children are instructed to read the word in the first session, to read the color in which the word is printed in the second session, and to name the printed color instead of the printed word in the final session. The total time spent reading the cards is checked during this test. Interference control (i.e., inhibition of habitual response) was measured in this test, and the T-score for age was registered for data analysis.

### *Children's Color Trails Test (CCTT)*

The CCTT measures alternating and sustained visual attention, sequencing, psychomotor speed, cognitive flexibility, planning, and inhibition-disinhibition.<sup>14</sup> The CCTT comprises two parts (namely, CCTT1, and CCTT2), which both require a pencil and paper. CCTT1 requires the children to quickly and correctly sequence numbers even with two different background colors between odd and even numbers, whereas CCTT2 requires the children to connect circles in ascending order while alternating between two different background colors. The score reflects the time from initiation to task completion. The difference interference was calculated as the difference between CCTT2 and CCTT1 task completion raw scores. The T-score for age was registered for data analysis.

### *Wisconsin Card Sorting Test (WCST)*

The WCST measures cognitive flexibility.<sup>15</sup> The children have four starting cards with different colors, shapes, and numbers and one test card on the computer. The children subsequently receive feedback after categorizing the cards according to color, shape, or number. In this study, the computer version of the Heaton's WCST was utilized, and T-scores for the total error, perseverative error, non-perseverative error, perseverative response, and conceptual-level response were used for the analyses.

## **Behavioral test**

Behavioral outcomes were evaluated using the Korean Child Behavior Checklist (K-CBCL). The K-CBCL comprises 119 items that should be answered by parents. These items are categorized into eight subscales (withdrawn/depressed, somatic complaints, anxiety/depression, social problems, thought problems, attention problems, rule-breaking behavior, aggressive behavior) and two broad scales (externalization and internalization). Higher scores indicate more problems, with T-scores  $\geq 60$  being considered as predictors of behavioral problems.<sup>16</sup>

The Korean ADHD Rating Scale (K-ARS) was used to screen ADHD risk.<sup>17</sup> The ARS comprises a total of 18 items—specifically, 9 items related to inattention and 9 items related to hyperactivity/impulsivity. A parent should complete this test using a 4-point scale: 0, none; 1, mild; 2, moderate; and 3, severe. Higher scores indicate greater severity. Inattention scores, hyperactivity/impulsivity scores, and total scores were calculated.

## **Statistical analysis**

All statistical analyses were performed using SPSS for Windows version 20.0 (IBM Corp., Armonk, NY, USA). Between-group comparisons were conducted using Student's *t*-tests and  $\chi^2$  tests. Analysis of covariance was used to assess FSIQ scores after adjusting for socioeconomic factors. Multiple logistic regression analysis with stepwise selection was performed to solve the

multicollinearity phenomenon in the analysis of independent risk factors for lower FSIQ scores. A  $P$  value  $< 0.050$  was considered to indicate statistical significance.

### Ethics statement

The present study protocol was reviewed and approved by the Seoul National University Hospital Institutional Review Board (IRB No. 1507-094-689). All participants provided written consent for the tests, and informed consent was obtained from their parents.

