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ARTICLE

Trends in the neurodevelopmental outcomes among preterm infants from 2003–2012: a retrospective cohort study in Japan

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Abstract

Objectives To determine the trends in mortality and the prevalence of abnormal neurodevelopmental outcomes among preterm Japanese infants.

Study design A retrospective multicenter cohort of 30,793 preterm infants born at a gestational age ≤32 weeks, between 2003 and 2012, in the Neonatal Research Network, Japan, was evaluated in the primary analysis. Finally, 13,661 infants were followed-up until 3 years of age and evaluated for neurodevelopmental outcomes, including cerebral palsy (CP), home oxygen therapy (HOT) use, and visual, hearing, and cognitive impairments. Multivariable logistic regression analysis was performed to determine the risk-adjusted trends in mortality and long-term neurodevelopmental outcomes.

Results The trends in overall mortality (adjusted odds ratio, (AOR): 0.92; 95% confidence interval, (CI): 0.89–0.94), the prevalence of CP (AOR: 0.95, 95% CI: 0.92–0.98), HOT use (AOR: 0.84, 95% CI: 0.75–0.93), and visual (AOR: 0.84, 95% CI: 0.81–0.87) and hearing impairments (AOR: 0.78, 95% CI: 0.63–0.97) showed a significant downward trend, while cognitive impairment showed no significant changes (AOR: 1.02, 95% CI: 0.99–1.05). Intravenous hyperalimentation was significantly correlated with visual impairment (AOR 0.74, 95% CI 0.59–0.91). Early establishment of enteral feeding was associated with improved long-term outcomes.

Conclusions Mortality was improved, and this did not lead to increased risks for abnormal neurodevelopmental outcomes. Nutritional support might improve long-term neurodevelopmental outcomes.

Introduction

While advances in perinatal and neonatal care management have led to increased survival rates among premature infants, worldwide [1–5], there have been concerns that the declining mortality may lead to an increase in the number of surviving infants with neurodevelopmental impairments. A recently conducted multicenter, multinational cohort of preterm infants among eight members of the International Network for Evaluating Outcomes, spanning nine countries, found that Japan had the lowest mortality [6]. However, few studies have examined the mortality and long-term neurodevelopmental outcomes among surviving premature infants using a large cohort. The findings of such studies would be important for clinicians, both in counseling and early-care decision-making for these high-risk infants. Furthermore, these findings might also be useful in identifying outcome variations in premature infants, across countries [6–8].

Therefore, the aim of our study was to characterize the recent trends in morbidity, mortality, and long-term neurodevelopmental outcomes, among preterm infants born at a gestational age (GA) ≤32 weeks, between 2003 and 2012, using data from the Neonatal Research Network, Japan (NRNJ) [9]. Furthermore, we also explored potential interventions associated with long-term neurodevelopmental outcomes.

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Materials and methods

Study design and population

This retrospective multicenter cohort study was carried out between 2003 and 2012. The 202 participating hospitals included large tertiary perinatal centers, designated as tertiary neonatal intensive care units (NICU), in Japan. The central internal review board at Tokyo Women's Medical University approved this study. Written informed consent was obtained from the parents or guardians of the participants. Data were collected anonymously, and unlinked from individual data before analysis.

Of the total 40,806 infants with a birth weight ≤1500 g, 10,013 cases (with congenital anomaly, missing medical records, and births outside hospitals) [10] and 155 cases of death in the delivery room were excluded. The final study population of 30,638 infants with a GA ≤32 weeks were then admitted to the NICU, and grouped into four GA categories (22–24, 25–27, 28–30, and 31–32 weeks). The characteristics of the participating hospitals over time are shown in Supplementary Table 1. To evaluate the neurodevelopmental outcomes among these infants, 13,661 infants with follow-up data at 3 years of age (from 132 tertiary perinatal centers) were analyzed while 14,971 infants (deaths at and after discharge, and those lost to follow-up by 3 years of age) were excluded (Fig. 1). The differences in variables between infants with and without follow-up data (13,661 vs. 14,971, respectively) are shown in Supplementary Tables 2 and 3.

Definitions

All study parameters were defined based on the NRNJ registration manual [2, 9]. Data on GA were obtained from obstetric histories with confirmation or corrections using ultrasound examination at health check-ups for pregnant women during the first trimester. Congenital anomaly was defined as a major life-threatening anomaly that did not include just external malformations. The study outcomes included neonatal outcomes (mortality and survival) and long-term neurodevelopmental outcomes at 3 years of age, such as the prevalence of cerebral palsy (CP) [11], home oxygen therapy (HOT) use, and visual, hearing, and cognitive impairments, as indicated by developmental testing, according to the Kyoto Scale of Psychological Development (KSPD) [12, 13]. Mortality was defined as death occurring among surviving in-born infants (born at any of the participating perinatal centers with no transfer to other hospitals after birth) admitted to the NICU, before discharge (deaths in the delivery room were excluded). CP was defined at 3 years of age at any level of severity, as reported by Bax [14]. Visual impairment was defined as blindness with no functional vision in one or both eyes. Hearing impairment was considered present when amplification was

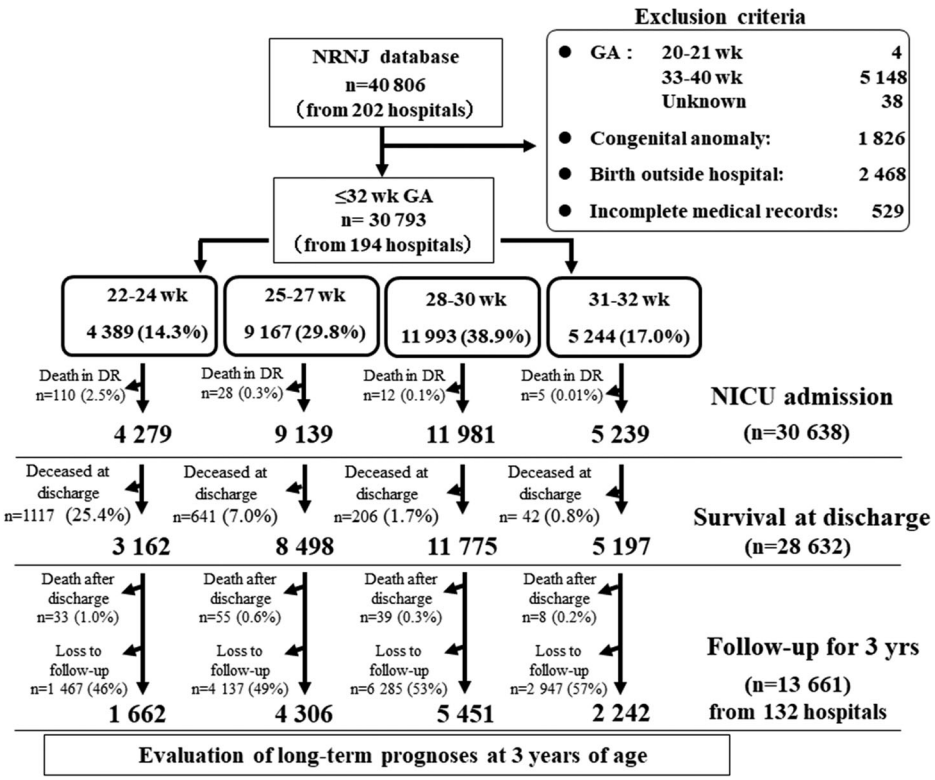

Fig. 1 Flow chart of the evaluated infants. Of the 40,806 infants registered to the participating neonatal centers in the NRNJ, from 2003 to 2012, 30,638 infants admitted to the NICU were categorized into the following four groups: 22–24, 25–27, 28–30, and 31–32 weeks' GA. Furthermore, 13,661 infants, followed up until 3 years of age, were evaluated for long-term outcomes. NICU neonatal intensive care unit, NRNJ Neonatal Research Network, Japan, GA gestational age, DR delivery room

required. A total Developmental Quotient score <70, equivalent to a Bayley III Cognitive Scale score <85, represented significantly delayed performance [13].

