Table 4. Long-term outcomes at three years of age according to era (N = 4,702)

Variables	2013–2014 (n = 1,463)	2015–2016 (n = 2,186)	2017 (n = 1,053)	*P* value
Mortality rate	0 (0–0)	0 (0–0)	0 (0–0)	0.669
Follow-up rate, wk	55 (53–56)	58 (56–60)	62 (60–64)	< 0.001
22–23	74 (39/53)	75 (41/55)	75 (24/32)	
24–25	66 (207/312)	66 (243/370)	69 (103/149)	
26–27	62 (319/516)	63 (460/734)	66 (213/322)	
28–29	50 (383/770)	56 (634/1,130)	60 (301/501)	
30–31	52 (305/589)	56 (459/821)	62 (235/382)	
≥ 32	48 (210/442)	53 (349/663)	56 (177/315)	
GA (mean), wk^{+days}	28^{+6}	29^{+1}	29^{+2}	
BWt (mean), g	1,072.15	1,094	1,109.8	
Weight < 5th percentile	26 (22–29)	21 (19–23)	21 (19–23)	0.138
Height < 5th percentile	29 (25–33)	24 (22–26)	23 (21–25)	0.063
Head circumference < 5th percentile	23 (18–27)	20 (17–22)	20 (17–22)	0.431
Re-hospitalization	28 (25–30)	30 (28–32)	29 (27–32)	0.332
Rehabilitative support	23 (21–25)	25 (23–27)	27 (24–29)	0.042
Language support	13 (12–15)	20 (18–21)	20 (17–22)	< 0.001
Blindness	0 (0–1)	0 (0–1)	1 (0–1)	0.431
Hearing loss	3 (2–4)	2 (1–2)	2 (1–2)	0.083
Sit alone	92 (89–94)	95 (93–96)	93 (92–94)	0.887
Walk independently	90 (87–92)	92 (91–93)	92 (90–93)	0.847
Cerebral palsy				
Yes	8 (6–11)	7 (6–8)	5 (4–6)	< 0.001
Unknown	2 (2–3)	4 (3–5)	3 (2–5)	0.130
BSID II, MDI < 70	25 (15–36)	24 (18–31)	21 (15–27)	0.490
BSID II, PDI < 70	48 (35–60)	34 (27–41)	29 (22–36)	0.073
BSID III, cognitive < 70	13 (0–35)	2 (0–7)	12 (6–17)	0.261
BSID III, language < 70	13 (0–35)	14 (3–24)	21 (15–28)	0.325
BSID III, motor < 70	13 (0–35)	9 (1–18)	17 (11–23)	0.324
K-DST, gross motor	15 (12–18)	12 (10–14)	14 (12–17)	0.716
K-DST, fine motor	13 (10–16)	13 (11–16)	16 (13–19)	0.172
K-DST, cognition	10 (8–13)	11 (9–13)	13 (11–16)	0.079
K-DST, language	13 (10–15)	16 (14–18)	19 (16–23)	0.001

Values are expressed as percentage (95% confidence interval).
GA = gestational age, BWt = birth weight, BSID = Bayley Scale of Infant Development, MDI = Mental Developmental Index, PDI = Psychomotor Developmental Index, K-DST = Korean Developmental Screening Test for Infants and Children.