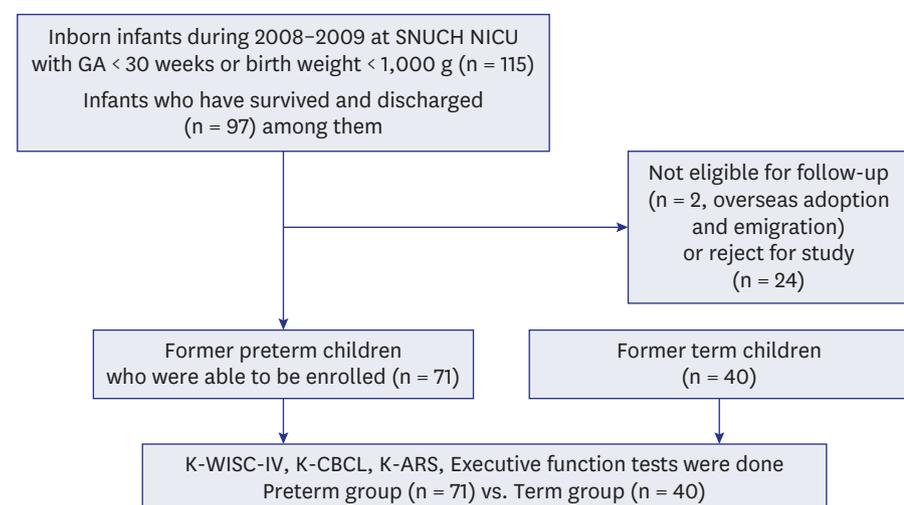
## RESULTS

A total of 115 infants were admitted to the NICU at SNUCH during the study period, and 97 infants survived to discharge. However, 26 children were not enrolled owing to loss of contact or the parents' refusal to participate in the study. Finally, 71 preterm children were enrolled; thus, the follow-up rate was 73.2%. All children in both the EP ( $n = 71$ ) and term control groups ( $n = 40$ ) completed all tests (Fig. 1).

### Demographic characteristic

Considering the possibility of selection bias, perinatal factors were compared between the EP study group and unenrolled EP infants ( $n = 24$ ). The enrolled EP infants had lower birth weights and higher maternal ages at birth than the unenrolled EP infants ( $P = 0.004$  and  $P = 0.002$ , respectively). Nevertheless, perinatal morbidities were not different between the enrolled and unenrolled EP infants (Table 1).

The mean gestational age and birth weight in the EP group were  $27.5 \pm 2.2$  ( $23^{+5}$ – $32^{+6}$ ) weeks and  $885 \pm 238$  (440–1,510) g, respectively. Maternal age at birth was significantly higher in the EP group ( $P = 0.018$ ). At the time of examination, age did not differ between groups, whereas weight and head circumference were significantly lower in the EP group ( $P = 0.007$  and  $P < 0.001$ , respectively). From a socioeconomic perspective, the EP group showed significantly lower maternal and paternal education levels ( $P = 0.002$  and  $P = 0.010$ , respectively) and



**Fig. 1.** Flow chart of the study.

SNUCH = Seoul National University Children's Hospital, NICU = neonatal intensive care unit, GA = gestational age, K-WISC-IV = Korean Wechsler intelligence scale for children–fourth edition, K-CBCL = Korean version of child behavior checklist, K-ARS = Korean version of attention-deficit/hyperactivity disorder rating scale.

**Table 1.** Perinatal characteristics of preterm infants

Perinatal factors	EP group (n = 71)	Unenrolled infants (n = 24)	P value
Gestational age, wk	27.5 ± 2.2	28.1 ± 1.8	0.223
Birth weight, g	885 ± 238	1,120 ± 342	0.004
Sex, male	41 (58)	13 (54)	0.760
SGA	16 (23)	4 (17)	0.542
Cesarean section	53 (75)	13 (54)	0.060
Multiple gestation	35 (51)	9 (38)	0.263
Antenatal steroid	55 (78)	21 (88)	0.288
Maternal age at birth, yr	34.8 ± 4.5	31.5 ± 3.9	0.002
Apgar score at 5 min	7 (5–7)	7 (6–8)	0.185
Cord pH	7.29 ± 0.12	7.25 ± 0.08	0.227
RDS	31 (44)	9 (38)	0.597
PDA ligation	4 (6)	2 (8)	0.558
Sepsis	14 (20)	4 (17)	0.742
NEC (≥ stage II)	6 (9)	2 (8)	0.986
IVH (≥ grade 3)	2 (3)	0 (0)	0.403
PVL	7 (10)	2 (8)	0.825
Postnatal steroid	1 (1)	1 (4)	0.416
Severe BPD	12 (17)	1 (4)	0.117
ROP laser	17 (24)	4 (21)	0.755
Admission duration, days	92.0 ± 79.9	66.9 ± 40.5	0.145
Weight at discharge, g	2,433 ± 520	2,572 ± 540	0.263
HC at discharge, cm	32.2 ± 1.7	32.9 ± 2.0	0.097
Cerebral palsy	5 (7)	2 (8)	0.834

Data are shown as mean ± standard deviation or number (%).