Trends in mortality and neurodevelopmental outcomes, by GA categories as percentages, were determined for the study participants, over the study period. With a low response rate (<60% from 2003 to 2005) in terms of HOT use, at 3 years of age in the NRNJ, the trends in HOT use were determined from 2006 to 2012.

Data were obtained on the antenatal characteristics of the participants, including maternal age, parity, multiple pregnancies, pregnancy-induced hypertension (PIH), maternal diabetic mellitus (DM), premature rupture of membrane (PROM), clinical chorioamnionitis (CAM), non-reassuring fetus status (NRFS), head presentation, antenatal steroid (ANS) use, and cesarean section. Data on the neonatal characteristics, including GA, birth weight, male sex, small for GA (SGA), and 1-minute Apgar score were also obtained. Furthermore, information on neonatal morbidities including the 5-minutes Apgar score, respiratory distress syndrome (RDS), pulmonary hemorrhage, air-leak syndrome, persistent pulmonary hypertension of the newborn (PPHN), patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD) at 36 weeks [15], adrenal insufficiency of prematurity (AOP), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP) [16], periventricular leukomalacia (PVL), sepsis, and necrotizing enterocolitis/interstitial perforation (NEC/IP) was obtained from each perinatal center's records. Data on the different interventions (intubation, mechanical ventilation, surfactant administration, high frequency oscillatory ventilation (HFOV), inhaled nitric oxide (iNO), steroids for BPD, indomethacin for PDA, PDA ligation, intravenous hyperalimentation, ROP treatment, time to establishment of enteral feeding (defined as the number of days till enteral feeding of 100 ml/kg/day was achieved), and HOT use at discharge were also obtained from each perinatal center's records.

Statistical analyses

Statistical analyses were conducted using JMP® 13 (SAS Institute Inc., Cary, NC, USA). Data were reported using the mean (continuous data) or the percentage (categorical data) and 95% confidence interval (95% CI). Variables with a non-normal distribution were expressed using median and interquartile range (IQR), and analyzed using Wilcoxon rank sum tests or Kruskal–Wallis one-way analysis of variance. The χ^2-test was performed for yearly trends in proportions (Cochran–Armitage test) over the past decade, as well as for the first (2003–2007) and second 5-year period (2008–2012) for categorical data (antenatal and neonatal correlates, morbidity, interventions, mortality, and long-term neurodevelopmental outcomes).

We examined the risk-adjusted trends in morbidity, intervention, mortality and long-term neurodevelopmental outcomes, over time, by adjusting for patients' background characteristics and related perinatal (antenatal and neonatal) risk factors; this is because, with the number of participating hospitals in the NRNJ increasing, annually, clinical conditions may change over time. To avoid bias among the registered hospitals in NRNJ, infants from the 38 originally participating hospitals, which were constantly tracked over the entire study period, were chosen.

Three levels of analysis were performed, as follows: the significant independent perinatal risk factors for mortality were determined using univariate logistic regression analysis (Analysis #1) among all the participating infants; multiple logistic regression analysis (Analysis #2) was performed to determine the risk-adjusted trends by adjusting for year and those significant perinatal factors determined in Analysis #1; multivariable logistic analysis (Analysis #3) was performed to determine the interventions associated with long-term neurodevelopmental outcomes by adjusting for year and the perinatal risk factors identified in Analysis #1. A p-value <0.05 was considered significant. The odds ratios (ORs) with 95% CIs were reported.

Results

A majority of the participants (99.5%) were admitted to the NICU soon after birth, with no differences across GA categories in the admission rates (Supplementary Table 4). The lowest GA group (22–24 weeks) had the highest intubation rate (93.2% [95% CI: 92.3–93.9]). The total mortality for all the participants was 6.5%, with a dramatic decrease, by GA category, from 26.1% (22–24 weeks) to 0.8% (31–32 weeks).

The trends in mortality and the prevalence of neurodevelopmental outcomes are shown in Fig. 2. A significant decrease in the overall trend (total) in mortality was observed, over time (from 9.0% in 2003 to 4.6% in 2012), and by GA categories (Fig. 2a). The overall prevalence of CP (from 12.3% in 2003 to 7.1% in 2012), HOT use (2.4% in 2006 to 0.9% in 2012), and visual impairment (11.4% in 2003 to 3.2% in 2012) showed a downward trend, over time. In the GA categories, similar patterns were shown for CP and visual impairment, but not HOT use (Fig. 2b–d). In the second 5-year period, among those with a GA of 22–24 weeks, the prevalence of CP showed an upward trend (Fig. 2b). Although no significant changes were observed for both hearing and cognitive impairments, over time (Fig. 2e, f), a significant decrease from 1.8% in 2008 to

