The Evidence from NRNJ database for VLBW (2003-2012)

-Vol 1- (2021 revision)

2021 revision		
P24	Chorioamnionitis and IVH3/4, Sepsis	Figures were exchanged. No change in the statements.
P59	CP in relation with PVL, IVH3,4 and Gestational weeks	Figures were exchanged. No change in the statements.
P62	Days of feeding at 100ml/kg/d and DQ(3 yrs)	Figures were exchanged. No change in the statements.
(P53)	「CP（3 years）or death」and perinatal factors	deleted
(P54)	“Relative” Odds（DQ/CP, CP/DQ) and perinatal factors	deleted
New data		
P12	Summary of Survival rate & Mortality	
P45	Summary of Cerebral Palsy Rate (3 years). Figures were exchanged. No change in the statements.	
P49	Summary of DQ <70, 70-84, 85-59 Outcome at 3 years for<24w, 24-27w, 28w-groups	

Masanori Fujimura, Satoshi Kusuda, Yumi Kono, Hidehiko Nakanishi, Shinya Hirano, Naohiro Yonemoto, for the Neonatal Research Network of Japan

Neonatal Research Network of Japan

2020

The Neonatal Research Network of Japan

OBJECTIVES

The objectives of this study were to describe the characteristics and morbidity of very low birth weight infants, to identify the medical intervention for these infants, and to evaluate the factors affecting the outcome of these infants [1, 2].

METHODS

A large multicenter neonatal research network that included level II and III NICUs from throughout Japan was established. The network included 202 centers and 40,806 infants weighing at or below 1,500 g, born or admitted to the centers in 2003-2012. Multivariate analyses using logistic regression for variables of VLBW were performed to calculate odds ratio of perinatal factors. All the factors included in the model are presented in the figure or table. In logistic regression analysis, the odds ratio was set 1 for the categorical data of >24w(>28w as appropriate), AFD, Apgar Score 5 m 7-10, female, inborn, and vaginal born. Statistical analyses were performed using EZR.

The NRNJ was supported by the Research Grant of Ministry of Health, Labour and Welfare of Japan, 2003-2012. The Japan Society of Neonatal Health and Development currently subsidize the NRNJ.

1. Satoshi Kusuda, Masanori Fujimura, Izumi Sakuma, Hirofumi Aotani, Kazuhiko Kabe, Yasufumi Itani, Hiroyuki Ichiba, Katsura Matsunami, Hiroshi Nishida and for the Neonatal Research Network of Japan. Morbidity and Mortality of Infants With Very Low Birth Weight in Japan: Center Variation. Pediatrics 2006;118;e1130-e1138; originally published online Sep 1, 2006

2. Kono Y, Yonemoto N, Nakanishi H, et al. Changes in survival and neurodevelopmental outcomes of infants born at <25 weeks' gestation: a retrospective observational study in tertiary centres in Japan. BMJ Paediatrics Open 2018;2:e000211. doi:10.1136/bmjpo-2017-000211

The Evidence from NRNJ database for VLBW(2003-2012) -Vol 1- (2021 revision)

Contents

Definitions

We compiled a network **database operation manual** to define the patient characteristics. In the manual, the day of birth was defined as day 0. **Neonatal mortality** was defined as death within 28 days of birth and mortality before discharge as death occurring before discharge from a participating NICU. **Gestational age** (GA) was determined in the following order: obstetric examination with ultrasonography, obstetric history based on last menstrual period, and then postnatal physical examinations of neonates. Infants weighing 10th percentile of the normal **birth weight** curve at each GA were defined as light for GA.2 Maternal diabetes mellitus (DM) or gestational DM (GDM) and maternal hypertension were determined according to the diagnostic criteria. **Premature rupture of membranes** (PROM) was defined as rupture of membranes before an onset of labor. **Clinical chorioamnionitis** was diagnosed based on the clinical findings, such as maternal fever, leukocytosis, and local pain. Histologic chorioamnionitis was defined according to the criteria reported by Blanc. **Antenatal steroid** (ANS) usage was defined as the administration of any corticosteroids to accelerate fetal lung maturity. **Surfactant** therapy meant pulmonary surfactant (Surfacten) given during the acute phase of respiratory problems. **Respiratory distress syndrome** was diagnosed based on the clinical and radiographic findings. **Chronic lung disease** (CLD) was defined when an infant received supplemental oxygen on the 28th day after birth (Page 71 for definition), and 36-week CLD was defined when an infant received supplemental oxygen at the 36th week postmenstrual age. **Postnatal steroid** (PNS) usage meant any steroids given during the hospital stay for the prevention or treatment of CLD. **Symptomatic patent ductus arteriosus** (PDA) was diagnosed based on both the echocardiographic findings and clinical evidence of a volume overload because of a left-to-right shunt. **Persistent pulmonary hypertension** of the newborn (PPHN) was defined as right-to-left shunt at the foramen ovale and/or ductus arteriosus without any anatomic malformations as detected by cardiac echocardiography. **Intraventricular hemorrhage** (IVH) was reported according to the classification of Papile et al. **Necrotizing enterocolitis** (NEC) was defined according to the classification of Bell et al: stage II or greater. Gastrointestinal perforation was diagnosed if free air was detected in the abdominal cavity by radiograph examination regardless of cause. **Sepsis** meant culture-proven septicemia or bacteremia at any time during the stay in the NICU. A **cystic periventricular leukomalacia** (PVL) diagnosis was made by using either head ultrasound or cranial MRI scans, performed either at 2 weeks of age or later. **Intrauterine infection** was diagnosed if any inflammatory response was detected in the infants at birth. **Retinopathy of prematurity** (ROP) was diagnosed if the infants were treated with laser coagulation, cryocoagulation therapy, or both. Patients were classified into **adrenal insufficiency of prematurity** (AOP) when any steroids were administered during the hospital stay for the treatment of a late-onset circulatory collapse of premature infants because of an impaired adrenal function. Major **congenital anomalies** did not include external malformation.

- Morbidity and Mortality of Infants With Very Low Birth Weight in Japan: Center Variation.
Satoshi Kusuda,MD, Masanori Fujimura,MD, Izumi Sakuma,MD, Hirofumi Aotani,MD, Kazuhiko Kabe,MD, Yasufumi Itani,MD, Hiroyuki Ichiba,MD, Katsura Matsunami,MD, Hiroshi Nishida,MD, for the Neonatal Research Network, Japan. PEDIATRICS Volume 118, Number 4, October 2006

NRNJ Database

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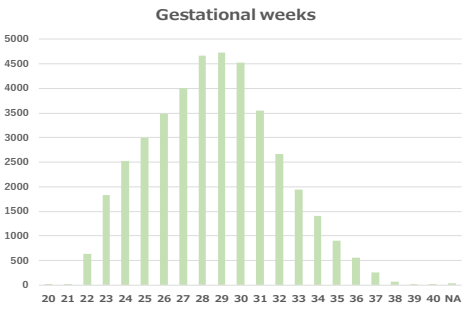
NRNJ Database

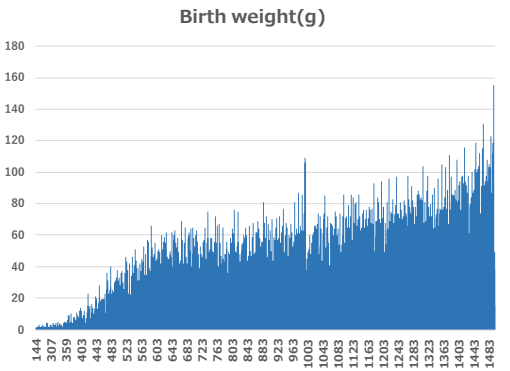
N=40,806 (2003－2012)

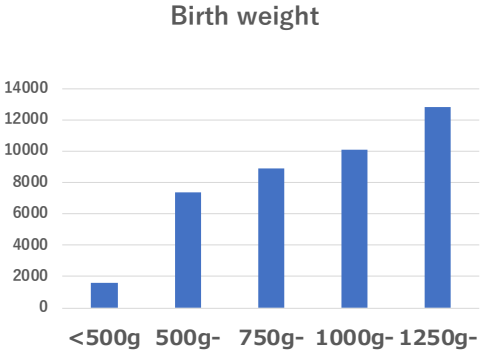
Gestational weeks and Birthweight(≦1500g)

Dataset928

Birth weight	20w	21w	22w	23w	24w	25w	26w	27w	28w	29w	30w	31w	32w	33w	34w	35w	36w	37w	38w	39w	40w	NA	Total	%
100g-				1	1																		2	0.0%
200g-			15	8	18	7	3	4															55	0.1%
300g-	2	1	48	48	37	54	36	26	12	8	6												278	0.7%
400g-			299	269	176	146	150	105	51	28	14	4	1	5		1						1	1250	3.1%
500g-		1	245	872	492	236	234	171	106	66	33	13	2		1							1	2473	6.1%
600g-			30	549	1059	552	287	284	208	111	74	35	15	6					1			3	3214	7.9%
700g-			1	71	587	1023	565	368	317	193	120	57	44	14	6	1	1					2	3370	8.3%
800g-				10	137	726	950	534	384	277	197	118	63	28	8	4	1	1	1	1		3	3443	8.4%
900g-				2	17	206	854	953	601	388	331	223	130	60	35	16	9	5				3	3833	9.4%
1000g-						29	310	800	862	533	387	277	217	132	54	38	10	6	1			2	3658	9.0%
1100g-						7	76	553	969	733	561	429	354	260	154	82	34	13	4	1	2	1	4234	10.4%
1200g-					1	4	17	156	691	995	773	580	447	321	241	147	69	32	6			7	4487	11.0%
1300g-						1	2	34	335	836	961	740	546	486	371	219	138	57	18	8		5	4757	11.7%
1400g-							2	16	137	564	1052	1051	846	624	527	388	287	139	37	8	2	7	5687	13.9%
1500g								1		2	6	11	4	6	9	6	2	2					49	0.1%
NA											2	7	2		1							3	15	0.0%
Total	2	2	639	1830	2525	2991	3486	4005	4673	4734	4517	3545	2671	1943	1407	902	551	255	68	18	4	38	40806	100
%	0.0%	0.0%	1.6%	4.5%	6.2%	7.3%	8.5%	9.8%	11.5%	11.6%	11.1%	8.7%	6.5%	4.8%	3.4%	2.2%	1.4%	0.6%	0.2%	0.0%	0.0%	0.1%	100	







Relations of Birth weight and Gestational weeks

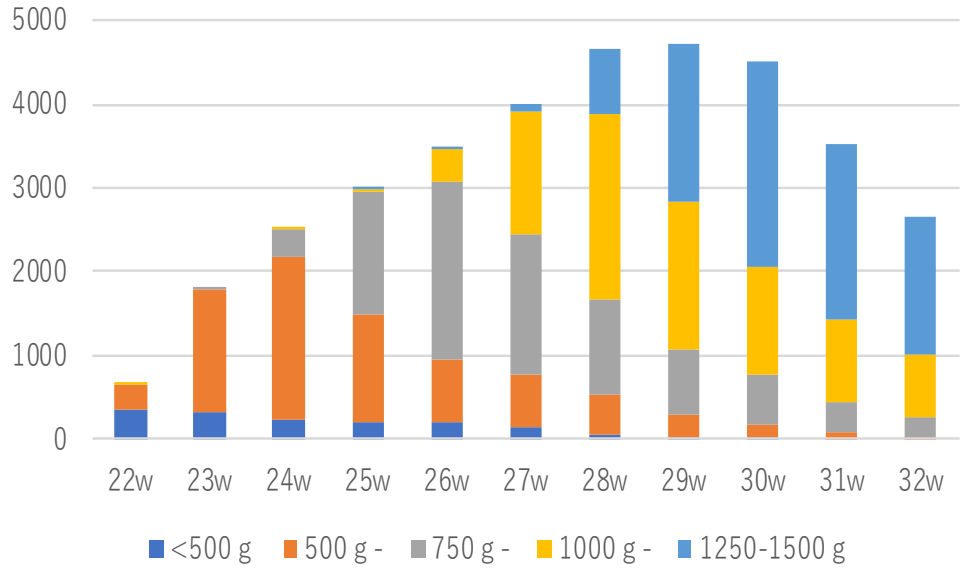
◆ Evaluation of very low birthweight infants starts by defining the position of gestational weeks and birth weight.

Dataset928

NRN Database
N=40,806 (2003－2012)
Gestational weeks and Birthweight(≦1500g)

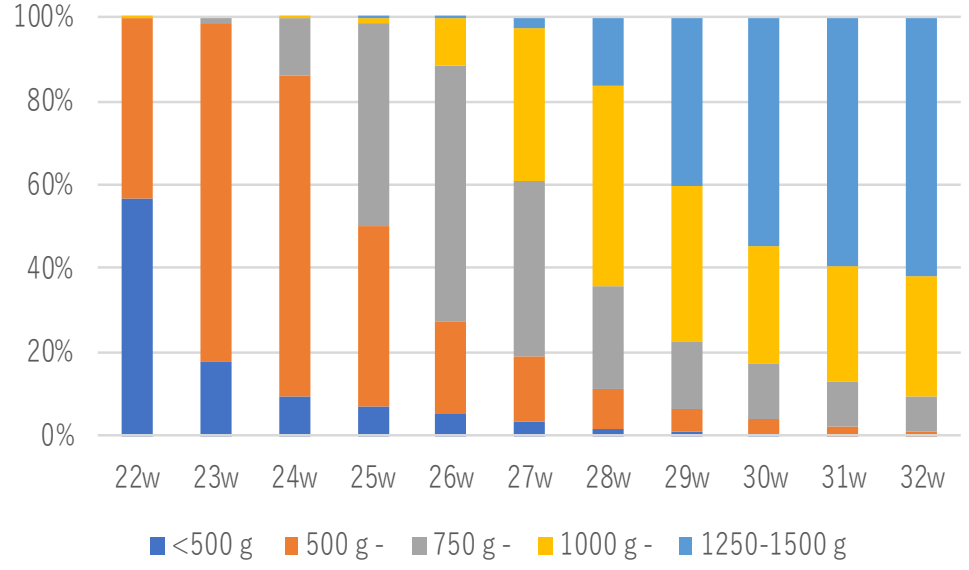
N

Birth weight and Gestational weeks



Ratio

Birth weight and Gestational weeks



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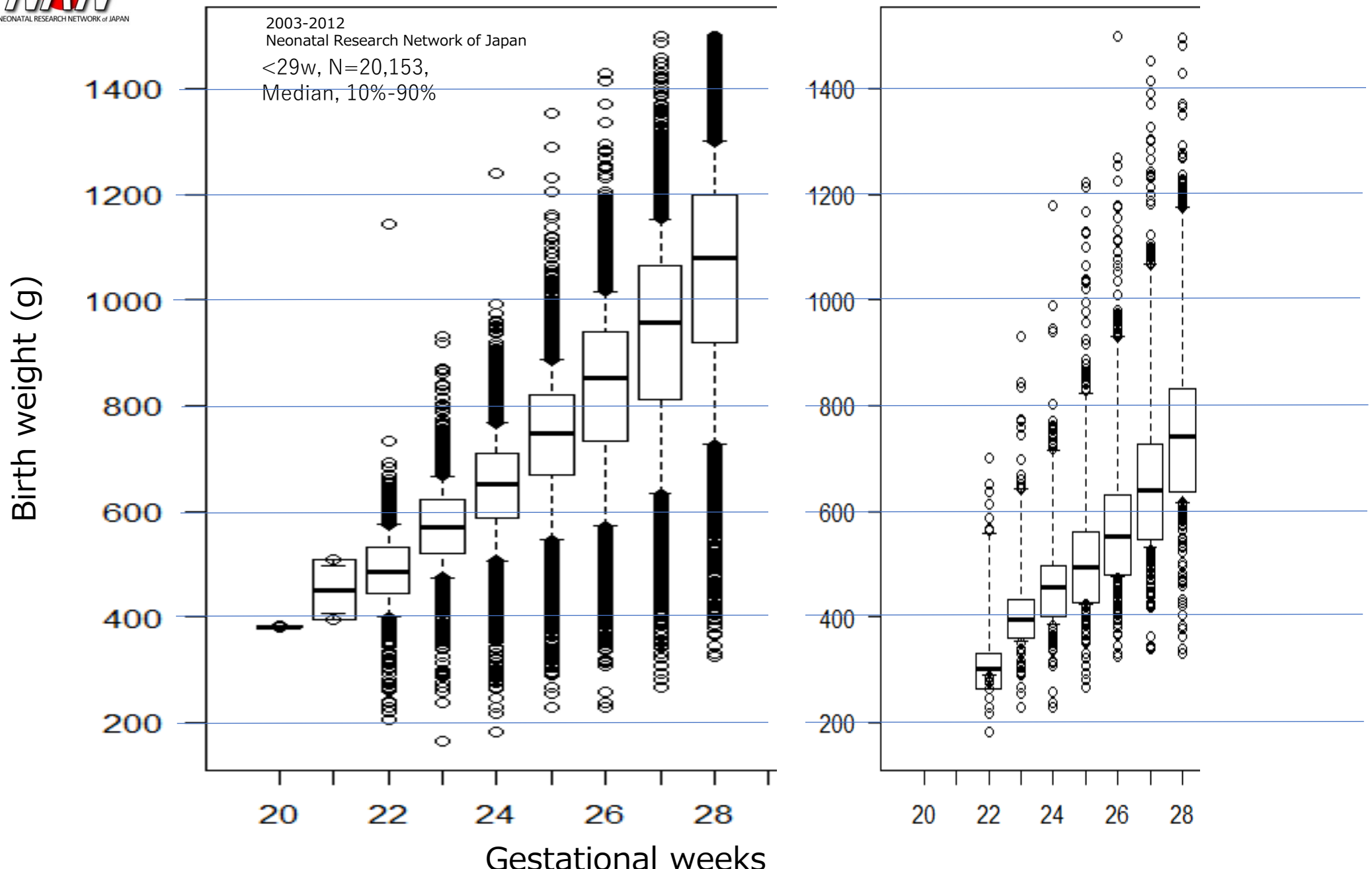
Fetal Growth (All) (SFD)



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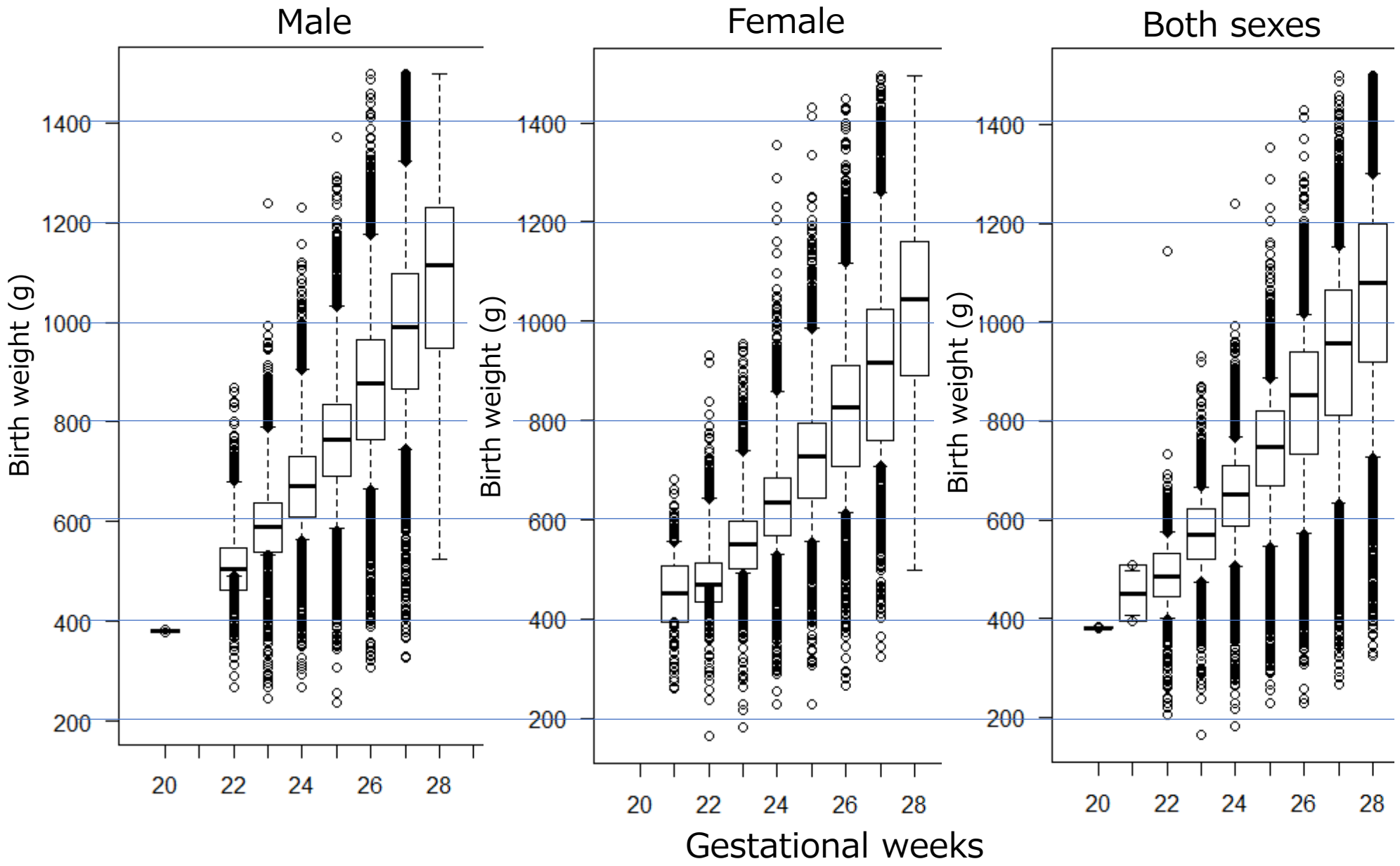
Fetal Growth/Gender (<29w, N=20,153, Median, 10%-90%)



Mortality

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Mortality(%) -Database-

Dataset928

◆ Tables show the number of infants (total, died), and the mortality rate(%)

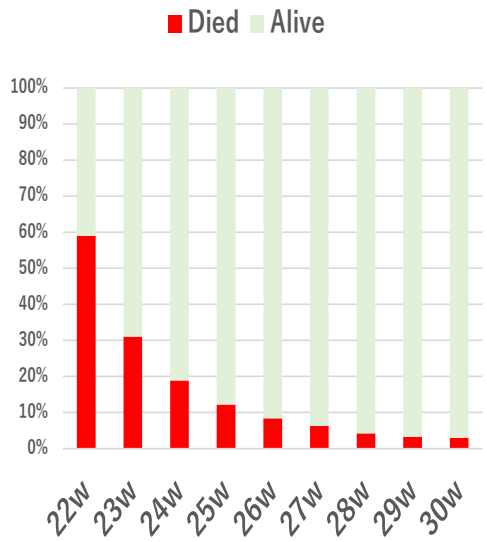
Died	20w	21w	22w	23w	24w	25w	26w	27w	28w	29w	30w	31w	32w	33w	34w	35w	36w	37w	38w	39w	40w	Total
100g				1	1																	2
200g			15	7	14	4	3	3														46
300g	2		40	27	18	20	23	9	10	5	4											158
400g			178	105	60	43	36	32	17	8	6	1		3		1						491
500g			130	263	103	45	29	28	16	10	6	4			1							636
600g			14	144	164	59	35	23	13	9	13	6	3						1			487
700g				15	95	91	41	29	22	14	9	2	8	2	2	1	1					333
800g				5	18	69	51	38	24	13	12	13	5	3	3					1		256
900g				1	4	28	45	31	23	15	7	7	14	6	3	1	1	4				190
1000g						4	15	25	13	26	17	8	13	11	7	5	4	1	1			150
1100g							10	20	21	18	11	18	9	11	14	8	3	3	3		1	150
1200g						1	3	8	19	14	19	13	14	6	11	11	7	6	1			133
1300g						1	1	3	10	11	13	9	18	15	14	17	15	18	4	4		154
1400g								2	9	12	18	18	15	16	15	19	11	16	10	3	1	165
Total	2		377	568	477	365	292	252	197	155	135	99	100	74	70	63	43	49	20	8	2	3356

All	20w	21w	22w	23w	24w	25w	26w	27w	28w	29w	30w	31w	32w	33w	34w	35w	36w	37w	38w	39w	40w	Total
100g				1	1																	2
200g			15	8	18	7	3	4														55
300g	2	1	48	48	37	54	36	26	12	8	6											278
400g			299	269	176	146	150	105	51	28	14	4	1	5		1						1250
500g		1	245	872	492	236	234	171	106	66	33	13	2		1							2473
600g			30	549	1059	552	287	284	208	111	74	35	15	6				1				3214
700g			1	71	587	1023	565	368	317	193	120	57	44	14	6	1	1					3370
800g				10	137	726	950	534	384	277	197	118	63	28	8	4	1	1	1			3443
900g				2	17	206	854	953	601	388	331	223	130	60	35	16	9	5				3833
1000g						29	310	800	862	533	387	277	217	132	54	38	10	6	1			3658
1100g						7	76	553	969	733	561	429	354	260	154	82	34	13	4	1	2	4234
1200g					1	4	17	156	691	995	773	580	447	321	241	147	69	32	6			4487
1300g						1	2	34	335	836	961	740	546	486	371	219	138	57	18	8		4757
1400g							2	16	137	564	1052	1051	846	624	527	388	287	139	37	8	2	5687
Total	2	2	639	1830	2525	2991	3486	4005	4673	4734	4517	3545	2671	1943	1407	902	551	255	68	18		440806

Mortality(%)	22w	23w	24w	25w	26w	27w	28w	29w	30w	31w	32w
100g		100.0%	100.0%								
200g	100.0%	87.5%	77.8%	57.1%	100.0%	75.0%					
300g	83.3%	56.3%	48.6%	37.0%	63.9%	34.6%	83.3%	62.5%	66.7%		
400g	59.5%	39.0%	34.1%	29.5%	24.0%	30.5%	33.3%	28.6%	42.9%	25.0%	0.0%
500g	53.1%	30.2%	20.9%	19.1%	12.4%	16.4%	15.1%	15.2%	18.2%	30.8%	0.0%
600g	46.7%	26.2%	15.5%	10.7%	12.2%	8.1%	6.3%	8.1%	17.6%	17.1%	20.0%
700g	0.0%	21.1%	16.2%	8.9%	7.3%	7.9%	6.9%	7.3%	7.5%	3.5%	18.2%
800g		50.0%	13.1%	9.5%	5.4%	7.1%	6.3%	4.7%	6.1%	11.0%	7.9%
900g		50.0%	23.5%	13.6%	5.3%	3.3%	3.8%	3.9%	2.1%	3.1%	10.8%
1000g				13.8%	4.8%	3.1%	1.5%	4.9%	4.4%	2.9%	6.0%
1100g				0.0%	13.2%	3.6%	2.2%	2.5%	2.0%	4.2%	2.5%
1200g			0.0%	25.0%	17.6%	5.1%	2.7%	1.4%	2.5%	2.2%	3.1%
1300g				100.0%	50.0%	8.8%	3.0%	1.3%	1.4%	1.2%	3.3%
1400g					0.0%	12.5%	6.6%	2.1%	1.7%	1.7%	1.8%

Summary of Survival rate & Mortality

	20w	21w	22w	23w	24w	25w	26w	27w	28w	29w
Total	2	2	639	1,830	2,525	2,991	3,486	4,005	4,673	4,734
Died	2		377	568	477	365	292	252	197	155
Alive	0	2	262	1,262	2,048	2,626	3,194	3,753	4,476	4,579
Survival %	0%	100%	41.0%	69.0%	81.1%	87.8%	91.6%	93.7%	95.8%	96.7%
Mortality %	100%	0.0%	59.0%	31.0%	18.9%	12.2%	8.4%	6.3%	4.2%	3.3%



30w	31w	32w	33w	34w	35w	36w	37w	38w	39w	40w	Total
4,517	3,545	2,671	1,943	1,407	902	551	255	68	18	4	40,806
135	99	100	74	70	63	43	49	20	8	2	3,356
4,382	3,446	2,571	1,869	1,337	839	508	206	48	10	2	37,450
97.0%	97.2%	96.3%	96.2%	95.0%	93.0%	92.2%	80.8%	70.6%	55.6%	50.0%	91.8%
3.0%	2.8%	3.7%	3.8%	5.0%	7.0%	7.8%	19.2%	29.4%	44.4%	50.0%	8.2%

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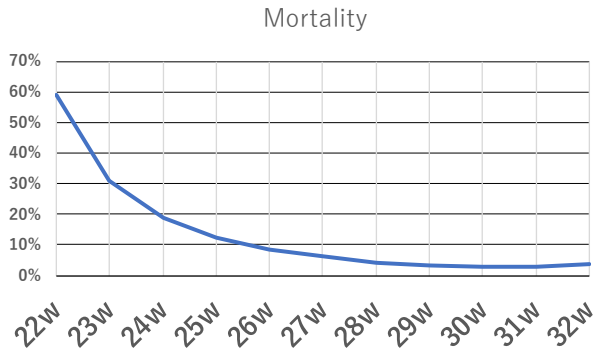
≦1500g

Mortality(%)

Gestational weeks and birth weight (g)



N indicate the lowest position in mortality for gestational week.

N indicate the lowest position in mortality for weight.