EP = extremely preterm, SGA = small-for-gestational age, RDS = respiratory distress syndrome, PDA = patent ductus arteriosus, NEC = necrotizing enterocolitis, IVH = intraventricular hemorrhage, PVL = periventricular leukomalacia, BPD = bronchopulmonary dysplasia, ROP = retinopathy of prematurity, HC = head circumference.

**Table 2.** Characteristics of studied children

Characteristics	EP group (n = 71)	Control group (n = 40)	P value
<b>Demographics at birth</b>			
Gestational age, wk	27.5 ± 2.2	39.5 ± 1.0	< 0.001
Birth weight, g	885 ± 238	3,299 ± 369	< 0.001
Sex, male	41 (58)	23 (58)	1.000
SGA	16 (23)	4 (10)	0.099
Maternal age at birth, yr	34.8 ± 4.5	32.8 ± 3.1	0.018
<b>Demographics at study</b>			
Age at study, yr	7.4 ± 0.5	7.5 ± 0.5	0.299
Weight at study, kg	22.4 ± 6.8	25.5 ± 3.0	0.007
Height at study, cm	118.0 ± 19.0	122.9 ± 17.9	0.186
HC at study, cm	50.9 ± 2.0	52.7 ± 1.3	< 0.001
<b>Socioeconomic variables</b>			
Intact family structure	69 (97)	40 (100)	0.284
Siblings number 0/1/2/3	22/31/13/5	7/28/5/0	0.037
Primary care giver, mother	68 (96)	37 (93)	0.399
Paternal smoking	33 (47)	12 (30)	0.090
Exclusive breastmilk feeding			
Until 6 months of age	5 (7)	19 (48)	< 0.001
Maternal education			
≤ High school	21 (30)	2 (5)	0.002
Paternal education			
≤ High school	14 (20)	1 (3)	0.010
Family income			
≤ 4,000,000 (KRW/mon)	25 (35)	6 (15)	0.023

Data are shown as mean ± standard deviation or number (%).

EP = extremely preterm, SGA = small-for-gestational age, HC = head circumference, KRW = Korean Won.

significantly lower family income level ( $P = 0.023$ ). Exclusive breast feeding until 6 months of age was significantly more frequent in the term control group ( $P < 0.001$ ; **Table 2**).

### Cognitive test/EF tests and behavioral outcomes

The mean FSIQ was significantly lower in the EP group than in the term control group ( $P < 0.001$ ). A similar pattern was observed for each index score. Because socioeconomic factors such as the rate of exclusive breastmilk feeding, maternal and paternal education levels, and income levels were different between the two groups (Table 2), the FSIQ scores were compared after adjusting for significant socioeconomic factors. The adjusted mean FSIQ score remained significantly lower in the EP group than in the term control group (89.9 with a standard error of 1.93 vs. 105.7 with a standard error of 2.61;  $P < 0.001$ ). In the EP group, 26 children had an FSIQ score below 85, and 9 children had an FSIQ score below 70, whereas only one child had an FSIQ score below 85 in the control group (Table 3). Among five children diagnosed with cerebral palsy in the EP group, one child exhibited an FSIQ score above 85,