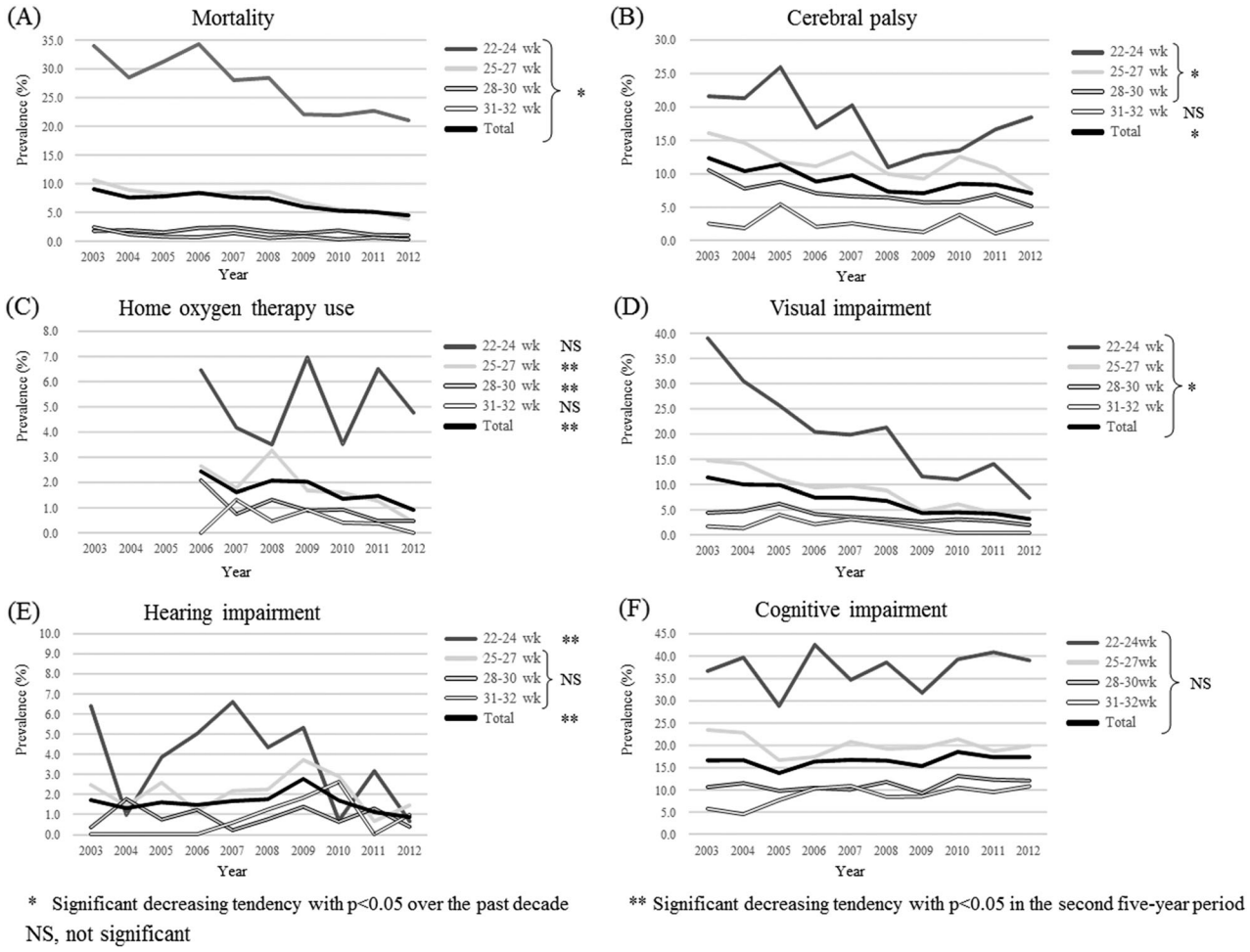

Fig. 2 Trends in **a** mortality and neurodevelopmental outcomes at 3 years of age, **b** CP, **c** HOT, **d** visual impairment, **e** hearing impairment, **f** cognitive impairment, by GA among all infants. *p*-Values were calculated by the Cochrane–Armitage χ^2-test. *Significant decrease in 2003–2012; **significant decrease in 2008–2012; NS not significant. CP cerebral palsy, HOT home oxygen therapy, GA gestational age

0.9% in 2012 was observed for hearing impairment, in the second 5-year period.

Table 1 shows the overall trends in the prevalence of antenatal and neonatal factors. Over time, a significant increase in the prevalence of ANS use and cesarean section was observed, while a decrease was noted for multiple pregnancies, especially in the second 5-year period; for GA, birth weight, and male sex, no significant differences were shown.

The overall trends in the prevalence of resuscitation, morbidity, intervention, and follow-up rate are shown in Table 2. Significant increases in prevalence, over time, were observed for resuscitation, as indicated by the intubation and NICU admission rates, even in the lowest GA group (22–24 weeks). Significant increases in prevalence, over time, were shown for RDS and BPD, at 36 weeks, especially in the second 5-year period. Similar findings of significant increases in prevalence were shown for symptomatic PDA, AOP, early-onset sepsis as well as NEC and/or IP, especially in the first 5-year period. For severe IVH, severe ROP, and PVL, a significant decrease in prevalence was shown, over time. Of the interventions (Table 2), intubation after birth, PDA ligation, HFOV, surfactant administration, indomethacin for PDA, ROP treatment, HOT use at discharge, and intravenous hyperalimentation showed an upward trend, over time. However, in the case of steroid treatment for BPD, a downward trend was shown, over time, especially in the second 5-year period.

In Analysis #1, where the independent perinatal risk factors of mortality were assessed (not shown), GA (adjusted odds ratio (AOR) 0.77, 95% CI 0.73–0.81), birth weight at increments of 100 g (AOR 0.74, 95% CI 0.71–0.78), male sex (AOR 1.37, 95% CI 1.23–1.52), Apgar score <4 at 1 min (AOR 2.24, 95% CI 2.01–2.51), multiple pregnancies (AOR 1.34, 95% CI 1.18–1.53), ANS (AOR 0.63, 95% CI 0.57–0.71), PIH (AOR 0.71, 95% CI

Table 1 Trends in the prevalence of antenatal and neonatal factors among in-born infants in the Neonaral Research Network, Japan