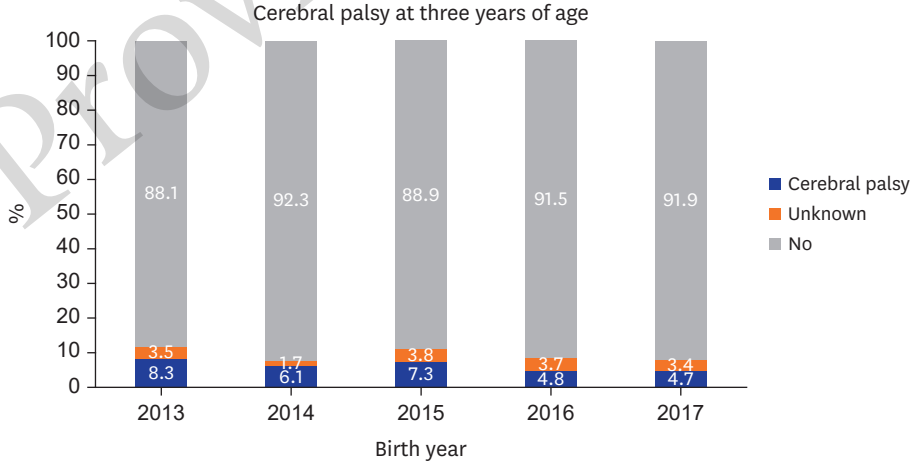

Fig. 2. Cerebral palsy at three years of age according to birth year. The incidence of cerebral palsy at three years of age has significantly decreased over time from 8.3% in infants born in 2013 to 4.7% in 2017. The follow-up rates of infants at three years of age were 55%, 58%, and 62% in infants born in 2013–2014, 2015–2016, and 2017, respectively. Blue bar, the rate of infants with cerebral palsy; orange bar, the rate of infants with 'unknown' cerebral palsy; and gray bar, the rate of infants without cerebral palsy.

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of cerebral palsy were 9.5% in infants with birth weights < 1,000 g and 5.1% in infants with birth weights of 1,000–1,500 g by NRNJ.[19] Similarly, in a recent meta-analysis, the prevalence of cerebral palsy in VLBWIs was 6.8%, 8.4% in infants with birth weight < 1,000 g, 4.2% in infants with birth weight 1,000–1,500 g, and 10.0% in extremely preterm infants with GA < 28 weeks.[20] In the Australian and New Zealand Neonatal Network (ANZNN),[21] at 2–3 years of age, the rates of cerebral palsy were lower than those in the present study, with 13%, 10%, 9%, 4%, and 4% in infants with a GA of < 24, 24, 25, 26, and 27 weeks, respectively. The rate of cerebral palsy in VLBWIs at 18–24 months of CA and at three years of age in Korea decreased over time in the present study. This result is in line with those of recent reports from other countries that observed a decreasing prevalence of cerebral palsy in VLBWIs as well as in term infants. In Japan, the prevalence of cerebral palsy has decreased over time to 1.88 per 1,000 live births in infants born between 1988 and 2007.[22] Among them, 70% were preterm or low-birth-weight infants. In Europe, the prevalence of cerebral palsy has also decreased, from 1.90 to 1.77 per 1,000 live births in infants born between 1980 and 2003.[23] Further, in VLBWIs, it decreased from 70.9 to 35.9 per 1,000 live births,[23] which is similar to the results of the present study. In addition, the Surveillance for Cerebral Palsy in Europe (SCPE) network reported that the prevalence of cerebral palsy in preterm infants born between 2004 and 2010 continues to decrease.[24] The rate of motor delay at 18–42 months of CA in ANZNN[21] was lower than that in the present study, which was 39%, 26%, 24%, 16%, and 13% in infants with a GA of < 24, 24, 25, 26, and 27 weeks, respectively, as reported by ANZNN. In the present study, the rate of infants requiring rehabilitative support at 18–24 months of CA decreased according to era. This finding was presumed to be affected by the decreased number of infants with cerebral palsy who continued to require rehabilitative motor support. But 34% and 25% of our VLBWIs required rehabilitative support at 18–24 months of CA and at three years of age, respectively. The follow-up rate at follow-up 2 increased over time in infants with each GA, not only in infants with larger GA. Therefore, decreased morbidities at follow-up 2 compared with follow-up 1 did not seem to be associated with increased follow-up of infants with larger GA.

The rate of infants with language developmental delays and requiring language support increased according to era. Further, infants with language developmental delay and requiring language support were increased at three years of age compared with those at 18–24 months of CA. This may result from the increased follow-up of severe infants at three years of age, increased concerns about language development at three years of age, or an actual increase in language developmental delay at three years of age. This trend is similar to the study by Stolt et al.[25] that VLBWIs with weak language skill increased at five years of age (20–27% of VLBWIs) compared with those at two years of age (16–18% of VLBWIs). Further, preterm infants have increased risk of atypical linguistic performances, which means language development in preterm infants is quite different from term infants.[26] Further studies on the increasing trends in language delay and language support are needed. According to an ANZNN,[21] the rate of cognitive delay at 18–42 months of CA was 34%, 26%, 18%, 15%, and 12% in infants with GA of < 24, 24, 25, 26, and 27 weeks, respectively. Moreover, the rate of language delay at 18–42 months of CA was higher than that of motor or cognitive delay at 56%, 40%, 32%, 28%, and 25% in infants with a GA of < 24, 24, 25, 26, and 27 weeks, respectively, as reported by ANZNN.[21]