**Table 3.** Cognitive and executive function outcomes

Tests	EP group (n = 71)	Control group (n = 40)	P value
K-WISC-IV			
FSIQ	89.1 ± 18.3	107.1 ± 12.7	< 0.001
FSIQ <sup>a</sup>	91.3 ± 16.3 <sup>a</sup>	107.1 ± 12.7	< 0.001 <sup>a</sup>
FSIQ 70–84	17 (24)	1 (3)	0.003
FSIQ < 70	9 (13)	0 (0)	0.019
Verbal comprehension index	94.2 ± 16.5	108.5 ± 11.5	< 0.001
Perceptual reasoning index	91.7 ± 19.7	108.5 ± 15.1	< 0.001
Working memory index	91.2 ± 16.4	103.0 ± 12.6	< 0.001
Processing speed index	86.3 ± 18.1	99.0 ± 15.1	< 0.001
Executive function tests (T scores)			
ATA, visual			
Omission errors	66.3 ± 21.1	55.7 ± 13.8	0.002
Commission errors	67.4 ± 18.7	62.3 ± 18.1	0.168
Response time	57.5 ± 19.6	55.5 ± 12.3	0.509
Response time SD	59.9 ± 19.3	55.1 ± 14.4	0.140
Any of T scores > 65	54 (76)	22 (55)	0.022
ATA, auditory			
Omission errors	62.0 ± 20.3	56.9 ± 16.7	0.190
Commission errors	59.9 ± 20.3	52.7 ± 15.6	0.041
Response time	45.9 ± 16.3	49.9 ± 12.2	0.147
Response time SD	49.9 ± 13.8	45.5 ± 12.3	0.096
Stroop			
Word	40.4 ± 12.4	48.8 ± 9.8	< 0.001
Word <sup>b</sup>	43.5 ± 9.9 <sup>b</sup>	49.5 ± 8.8 <sup>b</sup>	0.016 <sup>b</sup>
Color	40.9 ± 11.5	51.2 ± 10.5	< 0.001
Color <sup>b</sup>	44.9 ± 8.4 <sup>b</sup>	51.6 ± 10.4 <sup>b</sup>	0.006 <sup>b</sup>
Word-color	41.1 ± 11.1	50.5 ± 14.4	0.001
Word-color <sup>b</sup>	43.8 ± 9.7 <sup>b</sup>	50.9 ± 14.3 <sup>b</sup>	0.020 <sup>b</sup>
Interference	52.0 ± 11.7	47.6 ± 10.1	0.045
Interference <sup>b</sup>	49.6 ± 8.8 <sup>b</sup>	47.6 ± 10.3 <sup>b</sup>	0.435
CCTT			
CCTT1	43.5 ± 11.3	50.2 ± 10.0	0.003
CCTT2	45.3 ± 10.9	52.1 ± 8.9	0.002
Difference interference	47.4 ± 12.5	52.5 ± 8.8	0.017
WCST			
Total errors	43.7 ± 9.2	48.4 ± 11.5	0.020
Perseverative errors	45.0 ± 9.9	50.5 ± 9.4	0.005
Perseverative response	45.6 ± 9.4	50.5 ± 9.1	0.009
Conceptual level response	44.1 ± 9.4	49.2 ± 11.7	0.014

Data are shown as mean ± SD or number (%).

EP = extremely preterm, K-WISC-IV = Korean Wechsler intelligence scale for children-fourth edition, FSIQ = full-scale intelligence quotient, ATA = Advanced test of attention, SD = standard deviation, CCTT = Children's color trails test, WCST = Wisconsin card sorting test.

<sup>a</sup>After excluding five neurologically impaired children; <sup>b</sup>Only including FSIQ ≥ 85 children.

whereas the remaining children presented an FSIQ score below 70. Even after the exclusion of five neurologically impaired children, the mean FSIQ score of the EP group was still significantly lower than that of the term control group ( $P < 0.001$ ).

In the visual ATA, the EP group exhibited significantly higher omission errors than the term control group ( $P = 0.002$ ), and the number of children with T-scores exceeding 65 was significantly higher in the EP group than in the term control group (54 [76%] vs. 22 [55%];  $P = 0.022$ ). In the auditory ATA, the EP group exhibited significantly higher commission errors than the term control group ( $P = 0.041$ ). In the Stroop test, the EP group performed significantly worse on all three card tests than the term control group (all  $P < 0.001$ ); however, the interference score in the Stroop test was significantly higher in the EP group ( $P = 0.045$ ). The T-scores for CCTT1 and CCTT2 were significantly lower in the EP group ( $P = 0.003$  and  $P = 0.002$ , respectively), and the T-score for the difference in interference in the CCTT was also significantly lower in the EP group ( $P = 0.017$ ). The T-scores for the total error, perseverative error, perseverative response, and conceptual-level response in the WCST were significantly lower in the EP group ( $P = 0.020$ ,  $P = 0.005$ ,  $P = 0.009$ , and  $P = 0.014$ , respectively; **Table 3**). When analyzing the EP group after exclusion of five neurologically impaired children, the trend and significance of differences in EF outcomes between the groups were the same as above.