	2003		2004		2005		2006		2007		p* 2003–2007	**	2008		2009		2010		2011		2012		p* 2008–2012	**	p* 2003–2012	**
Antenatal factors	$n = 1642$[a]		$n = 2041$[a]		$n = 2320$[a]		$n = 2661$[a]		$n = 3263$[a]				$n = 3170$[a]		$n = 3330$[a]		$n = 3814$[a]		$n = 4184$[a]		$n = 4213$[a]					
Maternal age, mean [95% CI]	30.6 [30.3–30.8]		30.6 [30.4–30.9]		31.1 [30.8–31.3]		31.1 [30.8–31.3]		31.2 [31.0–31.4]		–	–	31.3 [31.1–31.5]		31.4 [31.2–31.6]		31.7 [31.5–31.8]		31.7 [31.5–31.9]		31.9 [31.7–32.0]		–	–	–	–
Primipara, % [95% CI], n[b]	57.6 [55.1–59.5]	1642	56.9 [54.8–59.1]	2041	57.3 [55.3–59.3]	2320	59.0 [57.2–60.9]	2661	55.2 [53.4–56.8]	3262	0.254	→	53.4 [51.7–55.2]	3170	51.8 [50.1–53.5]	3196	52.0 [50.4–53.6]	3773	52.3 [50.8–53.8]	4160	51.7 [50.2–53.2]	4206	0.290	→	0.001	↓
Multiple pregnancies, % [95% CI], n[b]	28.1 [26.0–30.3]	1642	30.1 [28.1–32.1]	2041	29.2 [27.4–31.1]	2320	27.6 [25.9–29.3]	2661	28.3 [26.8–29.9]	3263	0.397	→	25.7 [24.2–27.3]	3170	22.9 [21.5–24.3]	3330	23.6 [22.3–25.0]	3814	21.8 [20.6–23.1]	4184	23.6 [22.4–24.9]	4213	0.027	↓	0.001	↓
PIH, % [95% CI], n[b]	14.5 [12.9–16.3]	1642	15.5 [14.0–17.2]	2041	15.6 [14.1–17.1]	2320	16.4 [15.1–17.9]	2661	18.1 [16.9–19.5]	3263	0.001	↑	17.2 [15.9–18.6]	3170	18.3 [17.0–19.6]	3330	20.5 [19.3–21.8]	3794	21.3 [20.0–22.5]	4138	21.3 [20.1–22.6]	4177	0.001	↑	0.001	↑
DM, % [95% CI], n[b]	1.0 [0.6–1.6]	1642	1.6 [1.2–2.3]	2041	1.6 [1.1–2.1]	2320	1.6 [1.2–2.1]	2661	1.8 [1.4–2.4]	3263	0.053	→	1.3 [1.0–1.8]	3170	2.1 [1.7–2.6]	3330	2.7 [2.2–3.3]	3779	3.6 [3.1–4.2]	4099	4.3 [3.7–5.0]	4156	0.001	↑	0.001	↑
PROM, % [95% CI], n[b]	30.6 [28.5–32.9]	1642	29.1 [27.2–31.1]	2041	30.2 [28.3–32.1]	2320	28.4 [26.7–30.1]	2661	31.0 [29.5–32.6]	3263	0.720	→	29.9 [28.3–31.5]	3170	32.2 [30.6–33.8]	3330	33.2 [31.7–34.7]	3788	33.9 [32.5–35.3]	4153	32.1 [30.7–33.5]	4197	0.022	↑	0.001	↑
Clinical CAM, % [95% CI], n[b]	16.7 [15.0–18.6]	1642	18.8 [17.1–20.5]	2041	19.5 [17.9–21.1]	2320	16.9 [15.5–18.4]	2661	17.7 [16.4–19.0]	3263	0.749	→	17.8 [16.5–19.2]	3170	19.3 [18.0–20.7]	3330	21.0 [19.7–22.3]	3664	21.0 [19.8–22.4]	3806	21.6 [20.4–22.9]	3945	0.001	↑	0.001	↑
NRFS, % [95% CI], n[b]	23.3 [21.3–25.4]	1642	22.2 [20.5–24.1]	2041	23.6 [21.9–25.3]	2320	24.8 [23.2–26.4]	2661	22.6 [21.2–24.1]	3263	0.842	→	23.4 [22.0–24.9]	3170	22.3 [20.9–23.7]	3330	23.2 [21.9–24.6]	3703	25.9 [24.5–27.3]	3958	26.2 [24.9–27.6]	4062	0.001	↑	0.001	↑
Head presentation, % [95% CI], n[b]	73.0 [70.8–75.1]	1642	68.4 [66.3–70.4]	2041	69.2 [67.3–71.1]	2320	62.1 [60.2–63.9]	2661	66.9 [65.3–68.5]	3263	0.001	↓	67.3 [65.6–68.9]	3170	71.3 [69.8–72.8]	3330	70.3 [68.9–71.7]	3814	65.2 [63.7–66.6]	4184	64.5 [63.1–65.9]	4213	0.001	↓	0.001	↓
ANS use, % [95% CI], n[b]	41.8 [39.4–44.2]	1642	40.4 [38.3–42.6]	2041	39.4 [37.4–41.4]	2320	38.7 [36.8–40.5]	2661	44.9 [43.2–46.6]	3263	0.022	↑	48.5 [46.7–50.2]	3170	53.0 [51.3–54.7]	3330	55.5 [53.9–57.1]	3763	59.3 [57.8–60.8]	4061	62.4 [60.9–63.9]	4142	0.001	↑	0.001	↑
Cesarean section, % [95% CI], n[b]	71.6 [69.4–73.7]	1642	76.3 [74.4–78.1]	2041	75.7 [73.9–77.4]	2320	76.3 [74.6–77.8]	2661	77.0 [75.5–78.4]	3263	0.001	↑	76.3 [74.8–77.8]	3170	73.5 [72.0–75.0]	3330	80.8 [80.0–82.1]	3791	79.9 [78.7–81.1]	4150	81.4 [80.2–82.5]	4198	0.001	↑	0.001	↑
Neonatal factors	$n = 1642$[a]		$n = 2041$[a]		$n = 2320$[a]		$n = 2661$[a]		$n = 3263$[a]				$n = 3170$[a]		$n = 3330$[a]		$n = 3814$[a]		$n = 4184$[a]		$n = 4213$[a]					
Gestational age, mean [95% CI]	28.2 [28.0–28.3]		28.1 [28.0–28.2]		28.1 [28.0–28.3]		28.1 [28.0–28.2]		28.2 [28.1–28.3]		–	–	28.1 [28.0–28.2]		28.1 [28.0–28.2]		28.2 [28.2–28.3]		28.3 [28.2–28.4]		28.2 [28.2–28.3]		–	–	–	–
Birth weight, mean [95% CI]	993 [979–1008]		994 [981–1007]		999 [987–1011]		980 [968–991]		998 [988–1008]		–	–	988 [977–998]		993 [983–1003]		1009 [999–1018]		1010 [1001–1020]		1002 [993–1011]		–	–	–	–
SGA, %[95% CI], n[b]	21.5 [19.6–23.6]	1642	20.2 [18.5–22.0]	2041	18.9 [17.4–20.6]	2320	20.6 [19.1–22.2]	2661	19.0 [17.7–20.4]	3263	0.106	→	22.1 [20.7–23.6]	3170	21.4 [20.0–22.8]	3330	21.4 [20.1–22.7]	3782	22.6 [21.3–23.9]	4063	22.9 [21.6–24.2]	4114	0.181	→	0.001	↑
Male sex, % [95% CI], n[b]	53.0 [50.6–55.4]	1642	50.4 [48.2–52.6]	2035	50.6 [48.6–52.7]	2319	51.6 [49.7–53.5]	2661	50.9 [49.1–52.6]	3262	0.475	→	50.9 [49.2–52.7]	3170	52.0 [50.3–53.7]	3329	52.6 [51.0–54.1]	3813	52.6 [51.1–54.1]	4182	51.2 [49.7–52.7]	4209	0.764	→	0.378	→
1-min Apgar score < 4, % [95% CI], n[b]	27.4 [25.3–29.6]	1638	26.7 [24.8–28.7]	2034	25.1 [23.4–27.0]	2307	25.2 [23.5–26.8]	2628	25.9 [24.4–27.4]	3249	0.188	→	24.6 [23.1–26.2]	3127	26.1 [24.6–27.6]	3228	24.8 [23.5–26.2]	3810	26.7 [25.3–28.0]	4176	28.0 [26.6–29.3]	4209	0.001	↑	0.225	→

ANS antenatal steroid, *CAM* chorioamnionitis, *CI* confidence interval, *DM* diabetes mellitus, *NRFS* non-reassuring fetal status, *PIH* pregnancy-induced hypertension, *PROM* premature rupture of membranes, *SGA* small for gestational age

* p values were calculated by the Cochrane–Armitage χ^2-test

** ↑, significant increasing tendency; ↓, significant decreasing tendency; →, no significant change by the Cochrane–Armitage χ^2-test

[a]The number of infants, each year, of the 30,638 infants admitted to the NICU

[b]The obtained number of infants as a denominator for the % calculation, each year, of the 30,638 infants admitted to the NICU

Table 2 Trends in the resuscitation, morbidities, interventions, and follow-up rates of in-born infants in the Neonatal Research Network, Japan