Mortality(%)	20w	21w	22w	23w	24w	25w	26w	27w	28w	29w	30w	31w	32w	33w	34w	35w	36w	37w	38w	39w	40w
100g-				100	100																
200g-			100	88	78	57	100	75													
300g-	100	0	83	56	49	37	64	35	83	63	67										
400g-			60	39	34	29	24	30	33	29	43	25	0	60							
500g-		0	53	30	21	19	12	16	15	15	18	31	0								
600g-			47	26	16	11	12	8	6	8	18	17	20	0							
700g-			0	21	16	9	7	8	7	7	8	4	18	14	33						
800g-				50	13	10	5	7	6	5	6	11	8	11	38	0	0	0	0		
900g-				50	24	14	5	3	4	4	2	3	11	10	9	6	11	80			
1000g-						14	5	3	2	5	4	3	6	8	13	13	40	17			
1100g-						0	13	4	2	2	2	4	3	4	9	10	9	23	75	0	50
1200g-					0	25	18	5	3	1	2	2	3	2	5	7	10	19	17		
1300g-						100	50	9	3	1	1	1	3	3	4	8	11	32	22	50	
1400g-							0	13	7	2	2	2	2	3	3	5	4	12	27	38	50

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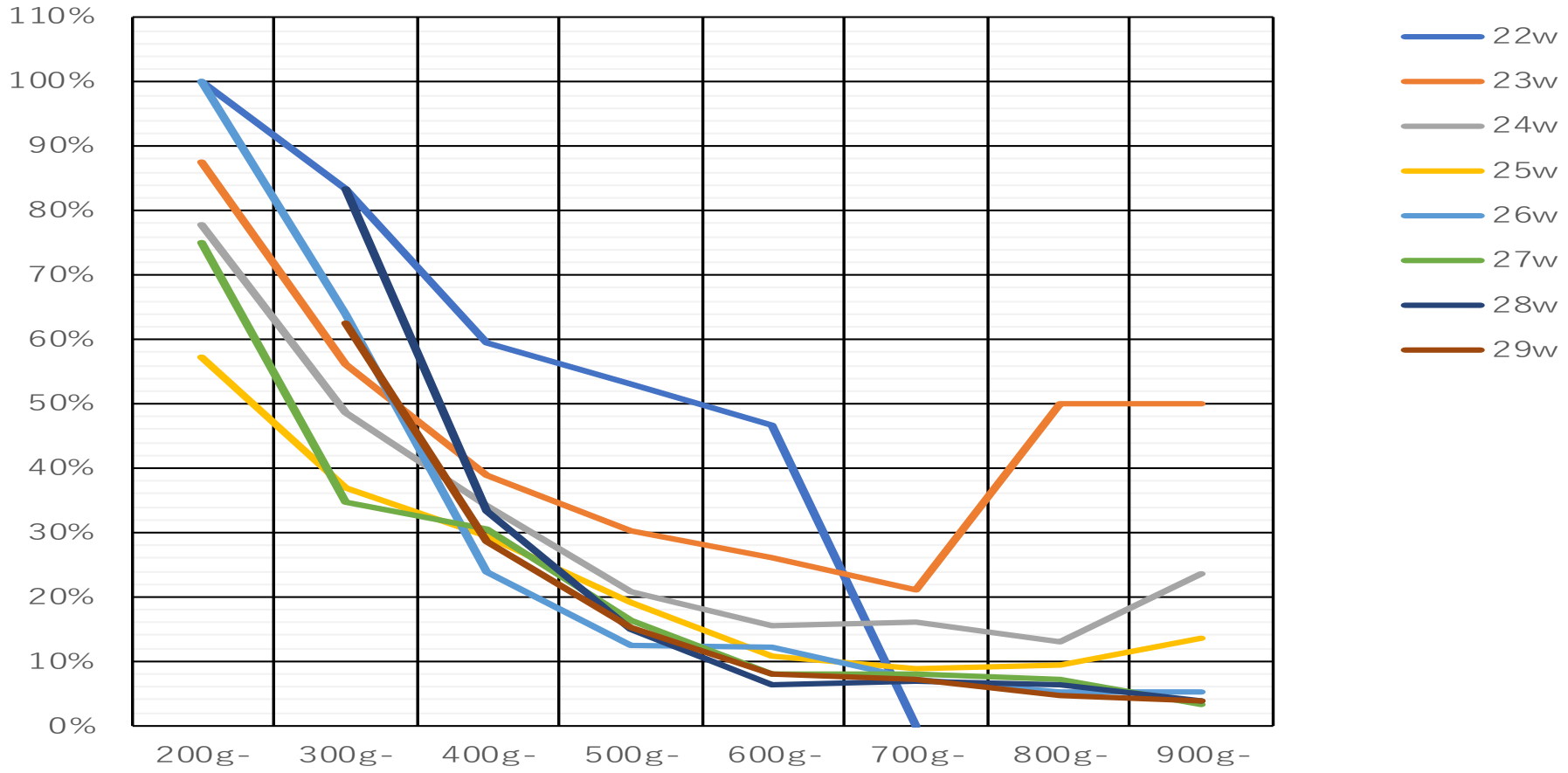
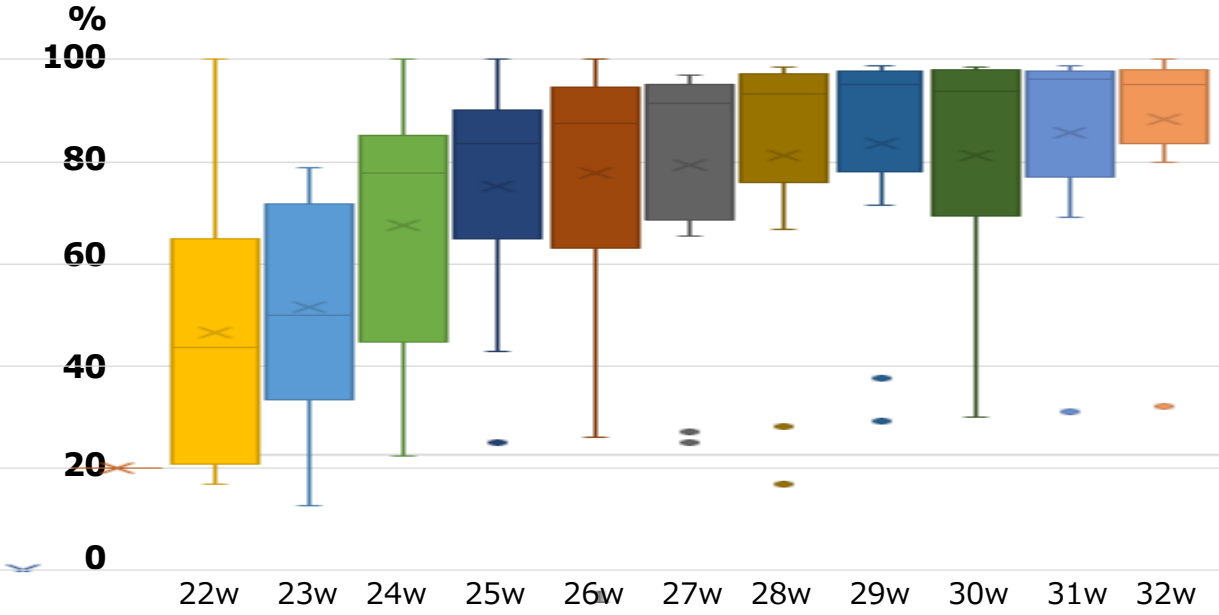
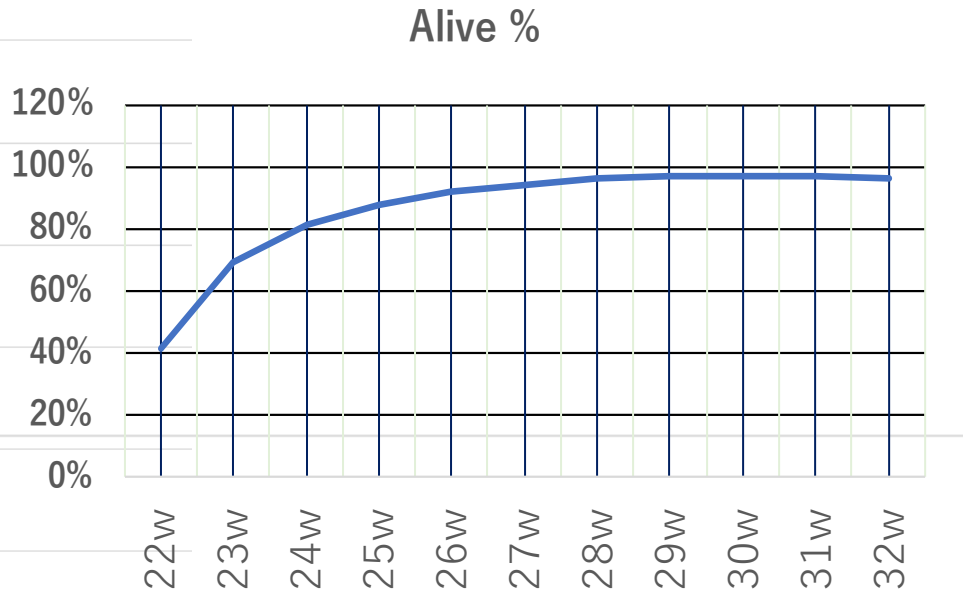
Mortality(%)

Gestational weeks and birth weight (g)



Survival Rate(%)

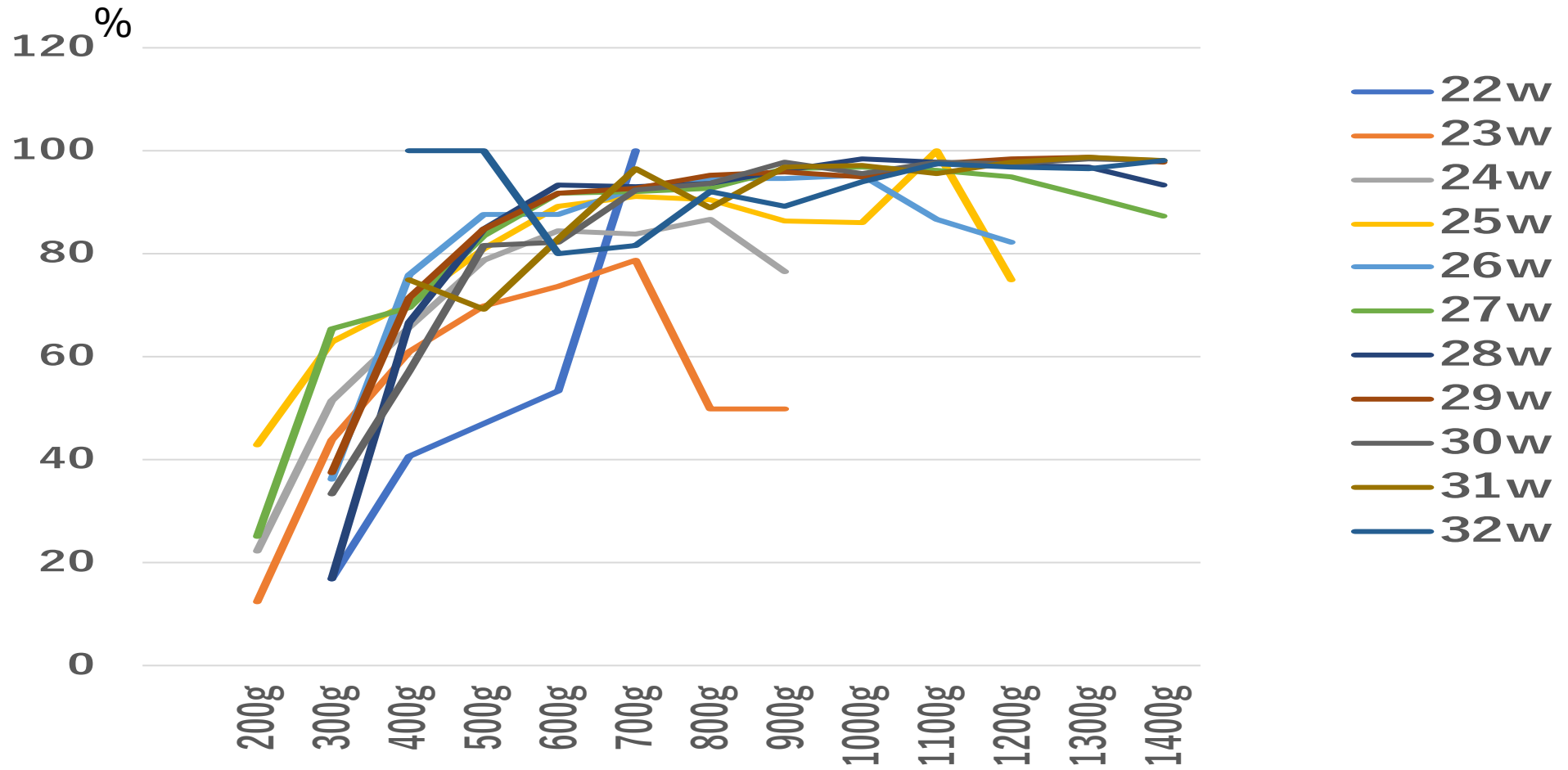




Survival Rate(%)	22w	23w	24w	25w	26w	27w	28w	29w	30w	31w	32w
100g	-	-	-	-	-	-	-	-	-	-	-
200g	-	12.5	22.2	42.9	-	25	-	-	-	-	-
300g	16.7	43.8	51.4	63	36.1	65.4	16.7	37.5	33.3	-	-
400g	40.5	61	65.9	70.5	76	69.5	66.7	71.4	57.1	75	100
500g	46.9	69.8	78.9	80.9	87.6	83.6	84.9	84.8	81.8	69.2	100
600g	53.3	73.6	84.4	89.3	87.8	91.9	93.3	91.9	82.4	82.9	80
700g	100	78.9	83.8	91.1	92.7	92.1	93.1	92.7	92.5	96.5	81.8
800g	-	50	86.9	90.5	94.6	92.9	93.8	95.3	93.9	89	92.1
900g	-	50	76.5	86.4	94.7	96.7	96.2	96.1	97.9	96.9	89.2
1000g	-	-	-	86.2	95.2	96.9	98.5	95.1	95.6	97.1	94
1100g	-	-	-	100	86.8	96.2	97.8	97.5	98	95.8	97.5
1200g	-	-	100	75	82.4	94.9	97.3	98.6	97.5	97.8	96.9
1300g	-	-	-	-	50	91.2	97	98.7	98.6	98.8	96.5
1400g	-	-	-	-	100	87.5	93.4	97.9	98.3	98.3	98.2

Survival Rate(%)
Gestational weeks and birth weight (g)

◆ Survival Rate(%) for each gestation and birth weight.



NEONATAL RESEARCH NETWORK of JAPAN

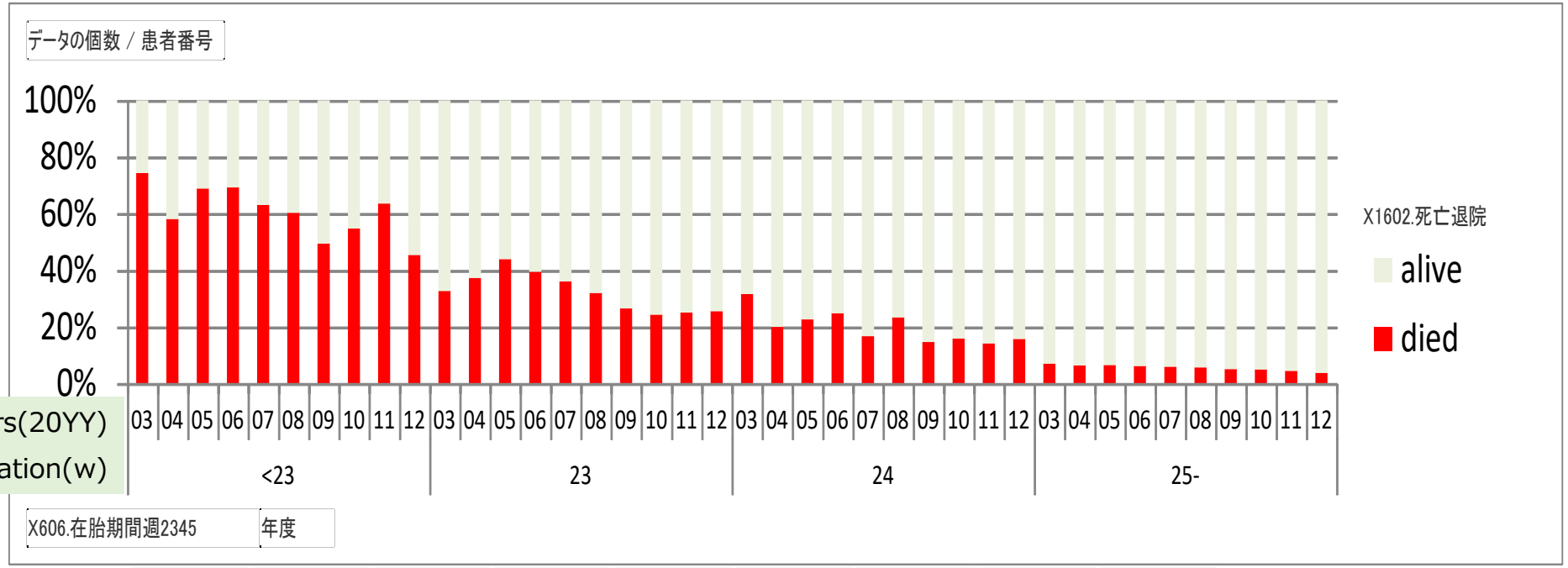
≦1500g

Annual trend of mortality for Ex-Preterm 22w, 23w, 24w & 25w-

◆ In 10 yeas mortality decreased in each gestation groups.

22w:	60 - 45%
23w:	40 - 25%
24w:	25 - 15%
25w-:	7.1 - 3.8%

Dataset928



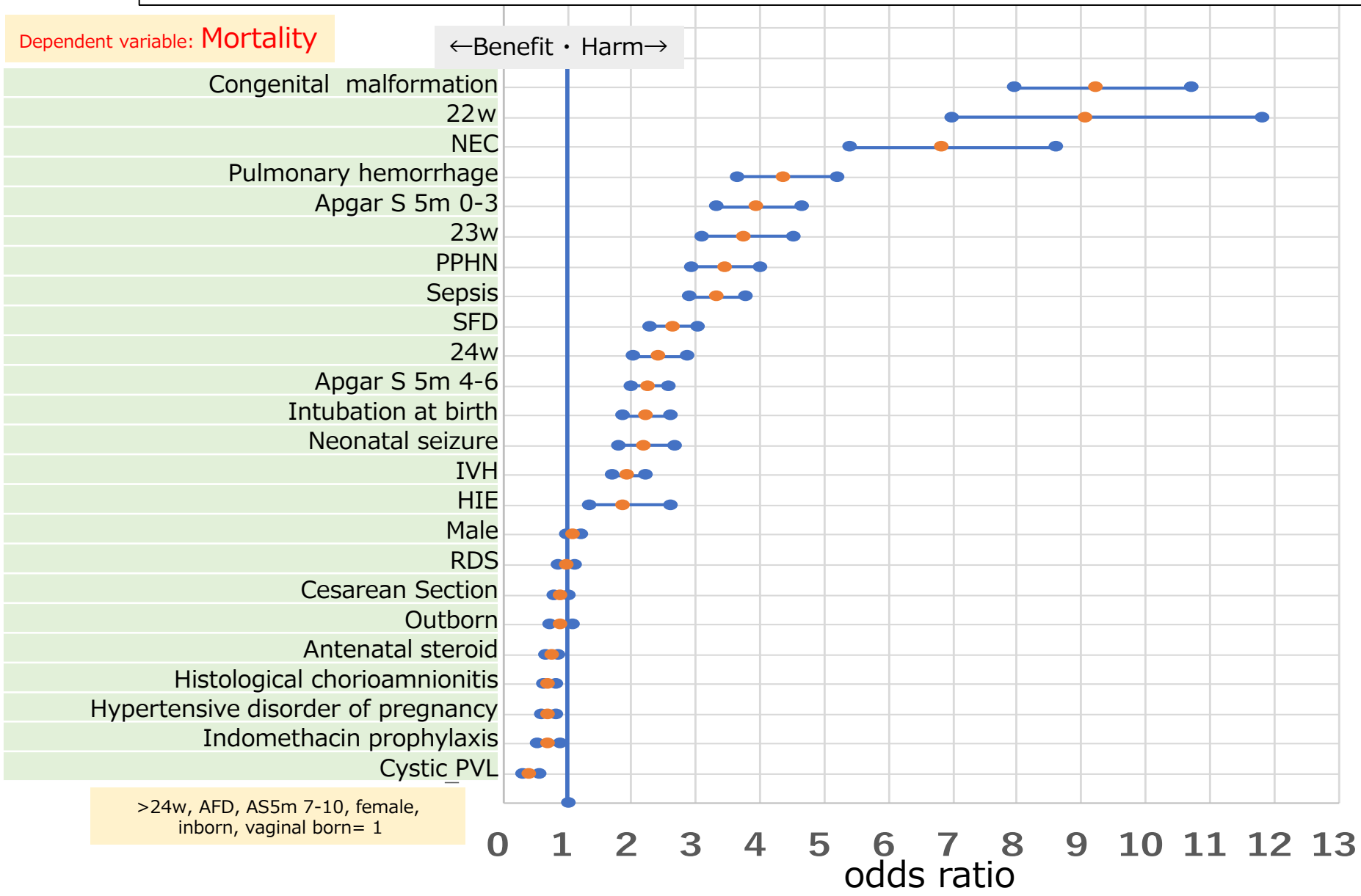
	20w	21w	22w	23w	24w	25w	26w	27w	28w
N=	2	2	639	1,830	2,525	2,991	3,486	4,005	4,673

Factors for neonatal mortality of VLBW

◆ The odds ratios of perinatal factors for the neonatal mortality of VLBW.

Dependent variable: Mortality

Dataset928

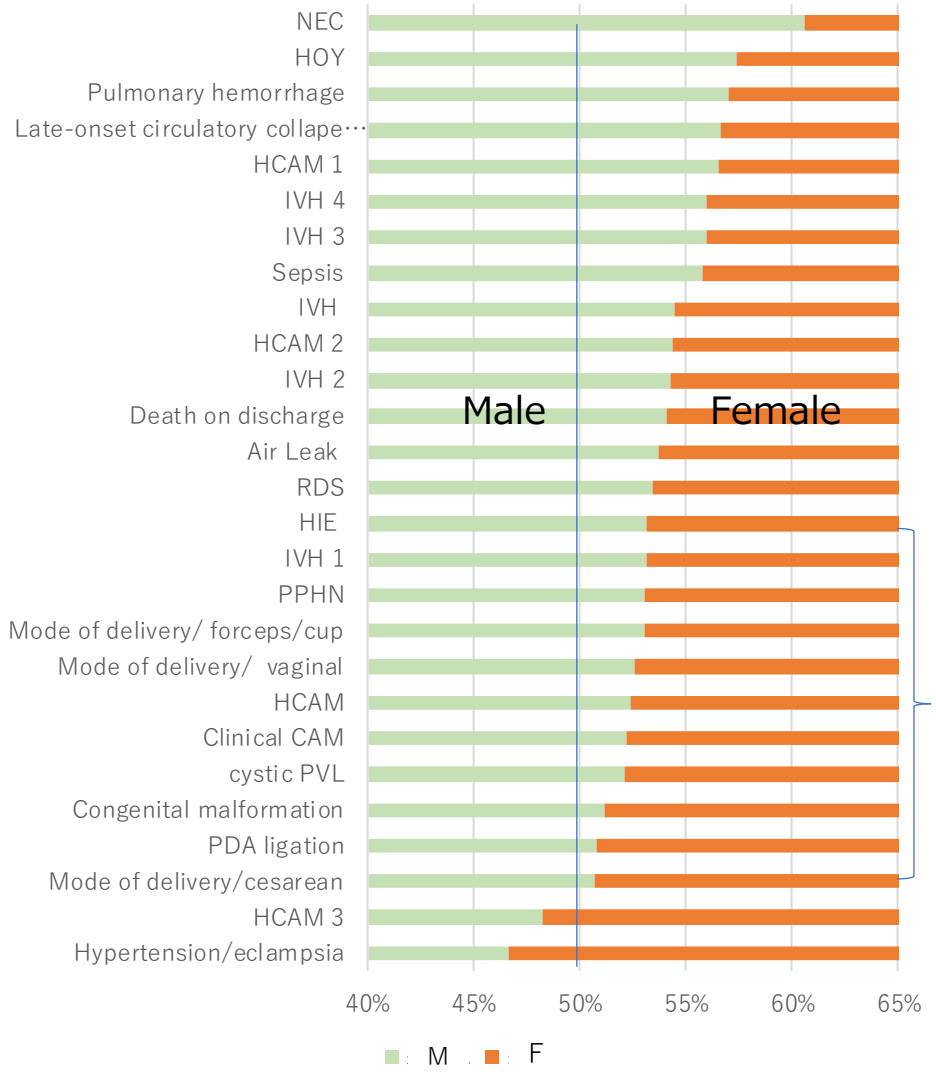


>24w, AFD, AS5m 7-10, female, inborn, vaginal born= 1

- Multivariate analysis using logistic regression for neonatal mortality of VLBW were performed to calculate odds ratio of perinatal factors. All the factors included in the model are presented in the figure.

Gender Ratio and Perinatal Factors

- Male over-represent most morbidities, except a few such as histological CAM grade-3 and hypertension/eclampsia.
- Histological CAM-1, -2, -3 differ in M/F ratio, which may indicate they are not homogeneous in nature or in origin.



NS

	Male	Female
NEC	60.6%	39.4%
HOT	57.4%	42.6%
Pulmonary hemorrhage	57.0%	43.0%
Late-onset circulatory collapse /Steroid	56.6%	43.4%
HCAM 1	56.5%	43.5%
IVH 4	56.0%	44.0%
IVH 3	56.0%	44.0%
Sepsis	55.8%	44.2%
IVH	54.5%	45.5%
HCAM 2	54.4%	45.6%
IVH 2	54.3%	45.7%
Death on discharge	54.1%	45.9%
Air Leak	53.7%	46.3%
RDS	53.4%	46.6%
IVH 1	53.1%	46.9%
HIE	53.1%	46.9%
PPHN	53.0%	47.0%
Mode of delivery/ forceps,cup	53.0%	47.0%
Mode of delivery/ vaginal	52.6%	47.4%
HCAM	52.4%	47.6%
Clinical CAM	52.2%	47.8%
cystic PVL	52.1%	47.9%
Congenital malformation	51.2%	48.8%
PDA ligation	50.8%	49.2%
Mode of delivery/cesarean	50.7%	49.3%
HCAM 3	48.2%	51.8%
Hypertension/eclampsia	46.6%	53.4%

High Risk Pregnancy

Hypertensive Disorder of Pregnancy and the morbidities of VLBW

◆ The Hypertensive Disorder of Pregnancy (HDP) is associated with lower morbidities of VLBW

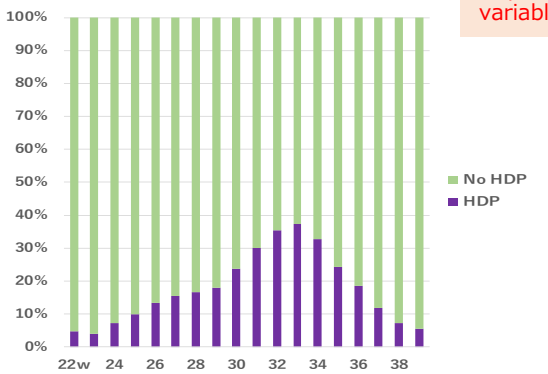
The peak incidence of HDP is 33 weeks.

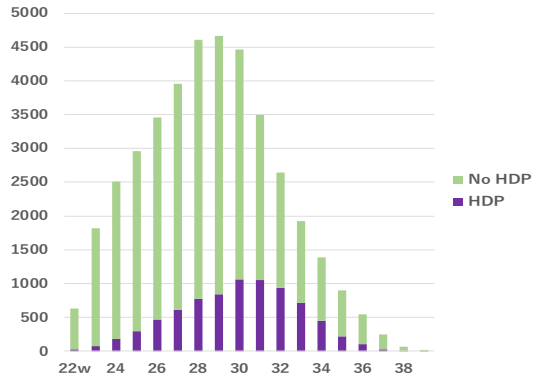
In HDP the IVH (and its severity) is significantly less.

In HDP the CLD type3 is significantly less.

In HDP the ROP treatment is significantly less.

HDP and GA



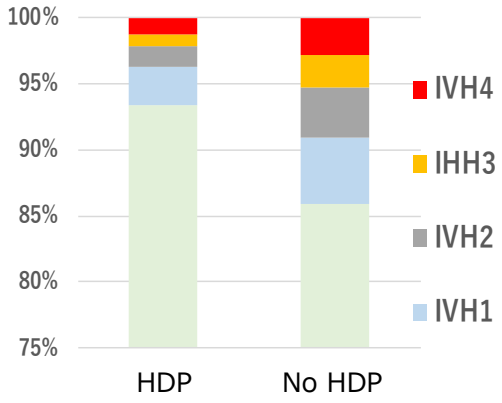


IVH and grade

Dependent variable: IVH3,4

	odds	95%CI		P
>=24w	1			
24w	1.27	1.07	1.5	0.005
23w	1.55	1.29	1.85	0.000
22w	2.34	1.8	3.04	0.000
HDP	0.802	0.649	0.992	0.042

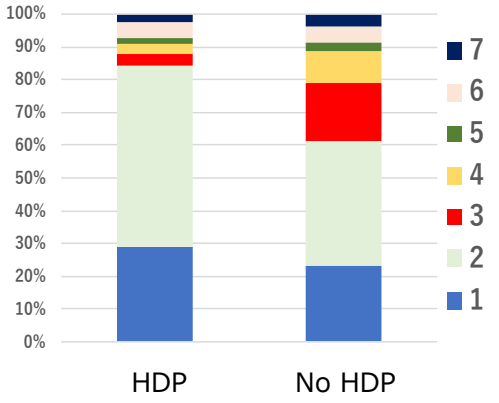
Logistic regression, adjusted for gestation



CLD types

HDP	1	2	3	3'	4	5
1	-	-	-	-	-	-
2	NS	-	-	-	-	-
3	<0.001	<0.001	-	-	-	-
3'	<0.001	<0.001	1	-	-	-
4	<0.02	<0.001	<0.001	NS	-	-
5	NS	NS	<0.001	<0.001	NS	-
6	0.001	<0.001	<0.001	NS	1	NS

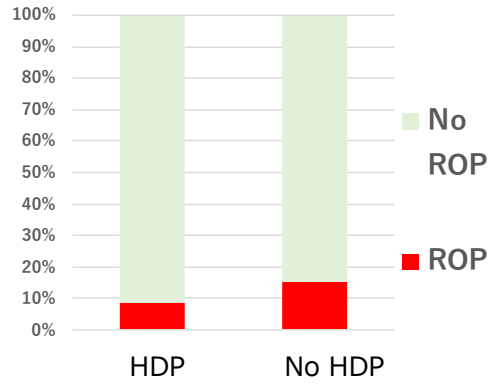
Mann-Whitney U test



ROP treatment

ROP	odds	95%CI		P
>=24w				
24w	5.26	4.79	5.78	0.000
23w	5.92	5.29	6.61	0.000
22w	5.19	4.23	6.36	0.000
HDP	0.656	0.6	0.716	0.000

Logistic regression, adjusted for gestation



□ Logistic regression analyses for IVH grades 3/4 and for ROP treatment were performed to calculate odds ratio of HDP against no-HDP adjusted with GA groups

Hypertensive Disorder of Pregnancy and outcome at 3 years

◆ In HDP the odds of Cerebral Palsy is 0.5.

◆ In HDP the odds of DQ<70 is 0.9.

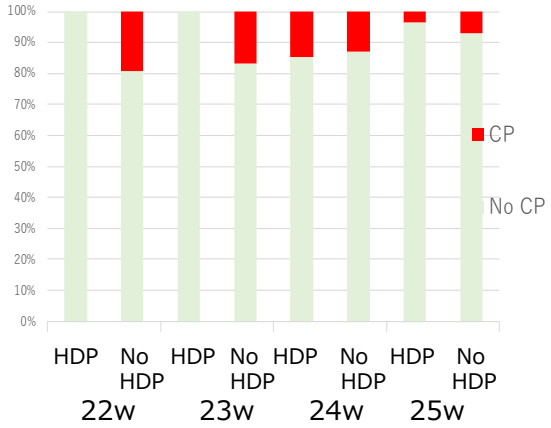
◆ In HDP the odds of Death at discharge is 0.7. No change even after controlled with gender.

◆ In HDP the odds of 3 yrs Visual Impairment is 0.8.