Except for the social problem domain, the K-CBCL scores were not different between the two groups ( $P = 0.001$ ). After establishing the cutoff values for the T-score ( $\geq 70$  for all domains except for internalization and externalization, which used  $\geq 60$ ), the two resultant groups showed no differences with respect to the number of abnormal T-scores, except for the social problem domain (8 [11%] vs. 0 [0%];  $P = 0.028$ ). Furthermore, the K-ARS scores did not differ between the EP and term control groups. The number of cases with a total score above 18 (the cutoff value for high ADHD risk) did not significantly differ between the EP and term control groups (10 [14%] vs. 4 [10%];  $P = 0.534$ ) (**Table 4**). When analyzing the EP group after exclusion of five neurologically impaired children, the trend and significance of differences in behavioral outcomes between the groups were the same as above.

**Table 4.** Behavioral outcomes

T scores	EP group (n = 71)	Control group (n = 40)	P value
<b>K-CBCL</b>			
Withdrawn/depressed	54.9 ± 6.1	53.3 ± 5.7	0.177
Somatic complaints	54.0 ± 5.9	53.9 ± 5.5	0.904
Anxiety/depression	56.2 ± 7.0	54.0 ± 6.4	0.111
Social problem	58.3 ± 8.3	53.7 ± 5.5	0.001
Score ≥ 70	8 (11)	0 (0)	0.028
Thought problem	54.9 ± 6.5	54.9 ± 6.6	0.947
Attention problem	54.9 ± 6.8	53.1 ± 5.0	0.124
Rule-breaking behavior	54.0 ± 5.2	54.5 ± 4.9	0.650
Aggressive behavior	54.2 ± 5.6	54.7 ± 6.3	0.665
Internalization	53.4 ± 9.9	50.8 ± 9.8	0.197
Externalization	50.2 ± 9.8	51.8 ± 8.9	0.396
<b>K-ARS</b>			
Inattention	5.3 ± 5.2	4.6 ± 3.9	0.460
Hyperactivity-impulsivity	3.3 ± 3.9	3.1 ± 3.3	0.804
Total score > 18	10 (14)	4 (10)	0.534

Data are shown as mean ± standard deviation or number (%).

EP = extremely preterm, K-CBCL = Korean version of child behavior checklist, K-ARS = Korean version of attention-deficit/hyperactivity disorder rating scale.

### FSIQ-related factors in the preterm group

The EP group was divided into two subgroups using a cutoff value of 85 for the FSIQ, and subgroup analysis was performed to delineate perinatal and socioeconomic risk factors in EP children with an FSIQ below 85. The low FSIQ group had a higher incidence of small-for-gestational age infants, albeit without statistical significance ( $P = 0.070$ ), and showed a significantly lower birth weight ( $P = 0.008$ ) than the normal FSIQ group, with no difference in gestational age at birth. Additionally, the low FSIQ group significantly more frequently presented with sepsis and necrotizing enterocolitis ( $P = 0.005$  and  $P = 0.037$ , respectively) and had a significantly longer duration of antibiotic use than the normal FSIQ group ( $P = 0.014$ ). The rate of laser treatment for ROP was significantly higher in the low FSIQ group than in the normal FSIQ group ( $P = 0.002$ ).

At NICU discharge, the weight, height, and head circumference Z-scores were significantly lower in the low FSIQ group than in the normal FSIQ group. Parental education level or family income level did not show any significant difference between the groups ( $P$  value of 0.051 for family income) (Table 5).