	2003		2004		2005		2006		2007		p^* 2003–2007	**	2008		2009		2010		2011		2012		p^* 2008–2012	**	p^* 2003–2012	**
Resuscitation	$n = 1668$[a]		$n = 2057$[a]		$n = 2351$[a]		$n = 2675$[a]		$n = 3271$[a]				$n = 3186$[a]		$n = 3340$[a]		$n = 3825$[a]		$n = 4197$[a]		$n = 4223$[a]					
Intubation at birth in total, % [95% CI], n[b]	50.1 [47.7–52.5]	1668	59.8 [57.7–61.9]	2057	57.0 [55.0–59.0]	2351	57.5 [55.7–59.4]	2675	57.5 [55.8–59.2]	3271	0.003	↑	59.4 [57.6–61.0]	3186	56.7 [55.0–58.4]	3340	60.7 [59.2–62.3]	3800	60.1 [58.6–61.6]	4133	63.8 [62.4–65.3]	4204	0.001	↑	0.001	↑
GA of 22–24 wk, % [95% CI], n[b]	85.8 [80.9–89.7]	240	97.9 [95.5–99.0]	287	94.6 [91.8–96.5]	368	91.5 [88.2–93.8]	386	92.6 [89.8–94.6]	458	0.419	→	93.9 [91.3–95.7]	458	87.6 [84.5–90.2]	502	94.7 [92.4–96.3]	507	96.0 [94.1–97.3]	578	95.0 [93.0–96.5]	600	0.001	↑	0.012	↑
NICU admission rate in total, % [95% CI], n[b]	98.4 [97.7–98.9]	1668	99.2 [98.7–99.5]	2057	98.7 [98.1–99.1]	2351	99.5 [99.1–99.7]	2675	99.8 [99.5–99.9]	3271	0.001	↑	99.5 [99.2–99.7]	3186	99.7 [99.4–99.8]	3340	99.7 [99.5–99.8]	3825	99.7 [99.5–99.8]	4197	99.8 [99.6–99.9]	4223	0.089	→	0.001	↑
GA of 22–24 wk, % [95% CI], n[b]	94.6 [91.0–96.8]	240	96.9 [94.1–98.3]	287	94.0 [91.1–96.0]	368	96.9 [94.6–98.2]	386	99.1 [97.8–99.7]	458	0.001	↑	96.9 [94.9–98.2]	458	98.4 [96.9–99.2]	502	98.0 [96.4–98.9]	508	97.9 [96.4–98.8]	581	99.0 [97.8–99.5]	601	0.056	→	0.001	↑
Morbidities	$n = 1642$[c]		$n = 2041$[c]		$n = 2320$[c]		$n = 2661$[c]		$n = 3263$[c]				$n = 3170$[c]		$n = 3330$[c]		$n = 3814$[c]		$n = 4184$[c]		$n = 4213$[c]					
5-min Apgar score < 4, % [95% CI], n[d]	5.9 [4.8–7.2]	1595	5.4 [4.5–6.5]	1993	5.4 [4.6–6.4]	2264	6.1 [5.3–7.1]	2600	5.2 [4.5–6.0]	3205	0.628	→	5.4 [4.7–6.2]	3096	4.7 [4.0–5.5]	3208	5.0 [4.4–5.7]	3795	5.4 [4.7–6.1]	4161	7.1 [6.3–7.9]	4192	0.001	↑	0.220	→
RDS, % [95% CI], n[d]	58.3 [55.9–60.6]	1642	59.5 [57.3–61.6]	2041	52.7 [50.7–54.7]	2320	58.5 [56.7–60.4]	2661	59.7 [58.0–61.3]	3263	0.230	→	62.7 [61.0–64.4]	3170	60.5 [58.9–62.2]	3330	66.0 [64.4–67.4]	3792	64.2 [62.7–65.6]	4170	66.5 [65.1–67.9]	4207	0.001	↑	0.001	↑
Pulmonary hemorrhage, % [95% CI], n[d]	4.2 [3.3–5.3]	1642	4.7 [3.8–5.7]	2041	3.6 [2.9–4.4]	2320	3.3 [2.7–4.0]	2661	3.7 [3.1–4.4]	3263	0.068	→	3.7 [3.1–4.4]	3170	3.0 [2.5–3.6]	3330	3.4 [2.9–4.0]	3787	3.7 [3.2–4.4]	4141	3.5 [3.0–4.1]	4183	0.633	→	0.080	→
Air leak syndrome, % [95% CI], n[d]	2.9 [2.2–3.8]	1642	3.1 [2.5–4.0]	2041	2.7 [2.1–3.5]	2320	2.5 [2.0–3.2]	2661	2.7 [2.2–3.3]	3263	0.350	→	2.7 [2.2–3.4]	3170	3.1 [2.6–3.7]	3330	2.5 [2.0–3.0]	3792	2.4 [2.0–2.9]	4120	2.6 [2.1–3.1]	4196	0.240	→	0.204	→
PPHN, % [95% CI], n[d]	4.3 [3.4–5.4]	1642	4.1 [3.3–5.1]	2041	4.2 [3.5–5.1]	2320	4.4 [3.7–5.2]	2661	5.1 [4.4–5.9]	3263	0.111	→	4.5 [3.8–5.3]	3170	5.3 [4.6–6.1]	3330	4.6 [4.0–5.4]	3786	5.7 [5.0–6.4]	4120	5.5 [4.8–6.2]	4195	0.051	→	0.001	↑
Symptomatic PDA, % [95% CI], n[d]	27.3 [25.2–29.6]	1642	32.7 [30.7–34.7]	2041	32.7 [30.8–34.7]	2320	34.1 [32.3–35.9]	2661	37.8 [36.1–39.4]	3263	0.001	↑	41.3 [39.6–43.0]	3170	38.6 [36.9–40.2]	3330	39.0 [37.5–40.6]	3792	39.7 [38.2–41.2]	4163	41.6 [40.2–43.1]	4198	0.351	→	0.001	↑
BPD at 36 wk, % [95% CI], n[d]	17.1 [15.4–19.0]	1642	17.4 [15.9–19.1]	2041	12.5 [11.2–13.9]	2319	16.3 [14.9–17.7]	2661	16.6 [15.3–17.9]	3259	0.730	→	16.3 [15.0–17.6]	3169	18.4 [17.2–19.8]	3329	21.5 [20.2–22.8]	3715	22.4 [21.1–23.7]	3871	21.2 [20.0–22.5]	4020	0.001	↑	0.001	↑
Late-onset AOP, % [95% CI], n[d]	4.9 [4.0–6.1]	1642	5.0 [4.2–6.1]	2041	7.0 [6.1–8.1]	2320	8.0 [7.0–9.1]	2661	8.6 [7.6–9.6]	3263	0.001	↑	9.8 [8.8–10.9]	3170	9.9 [9.0–11.0]	3330	9.8 [8.9–10.8]	3788	9.7 [8.8–10.6]	4123	9.8 [9.0-10.8]	4174	0.913	→	0.001	↑
IVH, % [95% CI], n[d]	14.1 [12.5-15.8]	1642	16.0 [14.5-17.7]	2041	14.4 [13.0–15.8]	2320	14.2 [12.9–15.6]	2661	13.6 [12.5–14.9]	3263	0.154	→	14.5 [13.3–15.8]	3170	13.4 [12.3–14.6]	3330	14.4 [13.3–15.5]	3790	13.6 [12.6–14.7]	4155	14.0 [13.0–15.1]	4193	0.714	→	0.152	→
Severe IVH, % [95% CI], n[d]	5.6 [4.5–6.8]	1637	6.6 [5.6–7.8]	2035	5.2 [4.4–6.2]	2288	5.8 [5.0–6.7]	2645	5.0 [4.3–5.8]	3253	0.122	→	4.7 [4.0–5.5]	3161	4.4 [3.7–5.1]	3319	4.9 [4.2–5.6]	3786	4.6 [4.0–5.3]	4150	4.3 [3.7–5.0]	4188	0.597	→	0.001	↓
Severe ROP, % [95% CI], n[d]	14.9 [13.2–16.8]	1570	15.5 [14.0–17.2]	1886	11.3 [10.0–12.7]	2241	12.1 [10.9–13.4]	2582	12.4 [11.3–13.6]	3241	0.001	↓	10.0 [9.0–11.1]	3148	12.3 [11.2–13.5]	3317	11.8 [10.8–12.9]	3724	11.6 [10.7–12.7]	4009	12.6 [11.6–13.7]	4022	0.041	↑	0.001	↓
PVL, % [95% CI], n[d]	3.8 [3.0–4.9]	1642	4.3 [3.5–5.3]	2041	4.1 [3.3–4.9]	2320	4.3 [3.6–5.1]	2661	3.8 [3.2–4.5]	3263	0.779	→	3.4 [2.8–4.1]	3169	3.1 [2.5–3.7]	3330	3.7 [3.1–4.3]	3785	3.3 [2.8–3.9]	4128	3.1 [2.6–3.6]	4188	0.608	→	0.001	↓
Sepsis, % [95% CI], n[d]	8.8 [7.5–10.2]	1642	8.7 [7.6–10.0]	2041	6.6 [5.7–7.7]	2320	8.7 [7.7–9.8]	2661	7.5 [6.7–8.5]	3263	0.196	→	8.5 [7.5–9.5]	3170	9.3 [8.4–10.3]	3330	9.1 [8.2–10.1]	3789	8.2 [7.4–9.1]	4109	8.8 [8.0–9.7]	4193	0.706	→	0.136	→
NEC/IP, % [95% CI], n[d]	2.1 [1.5–2.9]	1642	2.9 [2.3–3.8]	2041	3.1 [2.5–3.9]	2320	3.1 [2.5–3.9]	2661	3.5 [2.9–4.2]	3263	0.002	↑	3.8 [3.2–4.6]	3170	3.3 [2.7–3.9]	3330	3.8 [3.3–4.5]	3814	3.0 [2.5–3.6]	4184	4.0 [3.5–4.6]	4213	0.879	→	0.003	↑
Interventions	$n = 1642$[c]		$n = 2041$[c]		$n = 2320$[c]		$n = 2661$[c]		$n = 3263$[c]				$n = 3170$[c]		$n = 3330$[c]		$n = 3814$[c]		$n = 4184$[c]		$n = 4213$[c]					
Duration of mechanical ventilation (median, quartile)	7 (1–38)		8 (1–39)		6 (0–34)		5 (0–33)		6 (1–34)		–	–	7 (1–35)		7 (0–34)		7 (1–33)		6 (1–33)		7 (1–33)		–		– –	–
Surfactant, % [95% CI], n[d]	56.9 [54.5–59.3]	1642	58.6 [56.4–60.7]	2041	53.8 [51.7–55.8]	2320	57.9 [56.0–59.7]	2661	58.4 [56.7–60.1]	3263	0.299	→	60.3 [58.6–62.0]	3170	62.3 [60.6–63.9]	3330	62.8 [61.2–64.3]	3791	65.7 [64.2–67.1]	4086	67.3 [65.9–68.7]	4187	0.001	↑	0.001	↑
HFOV, % [95% CI], n[d]	28.0 [25.9–30.2]	1642	33.7 [31.6–35.7]	2041	29.0 [27.2–30.9]	2319	29.8 [28.1–31.5]	2660	30.9 [29.3–32.5]	3260	0.698	→	32.3 [30.7–34.0]	3165	32.7 [31.1–34.3]	3330	33.4 [31.8–35.0]	3511	39.9 [38.2–41.7]	3145	38.9 [37.3–40.5]	3476	0.001	↑	0.001	↑
iNO, % [95% CI], n[d]	3.8 [3.0–4.8]	1642	6.0 [5.1–7.1]	2041	5.3 [4.5–6.3]	2320	4.8 [4.1–5.7]	2661	8.4 [7.5–9.4]	3263	0.001	↑	6.9 [6.1–7.9]	3170	3.8 [3.2–4.6]	3330	4.0 [3.4–4.6]	3692	4.9 [4.2–5.6]	3914	5.6 [4.9–6.3]	4054	0.298	→	0.113	→
Steroid for BPD, % [95% CI], n[d]	33.4 [29.6–37.4]	572	31.2 [27.9–34.8]	698	27.6 [24.3–31.0]	686	33.3 [30.2–36.5]	857	32.2 [29.6–34.9]	1208	0.806	→	35.8 [33.1–38.7]	1117	35.5 [32.9–38.2]	1256	33.2 [30.9–35.5]	1565	32.7 [30.6–34.8]	1873	19.9 [18.5–21.3]	3085	0.001	↓	0.001	↓
Indomethacin for PDA, % [95% CI], n[d]	25.8 [23.7–27.9]	1642	31.3 [29.3–33.3]	2041	36.9 [35.0–38.9]	2320	35.7 [33.8–37.5]	2602	38.9 [37.2–40.7]	3103	0.001	↑	43.0 [41.2–44.8]	2930	41.9 [40.2–43.7]	3048	44.1 [42.4–45.7]	3423	43.0 [41.4–44.5]	3802	46.8 [45.2–48.4]	3716	0.001	↑	0.001	↑
PDA ligation, % [95% CI], n[d]	3.6 [2.8–4.6]	1642	5.2 [4.3–5.2]	2041	4.4 [3.6–5.3]	2319	5.0 [4.2–5.9]	2630	4.9 [4.2–5.7]	3255	0.146	→	6.4 [5.6–7.3]	3164	6.2 [5.4–7.1]	3330	7.4 [6.6–8.4]	3089	17.0 [15.3–18.9]	1633	17.4 [15.7–19.3]	1745	0.001	↑	0.001	↑
		1642		2041		2320		2661		3263	0.001	↑		3170		3330		3791		4103		4195	0.001	↑	0.001	↑