The rate of growth restriction, especially weight growth restriction at 18–24 months of CA, has decreased according to era. This may be partly due to aggressive nutritional support and improved NICU care. The rate of growth restriction decreased with increasing GA

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and then increased again in infants with GA ≥ 32 weeks. A direct comparison between the ANZNN report and the present study was not possible because of the methodological differences. However, this trend is similar to the ANZNN report that the decreased rate of growth restriction with increasing GA increased again in infants with larger GA (≥ 28 weeks). According to the report of ANZNN, the rates of weight growth restriction (weight < 10 percentile) at the 2–3 year follow-up were 30%, 20%, 18%, 16%, 15%, and 37% in infants with GA < 24, 24, 25, 26, 27, and ≥ 28 weeks, respectively.[21] The rates of height growth restriction (height < 10 percentile) at the 2–3 year follow-up were 35%, 31%, 26%, 24%, 23%, and 43% in infants with GA < 24, 24, 25, 26, 27, and ≥ 28 weeks, respectively. In addition, the rates of head circumference growth restriction (head circumference < 10 percentile) at the 2–3 year follow-up were 33%, 22%, 16%, 12%, 9%, and 23% in infants with GA < 24, 24, 25, 26, 27, and ≥ 28 weeks, respectively.[21] KNN registration was based on birth weight (< 1,500 g) not GA. Small-for-gestational age (SGA) infants with a GA ≥ 32 weeks and birth weight < 1,500 g may be included in the group of infants with a GA ≥ 32 weeks at enrollment. Therefore, extrauterine growth restriction might be affected by the enrollment rate of SGA infants, and SGA infants tend to have smaller head circumferences and remain lighter and shorter than appropriate-for-GA infants.[27] Further, the rate of growth restriction was higher at three years of age than at 18–24 months of CA in the present study. This result may be attributed to the higher follow-up rate of infants with respiratory distress syndrome, bronchopulmonary dysplasia, operation of patent ductus arteriosus, or periventricular leukomalacia,[28] who are at great risk for extrauterine growth restriction.[29] Also, this may be in line with the finding that the early achievement of catch-up growth is not sustained in some preterm infants.[27]

In the present study, we have presented long-term follow-up data according to GA. Therefore, additionally long-term outcomes according to birth weight were analyzed based on the annual reports of KNN 2020 (follow-up 1 of VLBWIs born in 2018, and follow-up 2 of VLBWIs born in 2017) (**Supplementary Tables 1** and **2**). Long-term outcomes were improved according to increasing birth weight both at follow-ups 1 and 2. At follow-up 2, VLBWIs who re-hospitalized, or required rehabilitative support were decreased, whereas those required language support were increased compared with follow-up 1. The incidence of cerebral palsy decreased abruptly according to increasing birth weight. The incidences of cerebral palsy and 'unknown' cerebral palsy at follow-up 1 were 4.5% and 2.4%, respectively in infants born in 2018, and those at follow-up 2 were 4.7% and 3.4%, respectively in infants born in 2017.

The present study has some limitations. First, this study was based on the annual reports of the KNN. Therefore, we could not control for all the confounding factors. For example, the enrollment rate of SGA infants in each GA group could not be controlled. Furthermore, direct statistical comparison with other neonatal networks was impossible because of methodological differences in long-term follow-up age, stratification of GA, and inclusion criteria of registrants. Second, infants with morbidities such as respiratory distress syndrome, bronchopulmonary dysplasia, operation of patent ductus arteriosus, periventricular leukomalacia, or retinopathy of prematurity were more commonly followed up.[28] Considering the long-term follow-up nature of this study, those selection bias was inevitable. Third, the higher mortality rate in the NICU among infants with a smaller GA may be related to a lower rate of long-term growth and neurodevelopmental impairment among survivors.[19] Despite these limitations, this study is significant because it is the first to evaluate the overall long-term growth and neurodevelopmental outcomes of VLBWIs in Korea using a nationwide large cohort.

In conclusion, the long-term outcomes of VLBWIs regarding weight growth and cerebral palsy, the most common motor disability in childhood, have improved serially since the establishment of the KNN. However, the rate of infants with language delays requiring language support has increased, according to era. Further research is needed on the increased trends of language delay and language support while improving motor outcomes.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Long-term outcomes at 18–24 months of corrected age according to birth weight in infants born in 2018

Click here to view

Supplementary Table 2

Long-term outcomes at three years of age according to birth weight in infants born in 2017

Click here to view

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