### Independent risk factors of low IQ in the preterm group

After adjusting for birth weight, multiple logistic regression analysis was performed to delineate independent risk factors for low FSIQ in the EP group. Following stepwise selection to solve multicollinearity, laser treatment for ROP and low discharge weight Z-score were

**Table 5.** Factors related to FSIQ in the preterm group (n = 71)

Factors	FSIQ < 85 (n = 26)	FSIQ ≥ 85 (n = 45)	P value
<b>Perinatal factors</b>			
Gestational age, wk	27.2 ± 2.4	27.7 ± 2.0	0.295
Birth weight, g	781 ± 149	946 ± 260	0.008
SGA	9 (35)	7 (16)	0.070
Antenatal steroid	17 (65)	38 (84)	0.070
RDS	12 (46)	19 (42)	0.748
PDA ligation	2 (8)	4 (9)	0.862
Sepsis	10 (38)	4 (9)	0.005
NEC (≥ stage 2)	5 (19)	1 (2)	0.037
IVH (≥ grade 3)	2 (8)	0 (0)	0.244
PVL	4 (15)	3 (6)	0.248
Severe BPD	5 (19)	7 (16)	0.691
ROP laser	12 (46)	5 (11)	0.002
Antibiotics duration, days	28.9 ± 23.8	14.4 ± 17.9	0.014
Admission duration, days	116.1 ± 124.2	78.1 ± 29.1	0.076
<b>Discharge status</b>			
Weight at discharge (Z-score)	-2.9 ± 1.5	-1.7 ± 1.2	0.001
Height at discharge (Z-score)	-3.3 ± 1.6	-1.9 ± 1.1	< 0.001
HC at discharge (Z-score)	-2.2 ± 1.2	-1.2 ± 0.9	0.001
<b>Socioeconomic factors</b>			
Maternal education			
≤ High school	3 (12)	11 (24)	0.481
Paternal education			
≤ High school	9 (35)	12 (27)	0.221
Family income			
≤ 4,000,000 (KRW/mon)	13 (50)	12 (27)	0.051

Data are shown as mean ± standard deviation or number (%).

FSIQ = full-scale intelligence quotient, SGA = small-for-gestational age, RDS = respiratory distress syndrome, PDA = patent ductus arteriosus, NEC = necrotizing enterocolitis, IVH = intraventricular hemorrhage, PVL = periventricular leukomalacia, BPD = bronchopulmonary dysplasia, ROP = retinopathy of prematurity, HC = head circumference, KRW = Korean Won.

**Table 6.** Independent risk factors of lower intelligence quotient in the preterm group

Adjusted by birth weight	Adjusted odds ratio	95% confidence interval
ROP laser	8.815	2.083–37.308
Discharge weight (Z-score)	0.488	0.282–0.843

ROP = retinopathy of prematurity.

identified as independent risk factors for low FSIQ in the EP cohort. EP children who received laser treatment for ROP had an 8.8-fold increased risk of a low FSIQ score, and a 1-point increase in discharge weight Z-score decreased the risk of a low FSIQ score by approximately half in this EP cohort (Table 6).

## DISCUSSION

In the study cohort, EP children exhibited significantly lower FSIQ score and level of EF than their term peers, 37% of which had mild-to-severe cognitive problems at school age, compared to only one child with mild cognitive problems in the control group. Except for social immaturity, the behavioral problems of EP children were not different from those of their term peers. In this study cohort, independent risk factors for FSIQ score < 85 in EP children were the presence of severe ROP and low discharge weight Z-score.