Table 2 (continued)

	2003		2004		2005		2006		2007		p^* 2003–2007	**	2008		2009		2010		2011		2012		p^* 2008–2012	**	p^* 2003–2012	**
Intravenous hyperalimentation, % [95% CI], n^d	32.6 [30.4–34.9]		43.3 [41.2–45.5]		45.7 [43.7–47.7]		51.5 [49.6–53.4]		55.3 [53.5–57.0]				61.7 [60.0–63.4]		66.5 [64.9–68.1]		76.6 [75.3–77.9]		81.8 [80.6–82.9]		86.2 [85.2–87.3]					
ROP treatment, % [95% CI], n^d	13.4 [11.8–15.1]	1642	16.3 [14.7–17.9]	2041	14.5 [13.1–16.0]	2319	16.6 [15.2–18.0]	2659	19.2 [17.9–20.6]	3260	0.001	↑	14.9 [13.7–16.2]	3166	17.1 [15.8–18.4]	3328	16.9 [15.7–18.1]	3661	16.1 [14.9–17.3]	3673	17.5 [16.3–18.7]	3887	0.039	↑	0.006	↑
Time to establishment of enteral feeding (days) (median, quartile)	12 (9–18)		12 (9–17)		11 (8–17)		12 (9–18)		12 (9–17)		–	–	12 (9–17)		12 (9–17)		11 (8–16)		11 (8–16)		11 (8–16)		–	–	–	–
HOT use at discharge, % [95% CI], n^d	4.5 [3.6–5.6]	1642	3.7 [3.0–4.6]	2041	3.4 [2.7–4.2]	2319	4.6 [3.9–5.5]	2659	4.2 [3.5–4.9]	3260	0.652	→	4.4 [3.7–5.1]	3167	5.5 [4.8–6.3]	3329	6.3 [5.5–7.1]	3708	6.7 [6.0–7.6]	3814	6.4 [5.7–7.2]	3941	0.001	↑	0.001	↑
Follow-up	$n = 1494^e$		$n = 1886^e$		$n = 2139^e$		$n = 1271^e$		$n = 1444^e$				$n = 2934^e$		$n = 3129^e$		$n = 3609^e$		$n = 3969^e$		$n = 4021^e$					
Follow-up rate at 3 years, % [95% CI], n^f	50.9 [48.4–53.5]	1494	53.2 [50.9–55.4]	1886	51.7 [49.6–53.8]	2139	52.2 [50.2–54.1]	2437	47.9 [46.1–49.7]	3014	0.008	↓	47.9 [46.1–49.7]	2934	48.5 [46.8–50.3]	3129	48.0 [46.3–49.6]	3609	43.7 [42.2–45.3]	3969	41.9 [40.4–43.4]	4021	0.001	↓	0.001	↓