Dependent variable:

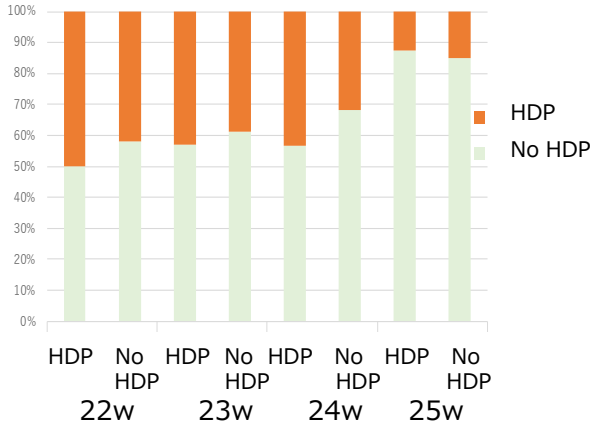
Cerebral Palsy

Cerebral Palsy	0dds	95%CI		P
>=25w	1			
24w	2.03	1.68	2.45	0.000
23w	3.14	2.55	3.86	0.000
22w	3.23	2.14	4.88	0.000
HDP	0.5	0.419	0.596	0.000



DQ<70 at 3 yrs

DQ<70	0dds	95%CI		P
>=25w	1			
24w	3.08	2.64	3.58	0.000
23w	4.42	3.67	5.32	0.000
22w	4.72	3.23	6.89	0.000
HDP	0.876	0.776	0.988	0.0316



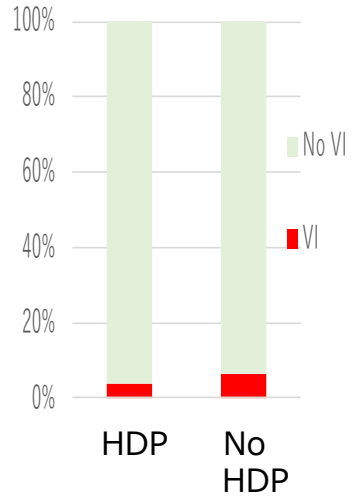
Death at discharge

Death at discharge	odds	95%CI		P
>=25w	1			
24w	3.73	3.26	4.28	0.000
23w	6.78	5.92	7.78	0.000
<23w	19.3	15.9	23.4	0.000
HDP	0.704	0.611	0.811	0.000

Death at discharge	odds	95%CI		P
>=25w	1			
24w	3.74	3.26	4.29	0.000
23w	6.79	5.92	7.78	0.000
22w	19.3	15.9	23.4	0.000
HDP	0.708	0.614	0.816	0.000
gender	1.11	1.01	1.22	0.026

Visual Impairment

3Yr VI	odds	95%CI		P
>=25w	1			
24w	3.94	3.24	4.8	0.000
23w	5.4	4.33	6.74	0.000
<23w	6.88	4.54	10.4	0.000
HDP	0.789	0.649	0.959	0.018



□ Logistic regression analyses for CP, for DQ<70, for death at discharge, and visual impairment(3 yr) were performed to calculate odds ratio of HDP against no- HDP adjusted with GA groups

Chorioamnionitis and NICU mortality, DQ at 3 years

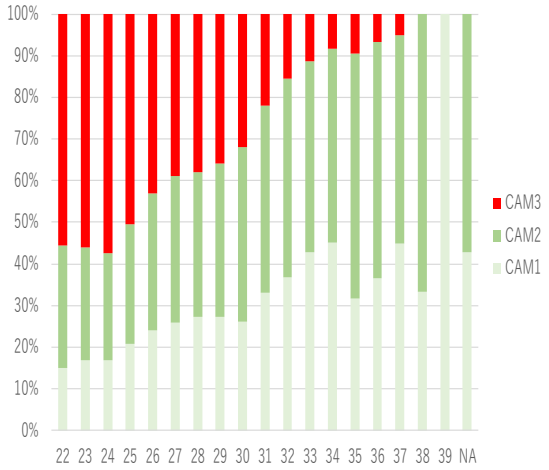
Histological Chorioamnionitis(HCAM:histology(Y/N), HisCAM:grade 0,1,2,3)

- Chorioamnionitis inversely correlates with gestational weeks.
- The more the positive histological CAM, the smaller NICU mortality.
- The more the HisCAM grade, the DQ significantly improve.

□ Logistic regression analyses for NICU mortality, for DQ<70 and for CP were performed to calculate odds ratio of CAM against no-CAM adjusted with GA groups

◆ CAM grade inversely correlates with GA.

CAM grade & GA



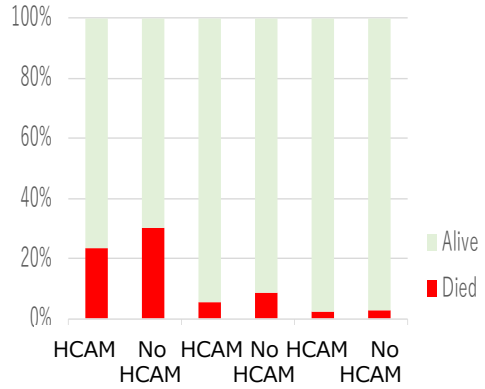
◆ PROM correlates with HCAM

HCAM	odds	95%CI		P
24-27w	2.44	2.32	2.58	0.000
<24w	4.04	3.66	4.46	0.000
PROM	2.87	2.72	3.03	0.000

◆ HCAM correlates smaller NICU mortality.

NICU mortality

Death at discharge	odds	95%CI		P
>27w	1			
24-27w	3.11	2.8	3.46	0.0000
<24w	14.8	13	16.9	0.0000
HCAM	0.705	0.632	0.787	0.0000

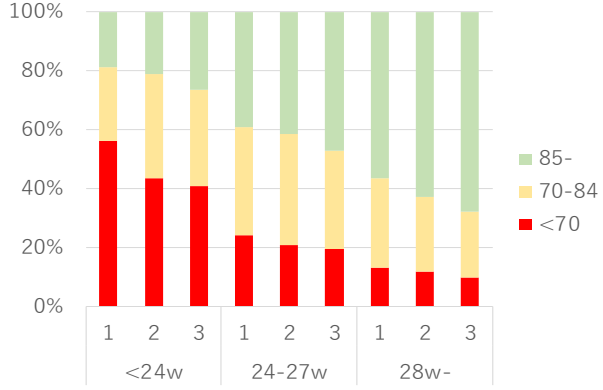


HCAM and GA groups

◆ The severer HisCAM grade the less DQ<70.

DQ<70

DQ (3Yr)	odds	95%CI		P
>27w	1			
24-27w	2.11	1.69	2.63	0.0000
<24w	6.46	4.8	8.7	0.0000
HisCAM	0.85	0.757	0.954	0.0056

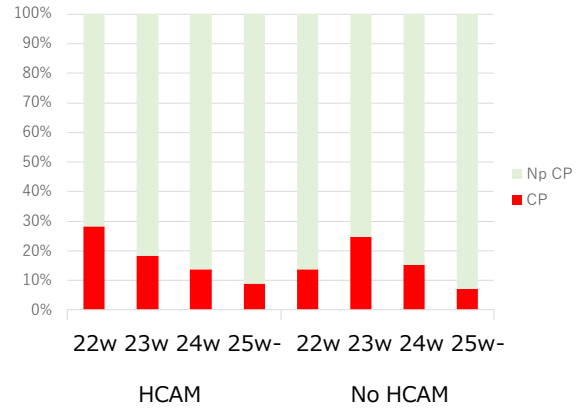


HisCAM grade1,2,3 and GA groups

◆ HCAM is not correlated with CP.

CP

CP	odds	95%CI		P
24-27w	2.46	2.18	2.79	0.000
<24w	4.92	4.02	6.02	0.000
HCAM	1	0.88	1.14	0.963



HCAM and GA groups

Chorioamnionitis and IVH3/4, Sepsis

Histological Chorioamnionitis(HCAM:histology(Y/N), HisCAM:grade 0,1,2,3))

◆ IVH3/4 is less in HCAM

◆ IVH3/4 is less in HisCAM of severe grade.

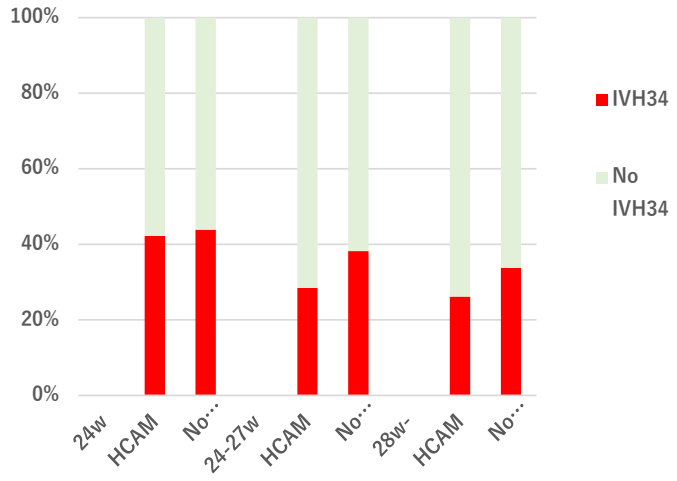
◆ Sepsis is not correlated with HisCAM grade.

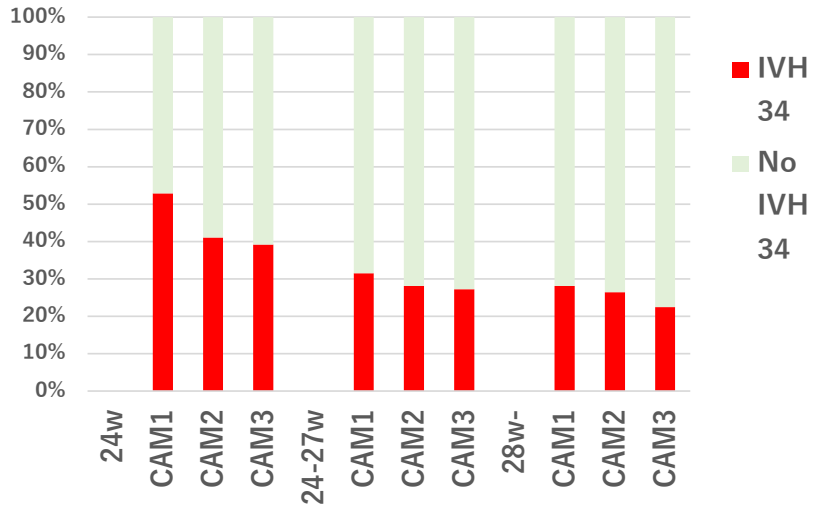
Dependent variable:

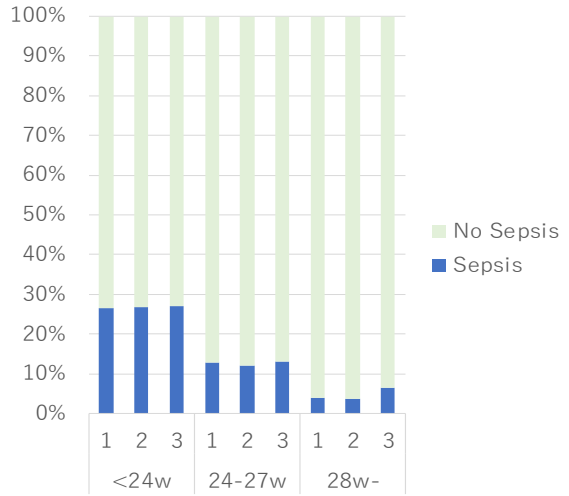
IVH3/4	odds	95%CI		P
>28w=1	1			
24-27w	1.4	1.16	1.68	0.0004
<24w	2.18	1.76	2.71	0.0000
HCAM	0.75	0.66	0.86	0.0000

IVH3/4	odds	95%CI		P
>28w=1	1			
24-27w	1.18	0.8	1.73	0.40
<24w	2.2	1.46	3.31	0.00
HisCAM	0.86	0.75	0.98	0.02

Sepsis	odds	95%CI		P
>28w=1	1			
24-27w	2.34	1.88	2.92	0.0000
<24w	5.89	4.59	7.55	0.0000
HisCAM	1.05	0.95	1.15	0.3270







Multiple births and mortality, cerebral palsy at 3 years

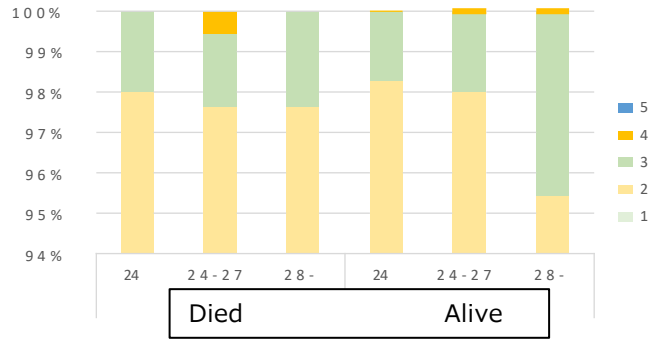
◆ Multiple births of extreme preterm have no correlations with mortality or cerebral palsy.

Number of fetuses

mortality	1	2	3	4	5	Total
died	1626	369	42	5		2042
<24w	397	119	11			527
24-27w	702	162	16	5		885
28w-	527	88	15			630
alive	26300	7593	1246	52	10	35201
<24w	1210	203	22	3		1438
24-27w	8807	1891	209	20	10	10937
28w-	16283	5499	1015	29		22826
Total	27926	7962	1288	57	10	37243

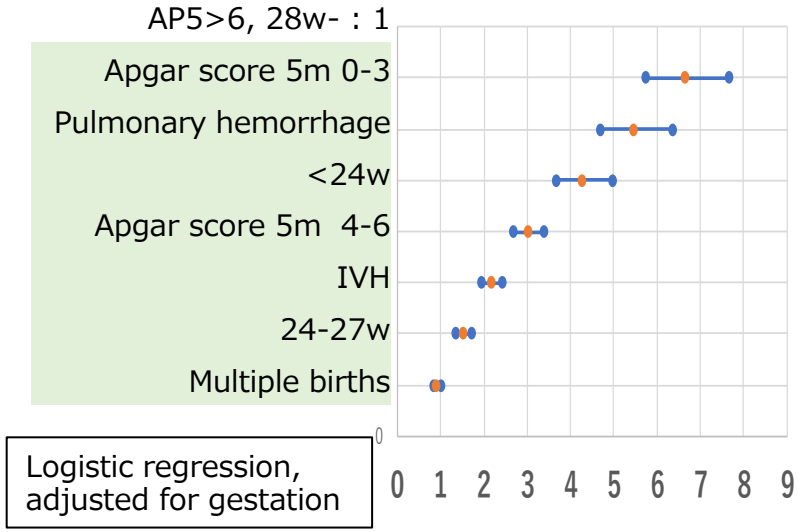
Per cent

mortality	1	2	3	4	5	Total
died	79.6%	18.1%	2.1%	0.2%	0.0%	100.0%
<24w	75.3%	22.6%	2.1%	0.0%	0.0%	100.0%
24-27w	79.3%	18.3%	1.8%	0.6%	0.0%	100.0%
28w-	83.7%	14.0%	2.4%	0.0%	0.0%	100.0%
alive	74.7%	21.6%	3.5%	0.1%	0.0%	100.0%
<24w	84.1%	14.1%	1.5%	0.2%	0.0%	100.0%
24-27w	80.5%	17.3%	1.9%	0.2%	0.1%	100.0%
28w-	71.3%	24.1%	4.4%	0.1%	0.0%	100.0%
Total	75.0%	21.4%	3.5%	0.2%	0.0%	100.0%



NICU death	odds	95%CI		P
28w-: 1				
Apgar score 5m 0-3	6.62	5.73	7.66	<0.001
Pulmonary hemorrhage	5.45	4.68	6.34	<0.001
<24w	4.26	3.66	4.95	<0.001
Apgar score 5m 4-6	3.00	2.67	3.37	<0.001
IVH	2.15	1.92	2.41	<0.001
24-27w	1.50	1.33	1.69	<0.001
Multiple births	0.89	0.81	0.99	0.03

NICU death



Logistic regression, adjusted for gestation

Number of fetuses

CP	1	2	3	4	Total
No CP	10757	2996	514	28	14295
<24w	473	76	9	3	561
24-27w	3753	786	85	5	4629
28w-	6531	2134	420	20	9105
CP	1026	286	23	5	1340
<24w	132	26	1		159
24-27w	520	124	10	3	657
28w-	374	136	12	2	524
Total	11783	3282	537	33	15635

Per cent

CP	1	2	3	4	Total
No CP	75.3%	21.0%	3.6%	0.2%	100.0%
<24w	84.3%	13.5%	1.6%	0.5%	100.0%
24-27w	81.1%	17.0%	1.8%	0.1%	100.0%
28w-	71.7%	23.4%	4.6%	0.2%	100.0%
CP	76.6%	21.3%	1.7%	0.4%	100.0%
<24w	83.0%	16.4%	0.6%	0.0%	100.0%
24-27w	79.1%	18.9%	1.5%	0.5%	100.0%
28w-	71.4%	26.0%	2.3%	0.4%	100.0%
Total	75.4%	21.0%	3.4%	0.2%	100.0%

CP	odds	95%CI		P
28w-	1			
24-27w	2.47	2.19	2.79	<0.001
<24w	4.93	4.05	6.01	<0.001
Number of fetus	1.01	0.91	1.13	0.81

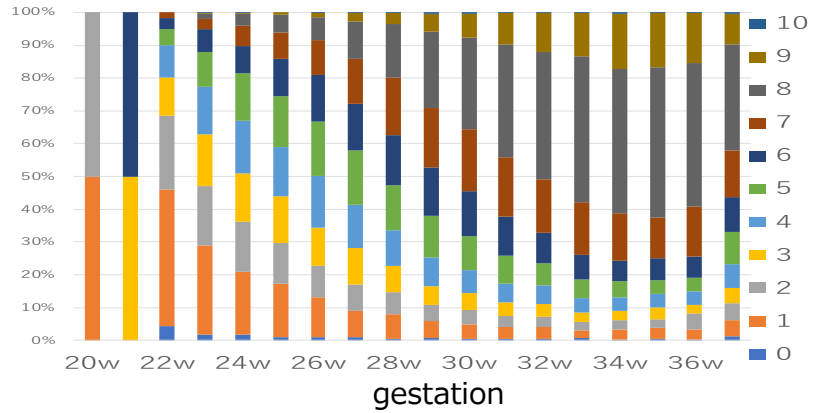
Neonatal Morbidities

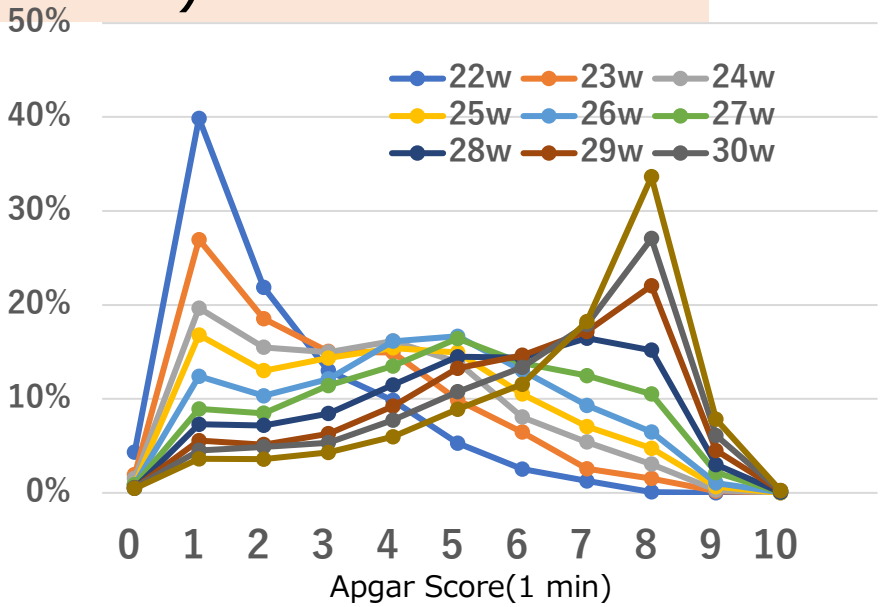
NEONATAL RESEARCH NETWORK of JAPAN

≦1500g

Apgar Score(1 min)

◆ Apgar Score(1 min) correlates significantly with gestation.





N

AS-1	20w	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	NA	総計
0			27	29	42	28	31	35	25	29	25	19	11	12	2	4	1	3					323
1	1		261	490	481	479	423	319	337	249	187	121	94	48	42	29	17	12	9	2		4	3605
2	1		141	323	379	364	327	317	319	228	204	120	82	49	41	24	26	13	6	1		1	2966
3		1	73	284	368	422	396	444	363	271	223	146	102	54	39	33	15	12	6	3	1	3	3259
4			61	262	399	440	550	521	504	411	311	197	150	83	59	36	22	18	3	1		4	4032
5			32	189	357	456	569	647	637	583	465	300	179	111	66	38	22	24	5			3	4683
6		1	21	125	206	337	483	560	705	691	611	413	244	147	88	58	35	27	7	2	1	3	4765
7			10	57	157	236	364	544	808	853	844	633	429	309	203	112	83	35	6	3	1	3	5690
8				29	90	159	242	449	751	1087	1255	1198	1023	853	611	407	236	81	18	6	1	2	8498
9				5	8	23	49	105	162	260	324	335	312	255	234	148	83	23	7				2333
10				1	1		3	4	1	15	13	9	6	4	4	2	1	1					65
NA			13	36	37	47	49	60	61	57	55	54	39	18	18	11	10	6	1			15	587
Total	**2**	**2**	**639**	**1830**	**2525**	**2991**	**3486**	**4005**	**4673**	**4734**	**4517**	**3545**	**2671**	**1943**	**1407**	**902**	**551**	**255**	**68**	**18**	**4**	**38**	**40806**
%	0.0%	0%	1.6%	4.5%	6.2%	7.3%	8.5%	9.8%	11.5%	11.6%	11.1%	8.7%	6.5%	4.8%	3.4%	2.2%	1.4%	0.6%	0.2%	0%	0%	0.1%	100.0%

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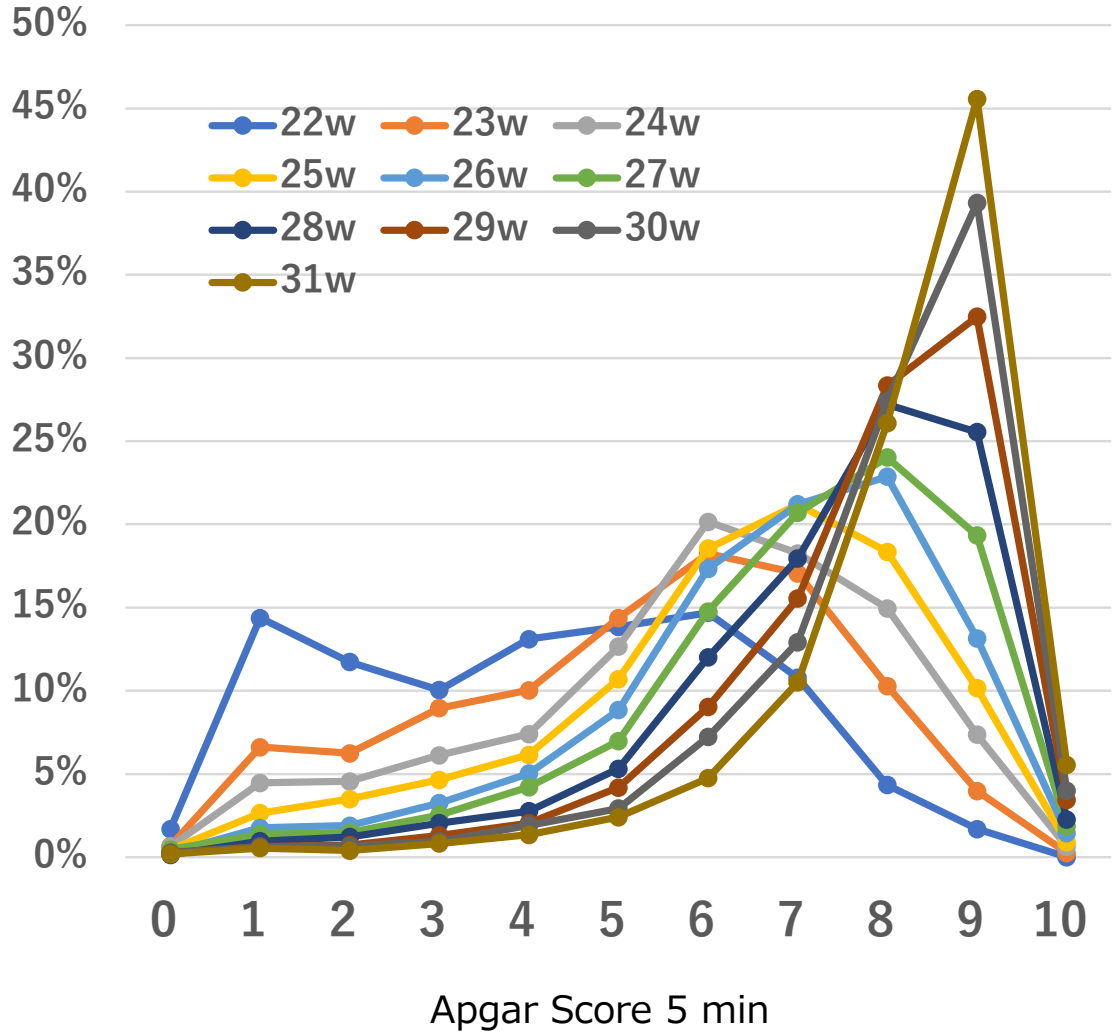
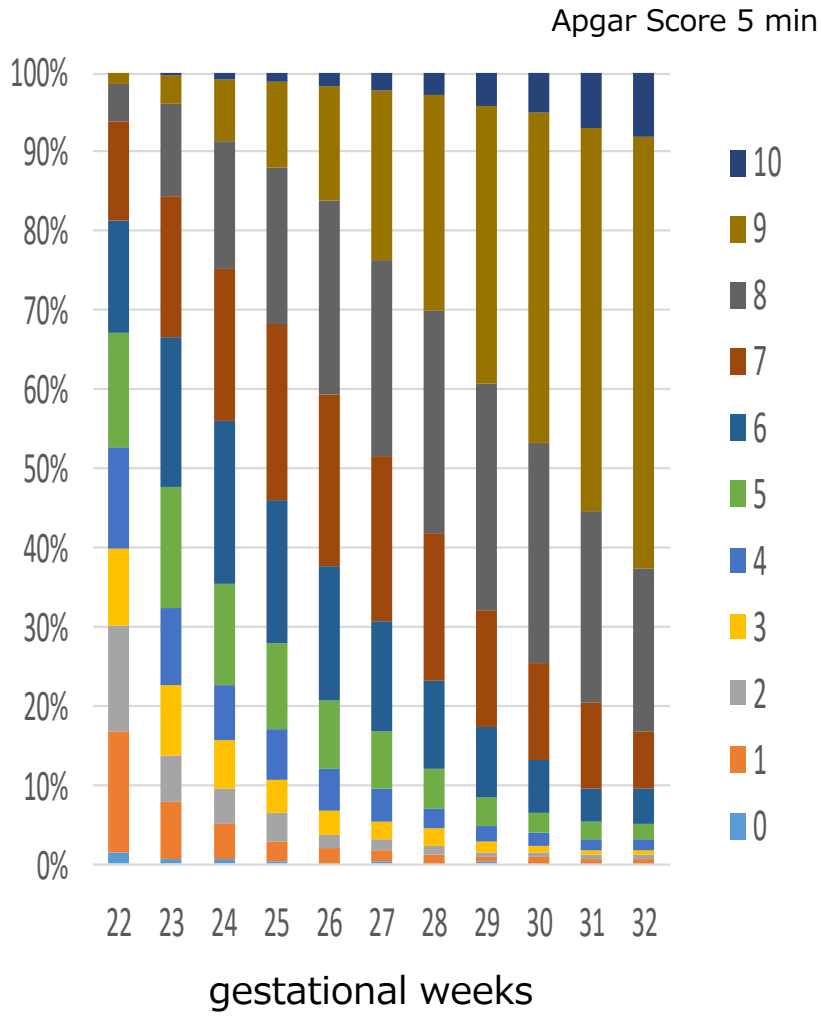
≦1500g

Apgar Score 5 min and gestational weeks

Dataset928





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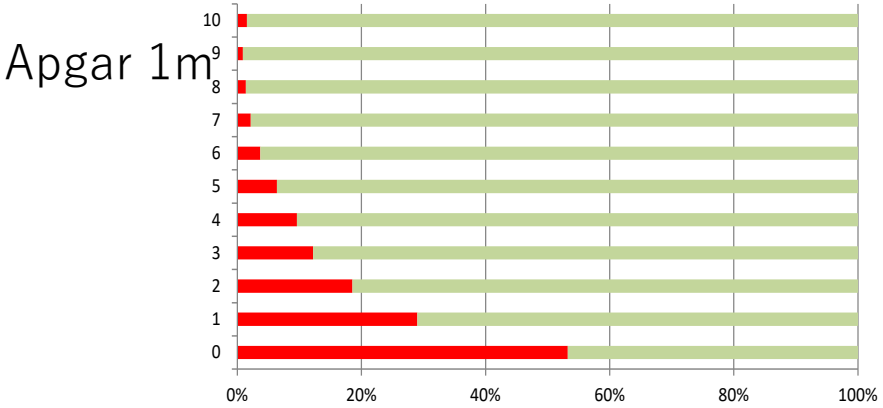
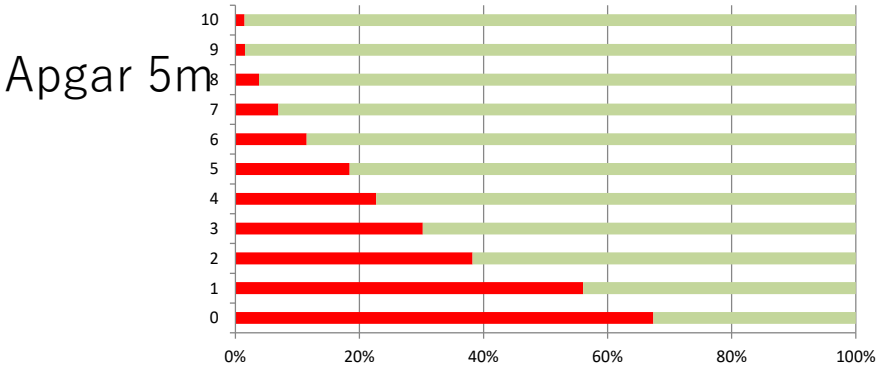
Apgar Score and mortality, cerebral palsy at 3 years

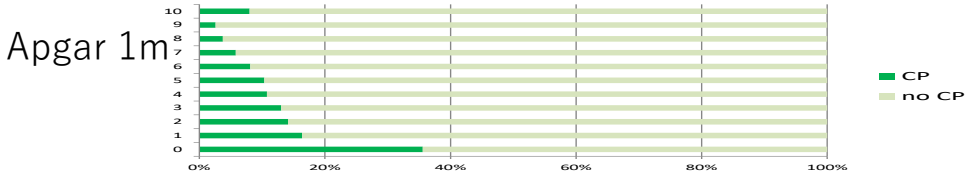
- Apgar Score inversely correlates with mortality, and the rate of CP.
- The correlation of AP 5 with CP remains for further analysis at AP <4*.