This is the first Korean study on the outcomes of school-aged children born EP. Recent developments in perinatal medicine and neonatal intensive care have considerably improved the survival of preterm infants in Korea.<sup>7</sup> Nonetheless, data from the Korean Neonatal Network, which is the national VLBW registry in Korea, indicated that approximately 60% of infants were followed up for 18–24 months (corrected age) and that only one-third of the infants who were followed up had undergone a formal developmental test.<sup>18</sup> A report from a single Korean NICU showed that 17% of VLBW children aged 3 to 5 years had a below-average FSIQ score (< 85).<sup>19</sup> However, there is limited information on the longer-term prognosis of this high-risk population. The cognitive outcomes in this study implicate a substantial social burden on preterm children. In this study, 13% and 24% of preterm children had an IQ < 70 and 70 ≤ IQ < 85, respectively; these results are comparable to the findings of the Victorian EP cohort study,<sup>20</sup> which reported IQ < -2 SD and IQ -2 SD to -1 SD in 10–14% and 19–33% of children, respectively, at 8 years of age. Similar to our study, the EPIPAGE study,<sup>21</sup> which included children born before 33 weeks of gestation, reported that 11% and 20% of children exhibited an IQ < 70 and 70 ≤ IQ < 85, respectively, at 5 years of age. Moreover, owing to the upward drift in the tendency of IQ scores over time, their term peers' cognitive outcomes are important with respect to comparison. The FSIQ score was significantly lower, even in EP children with an IQ ≥ 85 (n = 45), than in term-birth controls with each index score showing a similar pattern. Furthermore, among the EP tests, EP children with an IQ ≥ 85 exhibited significantly lower Stroop test results than term-birth controls (data not shown). Therefore, IQ ≥ 85 in EP children does not guarantee a reassuring cognitive outcome. While IQ is not a proxy for learning potential, EF has been suggested to be a better indicator of academic success.<sup>22</sup> In the study cohort, EP children exhibited significantly lower EF outcomes based on the Stroop test, CCTT, and WCST results than normal term-birth controls. Only the interference score in the Stroop test was higher in the EP group, which may reflect less disturbance in color selection due to reduced literacy in the EP group. The results indicate deficits in inhibition control, sequencing, psychomotor speed, and cognitive flexibility among preterm children. A previous meta-analysis of EF showed that the scores of VP

children for verbal fluency, working memory, and cognitive flexibility were below the scores of term-birth controls by 0.3–0.7 SD.<sup>4</sup> The Victorian Study Group had recently reported high rates of abnormal scores for working memory (up to 37%) and planning and organizing areas (up to 29%), although a parent-completed questionnaire was used.<sup>23</sup> Arguments exist among researchers that poor EF in VP infants might reflect a delay rather than a deficit. Nevertheless, a large geographic cohort study involving EP and ELBW infants revealed that most children exhibit stable EF from 8 to 18 years of age.<sup>24</sup> Additionally, studies in young adulthood have reported difficulties in selective attention, inhibitory control, cognitive flexibility, and working memory. Therefore, EF difficulties in preterm children are generally regarded as evident before they enter the classroom and persist throughout their lifespan.<sup>5</sup>

Increased inattention and internalizing behaviors have been documented in preterm children.<sup>4</sup> In the study cohort, omission errors in the visual ATA, which represent attention components among the EF tests, were significantly greater in EP children. However, the K-CBCL and K-ARS results did not indicate significant inattention problems in EP children. The K-CBCL and K-ARS are parent-reported tests, whereas the ATA is a performance-based test; thus, the test method might have resulted in such discrepancies. Four EP children were on medication for ADHD diagnosis, and all scored over 19 in the K-ARS; in contrast, no children in the term control group were diagnosed with ADHD. Even when including children with an ADHD diagnosis, the results of the parent-reported tests did not indicate significant between-group differences. Social immaturity is a component of internalizing behaviors; together with other meta-analyses, the present study identified significant problems in social immaturity in the EP group.

Low cognitive function in preterm infants is a complex multifactorial issue. Both biological and environmental factors can influence the cognitive outcomes of preterm children. The EPIPAGE study showed that social factors such as low social status and lack of breastfeeding predicted both mild and severe cognitive deficiencies, whereas medical factors such as cerebral lesions predicted the most severe cognitive deficiencies.<sup>25</sup> A systematic review pointed out that perinatal risk factors for the cognitive development of VP children seem to diminish over time as environmental factors become more evident; thus, parental education status influences the cognitive outcomes of preterm children.<sup>26</sup> Nevertheless, after adjustments for birth weight, the presence of severe ROP and low discharge weight, which are early biological factors, were identified as independent risk factors for low cognitive outcomes of preterm children in this study cohort.