GA gestational age, *NICU* neonatal intensive care unit, *AOP* adrenal insufficiency of prematurity, *BPD* bronchopulmonary dysplasia, *HFOV* high frequency oscillatory ventilation, *HOT* home oxygen therapy, *iNO* inhaled nitric oxide, *IP* intestinal perforation, *IVH* intraventricularhemorrhage, *NEC* necrotizing enterocolitis, *PDA* patent ductus arteriosus, *PPHN* persistent pulmonary hypertension of the newborn, *PVL* periventricular leukomalacia, *RDS* respiratory distress syndrome, *ROP* retinopathy of prematurity

* p-Values were calculated by the Cochrane–Armitage χ^2-test

** ↑, significant increasing tendency; ↓, significant decreasing tendency; →, no significant change by the Cochrane–Armitage χ^2-test

[a]The number of infants, each year, of the 30,793 liveborn infants

[b]The obtained number of infants as a denominator for the % calculation, each year, of the 30,793 liveborn infants

[c]The number of infants, each year, of the 30,638 infants admitted to the NICU

[d]The obtained number of infants as a denominator for % calculation, each year, of the 30,638 infants admitted to the NICU

[e]The number of surviving infants at discharge, each year

[f]The number of infants as a denominator for the % calculation, each year, of the 28,632 surviving infants at discharge

0.59–0.85), clinical CAM (AOR 0.84, 95% CI 0.74–0.96), NRFS (AOR 1.54, 95% CI 1.37–1.74), and cesarean section (AOR 0.82, 95% CI 0.73–0.94) remained independent predictors of mortality. These factors adjusted for year, were then used to determine the risk-adjusted trends, over time.

As shown in Table 3 (Analysis #2), over time, in the risk-adjusted trends in the prevalence of morbidities, the significant upward trend persisted for RDS, PPHN, BPD (28 days and 36 weeks), PDA, late-onset AOP, and NEC/IP, and a significant decrease was noted for severe IVH, severe ROP and PVL. In terms of interventions, over time, the significant upward trend persisted for HFOV, surfactant administration, indomethacin for PDA, PDA ligation, intravenous hyperalimentation, ROP treatment, and HOT use. Importantly, for mortality and long-term neurodevelopmental outcomes, over time, the significant downward trend persisted for mortality, the prevalence of CP, HOT use, and visual and hearing impairment, while no significant changes were noted for cognitive impairment.

As shown in Table 4 (Analysis #3), in the adjusted model, nutritional support remained correlated with long-term neurodevelopmental outcomes with intravenous hyperalimentation remaining an independent correlate of visual impairment (AOR 0.74, 95% CI 0.59–0.91). Furthermore, the AOR of time to establishment of enteral feeding (with 5-day increments) for all disabilities suggested that the shorter the time to the establishment of full enteral feeding, the lower the prevalence of abnormal long-term neurodevelopmental outcomes (Table 4).

Table 3 Risk-adjusted trends in the morbidities, intervention, mortality, and long-term neurodevelopmental outcomes of the in-born patients from the 38 originally participating hospitals

	AOR	95% CI
Morbidities		
RDS	1.05	1.03–1.06
PPHN	1.03	1.01–1.06
Symptomatic PDA	1.06	1.05–1.08
BPD at 36 wk	1.05	1.03–1.07
Late-onset AOP	1.08	1.06–1.11
Severe IVH	0.96	0.93–0.99
Severe ROP	0.97	0.96–0.99
PVL	0.95	0.92–0.98
NEC/interstitial perforation	1.04	1.01–1.08
Intervention		
Surfactant	1.06	1.05–1.07
HFOV	1.06	1.04–1.07
iNO	1.02	0.99–1.05
Indomethacin for PDA	1.12	1.10–1.13
PDA ligation	1.16	1.13–1.20
Steroid for BPD	0.99	0.97–1.01
Intravenous hyperalimentation	1.31	1.30–1.33
ROP treatment	1.02	1.00–1.04
HOT use at discharge	1.10	1.07–1.13
Mortality		
Deceased at discharge	0.92	0.89–0.94
Long-term neurodevelopmental outcomes at 3 years of age		
CP	0.95	0.92–0.98
HOT use*	0.84	0.76–0.94
Visual impairment	0.84	0.81–0.87
Hearing impairment*	0.79	0.63–0.97
Cognitive impairment	1.02	0.99–1.05

Year, gestational age, birthweight, male sex, Apgar score <4 at 1 min, multiple pregnancy, antenatal steroid use, pregnancy induced hypertension, clinical chorioamnionitis, non-reassuring fetus status, and cesarean section were used to adjust for changes in the background risks, over time

AOR adjusted odds ratio, *AOP* adrenal insufficiency of prematurity, *BPD* bronchopulmonary dysplasia, *CI* confidence interval, *CP* cerebral palsy, *DQ* developmental quotient, *HFOV* high frequency oscillatory ventilation, *HOT* home oxygen therapy, *iNO* inhaled nitric oxide, *IVH* intraventricular hemorrhage, *NEC* necrotizing enterocolitis, *PDA* patent ductus arteriosus, *PPHN* persistent pulmonary hypertension of the newborn, *PVL* periventricular leukomalacia, *RDS* respiratory distress syndrome, *ROP* retinopathy of prematurity

* AOR was calculated among patients in the second 5-year period, 2008–2012

Discussion

An important contribution of our study is that it elucidated the trends, over time, in the prevalence of abnormal long-term neurodevelopmental outcomes, among in-born preterm infants, excluding births occurring outside the participating hospitals, which were strongly associated with the survival of extremely preterm infants [10]. As shown in Supplementary Table 1, in accordance with increased number of participating hospitals, the number of infants increased: however the average number of infants per hospital decreased. This suggests that more hospitals with low numbers of NICU beds had gradually been increased in the NRNJ, over the study period. As the NRNJ database covered almost 70% of all nationally delivered preterm infants with a birth weight ≤1500 g, in 2012, our study seems to correspond to a nationwide survey of premature infants in Japan.