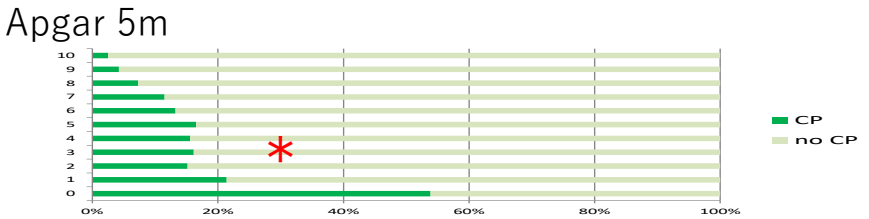
Death

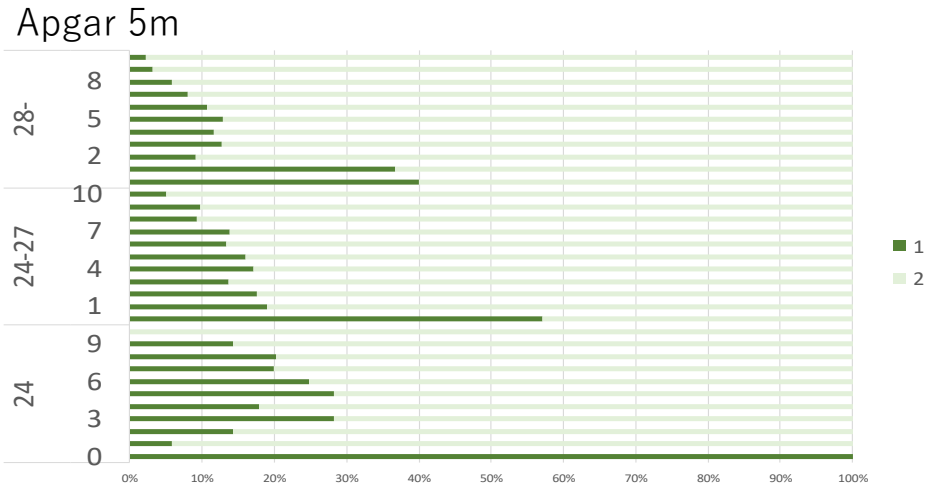




Cerebral palsy(3 yrs)







Pulmonary hemorrhage and RDS

Pulmonary Hemorrhage

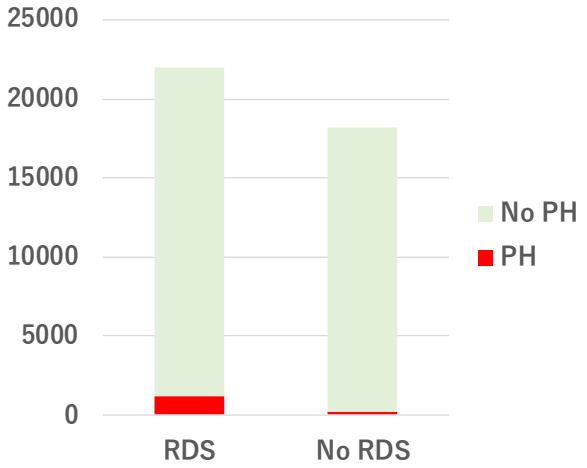
- 5.4% of RDS are associated with PH.

- PH shows odds 7.5 for death, which is five times of RDS.

	PH	No PH	総計	PH(%)
RDS	1185	20767	21952	5.4%
No RDS	186	17983	18169	1.0%
total	1371	38750	40121	

Dependent variable:

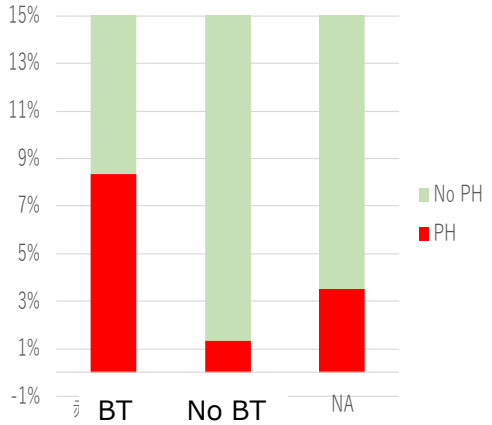
Death				
>=25w:1	odds	95%CI		P
Antenatal steroid	0.660	0.598	0.729	0.000
24w	3.400	2.940	3.920	0.000
23w	5.930	5.140	6.850	0.000
22w	16.300	13.300	20.100	0.000
RDS	1.280	1.150	1.420	0.000
Pulmonary hemorrhage	7.470	6.460	8.630	0.000



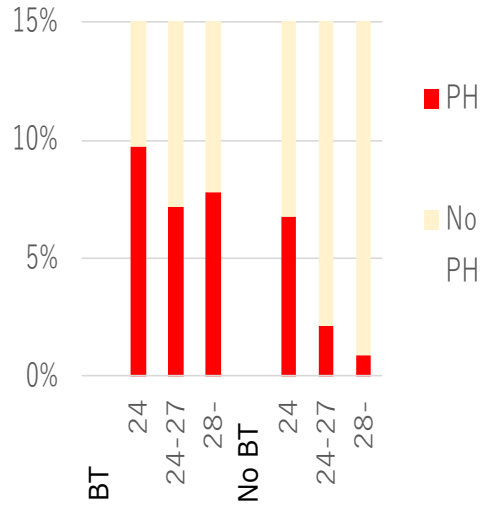
Pulmonary hemorrhage and blood transfusion

① Blood transfusion is significantly associated with pulmonary hemorrhage.
② The association remains even in larger gestation.

①

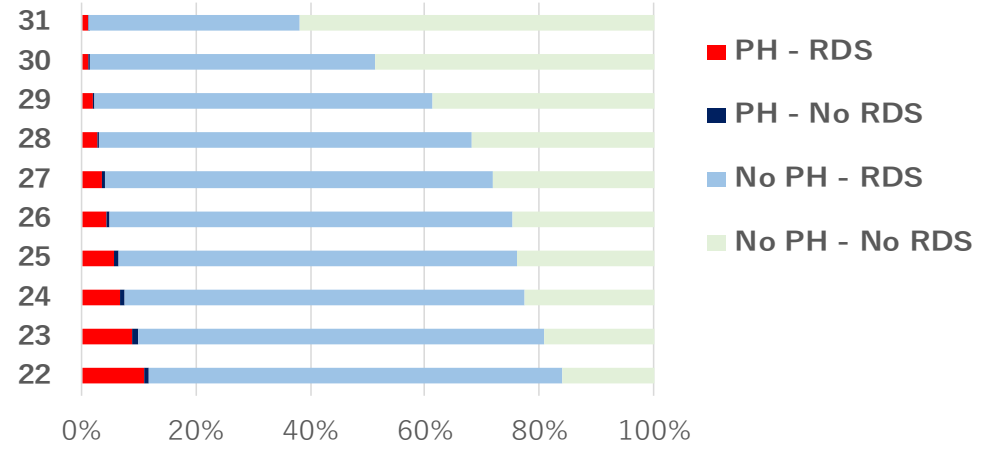


②



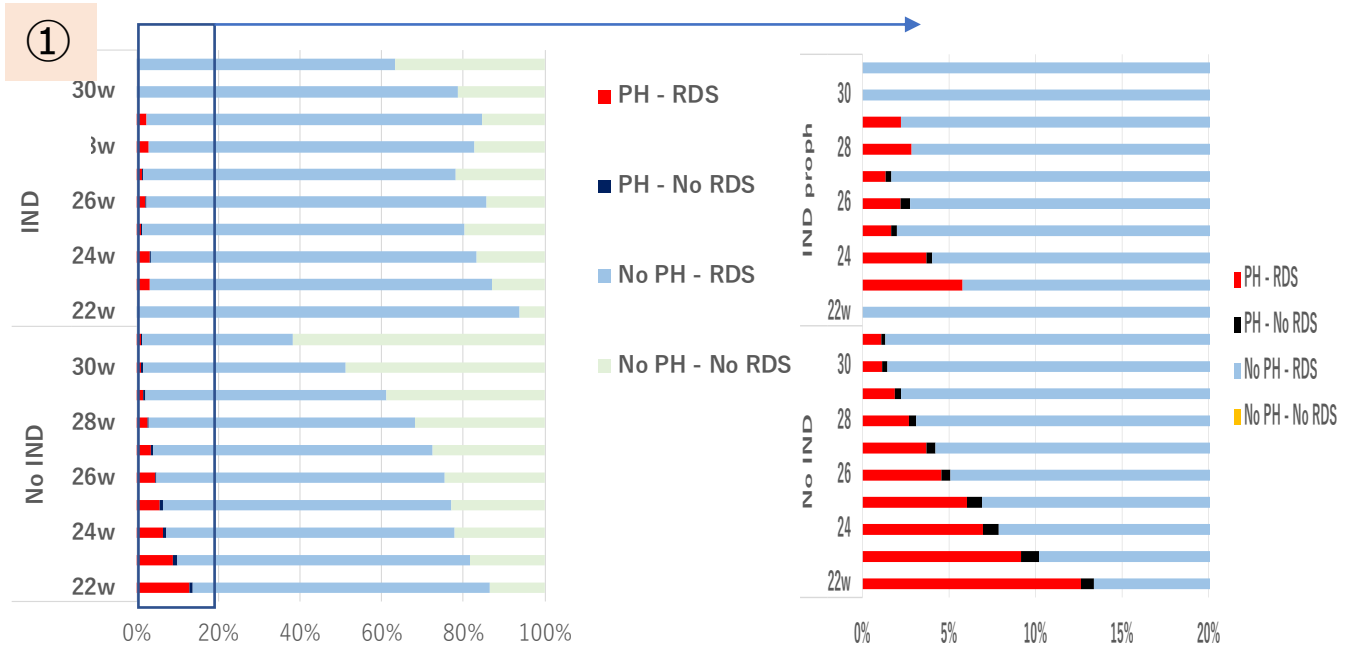
Pulmonary hemorrhage and Indomethacin

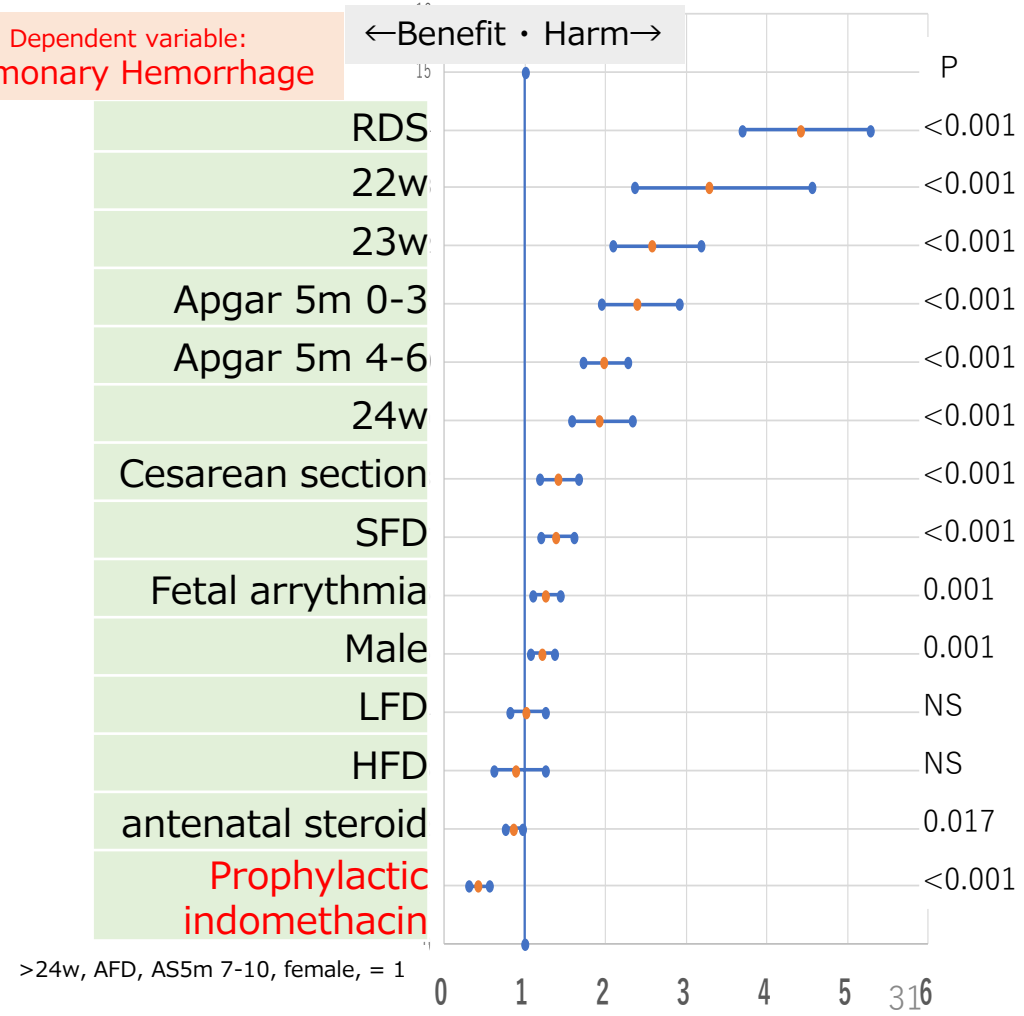
◆ Majority of PH are associated with RDS.



① The rate of PH significantly decreases with the prophylactic low dose indomethacin*.

*Starting within 6 hours of birth 3 doses of indomethacin IND are given with 6 hours continuous i.v. glucose infusion every 24 hours. IND is given at the dose of 0.1 mg/kg-wt/dose.



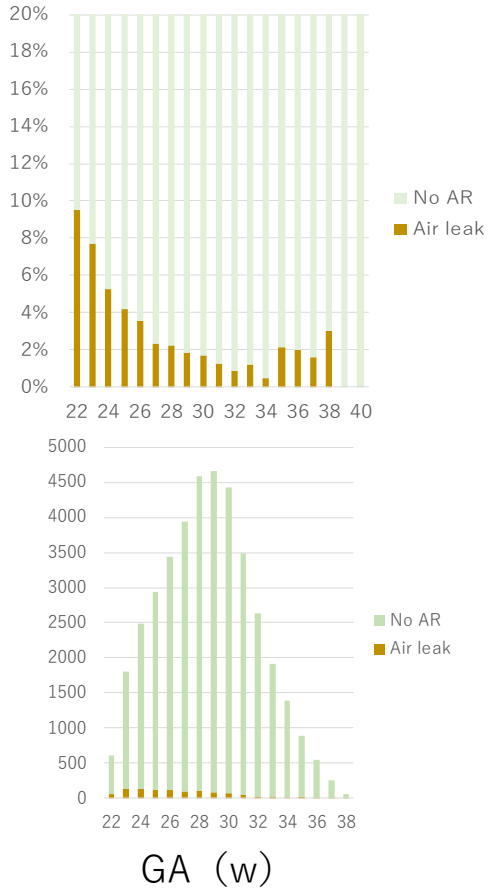


>24w, AFD, AS5m 7-10, female, = 1

Air Leak

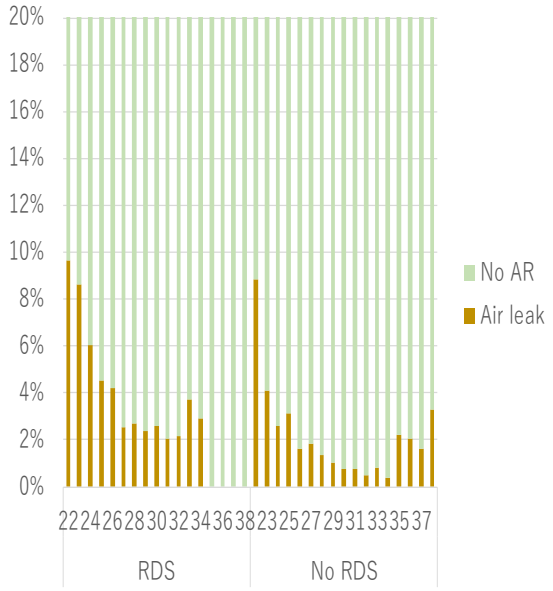
◆ Smaller gestation is associated with AL. AL is further associated with other illnesses (RDS, Pulmonary hemorrhage、PPHN).

Smaller gestation　　RDS　　Pulmonary hemorrhage　　PPHN

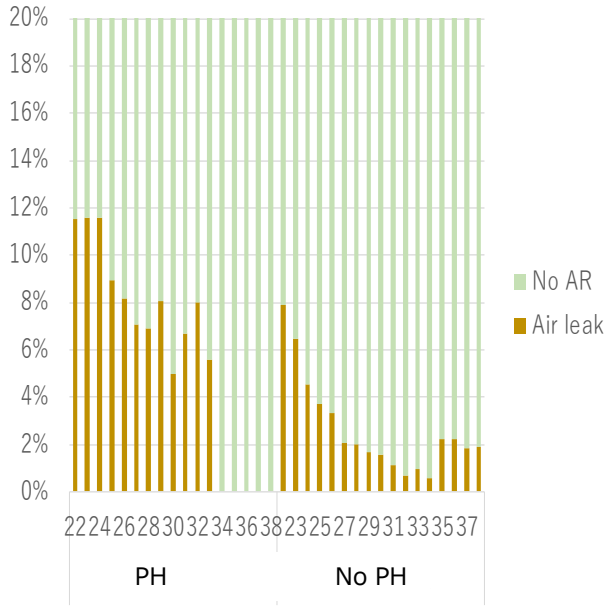


Dependent variable:

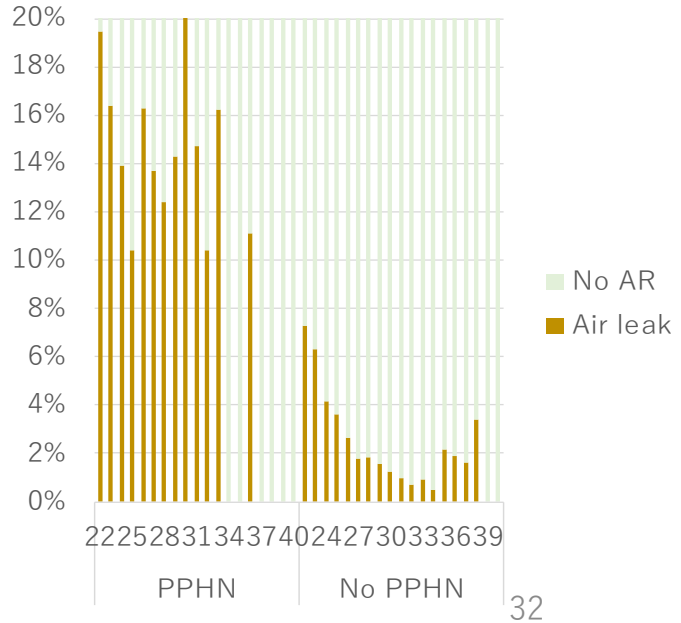
AR	odds	95%CI		P
＞28w	1 ar			
24-27w	1.86	1.6	2.16	0.0000
＜24w	3.81	3.1	4.69	0.0000
RDS	2.19	1.85	2.58	0.0000



AR	odds	95%CI		P
＞28w	1			
24-27w	1.8	1.55	2.09	0.0000
＜24w	3.48	2.82	4.29	0.0000
RDS	2.09	1.77	2.46	0.0000
PH	2.63	2.11	3.29	0.0000

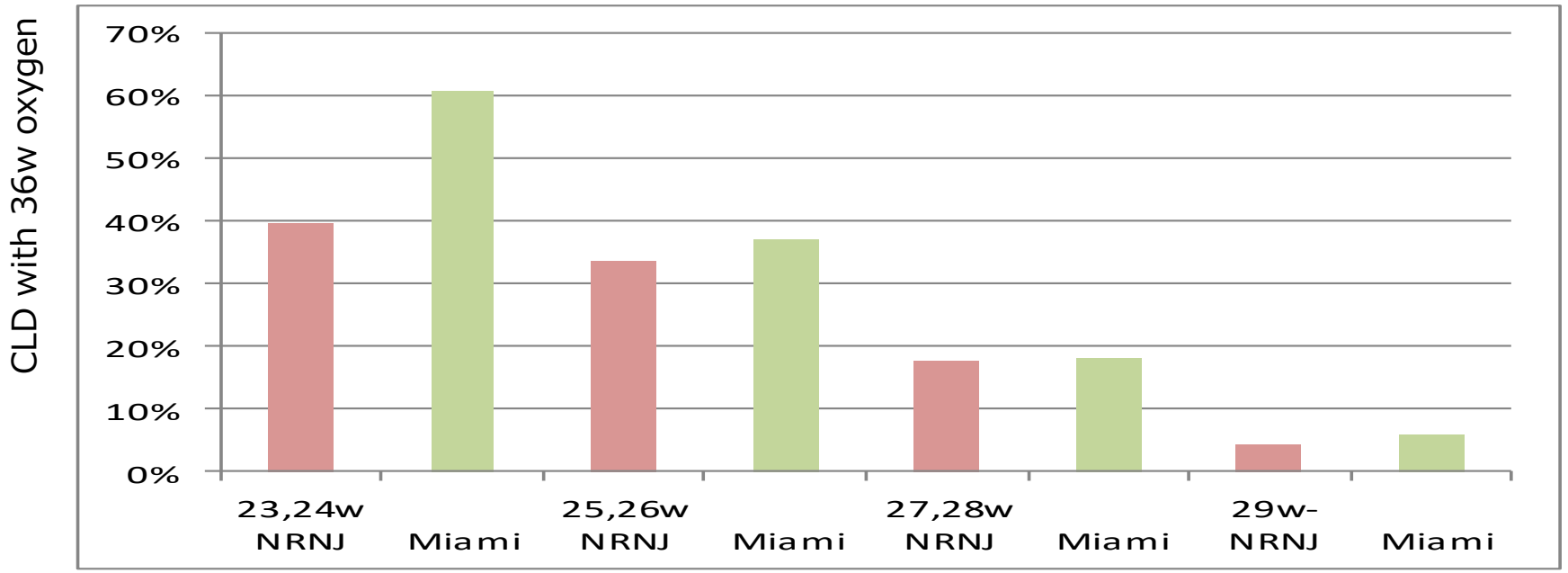


AR	odds	95%CI		P
＞28w	1			
24-27w	1.59	1.37	1.85	0.0000
＜24w	2.68	2.16	3.32	0.0000
RDS	2.01	1.71	2.38	0.0000
PH	2.16	1.72	2.71	0.0000
PPHN	5.07	4.27	6.02	0.0000



BPD36w (Japan vs Miami US)
NRNJ*(N=6,605) & Miami** (N=1,539)

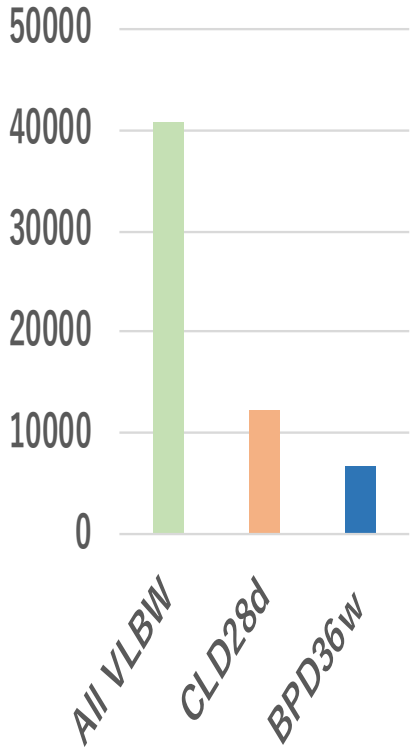
◆ The incidence of BPD36w in NRNJ are less compared with those of Univ Miami.



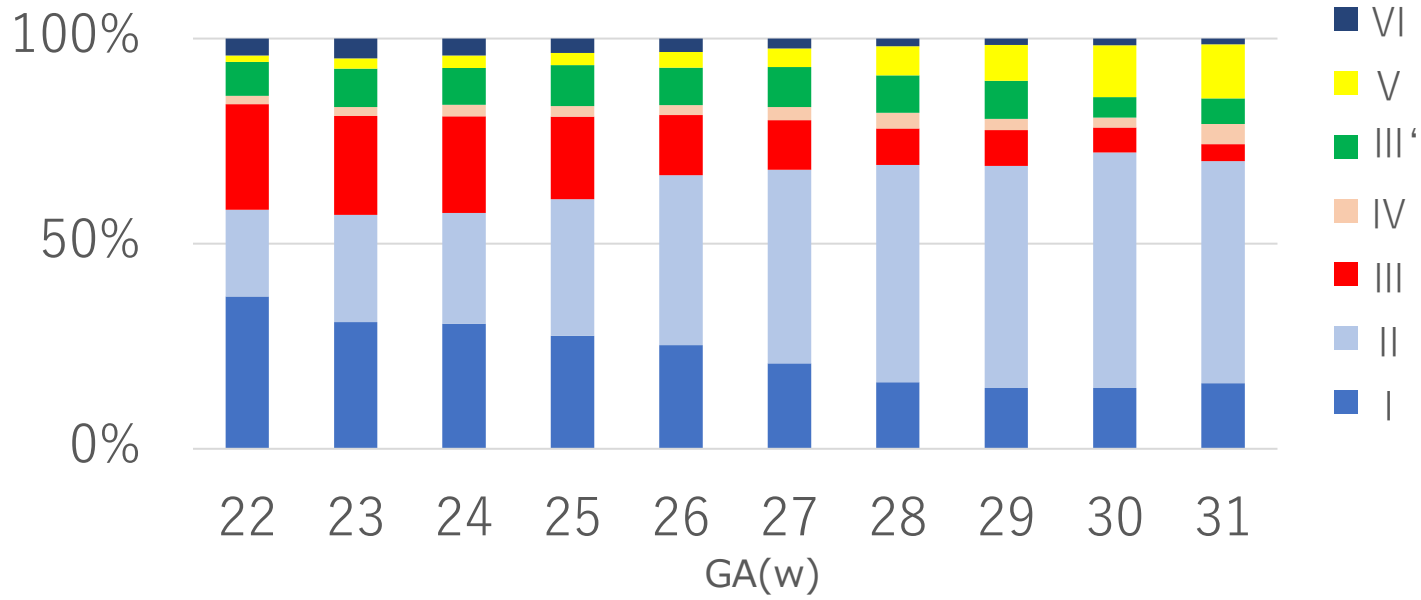
(*Fujimura, 2019. **Bancalari E, Am J Perinatol 2018;35:537-540)

Chronic lung disease（CLD28d）and gestational weeks

◆ CLD type III inversely correlates with GA.



CLD type III	odds	95%CI	P
GA(w)	0.819	0.8 - 0.838	<0.0001



□ CLD28 days (Ogawa's Classification*) N= 12,297

CLD type III; Bubbly/cystic appearance on chest X-ray (see page 72)

(* Ogawa Y, Fujimura M, Goto A et al. Epidemiology of neonatal chronic lung disease in Japan. Acta Pediatr Jpn. 1992; 34: 663-667)

CLD28d Type III in relation with HOT and Chorioamnionitis grade III

(see page 71)

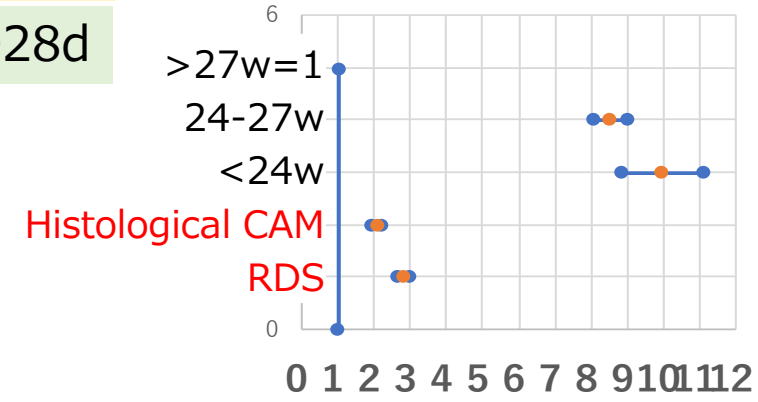
① CLD28d is significantly associated with RDS and histological chorioamnionitis.

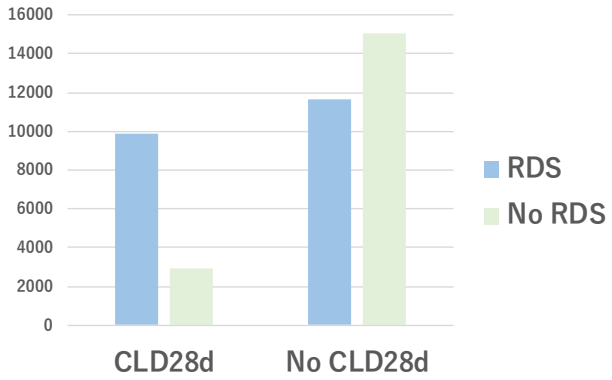
② CLD type III is largest in HOT rate and significantly associated with histological CAM grade III.

③ For CLD type III the odds ratio of RDS is 0.27. For BPD36w the odds for RDS is 1.1.

Dependent variable:

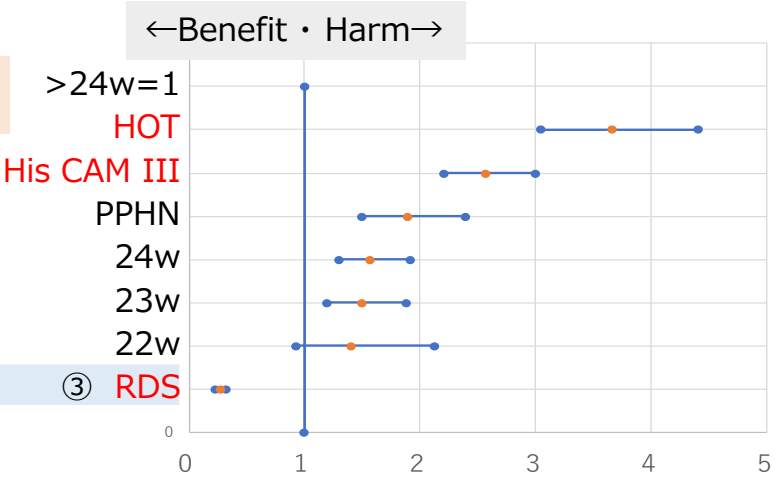
① CLD28d



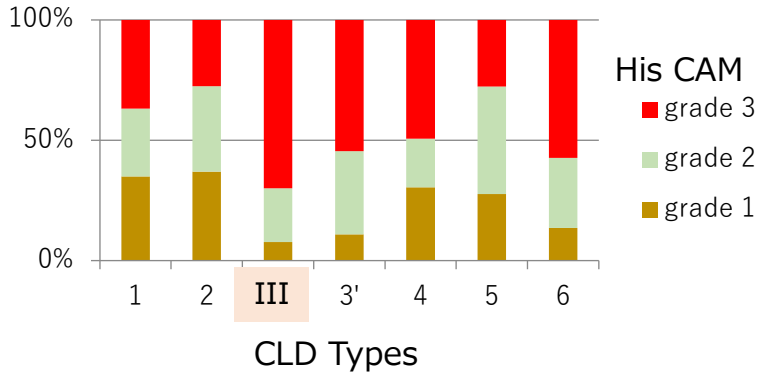


Dependent variable:

② CLD type III

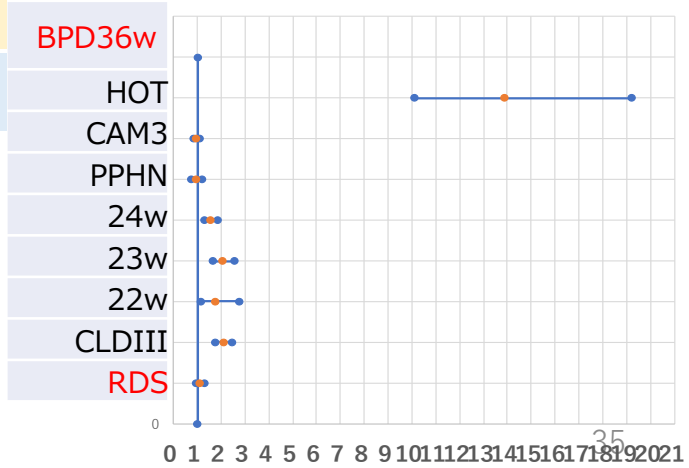


②



Dependent variable:

③



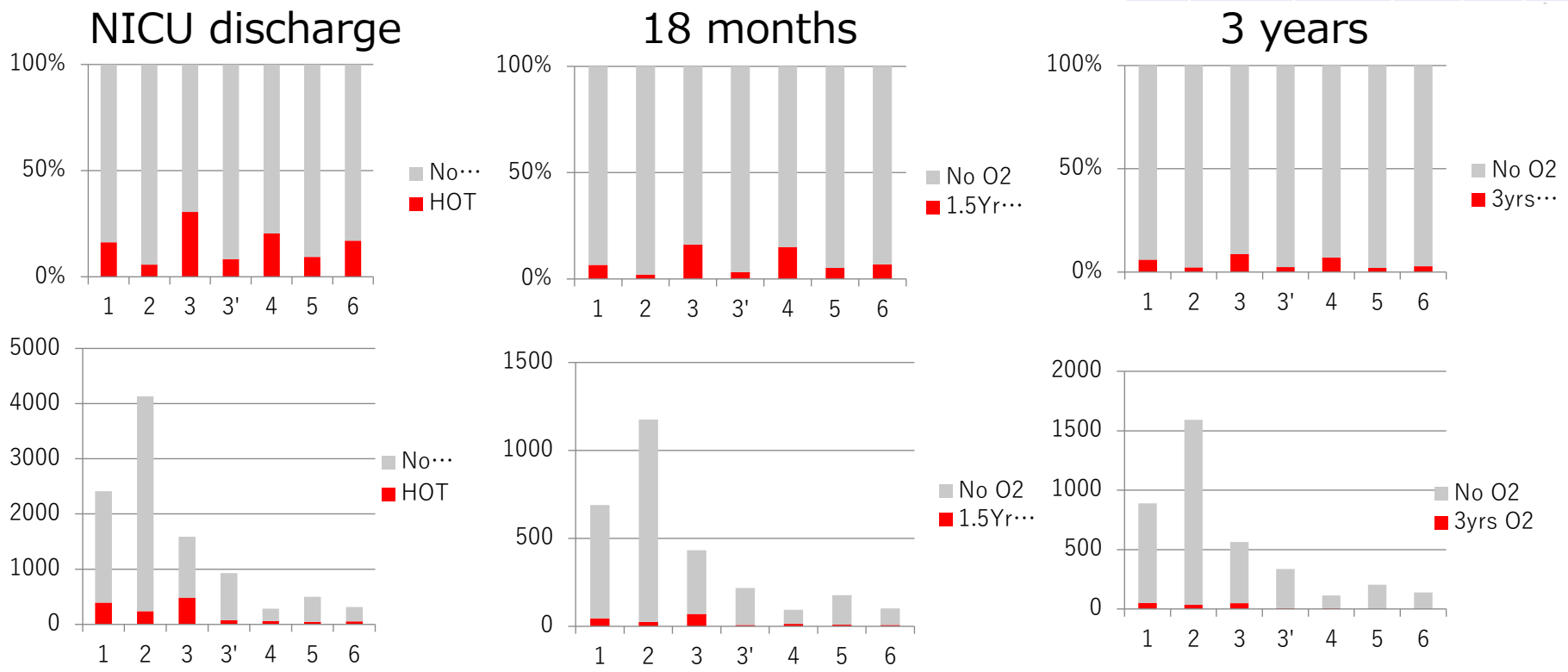
CLD types and Home Oxygen therapy

- The HOT rates are significantly larger in CLD type III up to 3 years.