Severe ROP can be defined as ROP treated with laser photocoagulation. Several cohort studies have indicated the association of severe ROP with poor cognitive outcomes in preterm children.<sup>27-30</sup> An unfavorable early biological injury promoting ROP may concurrently aggravate the developing brain. Severe ROP has been reported to be related to poor white-matter maturation, irrespective of PVL or IVH, and is independent of visual outcomes.<sup>31</sup> Insulin-like growth factor-1 concentration has been suggested to be related to ROP and white-matter development, using the retina as a “window into the brain.”<sup>31</sup>

A low discharge weight Z-score, which mainly results from extrauterine growth restriction, is common among EP infants and may reflect various factors, including genetic factors, inadequate nutrition, morbidities affecting nutrient requirements, endocrine problems, and treatments.<sup>32,33</sup> Several studies have confirmed that low discharge weight in preterm infants is a risk factor for poor neurodevelopmental outcomes, which is similar to the results of our

study. In particular, Franz et al.<sup>34</sup> reported that the weight SD score at birth and an increase in the weight SD score from birth to discharge influenced the mental processing composite score among VLBW infants at approximately 6 years of age, whereas Belfort et al.<sup>35</sup> showed that greater weight gain to term was related to better neurodevelopmental outcomes at a corrected age of 18 months among VP infants. The Neonatal Research Network of Japan analyzed weight growth velocity during NICU hospitalization as a predictive factor for neurodevelopmental impairment at 3 years of age.<sup>36</sup>

As IVH and PVL were not frequent in our study cohort, cerebral morbidity did not therefore appear to be a determinant of low cognitive outcomes. Additionally, majority of the study cohort had an intact family structure, and socioeconomic status and parental education levels were not remarkably different. These cohort characteristics seem to have diminished the environmental impact on cognitive outcomes in this study.

In our analysis, we focused on risk factors for low cognitive outcomes using the FSIQ cutoff value. EF outcomes were correlated with FSIQ scores in the study cohort; furthermore, after controlling for FSIQ score, each of the indices in the EP group was not significantly different between groups (data not shown). This is understandable, considering that the Wechsler Intelligence Scale for Children-Fourth Edition contains Working Memory Index and Processing Speed Index subscales, both of which are highly associated with EF, including working memory, cognitive flexibility, and attentional control. Nonetheless, we should bear in mind that an IQ test would not appropriately evaluate EF<sup>37</sup> and controlling for IQ when assessing group differences in EF might result in overcorrected results.<sup>38</sup> The present study has some limitations. First, this study was conducted at a single center and included relatively fewer patients than other large-scale follow-up studies, such as the Victorian, EPICure, and EPIPAGE studies. Second, because term-birth controls were voluntarily recruited at the time of this study, perinatal data were not longitudinally collected and socioeconomic status was not matched to the preterm cohort. Nonetheless, this cohort study also has several strengths. First, the follow-up rate was comparable to that reported by other large-scale studies. Second, this study included a contemporary term-control group, thereby ensuring that comparisons were not outdated.

In conclusion, low FSIQ and low EF were common among EP children, and 37% of them had mild-to-severe cognitive problems at school age. Except for social immaturity, the behavioral problems of children born preterm were not evident, as compared to those of their term peers. In this study cohort, independent risk factors for FSIQ < 85 among EP children were the presence of severe ROP and a low discharge weight Z-score. As the first Korean study with long-term follow-up that evaluated the cognitive and behavioral outcomes of school-aged children born EP, the findings of this study can be used as basic data by the international community. Further persistent efforts to manage the long-term outcomes of EP infants and research on EF interventions are required.

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