We investigated the recent trends in mortality and abnormal neurodevelopmental outcomes, and demonstrated that the increased survival of preterm infants was not associated with a concomitant increase in long-term disabilities. However, there were concerns over some of the GA categories. For example, the prevalence of HOT use at 3 years of age, in the 22–24 weeks GA group, showed no downward trend. It is thought that preterm infants with a GA of 22–24 weeks, originally born with an

Table 4 Interventions associated with long-term neurodevelopmental outcomes at 3 years of age among the in-born infants from the original 38 participating hospitals over time

Intervention	CP		Visual impairment		Hearing impairment 2008–2012**		HOT 2008–2012***		Cognitive impairment	
	AOR*	95% CI	AOR*	95% CI	AOR*	95% CI	AOR*	95% CI	AOR*	95% CI
Surfactant	1.69	1.39–2.07	1.49	1.18–1.88	1.75	0.78–3.92	1.51	0.74–3.08	1.13	0.96–1.33
HFOV	1.14	0.95–1.37	1.18	0.95–1.45	1.77	0.90–3.47	1.76	0.95–3.26	1.14	0.97–1.33
iNO	1.22	0.86–1.73	1.18	0.80–1.76	0.89	0.27–2.99	2.28	1.13–4.57	1.15	0.86–1.54
Indomethacin	1.31	1.09–1.57	1.23	0.99–1.52	1.71	0.86–3.40	0.90	0.49–1.67	1.15	0.99–1.34
PDA ligation	1.51	1.16–1.97	1.53	1.15–2.03	2.16	0.91–5.10	1.81	0.91–3.59	1.39	1.10–1.77
Steroid for BPD	1.09	0.86–1.39	1.06	0.82–1.36	0.63	0.27–1.47	2.45	1.36–4.43	1.38	0.90–1.33
Intravenous hyperalimentation	1.03	0.85–1.24	0.74	0.59–0.91	1.35	0.60–3.05	1.17	0.57–2.43	1.10	0.94–1.29
Time to establishment of enteral feeding (5 days increment)	1.13	1.09–1.16	1.06	1.02–1.10	1.11	1.04–1.18	1.11	1.04–1.18	1.09	1.06–1.13
ROP treatment	1.41	1.16–1.71	3.73	3.03–4.59	1.21	0.60–2.47	1.34	0.77–2.36	1.40	1.19–1.64

AOR adjusted odds ratio, *BPD* bronchopulmonary dysplasia, *CI* confidence interval, *CP* cerebral palsy, *HOT* home oxygen therapy, *HFOV* high-frequency oscillatory ventilation, *iNO* inhaled nitric oxide, *PDA* patent ductus arteriosus, *ROP* retinopathy of prematurity

*Adjusted for year, gestational age, birth weight, male sex, Apgar score <4 at 1 min, multiple pregnancy, antenatal steroid use, pregnancy induced hypertension, clinical chorioamnionitis, non-reassuring fetus status, and cesarean section

** Evaluated in the second half, 2008–2012, because trends in its prevalence showed decreasing tendency during those terms

*** Evaluated in the second half, 2008–2012, because there were lots of missing data, in the first half, 2003–2007

extremely premature lung structure and function, may not achieve the complete recovery of their lungs by 3 years of age. Hence, it is thought that it might be difficult to stop HOT use in these infants, by 3 years of age. The overall trend in the prevalence of cognitive impairment, which showed no change, over time, in this study, is similar to that observed in a report of periviable infants (GA of 22–24 weeks) with cognitive impairment in 2000–2011 [17]. This was thought to be due to the threshold of NICU admissions, especially for extremely premature infants. However, the absence of an increasing rate of disabilities, despite the increased number of surviving infants in this study, might reflect the advances in perinatal care in Japan. It is unknown why the trend in CP, in the 22–24 weeks GA group, showed a significantly increasing tendency, especially in the second 5-year period. The prevalence of CP in our study was similar to that observed in another study which showed an increasing tendency [17]. Thus, further studies involving longer follow-up periods are needed among this group.

The findings of this study seem to support the notion that nutritional management is important for improved long-term neurodevelopmental outcomes among preterm infants [18, 19]. Parenteral nutrition and early postnatal enteral feeding could help improve the development of gastrointestinal function, which might lead to a reduction in the time to full feeding commencement [20, 21]. In our study, the time to establish full enteral feeding was inversely correlated with long-term neurodevelopmental disabilities, supporting the importance of the early establishment of enteral feeding for long-term neurodevelopmental outcomes. The induction of intravenous hyperalimentation was associated with visual impairment (AOR 0.73 95% CI 0.59–0.90). Nutritional conditions including the levels of the systemic insulin-like growth factor 1 (IGF-1) are correlated with the pathogenesis of ROP [22]. Preterm infants with poor postnatal nutrition and growth have low circulating tissue concentrations of IGF-1 [23], which is associated with severe ROP [24].

The constant high rate of intubation after birth and NICU admission, among those with a GA of 22–24 weeks, might be one of the unique aspects of intensive care for extremely preterm infants, in Japan. The resuscitation and ongoing management of infants born at a GA <24 weeks widely vary among countries due to great concerns about the increased number of surviving infants with neurodevelopmental impairments [25, 26]. Our results seem to suggest the use of aggressive management for extremely preterm infants by neonatologists in Japan.

In Japan, echocardiography is routinely performed for hemodynamic management of preterm infants, and this might influence the early detection of PDA, which might explain the decreasing tendency of severe IVH and PVL found in our study [27].

Some of the temporal differences in the antenatal characteristics are interesting. Similar to previously published epidemiologic data [28, 29], the prevalence of DM was found to increase, over time, in our study cohort. As

maternal age is thought to be correlated with DM [30], our data were consistent with those available in the existing literature. Moreover, the current screening and diagnosis of DM, updated in 2010 [31], might also have contributed to the prevalence of DM, over time, in our study cohort. The clinical explanation for our observation in the increase in the prevalence of clinical CAM is unclear. This could possibly be attributed to the fact that the screening and diagnosis of clinical CAM by attending obstetricians, over time, are being conducted in a more careful manner [32]. The prevalence of ANS use in Japan is very low compared to that in other countries; [6] this could be because ANS used to be off-label in Japan until 2009. Considering the advantages of ANS use even for the long-term prognosis of infants born at a GA <24 weeks [33], the increased promotion of ANS use in preterm infants might lead to improved mortality outcomes and long-term prognoses, in Japan.

This study has some limitations, the most important being the low follow-up rate (48% at 3 years of age among surviving in-born infants across all institutions, over time). Moreover, infants with follow-up data at 3 years of age had a significantly lower GA and birth weight, and had more morbidities than those without follow-up data (Supplementary Tables 2 and 3). Therefore, in our study, worse-affected infants might have had higher rates of regular hospital follow-ups, which might have led to an overestimation of the long-term outcomes. Although loss to follow-up is actually a common problem in most cohort studies [34–36], concerted efforts must be made to improve the follow-up rate in the NRNJ. Regardless of this, this large cohort study still showed sufficient power in determining the prevalence and correlates of long-term neurodevelopmental outcomes, based on careful interpretation. Second, due to the retrospective design of this study, it might be difficult to determine which of the interventions improved long-term neurodevelopmental outcomes. The high AORs of medical interventions for abnormal long-term outcomes might simply suggest that the most ill infants had received those interventions. For the analysis of the risk-adjusted trends, over time, we targeted inborn infants from 38 of the originally participating hospitals in the NRNJ, for the entire study period. These outcomes should be carefully interpreted, as center-related variations inside the network cannot be completely ruled out, as is the case in most cohort studies [9]. We performed multiple testing in the study, wherein the model adjusts for some factors, such as ANS use and cesarean section, that are likely causally related to the changes in the outcomes, over time. However, those changeable factors should be included for the evaluation of the trends in the outcomes, over time, because they are actually important perinatal factors, as indicated by the univariate logistic regression analysis for mortality [33, 37].

In conclusion, this large retrospective cohort study determined the trends in mortality and long-term neurodevelopmental outcomes among preterm infants born at a GA ≤32 weeks, over the past decade, in Japan. The trends in terms of the neurodevelopmental outcomes showed a significant downward trend, over time, with the same trend in mortality, suggesting that the increased number of surviving preterm infants were not associated with an increased risk of abnormal neurodevelopmental outcomes. Nutritional support such as intravenous hyperalimentation might be important, and lead to a decreased prevalence of visual impairment, while the early establishment of enteral feeding might lead to improved long-term neurodevelopmental outcomes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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