HOT

CLD types at NICU discharge	CLD types 1	2	3	3'	4	5
2	<0.0001	-	-	-	-	-
3	<0.0001	<0.0001	-	-	-	-
3'	<0.0001	<0.01	<0.0001	-	-	-
4	1	<0.01	<0.01	<0.0001	-	-
5	<0.001	<0.01	<0.0001	1	<0.001	-
6	1	<0.0001	<0.0001	<0.0001	1	<0.01

CLD types at 3yrs	CLD types 1	2	3	3’	4	5
2	<0.0001	-	-	-	-	-
3	NS	<0.0001	-	-	-	-
3’	NS	NS	<0.02	-	-	-
4	NS	<0.04	NS	NS	-	-
5	NS	NS	<0.03	NS	NS	-
6	NS	NS	NS	NS	NS	NS



CLD Types by Ogawa’s Classification

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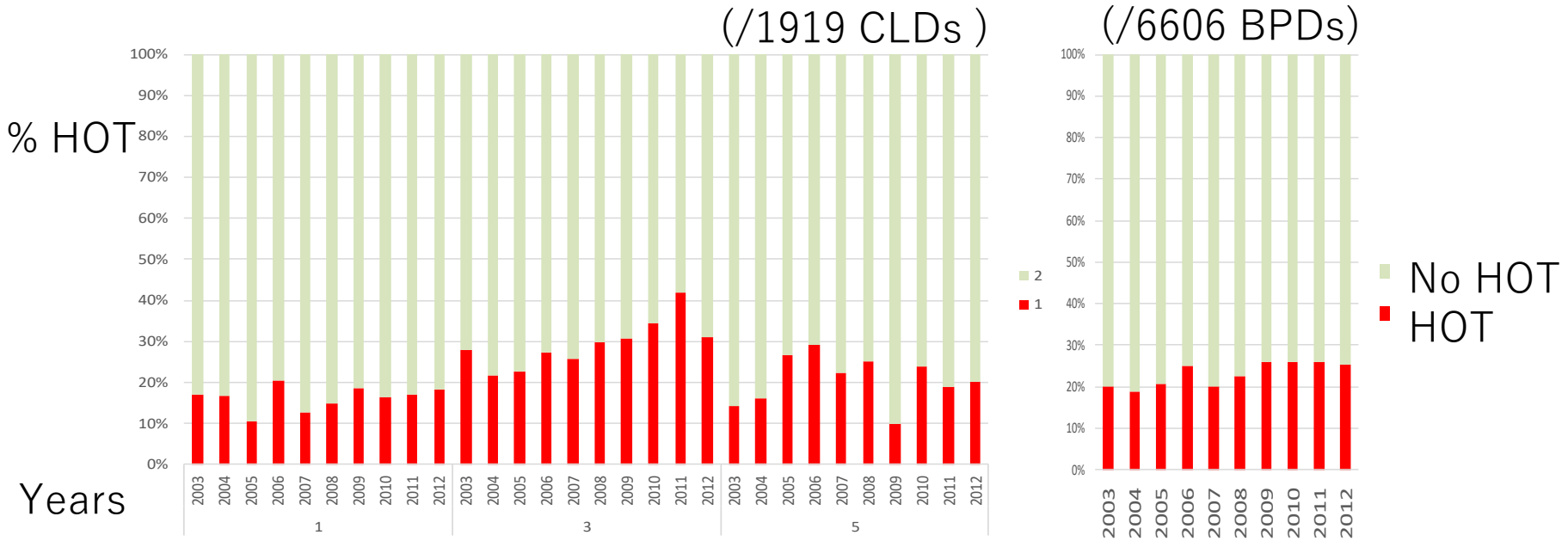
Annual trend of Home Oxygen therapy
(CLD type 1, 3, 4 & BPD36w)

◆ Hot is increasing in CLD type 3 and BPD36w.



CLD type 1	type 3	type 4	BPD36w
HOT	HOT	HOT	HOT
odds 1.03	odds 1.08	Odds 1.02	odds 1.05
95%CI 0.994 - 1.07	95%CI 1.04 - 1.12	95%CI 0.916 - 1.13	95%CI 1.02 - 1.07
P NS	P <0.0001	P NS	P <0.0001

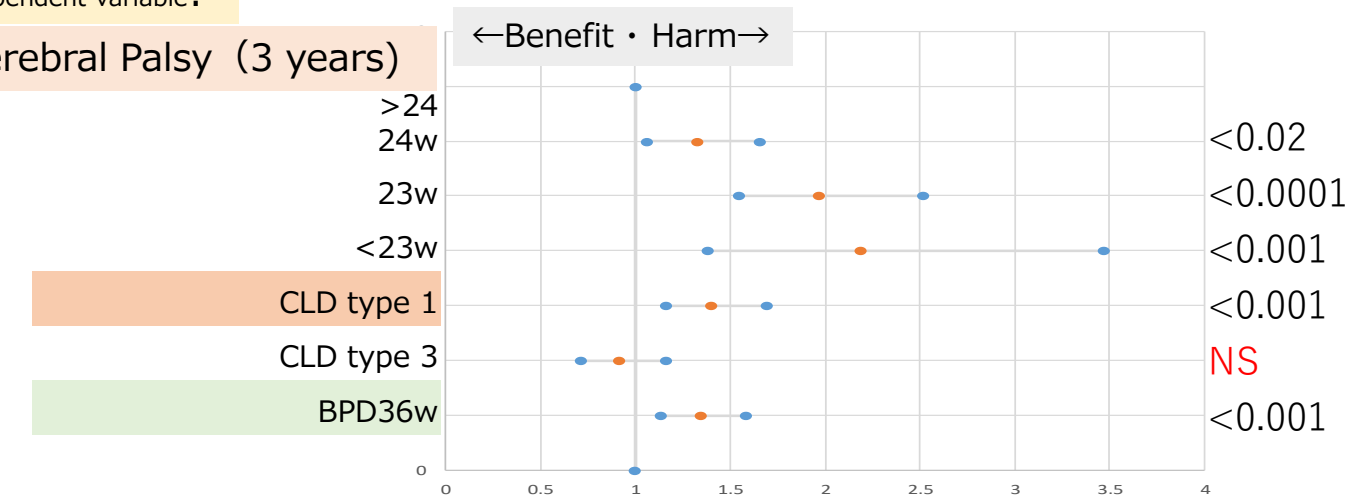
Logistic regression, adjusted for gestation

CLD type1、3 & BPD36w and Cerebral Palsy（3 years）

- The odds ratio of CP for CLD type 1 is 1.4.
- CP odds for BPD36w is 1.34.
- No correlations between CLD type 3 and CP.

Dependent variable:

Cerebral Palsy（3 years）



Logistic regression, adjusted for gestation

◆ Summary of CLD

1. CLD type III is characteristic with bubbly/cystic appearance on chest X-ray. （see page 72）
2. CLD28d is significantly associated with RDS and histological chorioamnionitis.
3. CLD type III is largest in HOT rate and significantly associated with histological CAM grade III.
4. For CLD type III the odds ratio of RDS is 0.27, whereas for BPD36w the odds for RDS is 1.1.
5. CLD type 3 and BPD36w differs in the risk of CP.
6. The Ogawa's classification of Chronic lung disease（CLD28）shows unique characteristics of CLD.

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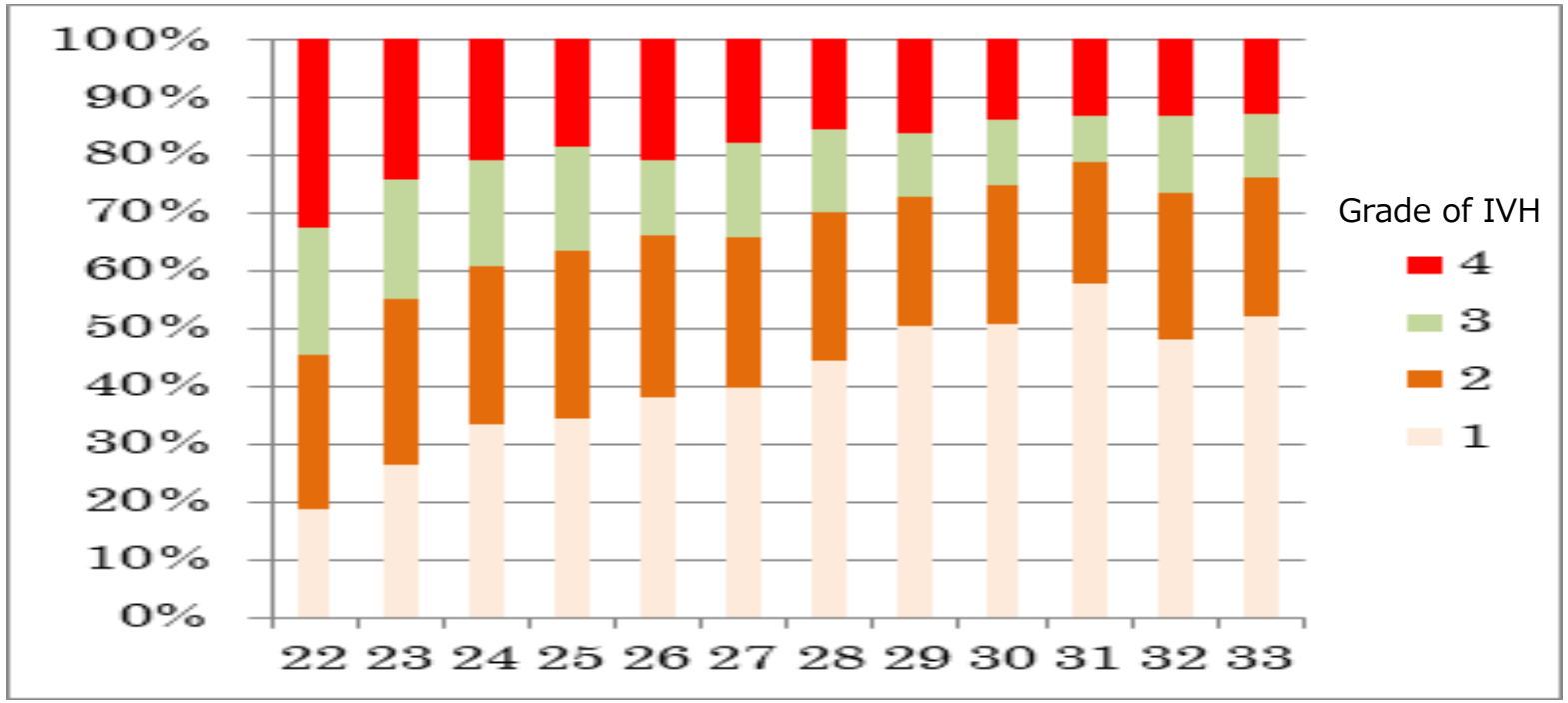
Grade of IVH and gestational weeks

Intraventricular Hemorrhage

- Grade of IVH correlates to gestational age.
- Such precise correlation is shown possible only by using big data like NRNJ data-base.

Dependent variable:

IVH grade	odds	95%CI
gestational weeks	0.814	0.798 - 0.83



gestational weeks

Place of birth and IVH

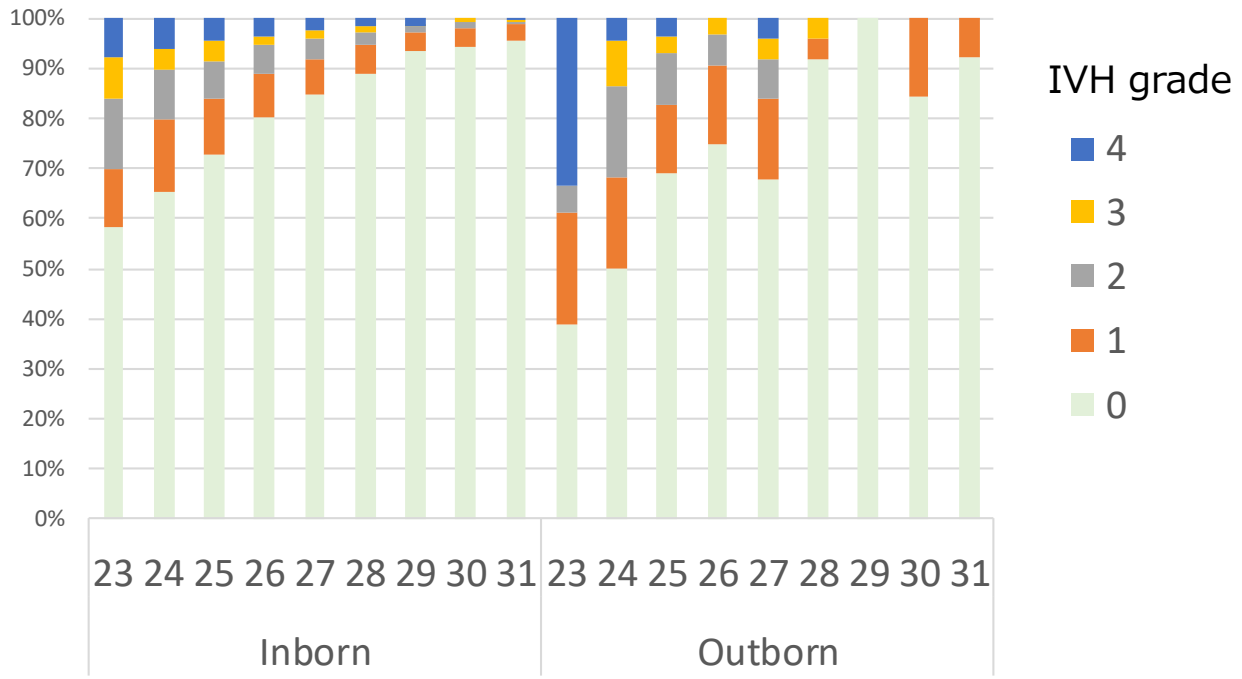
Intraventricular Hemorrhage

◆ Outborn preterm infants show higher incidence for gestational weeks.

Dependent variable:

IVH grade	odds	95%CI	
24-27w	5.45	5.07	5.86
<24w	15.4	13.8	17.1
outborn	1.6	1.43	1.78

(>27w＝1)



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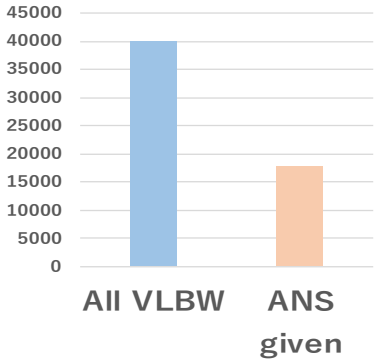
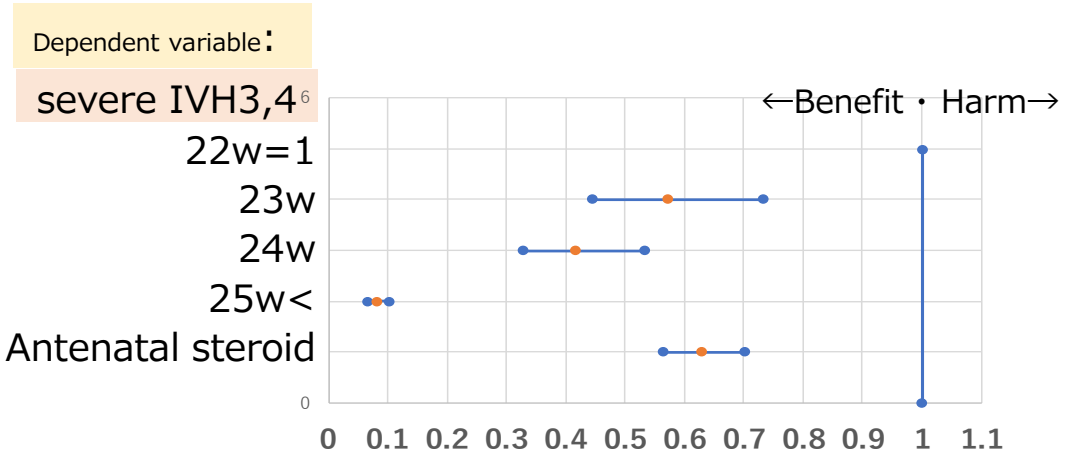
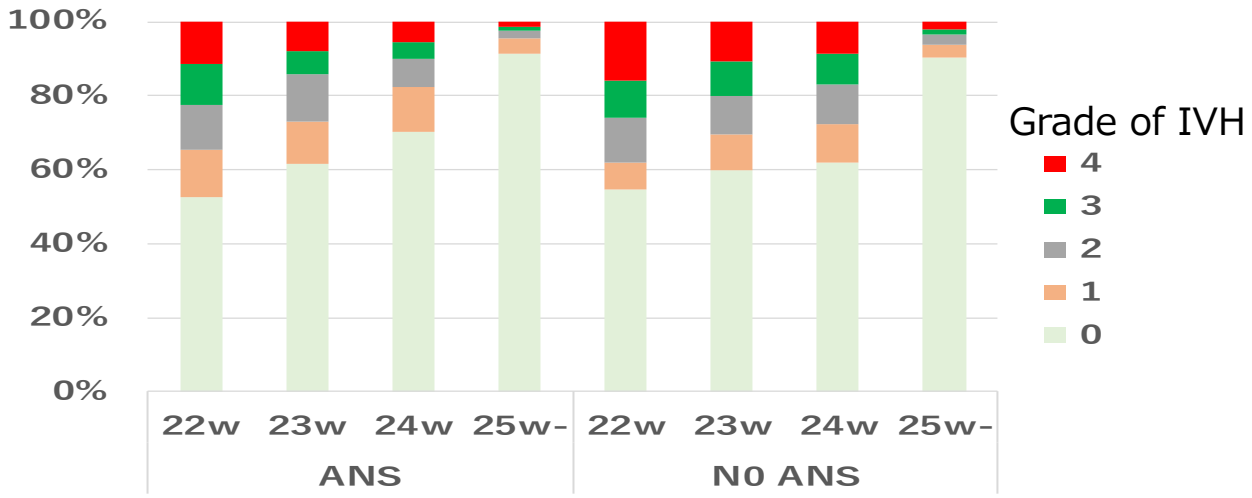
Antenatal steroid and IVH

◆ Antenatal steroid is effective in preventing severe type of IVH3,4.



Dependent variable:
severe IVH3,4





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PVL and Gestational weeks

Periventricular Leukomalacia

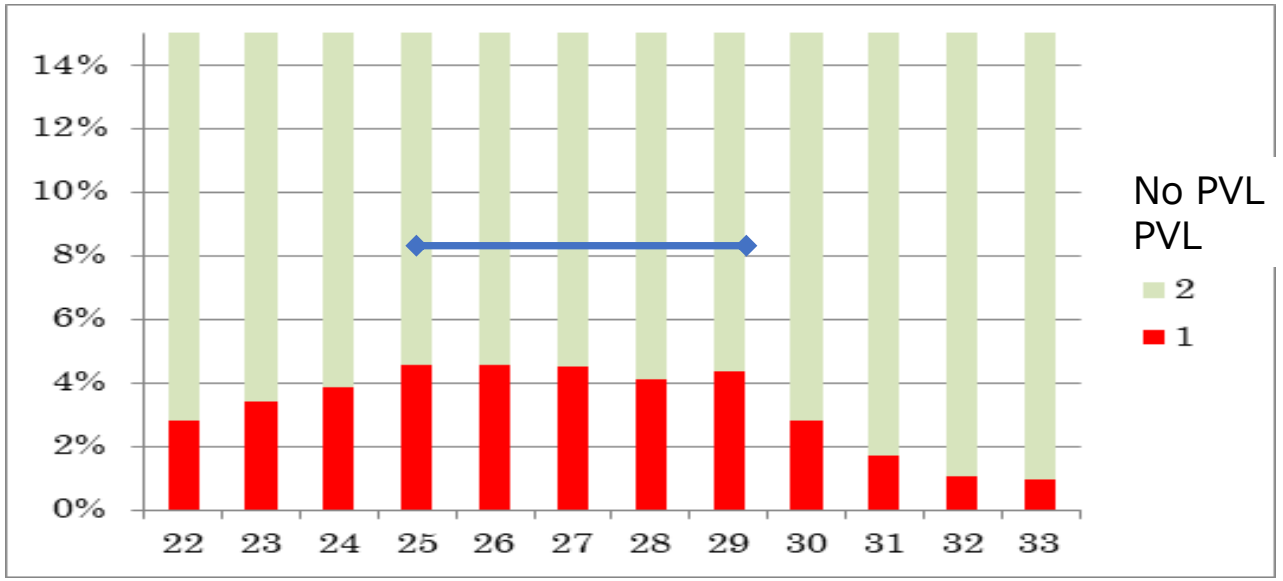
◆ The peak gestation for PVL risk is 25-29weeks.

Dependent variable:

Periventricular Leukomalacia

	odds	95%CI
<24w	1.28	1.01 - 1.62
24-27w	1.74	1.55 - 1.95
28w-	1	

Logistic regression



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Antenatal steroid and PVL prevention

Periventricular Leukomalacia

◆ Antenatal steroid significantly reduces PVL for 24-27w of gestation.

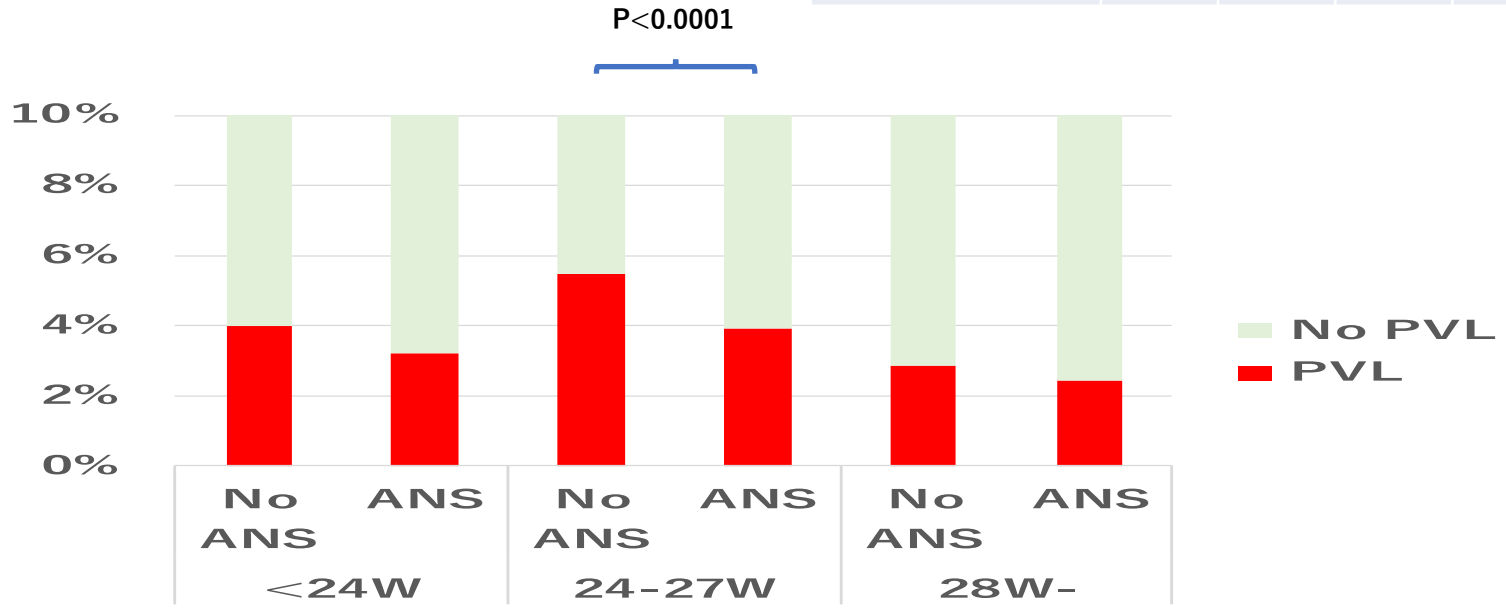
Dependent variable:

PVL	Odds	95%CI	
Antenatal steroid	0.755	0.673	0.848
Gestational weeks	0.882	0.866	0.898

Logistic Regression

PVL	PVL	No PVL	Total		χ2
<24w	80	2300	2380		
ANS	26	824	850	3.10%	NS
No ANS	54	1476	1530	3.50%	
24-27w	569	12142	12711		
ANS	245	6150	6395	3.80%	<0.0001
No ANS	324	5992	6316	5.10%	
28w-	648	24050	24698		
ANS	254	10176	10430	2.40%	NS
No ANS	394	13874	14268	2.80%	

X 2 test



Cerebral Palsy, DQ, Outcomes

Neonatal Research Network of Japan (2003-12)

Number of VLBW infants	a	40,806				100%
Discharged alive from NICU	b	37,450				91.8%
Died in NICU	c	3,356				9.0%
Died after discharge until 3 years	d	187				0.5%
Number of children at 3 years	e=b-d	37,263				100%
Examined for cerebral palsy	f	15,649		CP examined	f/e	42.0%
tested for DQ	g	13,520		DQ tested	g/e	36.3%

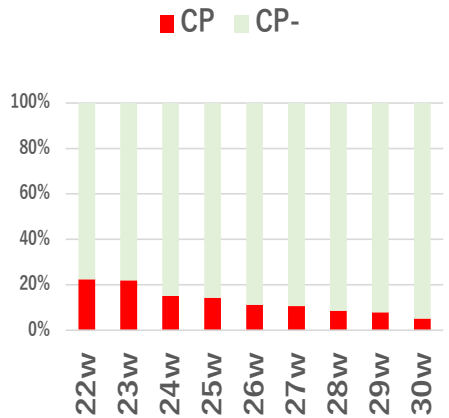
Cognitive functions were assessed using the Kyoto Scale of Psychological Development (KSPD) test. The latest version of the KSPD was standardised in 2001 for Japanese children, and the mean and 1 SD of the developmental quotient (DQ) were 100.6 and 13.4, respectively. A DQ score of KSPD <70, which represents a 70% achievement of standardised performance for the chronological age, was interpreted as significantly delayed according to the protocol by the Japan Neonatal Follow-up Study Group. A DQ score of KSPD <70 is equivalent to a Bayley III cognitive score <85. This test was administered by certified psychologists blinded to perinatal details at each centre; however, they were aware that participants were extremely preterm infants.

Kono Y, *et al*. *BMJ Paediatrics Open* 2018;2:e000211. doi:10.1136/bmjpo-2017-000211

Summary of Cerebral Palsy Rate (3 years)

- CP rate increases inversely to gestation.
- The larger mortality among smaller gestation effect downward trend of CP rate at 3 years

Gestational weeks	22w	23w	24w	25w	26w	27w	28w	29w	30w
CP	30	129	144	172	165	176	159	154	92
Total	134	586	953	1,205	1,477	1,651	1,857	1,955	1,792
CP %	22.4%	22.0%	15.1%	14.3%	11.2%	10.7%	8.6%	7.9%	5.1%



31w	32w	33w	34w	35w	36w	37w	38w	39w	NA	Total
42	30	14	6	12	8	4	2	1	1	1,341
1,345	1,004	697	468	277	159	57	14	4	14	15,649
3.1%	3.0%	2.0%	1.3%	4.3%	5.0%	7.0%	14.3%	25.0%	7.1%	8.6%

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Cerebral Palsy (3 years) -Gestation/ Birthweight Database-

◆ Tables show the number of infants (total, cerebral palsy), and the cerebral palsy rate(%)

CP	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	NA	Total
300g-	2	3	1	4	2	2	1	1	1											17
400g-	13	15	13	8	12	6	1	2												70
500g-	14	62	28	11	6	7	5	3	3											139
600g-	1	42	55	34	23	10	4	2	2	1										174
700g-		7	37	60	24	21	8	5	4											166
800g-			9	40	34	18	13	6	3				1							124
900g-			1	14	43	37	22	9	4	3				1						134
1000g-					16	40	30	9	3	5	1	2	1	1	1					109
1100g-				1	5	22	28	25	8	1	7	4	1		1					103
1200g-						11	23	32	15	5	7	1	1	1	2	4				102
1300g-						2	15	34	22	7	7	7		2	1			1	1	99
1400g-							9	26	27	20	8		2	7	3		2			104
Total	30	129	144	172	165	176	159	154	92	42	30	14	6	12	8	4	2	1	1	1341

all	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	NA	Total
100g																				
200g			2	2																4
300g	6	7	8	15	8	11	1	2	2											60
400g	62	75	53	46	63	42	15	13	4											373
500g	59	287	173	102	98	77	42	24	11	3	1									877
600g	5	191	420	219	126	112	85	43	33	8	4	2								1248
700g	1	23	242	426	253	156	135	84	60	23	17	4	2						1	1427
800g		2	49	305	391	220	170	118	85	40	27	10	3	1			1		2	1424
900g		1	6	76	356	398	242	162	139	106	39	21	9	7						1562
1000g				10	145	348	333	226	165	127	85	44	15	16	1	3				1518
1100g	1			2	29	213	397	316	222	162	144	100	51	19	6	3			1	1666
1200g				2	7	56	256	408	290	243	172	106	91	53	24	10	2		4	1724
1300g						12	133	327	389	264	216	188	115	65	41	7	3	3	3	1766
1400g					1	6	48	231	390	367	298	222	178	113	86	33	8	1	3	1985
Total	134	586	953	1205	1477	1651	1857	1955	1792	1345	1004	697	468	277	159	57	14	4	14	15649

%CP	22w	23w	24w	25w	26w	27w	28w	29w	30w	31w	32w	33w	34w	35w	36w	37w	38w	39w
100g																		
200g			0%	0%														
300g	33%	43%	13%	27%	25%	18%	100%	50%	50%									
400g	21%	20%	25%	17%	19%	14%	7%	15%	0%									
500g	24%	22%	16%	11%	6%	9%	12%	13%	27%	0%	0%							
600g	20%	22%	13%	16%	18%	9%	5%	5%	6%	13%	0%	0%						
700g	0%	30%	15%	14%	9%	13%	6%	6%	7%	0%	0%	0%	0%					
800g		0%	18%	13%	9%	8%	8%	5%	4%	0%	0%	0%	33%	0%			0%	
900g		0%	17%	18%	12%	9%	9%	6%	3%	3%	0%	0%	0%	14%				
1000g				0%	11%	11%	9%	4%	2%	4%	1%	5%	7%	6%	100%	0%		
1100g				50%	17%	10%	7%	8%	4%	1%	5%	4%	2%	0%	17%	0%		
1200g				0%	0%	20%	9%	8%	5%	2%	4%	1%	1%	2%	8%	40%	0%	
1300g						17%	11%	10%	6%	3%	3%	4%	0%	3%	2%	0%	0%	33%
1400g					0%	0%	19%	11%	7%	5%	3%	0%	1%	6%	3%	0%	25%	0%

NEONATAL RESEARCH NETWORK of JAPAN

≦1500g

Cerebral Palsy Rate (3 years)

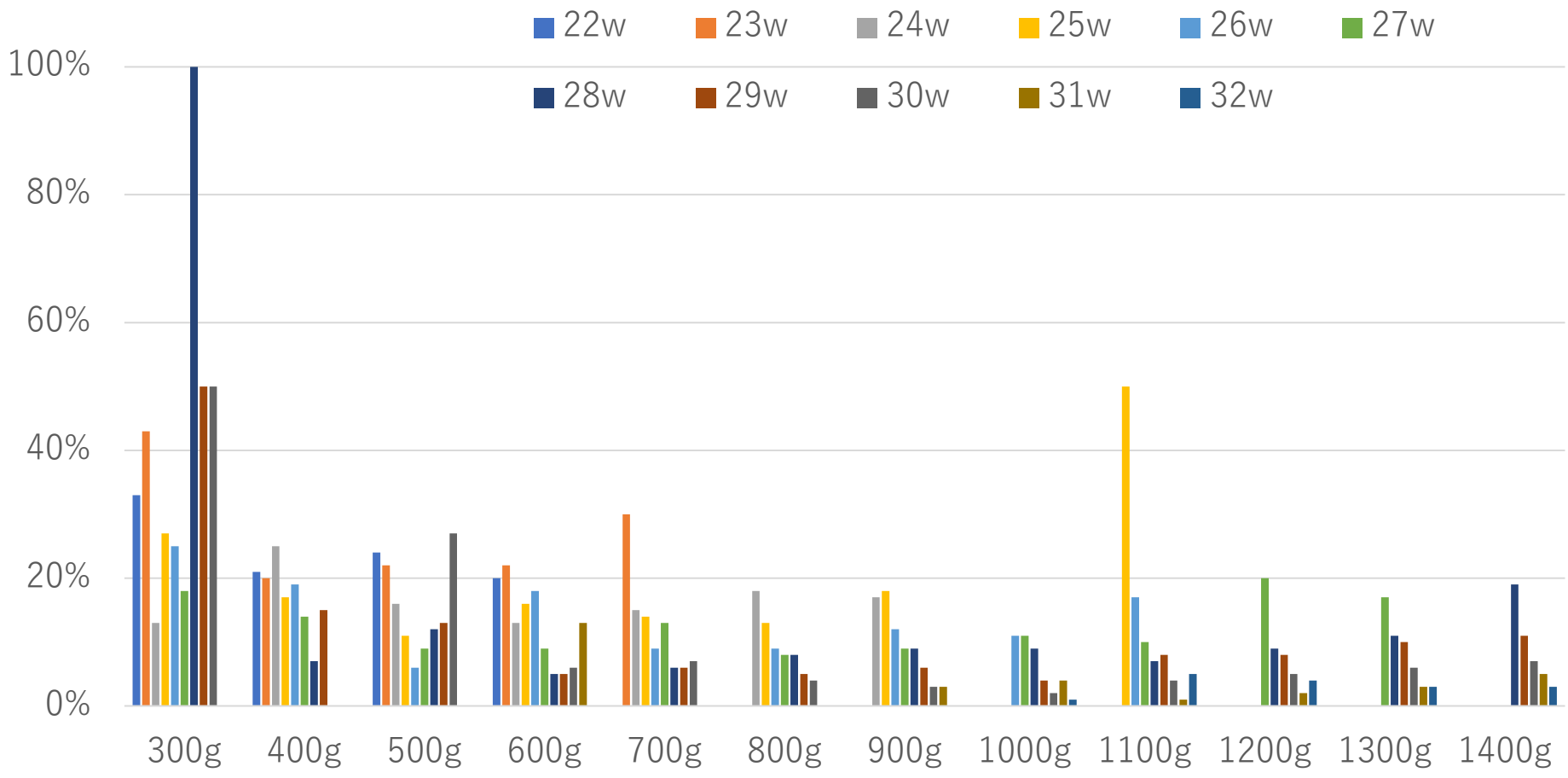
Neonatal Research Network of Japan,
≦1,500g, N=15,649 (2003-12)

Cerebral Palsy Rate (3 years) : 10%≦ 20%≦

%CP	22w	23w	24w	25w	26w	27w	28w	29w	30w	31w	32w	33w	34w	35w	36w	37w	38w	39w
100g																		
200g			0%	0%														
300g	33%	43%	13%	27%	25%	18%	100%	50%	50%									
400g	21%	20%	25%	17%	19%	14%	7%	15%	0%									
500g	24%	22%	16%	11%	6%	9%	12%	13%	27%	0%	0%							
600g	20%	22%	13%	16%	18%	9%	5%	5%	6%	13%	0%	0%						
700g	0%	30%	15%	14%	9%	13%	6%	6%	7%	0%	0%	0%	0%					
800g		0%	18%	13%	9%	8%	8%	5%	4%	0%	0%	0%	33%	0%			0%	
900g		0%	17%	18%	12%	9%	9%	6%	3%	3%	0%	0%	0%	14%				
1000g				0%	11%	11%	9%	4%	2%	4%	1%	5%	7%	6%	100%	0%		
1100g				50%	17%	10%	7%	8%	4%	1%	5%	4%	2%	0%	17%	0%		
1200g				0%	0%	20%	9%	8%	5%	2%	4%	1%	1%	2%	8%	40%	0%	
1300g						17%	11%	10%	6%	3%	3%	4%	0%	3%	2%	0%	0%	33%
1400g					0%	0%	19%	11%	7%	5%	3%	0%	1%	6%	3%	0%	25%	0%

Cerebral Palsy Rate at 3 years

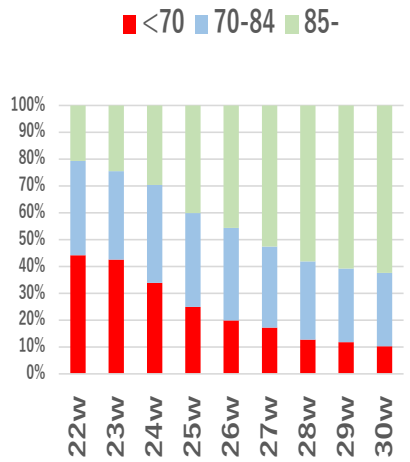
- In a group of 300g, the larger gestations are associated with larger rate of CP.
- For ≧600g, the CP rate is smaller in larger gestation.



Summary of DQ <70, 70-84, 85-

- DQ <70 rate increases inversely to gestation.
- The larger mortality among smaller gestation effect downward trend of DQ <70 rate at 3 years

	22w	23w	24w	25w	26w	27w	28w	29w	30w
All DQ	111	498	840	1,067	1,313	1,440	1,627	1,700	1,556
<70	49	212	285	266	261	248	208	200	160
70-84	39	164	306	373	453	434	473	466	425
85-	23	122	249	428	599	758	946	1,034	971
% <70	44.1%	42.6%	33.9%	24.9%	19.9%	17.2%	12.8%	11.8%	10.3%
%70-84	35.1%	32.9%	36.4%	35.0%	34.5%	30.1%	29.1%	27.4%	27.3%
% 85-	20.7%	24.5%	29.6%	40.1%	45.6%	52.6%	58.1%	60.8%	62.4%



	31w	32w	33w	34w	35w	36w	37w	38w	39w	NA	Total
All DQ	1,150	844	576	395	209	127	40	12	3	12	13,520
<70	117	88	49	44	30	13	7	2	1	4	2,244
70-84	320	212	140	87	35	37	9	3		5	3,981
85-	713	544	387	264	144	77	24	7	2	3	7,295
% <70	10.2%	10.4%	8.5%	11.1%	14.4%	10.2%	17.5%	16.7%	33.3%	33.3%	16.6%
%70-84	27.8%	25.1%	24.3%	22.0%	16.7%	29.1%	22.5%	25.0%	0.0%	41.7%	29.4%
% 85-	62.0%	64.5%	67.2%	66.8%	68.9%	60.6%	60.0%	58.3%	66.7%	25.0%	54.0%

NEONATAL RESEARCH NETWORK of JAPAN

DQ<70 (3 years) -Database-

Gestation/ Birthweight

(All subjects DQ examined, DQ<70, DQ 70-84, DQ 85-)

All DQ	22w	23w	24w	25w	26w	27w	28w	29w	30w	31w	32w	33w	34w	35w	36w	37w	38w	39w	NA	Total
200g-			2	1																3
300g-	4	7	10	12	7	6		2												48
400g-	51	65	48	42	54	32	11	8	4		1									316
500g-	50	240	151	89	89	69	33	20	8	3	1									753
600g-	4	165	371	200	112	105	75	31	29	7	4	2								1105
700g-	1	19	213	379	224	139	126	79	52	22	17	3	2						1	1277
800g-		2	42	261	356	193	147	103	77	35	20	9	3	1					2	1251
900g-			3	70	314	350	219	141	117	97	33	19	8	7						1378
1000g-				9	125	299	279	198	141	102	75	32	14	12	1	2				1289
1100g-				3	26	183	349	279	192	131	118	85	45	18	4	2		1		1437
1200g-				1	5	49	230	362	259	213	152	79	80	40	18	5	2		4	1499
1300g-						10	122	272	343	232	176	153	94	48	36	4	3	2	2	1497
1400g-					1	5	36	204	332	306	246	194	147	83	68	26	7		3	1658
Total	111	498	840	1067	1313	1440	1627	1700	1556	1150	844	576	395	209	127	40	12	3	12	13520
%	0.8%	3.7%	6.2%	7.9%	9.7%	10.7%	12.0%	12.6%	11.5%	8.5%	6.2%	4.3%	2.9%	1.5%	0.9%	0.3%	0.1%	0%	0.1%	100.0%

<70	22w	23w	24w	25w	26w	27w	28w	29w	30w	31w	32w	33w	34w	35w	36w	37w	38w	39w	NA	Total
200g-			1	1																2
300g-	2	4	6	6	5	3		1												27
400g-	26	30	19	17	15	12	4	2	4		1									130
500g-	21	99	51	23	24	20	10	6	2											256
600g-		71	126	53	22	25	8	7	5	3	3	1								324
700g-		8	66	93	44	29	21	16	12	2	3								1	295
800g-			15	50	65	22	20	11	13	7	6	3	2							214
900g-			1	19	59	54	21	18	15	16	6	2	1	2						214
1000g-				2	26	41	41	20	11	11	8	3	2	2	1					168
1100g-				2	1	25	40	35	20	9	12	12	6	2	1	1		1		167
1200g-						12	23	41	22	17	14	4	11	5	1	1			3	154
1300g-						4	15	23	27	29	16	9	7	5	3	1				139
1400g-						1	5	20	29	23	19	15	14	14	7	4	2			153
Total	49	212	285	266	261	248	208	200	160	117	88	49	44	30	13	7	2	1	4	2244

70-84	22w	23w	24w	25w	26w	27w	28w	29w	30w	31w	32w	33w	34w	35w	36w	37w	38w	NA	Total
200g-			1																1
300g-		1	3	3	2	3		1											13
400g-	15	21	17	12	27	9	5	4											110
500g-	19	76	56	37	27	26	10	6	4	1	1								263
600g-	3	60	135	59	41	28	35	9	11	2	1								384
700g-	1	5	80	142	77	38	35	22	12	10	7	2	1						432
800g-		1	14	95	116	60	42	31	26	9	5	2	1	1				2	405
900g-				22	105	106	61	46	38	37	7	7	3	2					434
1000g-				2	45	90	79	56	47	26	28	8	4	1					386
1100g-					9	60	99	77	50	41	25	24	11	2	1	1			401
1200g-				1	3	11	68	100	63	59	37	18	15	7	6	1			389
1300g-						2	30	71	94	53	45	24	24	10	11	1	1	2	368
1400g-						1	1	9	43	78	80	56	55	27	12	19	6	2	1	390
Total	39	164	306	373	453	434	473	466	425	320	212	140	87	35	37	9	3	5	3981

85<	22w	23w	24w	25w	26w	27w	28w	29w	30w	31w	32w	33w	34w	35w	36w	37w	38w	39w	NA	Total
300g-	2	2	1	3																8
400g-	10	14	12	13	12	11	2	2												76
500g-	10	65	44	29	38	23	13	8	2	2										234
600g-	1	34	110	88	49	52	32	15	13	2		1								397
700g-		6	67	144	103	72	70	41	28	10	7	1	1							550
800g-		1	13	116	175	111	85	61	38	19	9	4								632
900g-			2	29	150	190	137	77	64	44	20	10	4	3						730
1000g-				5	54	168	159	122	83	65	39	21	8	9		2				735
1100g-				1	16	98	210	167	122	81	81	49	28	14	2					869
1200g-					2	26	139	221	174	137	101	57	54	28	11	3	2		1	956
1300g-						4	77	178	222	150	115	120	63	33	22	2	2	2		990
1400g-						3	22	141	225	203	171	124	106	57	42	16	3		2	1115
Total	23	122	249	428	599	758	946	1034	971	713	544	387	264	144	77	24	7	2	3	7295

NEONATAL RESEARCH NETWORK of JAPAN

Gestation/ Birthweight
DQ<70 (3 years)

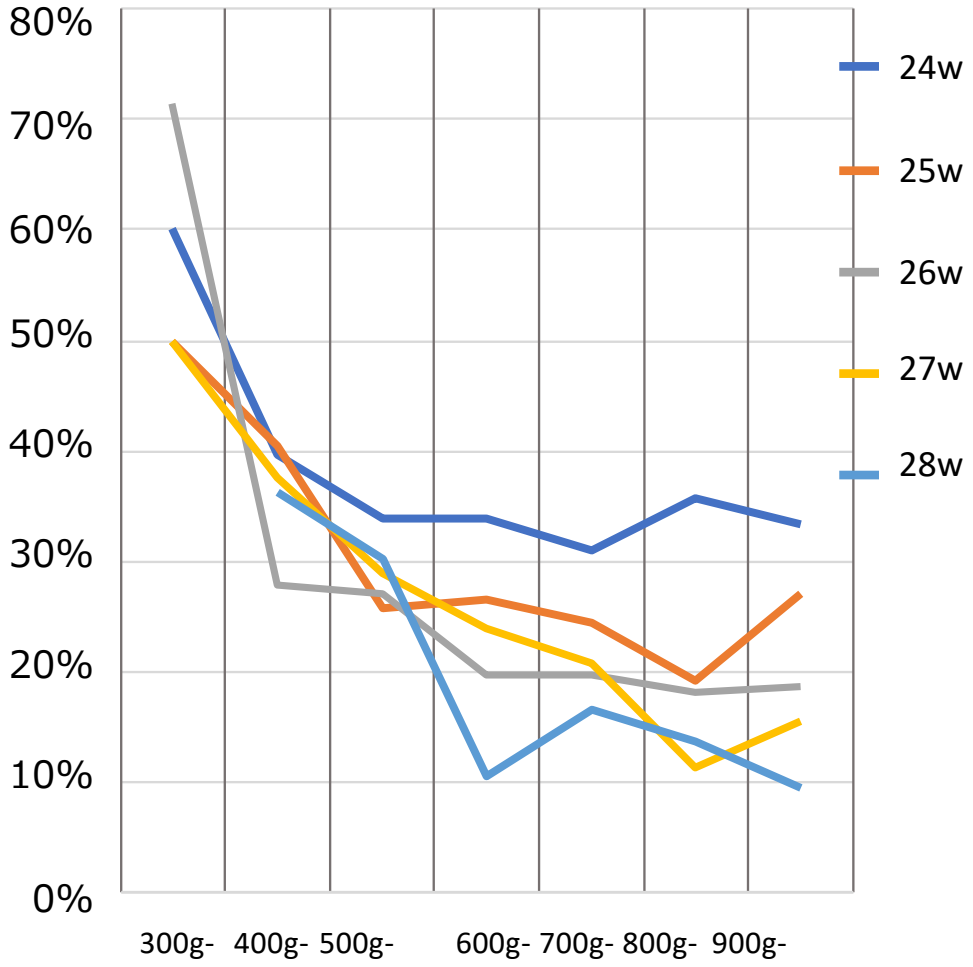
Neonatal Research Network of Japan,
≦1,500g, N=13,520 (2003-12)

DQ<70 (3 years): 20%< 30%<

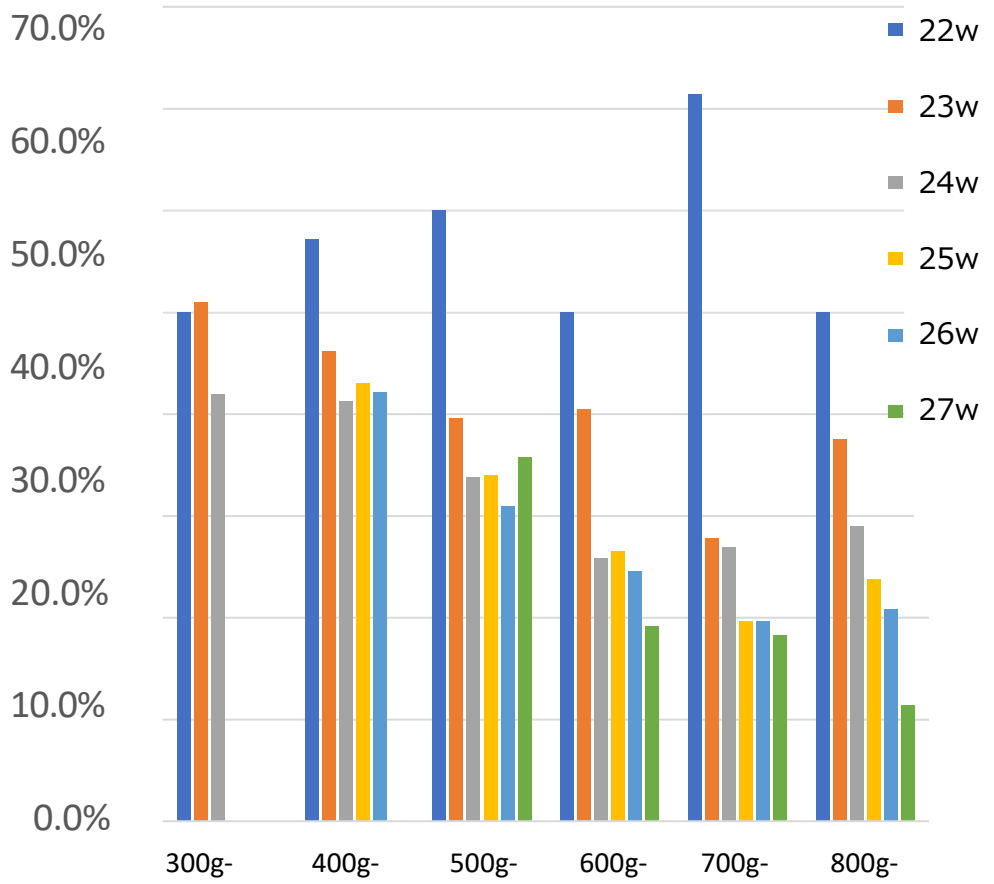
<70 %	22w	23w	24w	25w	26w	27w	28w	29w	30w	31w	32w	33w	34w	35w	36w	37w	38w	39w
200g-			50.0%	100.0%														
300g-	50.0%	57.1%	60.0%	50.0%	71.4%	50.0%		50.0%										
400g-	51.0%	46.2%	39.6%	40.5%	27.8%	37.5%	36.4%	25.0%	100.0%		100.0%							
500g-	42.0%	41.3%	33.8%	25.8%	27.0%	29.0%	30.3%	30.0%	25.0%	0.0%	0.0%							
600g-	0.0%	43.0%	34.0%	26.5%	19.6%	23.8%	10.7%	22.6%	17.2%	42.9%	75.0%	50.0%						
700g-	0.0%	42.1%	31.0%	24.5%	19.6%	20.9%	16.7%	20.3%	23.1%	9.1%	17.6%	0.0%	0.0%					
800g-		0.0%	35.7%	19.2%	18.3%	11.4%	13.6%	10.7%	16.9%	20.0%	30.0%	33.3%	66.7%	0.0%				
900g-			33.3%	27.1%	18.8%	15.4%	9.6%	12.8%	12.8%	16.5%	18.2%	10.5%	12.5%	28.6%				
1000g-				22.2%	20.8%	13.7%	14.7%	10.1%	7.8%	10.8%	10.7%	9.4%	14.3%	16.7%	100.0%	0.0%		
1100g-				66.7%	3.8%	13.7%	11.5%	12.5%	10.4%	6.9%	10.2%	14.1%	13.3%	11.1%	25.0%	50.0%		100.0%
1200g-				0.0%	0.0%	24.5%	10.0%	11.3%	8.5%	8.0%	9.2%	5.1%	13.8%	12.5%	5.6%	20.0%	0.0%	
1300g-						40.0%	12.3%	8.5%	7.9%	12.5%	9.1%	5.9%	7.4%	10.4%	8.3%	25.0%	0.0%	0.0%
1400g-					0%	20%	14%	10%	9%	8%	8%	8%	10%	17%	10%	15%	29%	

NEONATAL RESEARCH NETWORK of JAPAN

Gestation/ Birthweight
DQ<70 (3 years)



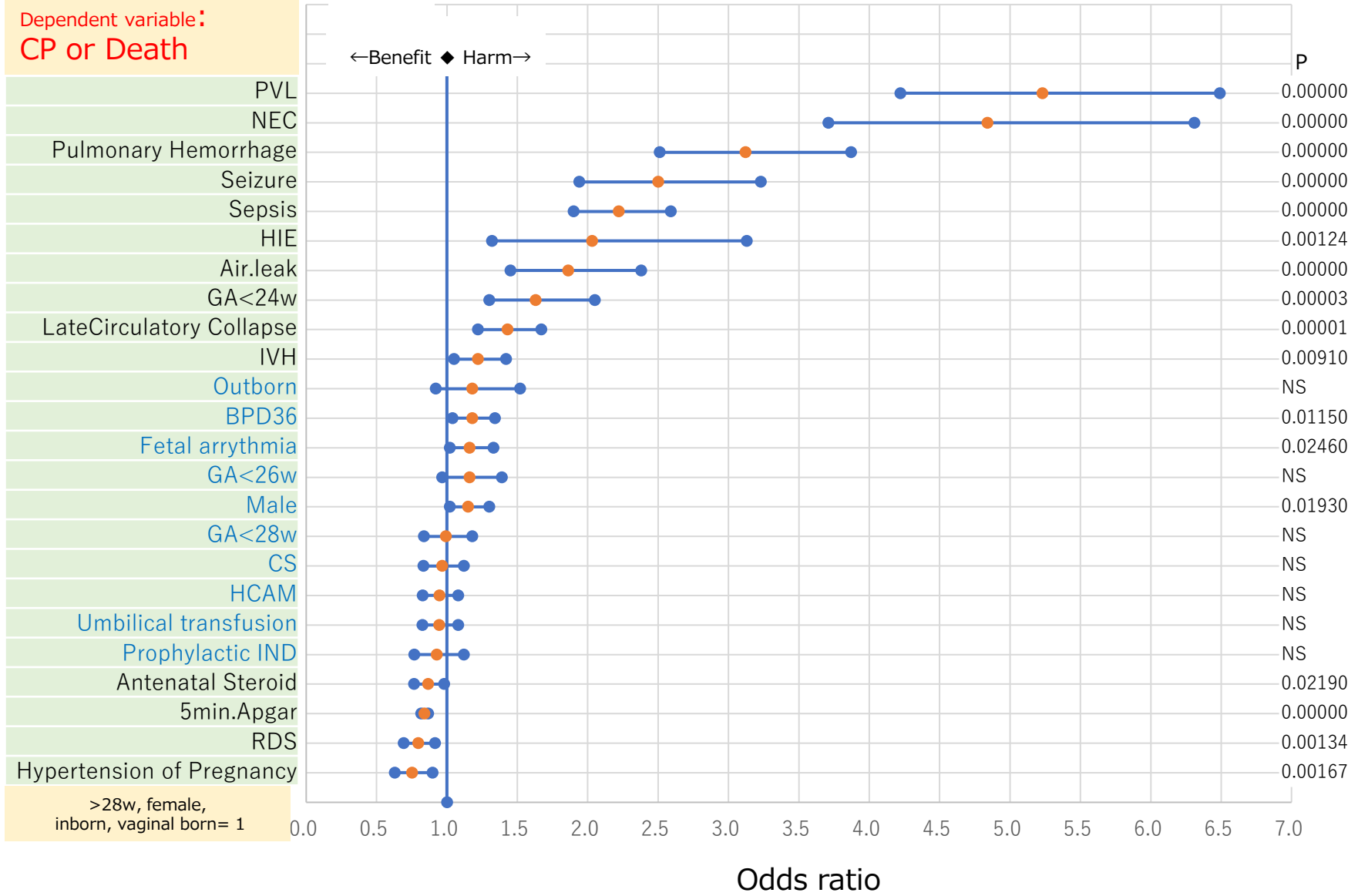
◆ The bars indicate the DQ<70 rates for each b-wt/gestation groups



「CP（3 years）or death」and perinatal factors

- The odds ratio of perinatal factors for the composite outcome of CP or death.
- PVL and NEC are the most significant factors for CP or death at 3 years.

Dependent variable:
CP or Death

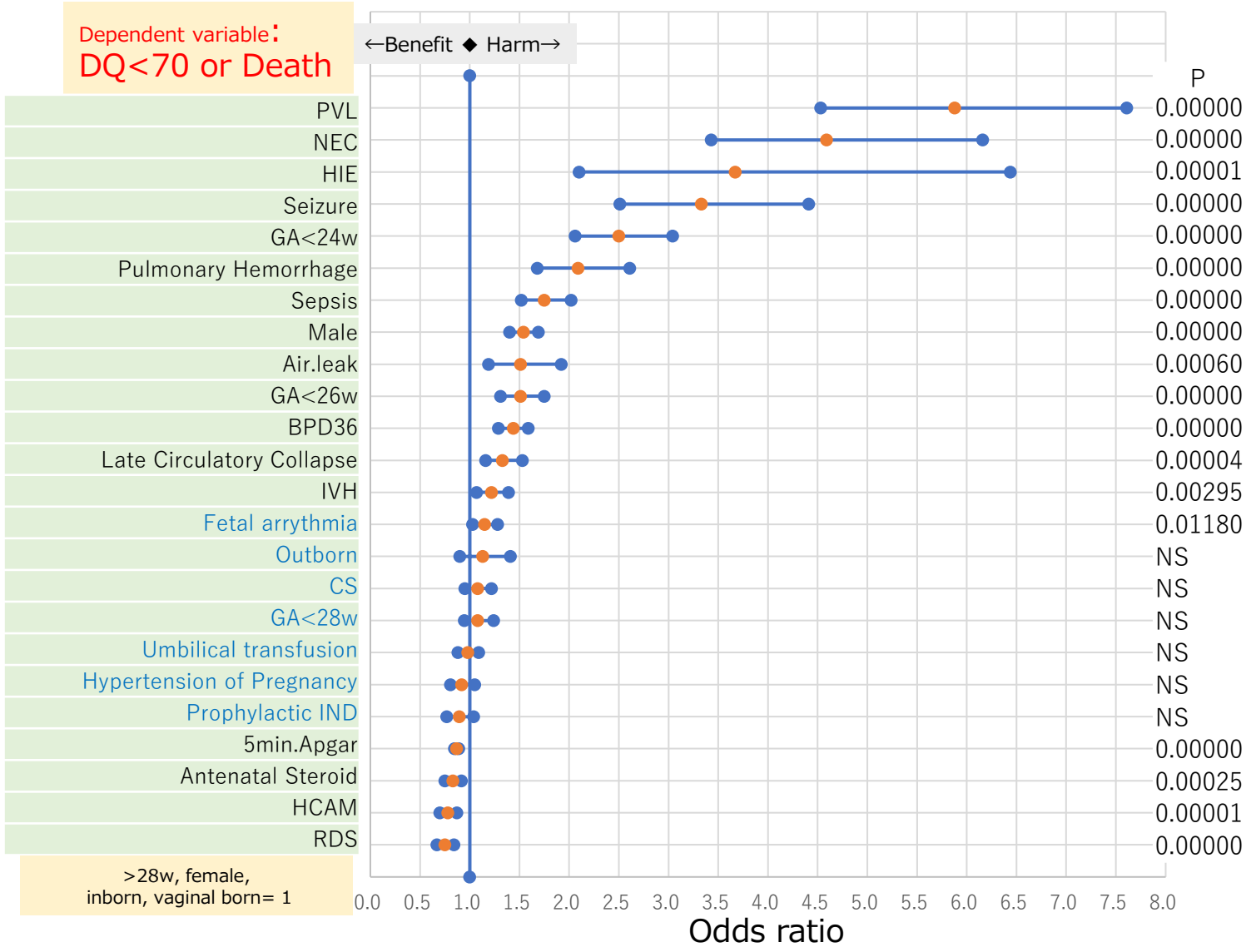


>28w, female,
inborn, vaginal born= 1

- Multivariate analysis using logistic regression for composite outcome of 「CP（3 years）or death」of VLBW were performed to calculate odds ratio of perinatal factors. All the factors included in the model are presented in the figure.

「DQ<70（3 years）or death」and perinatal factors

- The odds ratio of perinatal factors for the composite outcome of DQ<70（3 years）or death.
- NEC and PVL are the most significant factors for CP or death at 3 years.



Dataset928

- Multivariate analysis using logistic regression for composite outcome of「DQ<70（3 years）or death」of VLBW were performed to calculate odds ratio of perinatal factors. All the factors included in the model are presented in the figure.

NEONATAL RESEARCH NETWORK of JAPAN

≦1500g

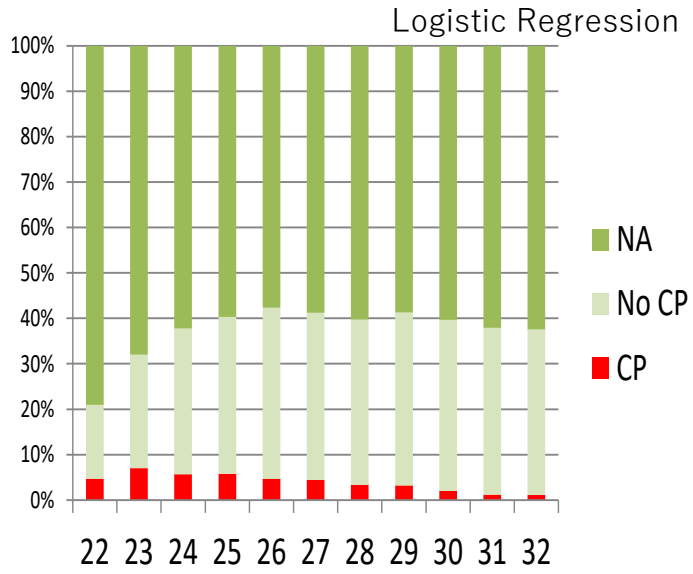
Cerebral palsy and gestational weeks

- Cerebral palsy, one of the major targets in neonatal medicine, decreases as gestations increase.
- The larger mortality among smaller gestation effect downward trend of CP rate at 3 years

All infants ≦1500g

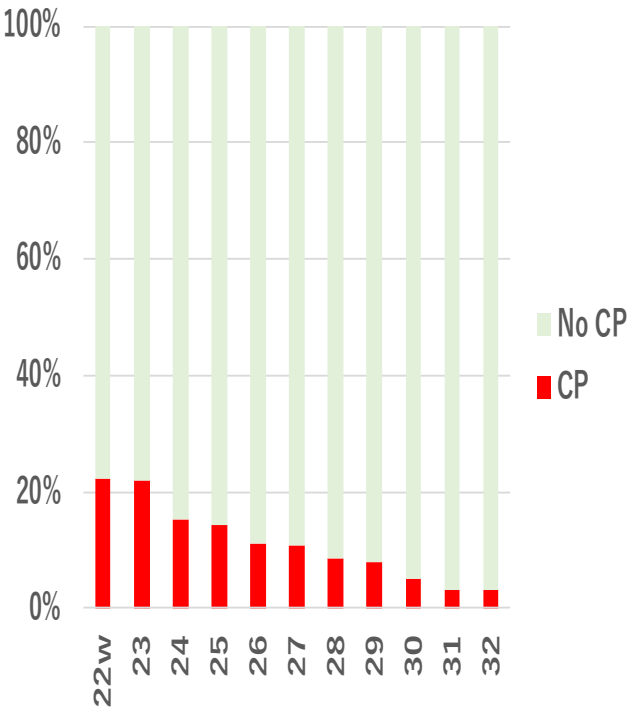
N; CP 1,341, No CP 14,308, NA 25,157

CP	odds	95%CI
Gestation	0.814	0.798 - 0.83



VLBW with examination for CP

GA	CP N
22w	30
23	129
24	144
25	172
26	165
27	176
28	159
29	154
30	92
31	42
32	30



NEONATAL RESEARCH NETWORK of JAPAN

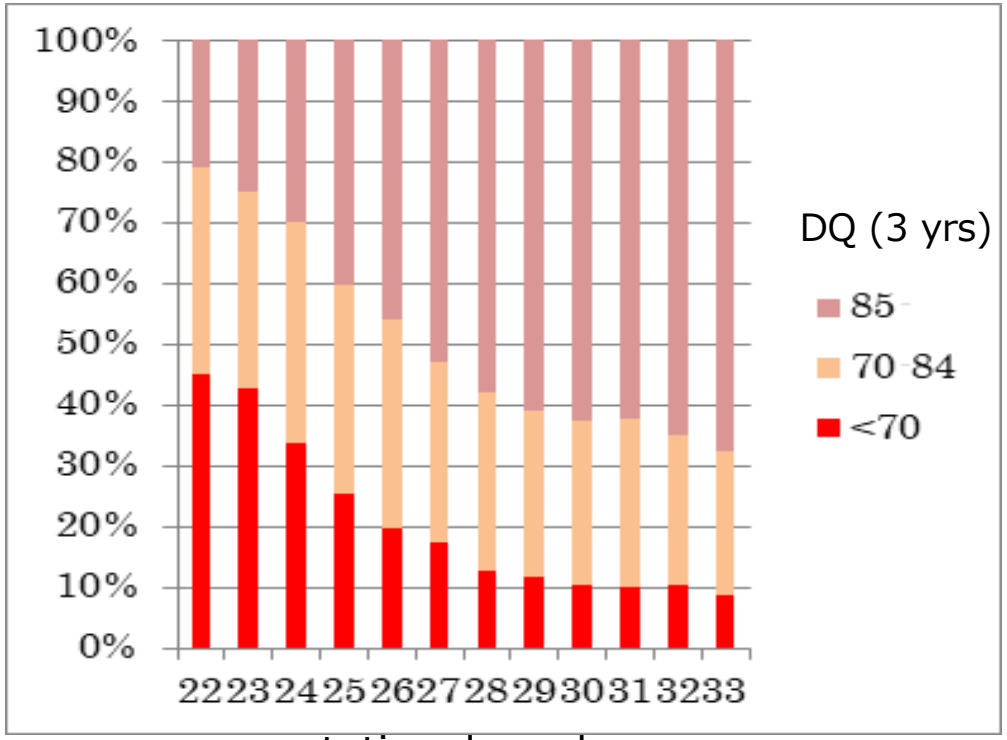
≦1500g

DQ at 3 years and gestational weeks

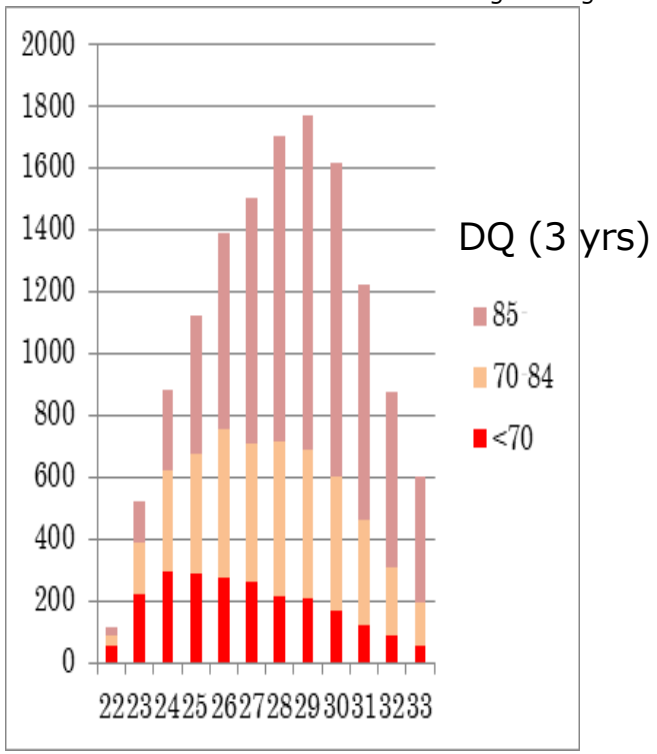
◆ The proportion of children DQ<70 starts to increase below 28 weeks.

Dependent variable	DQ<70			
≧28w: 1	odds	95%CI		P
24-27w	2.35	2.13	2.58	<0.0001
<24w	5.97	5.02	7.11	<0.0001

logistic regression



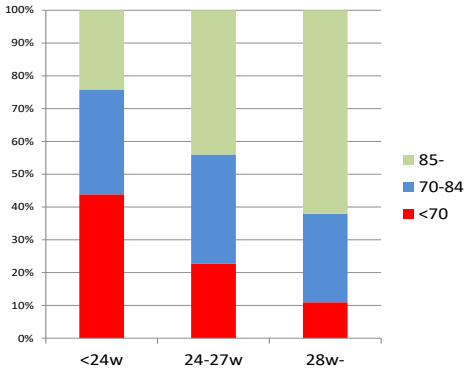
gestational weeks



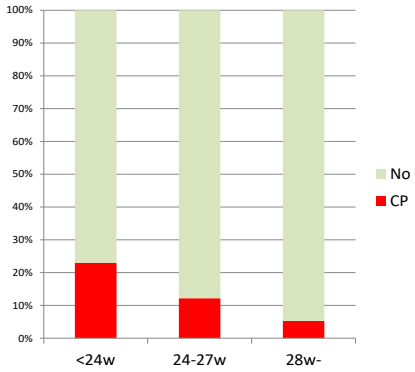
Outcome at 3 years for<24w, 24-27w, 28w-groups

◆ The handicap rate increases as the gestation decreases.

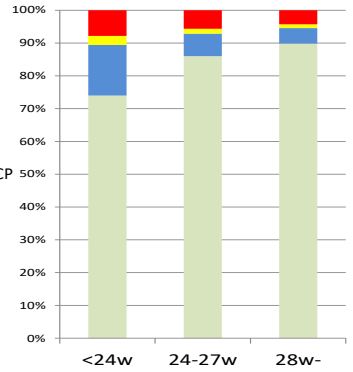
DQ



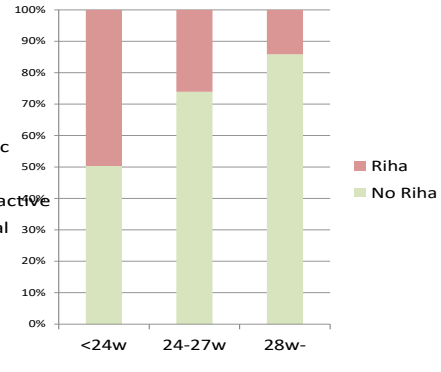
CP



Behavior

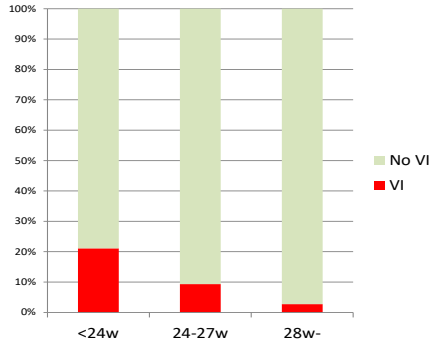


Rehabilitation

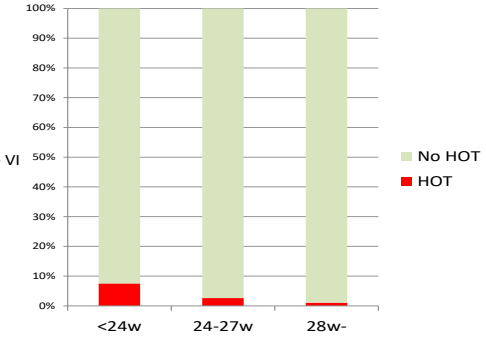


◆ The handicaps of preterm are in various directions.

Visual Impairment



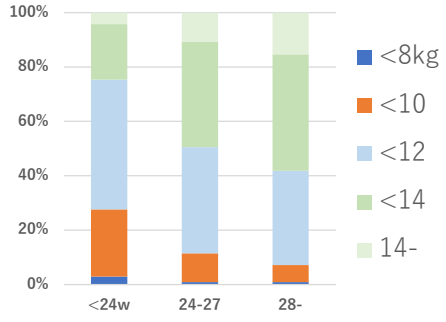
HOT

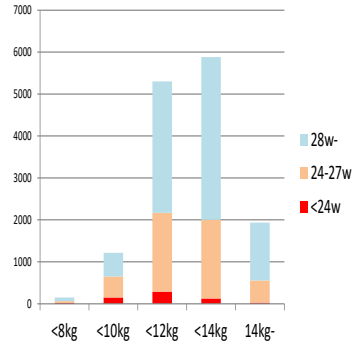


◆ In 30% of <24weeks, 3 year body weight is less than 10kg

Weight(kg) at 3 yrs

Dataset928





Annual trend of CP, Gestation, and PVL

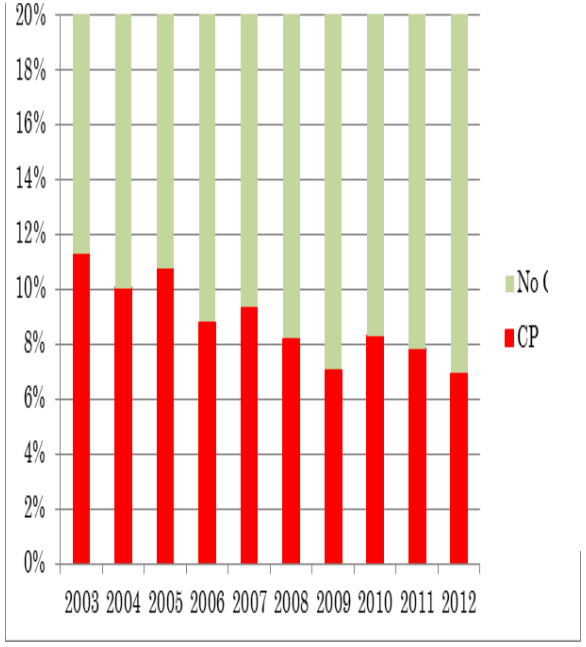
◆ Cerebral palsy decreases 0.4% every year. PVL also decreased 1% in 10 years, while no change in gestation

CP

Dependent variable:

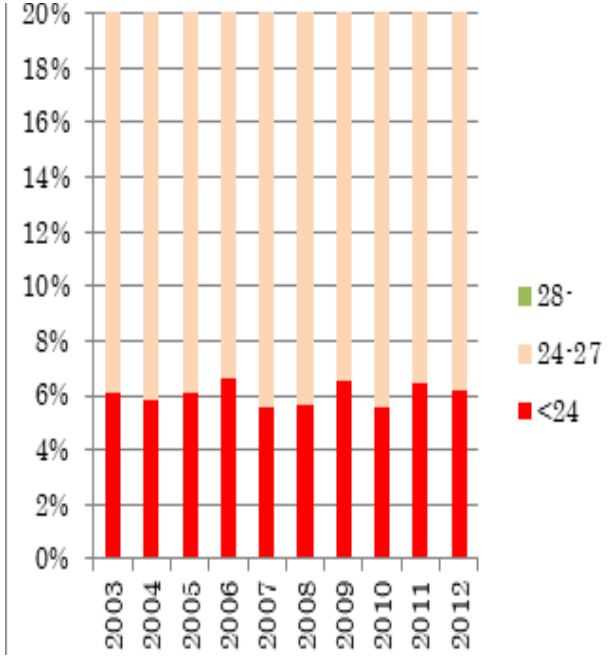
CP	odds	95%CI
Yr	0.948	0.929 - 0.967

Adjusted for gestation



Gestation(w)

◆ The ratio of <24w remains the same for 10years

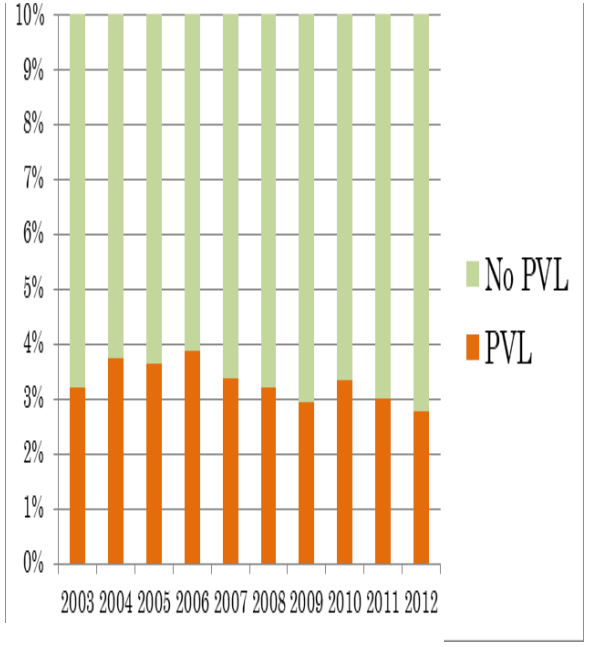


PVL

Dependent variable:

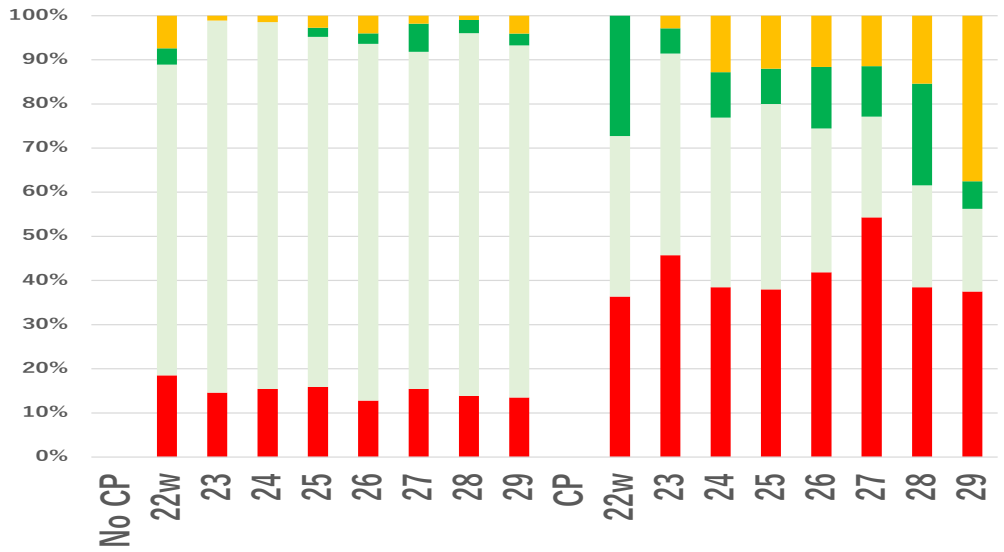
PVL	odds	95%CI
Yr	0.971	0.952 - 0.99

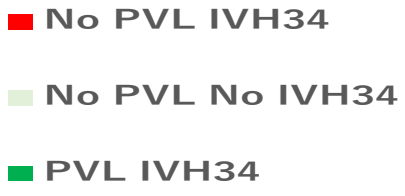
Adjusted for gestation

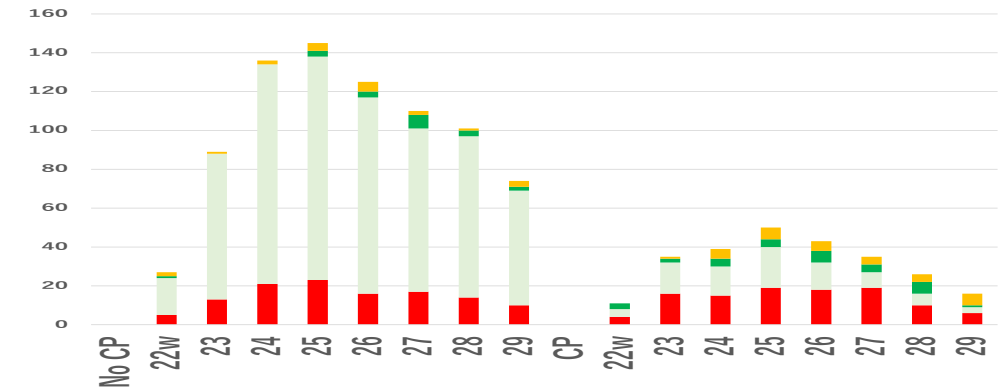


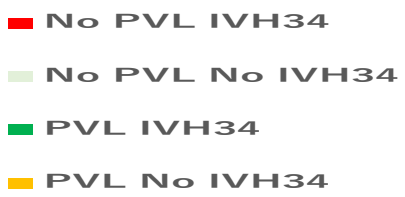
CP in relation with PVL, IVH3,4 and Gestational weeks

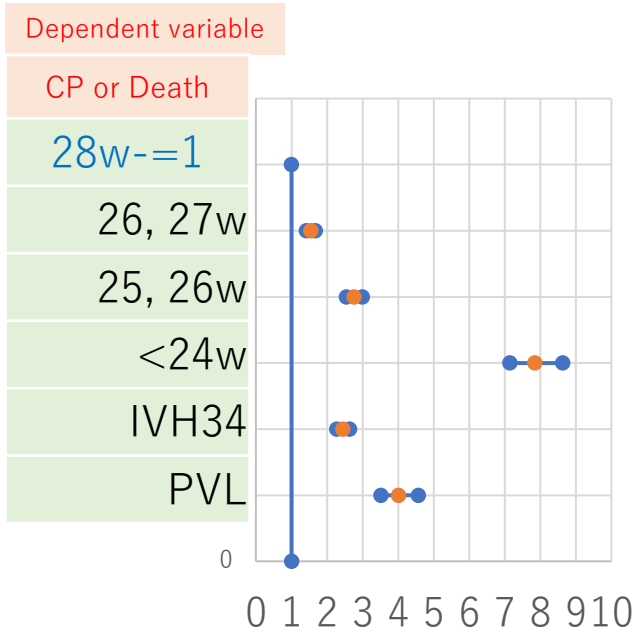
- The odds of PVL is 4.0 for CP compared with 2.4 of IVH3,4 by the logistic regression analysis.
- There is a sharp rise of PVL in 28 and 29 weeks of gestation.







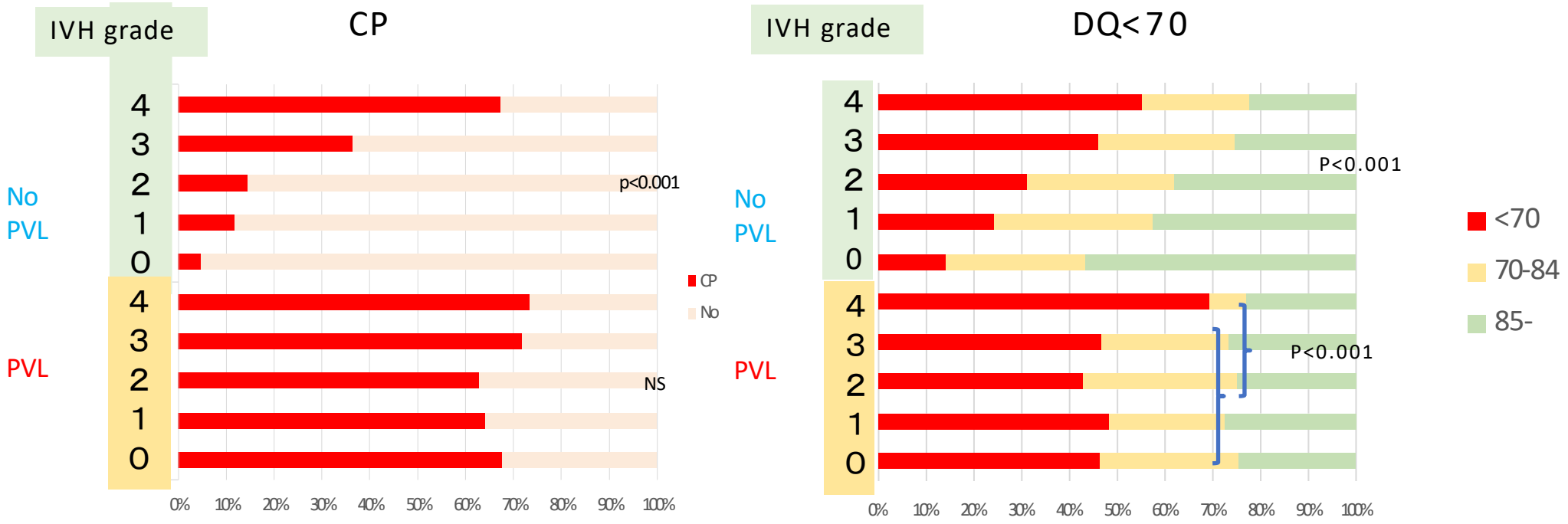




IVH grade, PVL and outcome at 3 years

Intraventricular Hemorrhage, Periventricular leukomalacia

- In No PVL group CP and DQ<70 increase correlating the IVH grade.
- PVL is a powerful determinant of CP and DQ<70.
- In PVL group IVH grade shows no correlation with CP, and only IVH 4 – IVH 3,2,1,0 correlate with DQ<70.



Fetal growth and DQ at 3 yrs (<28 weeks)

- In this page, all analyses were made for infants who were born <28 weeks.
- ◆ DQ of SFD children at three years are significantly small compared to AFD and LFD.

DQ

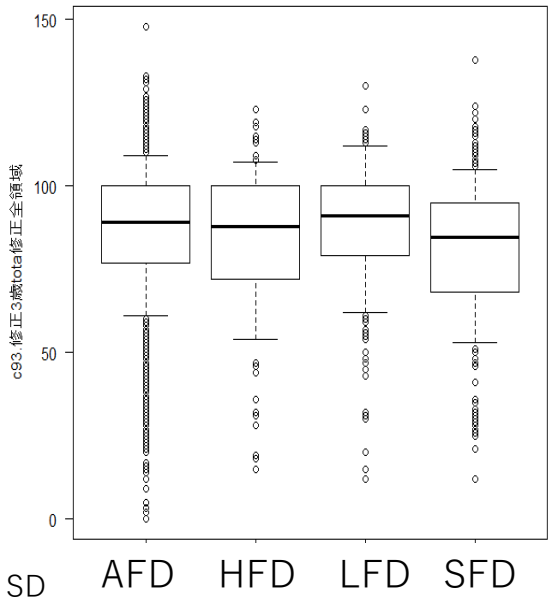
	mean	sd
AFD	86.5	20.6
HFD	83.1	22.3
LFD	87.2	20.1
SFD	81.0	21.0

summary.anova

P

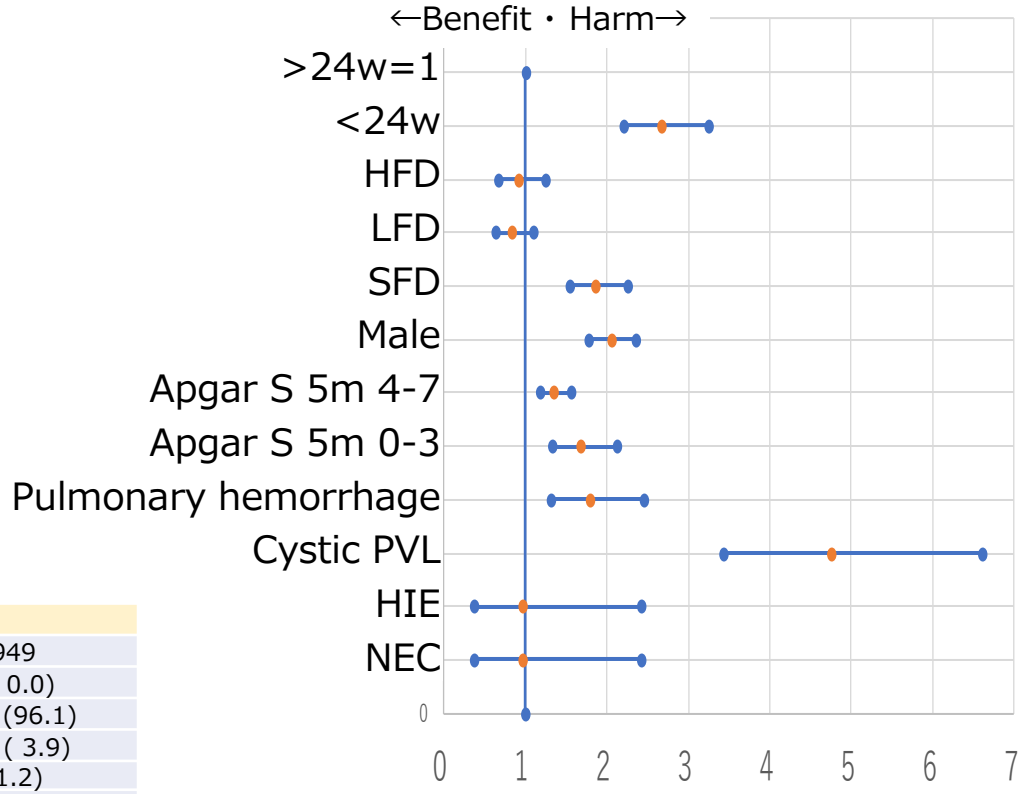
	AFD	HFD	LFD
HFD	0.42	-	-
LFD	1.00	0.46	-
SFD	<0.001	1.00	<0.01

Pairwise comparisons using t tests with pooled SD



DQ<70 at 3 yrs

Logistic regression, adjusted for gestation



-Neonatal-		AFD	HFD	LFD	SFD
n		11321	846	1251	1949
Gestation (%)	28w-	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	24-27w	8525 (84.1)	539 (73.4)	972 (93.2)	1693 (96.1)
	<24w	1616 (15.9)	195 (26.6)	71 (6.8)	68 (3.9)
Gestation		25.1 (1.5)	24.7 (1.6)	25.5 (1.3)	25.9 (1.2)
Birth weight		796.1 (182.8)	945.5 (236.4)	625.9 (133.4)	556.7 (138.9)

Mean(sd)

Days of feeding at 100ml/kg/d and DQ(3 yrs)

Dataset928

◆ Days of feeding reaching at 100 ml/kg/d correlate with DQ(3 yrs)<70.

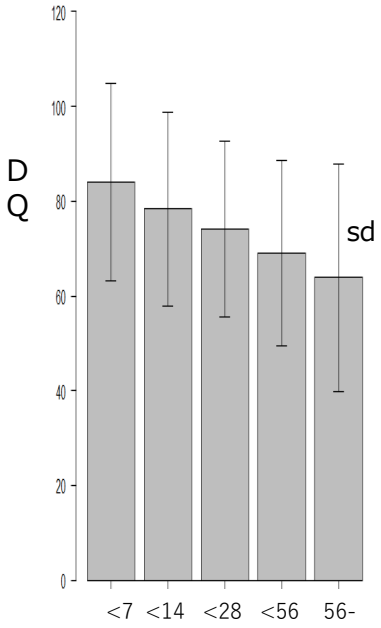
N of cases

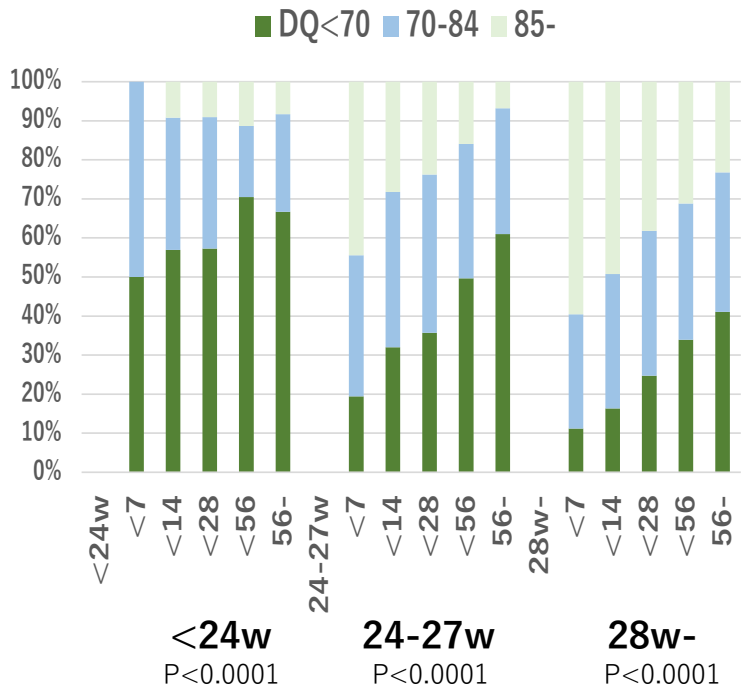
Days of feeding at 100ml/kg/d	DQ<70	70-84	85-
<7 days	131	324	896
<14	756	1646	3226
<28	676	1035	1536
<56	220	223	271
56-	60	52	51

Mean of DQ

Days of feeding at 100ml/kg/d	DQ mean	sd
<7日	84.1	20.9
<14	78.4	20.4
<28	74.1	18.5
<56	69.0	19.5
56-	63.8	24.1

P<0.0001

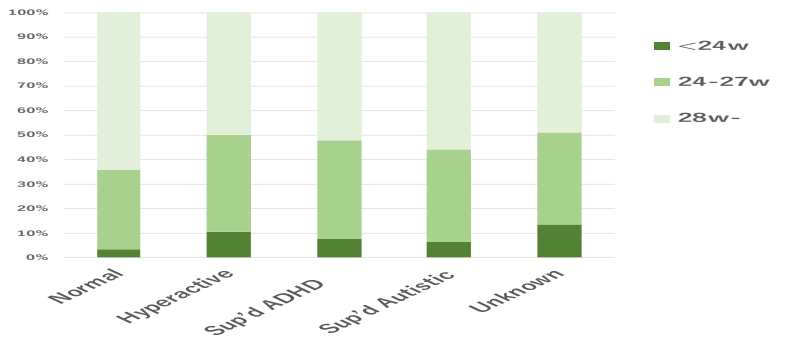


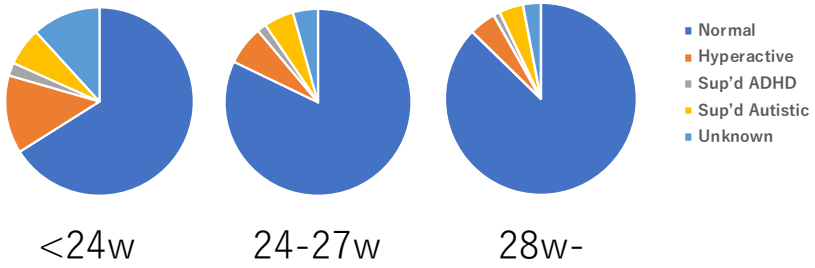


Behavior at 3 years and perinatal factors

◆ Behaviors at 3 years are significantly related to extreme preterm, PVL, HIE, gender, NEC, SFD, & IVH.

	Normal	Hyper active	Suspected ADHD	Suspected Autistic	Un kno wn	NA	Total
<24w	354	72	12	35	63	1836	2372
24-27w	3277	269	64	206	173	8411	12400
28w-	6528	338	83	304	225	16878	24356
Total	10159	679	159	545	461	27125	39128

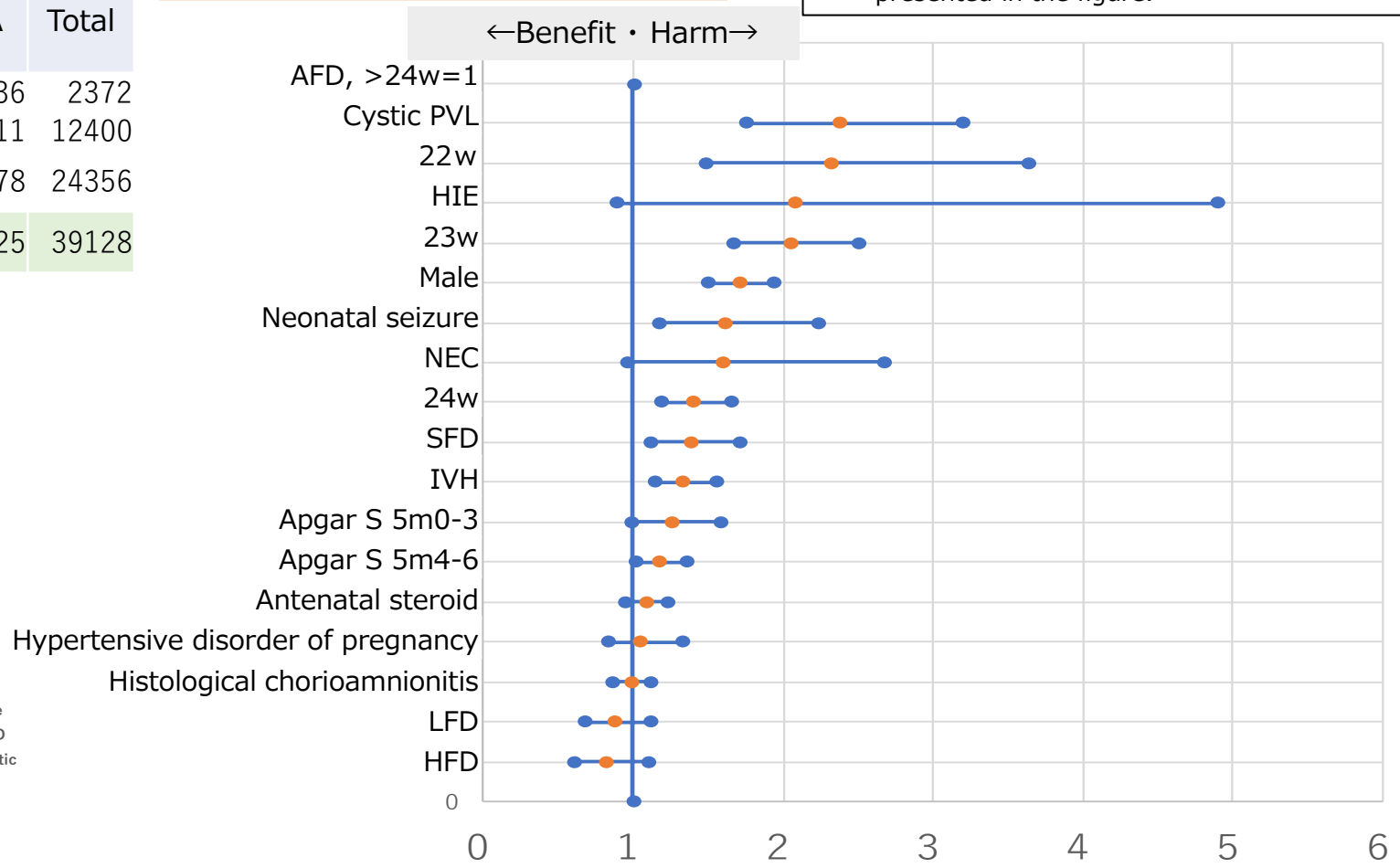




Dependent variable:

Abnormal child behavior (3 yrs)

□ All the factors included in the model are presented in the figure.

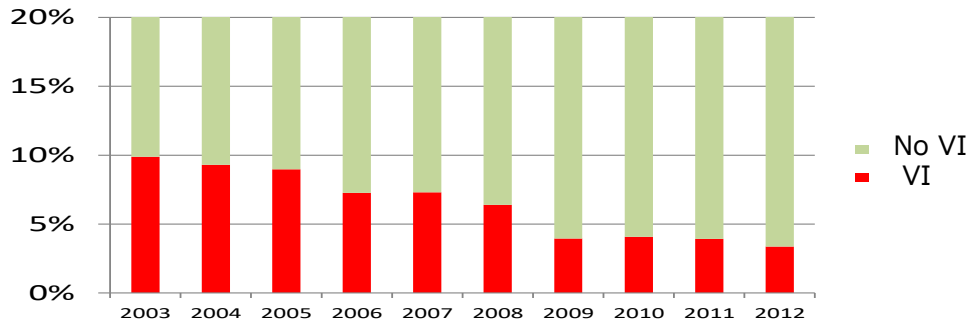


□ infants who were born <28 weeks.

Annual trend of Visual Impairment（3 yrs)

◆ Visual Impairment（3 yrs) decreased rapidly scince 2008.

Visual Impairment（3 yrs)

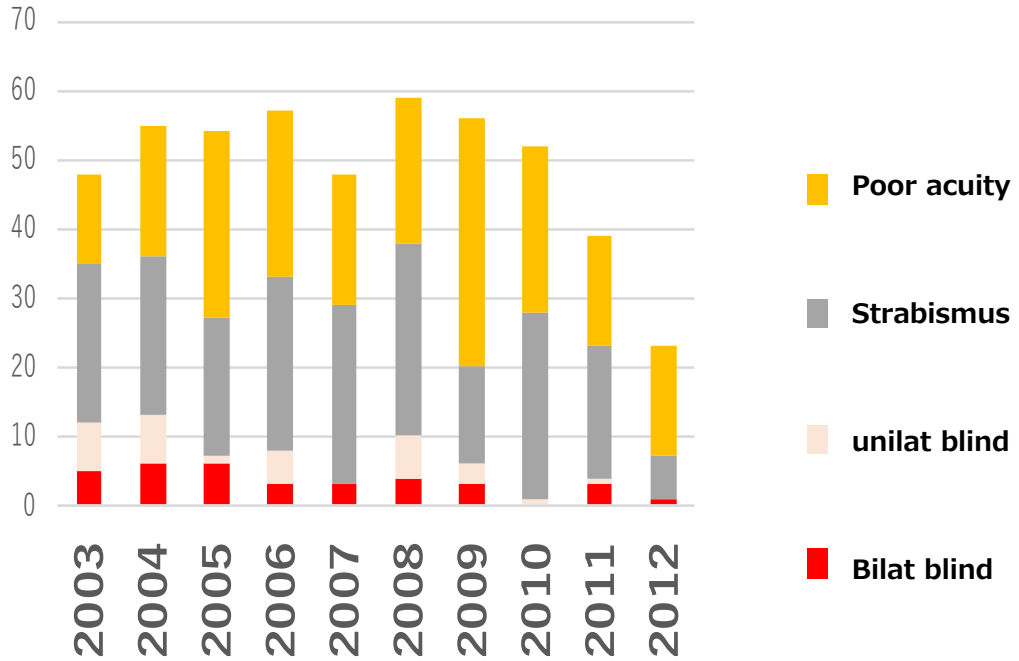


	none	Bil blind	Unil blind	Poor acuity	Strabis mus	total
2003	670	5	7	23	13	718
2004	903	6	7	23	19	958
2005	994	6	1	20	27	1048
2006	1092	3	5	25	24	1149
2007	1078	3		26	19	1126
2008	1089	4	6	28	21	1148
2009	1233	3	3	14	36	1289
2010	1260		1	27	24	1312
2011	1144	3	1	19	16	1183
2012	588	1		6	16	611
total	10051	34	31	211	215	10542

Dependent variable:

VI	odds	95%CI
years	0.870	0. 849 - 0.891

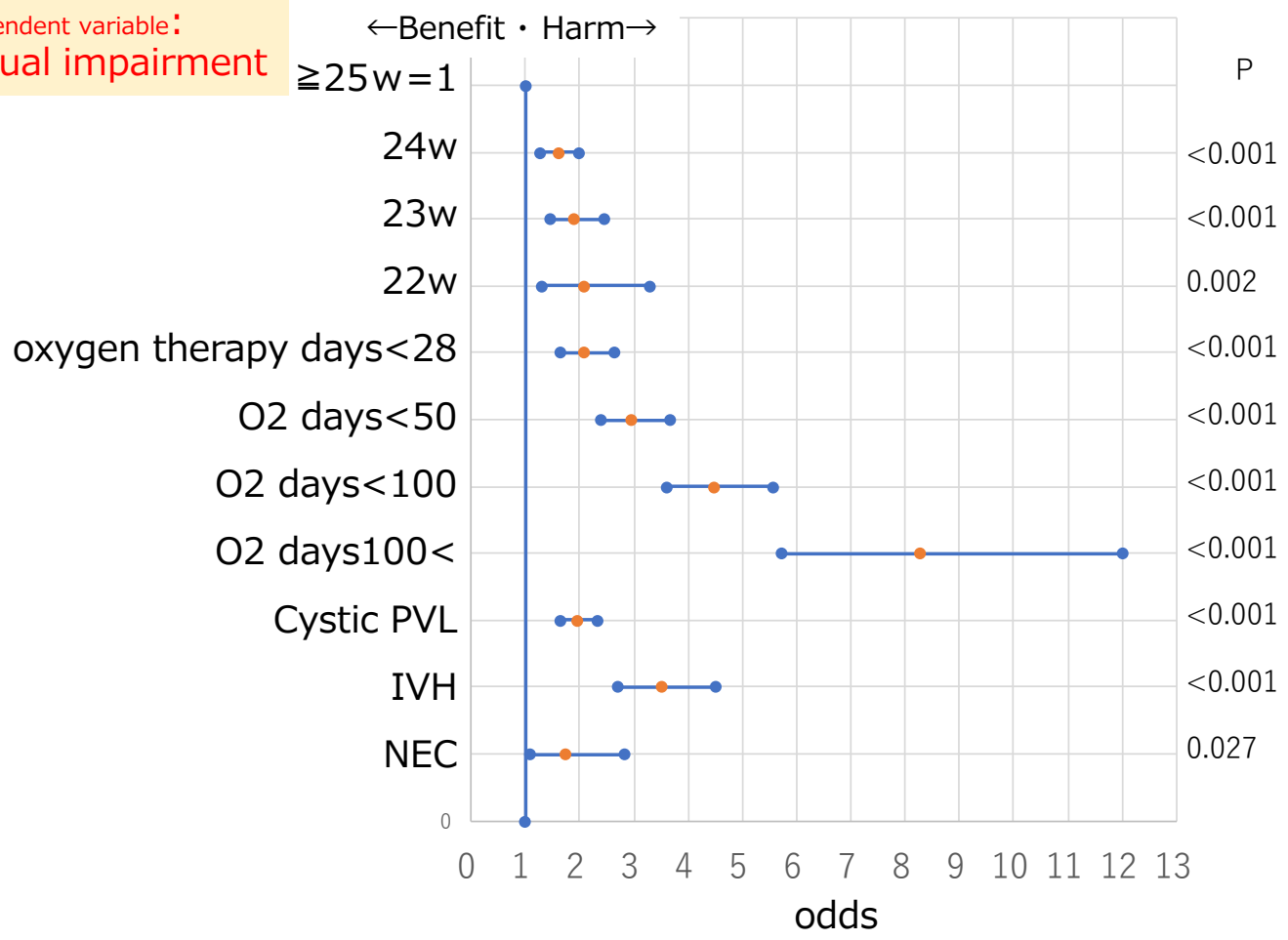
Adjusted for gestation



Visual impairment（3 yrs）and perinatal factors

- There are significant correlation between VI and days of oxygen therapy.
- CP causative factors(PVL, IVH, NEC) are also related with VI.

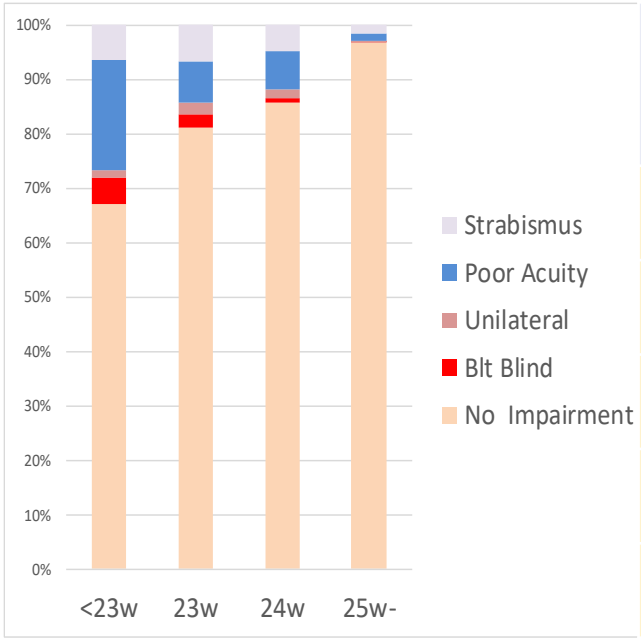
Dependent variable:
Visual impairment



- Logistic regression analyses for visual impairment（3 yrs）were performed to calculate odds ratio of oxygen therapy and neonatal factors adjusted with GA groups. All the factors included in the model are presented in the figure.

Visual impairment（3 yrs) and extreme preterm

◆ High incidence of visual impairment（3 yrs) (unilateral and bilateral blindness、poor acuity、strabismus) are seen for children born <25 weeks.



	normal	Bilateral blind	Unilateral blind	Poor acuity	strabismus	Total
22w	43	3	1	13	4	64
23w	330	9	9	31	27	406
24w	551	5	11	44	31	642
25w-	9118	17	10	123	153	9421
Total	10042	34	31	211	215	10533

Visual impairment（3 yrs) and GA, PPHN

- Extreme preterm is highly correlated with VI （3 yrs).
- PPHN correlates with VI（3 yrs)（ Nakanishi H, 2018).

VI (3yr) :Unilateral or bilateral blindness

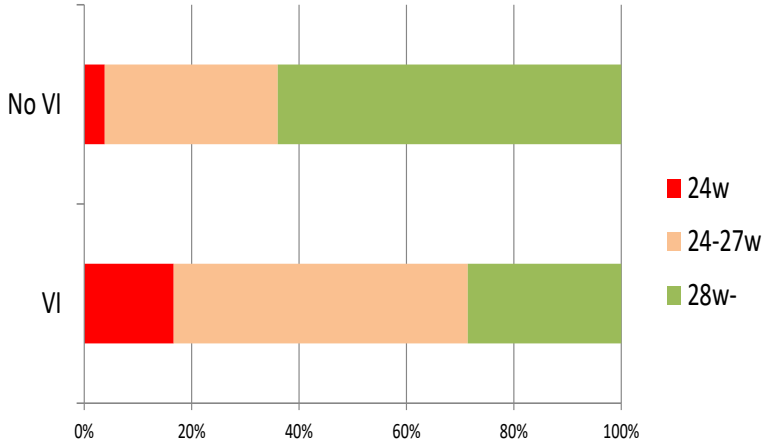
Dependent variable:

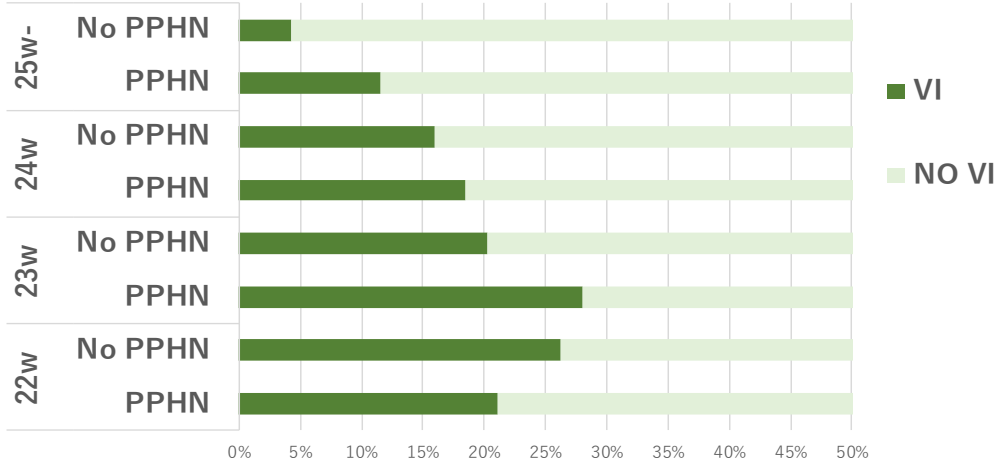
VI	odds	95%CI
24-27w	3.81	3.26 - 4.45
<24w	9.79	7.85 - 12.20

Dependent variable:

VI	odds	95%CI
24-27w	3.75	3.20 - 4.38
<24w	9.28	7.43 - 11.60
PPHN	1.78	1.36 - 2.33

Logistic Regression





(Nakanishi H, Persistent pulmonary hypertension of the newborn in extremely preterm infants: a Japanese cohort study. Arch Dis Child Fetal Neonatal Ed, 2018;0:F1–F8.)

Annual trend of use of glasses（3 yrs)

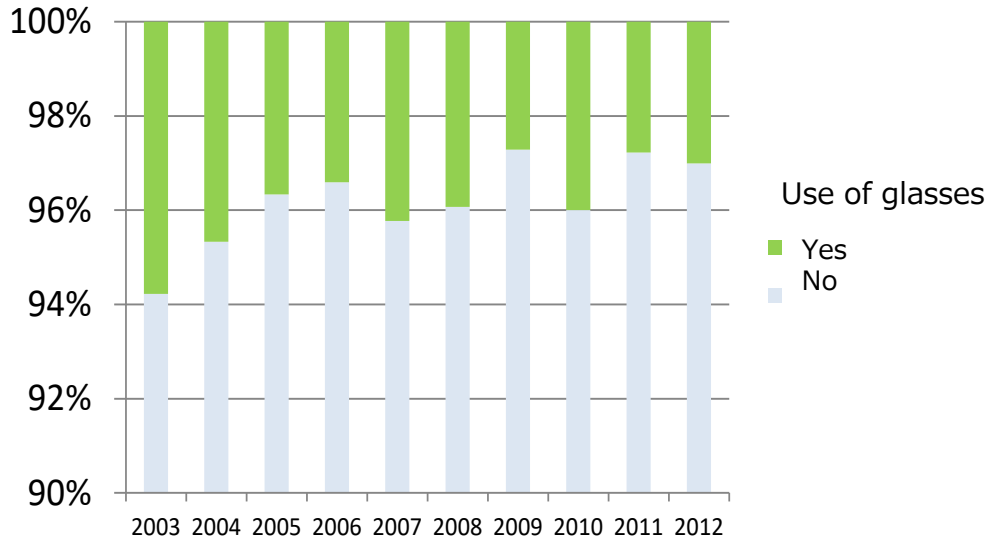
◆ Use of glasses is decreasing.

Use of glasses (3yrs)

	none	glasses	Total
2003	864	53	917
2004	1163	57	1220
2005	1236	47	1283
2006	1388	49	1437
2007	1314	58	1372
2008	1345	55	1400
2009	1434	40	1474
2010	1512	63	1575
2011	1401	40	1441
2012	1582	49	1631
Total	**13239**	**511**	**13750**

	odds	95%CI
Years	0.937	0.906 - 0.968

Adjusted for gestation



Annual trend of use of hearing aids（3 yrs)

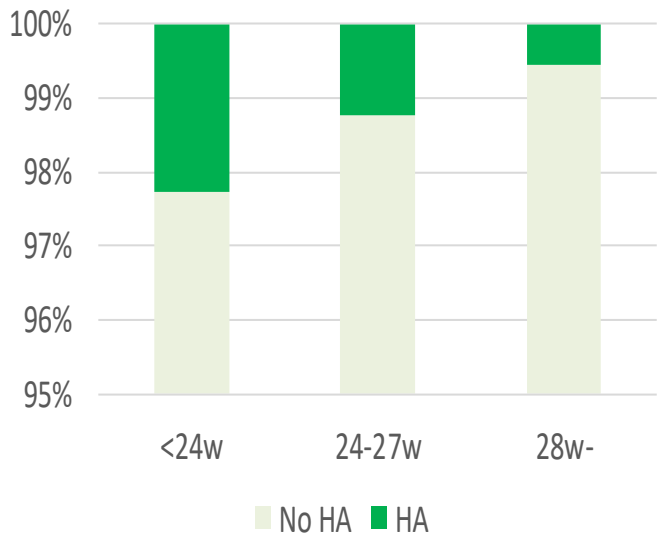
◆ Use of hearing aids（3 yrs) remains about 1% in extreme preterm.

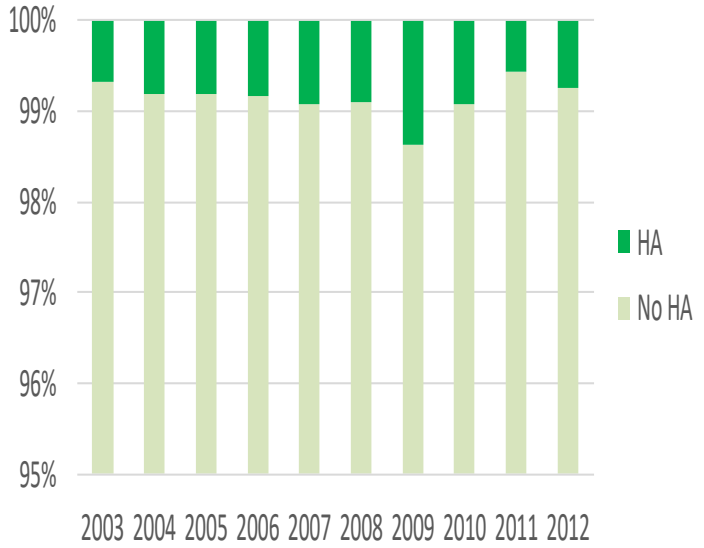
HA	no HA	HA
<24w	599	13
24-27w	4304	50
28w-	7955	41
Total	12858	104

Dependent variable:

HA	odds	95%CI	
Years	0.999	0.926 - 1.06	NS

Adjusted for gestation





Blood pressure （3 yrs) and fetal growth

◆ Blood pressure of VLBW(3yrs) shows no differences in types of fetal growth (<28w).

(<28w) n=15,367

Systolic	Mean	sd	P
AFD	101.0	13.5	0.5
HFD	102.6	13.6	
LFD	99.6	12.6	
SFD	100.6	13.0	

Dyastolic	Mean	sd	P
AFD	59.3	12.1	0.2
HFD	60.1	15.4	
LFD	60.1	11.5	
SFD	58.6	12.7	

AFD; Appropriate for date

HFD; Heavy for date

LFD; Light for data

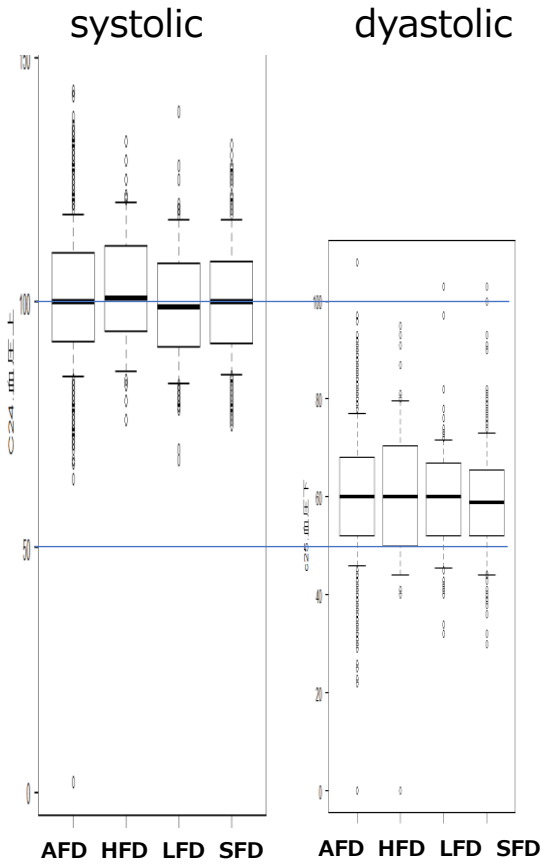
SFD; Small for date

Mean (sd)

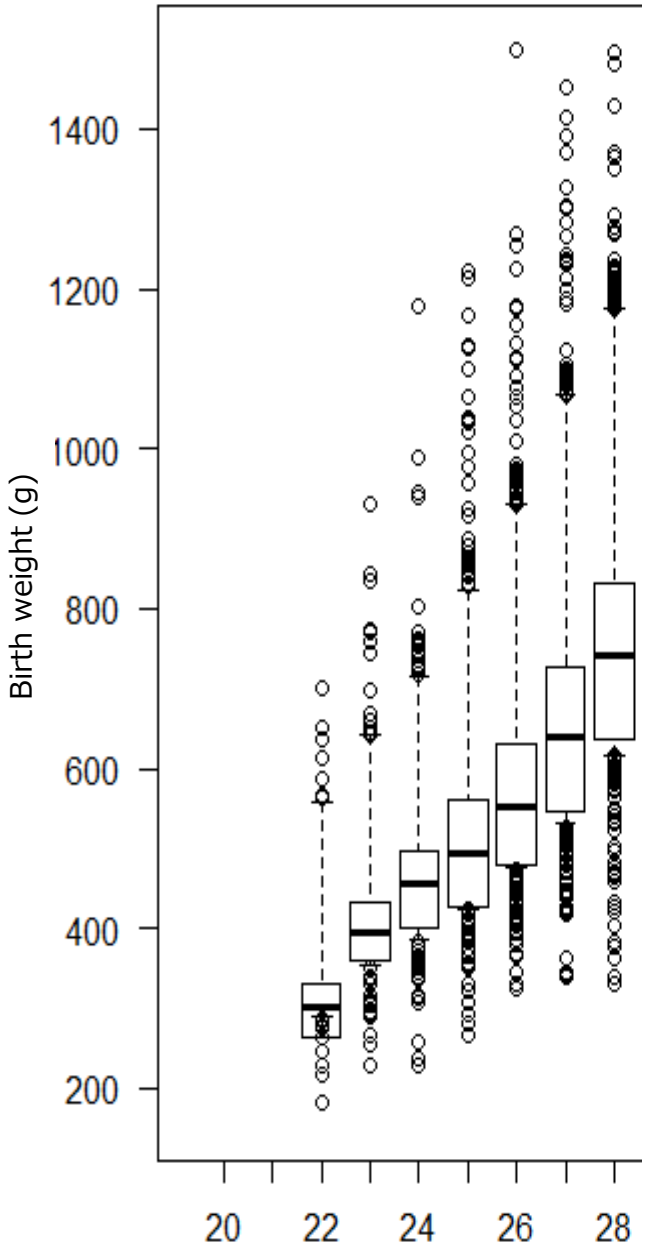
Neonatal data	AFD	HFD	LFD	SFD
n	11321	846	1251	1949
Gestation(w)	25.1 (1.5)	24.7 (1.6)	25.5 (1.3)	25.9 (1.2)
Birth weight(g)	796 (182)	945 (236)	625 (133)	556 (138)

Three years	AFD	HFD	LFD	SFD
n	11321	846	1251	1949
weight	12.0 (2.6)	12.8 (4.8)	11.5 (3.9)	11.0 (5.7)
height	89.1 (4.2)	90.4 (4.2)	88.3 (4.0)	86.3 (4.4)
head circumference	48.2 (2.0)	48.7 (1.9)	47.4 (1.8)	46.8 (2.0)

Bood Pressure (3 yrs) (<28w)



(SFD only)



The Evidence from NRNJ database for VLBW(2003-2012) -Vol 1 (2021 revision)-

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Definition

Classification of Chronic Lung Disease *

＊Oxygen therapy >28days of age

Type of CLD	RDS	High serum IgM、Chorioamnionitis, Funicitis	Bubbly/cystic Chest X-ray >28days
Ⅰ	＋	—	＋
Ⅱ	＋	—	—
Ⅲ	—	＋	＋
Ⅳ	—	Unknown	＋
Ⅲ’	—	＋	—
Ⅴ	—	—	—
Ⅵ			

CLD Group, MCH Grant（Yunosuke Ogawa 1992、Masanori Fujimura 1996).

Ogawa Y, Fujimura M et al. Epidemiology of Neonatal Chronic Lung Disease in Japan. Acta Paediatr Jpn 1992;34:663-667

CLD type III;
Bubbly/cystic appearance on chest X-ray