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Outcomes of Infants with Very Low Birth Weight Associated with Birthplace Difference: A Retrospective Cohort Study of Births in Japan and California

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Objective To determine whether outcomes among infants with very low birth weight (VLBW) vary according to the birthplace (Japan or California) controlling for maternal ethnicity.

Study design Severe intraventricular hemorrhage (IVH) and mortality were ascertained for infants with VLBW born at 24-29 weeks of gestation during 2008-2017 and retrospectively analyzed by the country of birth for mothers and infants (Japan or California).

Results Rates of severe IVH, mortality, or combined IVH/mortality were lower in the 24 095 infants born in Japan (5.1%, 5.0%, 8.8% respectively) compared with infants born in California either to 157 mothers with Japanese ethnicity (12.5%, 9.7%, 17.8%) or to a comparison group of 6173 non-Hispanic white mothers (8.4%, 8.8%, 14.6%). ORs for adverse outcomes were increased for infants born in California to mothers with Japanese ethnicity compared with infants born in Japan for severe IVH (OR, 3.31; 95% CI, 1.93-5.68), mortality (3.73; 95% CI, 2.03-6.86), and the combined outcome (3.26; 95% CI, 2.02-5.27). The odds of these outcomes also were increased for infants born in California to non-Hispanic white mothers compared with infants born in Japan. Outcomes of infants born in California did not differ by Japanese or non-Hispanic white maternal ethnicity.

Conclusions Low rates of severe IVH and mortality for infants with VLBW born in Japan were not seen in infants born in California to mothers with Japanese ethnicity. Differences in systems of regional perinatal care, social environment, and the quality of perinatal care may partially account for these differences in outcomes. *(J Pediatr 2021;229:182-90)*.

Owing to advances in neonatal medicine, the prognosis is improving for infants with very low birth weights (VLBW). However, it is still not fully satisfactory.[1-3] Furthermore, the prognosis for high-risk infants varies among facilities, countries, and races/ethnicities.[4-6] Differences in prognosis by country of birth are presumed to involve not only the regional perinatal medical system but also the social environment, lifestyle, and perhaps genetic endowment.[7,8] Infants born in Japan had better outcomes than those born in the state of California for the incidence of severe intraventricular hemorrhage (IVH), a serious complication of prematurity that often results in death or developmental disability and neonatal mortality.[9-11]

The goal of this study was to identify factors that might explain this observation by evaluating rates of severe IVH and mortality before neonatal intensive care unit discharge among infants with VLBW born in Japan compared with those born in California to mothers with Japanese ancestry and to a comparison group of infants with non-Hispanic white mothers. To explore the effect of genetic factors, neonatal outcomes for infants born in Japan were compared with those of infants born in California to first-generation mothers born in Japan. We hypothesized that if genetic differences contributed to outcomes of infants born in Japan, these outcomes would carry over into the outcomes of infants born in California to mothers born in Japan. We also assessed the potential impact of differential risk factors in these 2 cohorts. To assess the impact of acculturation, we compared risk factors and outcomes of infants born in California to mothers who were born in Japan or later generation mothers of Japanese ethnicity who were born in the US or other countries. In all analyses, we also used a comparison group of infants born in California to non-Hispanic white mothers.

Methods

We performed a retrospective cohort analysis of clinical data obtained from the Neonatal Research Network of Japan (NRNJ, http://plaza.umin.ac.jp/nrndata/

BMI	Body mass index
CPQCC	California Perinatal Quality Care Collaborative
IVH	Intraventricular hemorrhage
NRNJ	Neonatal Research Network of Japan
VLBW	Very low birth weight

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indexe.htm) and the California Perinatal Quality Care Collaborative (CPQCC, https://www.cpqcc.org/nicu/nicu-reports).

Approximately 150 hospitals have participated in the NRNJ since 2003, collecting information on short- and long-term outcomes from infants born with a birth weight of ≤1500 g. More than 70 000 infants have been registered in the NRNJ database covering >60% of infants with VLBW born in Japan. There is no variable regarding ethnicity in the NRNJ dataset, but according to the Vital Statistics in Japan, >97% of infants were born to mothers of Japanese ethnicity. Because early entry into prenatal care and access to care in Japan is almost universal, the NRNJ does not include data on payer status or trimester of entry into prenatal care.

In California, approximately 130 hospitals are members of CPQCC, caring for more than 95% of all infants with VLBW. We used demographic and clinical data from NRNJ and CPQCC to assess outcomes and adjust for clinical case mix. We used the California birth certificate to obtain self-identified nativity, maternal and paternal race and ethnicity, and maternal body mass index (BMI) for the California-born infants. These vital statistics data were then linked to the CPQCC demographic and clinical outcomes data using a probabilistic linkage algorithm.

Study Cohort

The study cohort included all registered infants with VLBW born at 24-29 weeks of gestation in Japan and California during 2008-2017. We excluded infants born at <24 weeks of gestation because the resuscitation policy toward infants born at <24 weeks differed between the networks. We excluded infants born >29 weeks, because there was a higher percentage of more mature, growth-restricted infants with VLBW in the NRNJ cohort. Infants with major congenital anomalies in both cohorts and infants without vital statistics data in California were also excluded. After exclusion of ineligible infants, 4 groups were defined for data analyses: infants born in Japan, infants born in California to mothers born in Japan (first generation), infants born in California to mothers with Japanese ethnicity but who were born in the US or another country (later generation), and a comparison group of infants born in California to non-Hispanic white mothers.

To assess the potential impact of differential risk profiles, we compared the percentage and contribution of maternal risk factors (hypertension, chorioamnionitis, diabetes), healthcare differences (antenatal steroid use, cesarean delivery, neonatal transport to a higher level of care) and a social risk factor (teen age pregnancies) in the study groups.

To assess the potential impact of acculturation, we compared the risk profiles and neonatal outcomes for infants born to first generation mothers who were born in Japan to those of Japanese ancestry who were born in the US (later generations). We also compared differences in the percent of fathers reporting Japanese ethnicity.

BMI also was evaluated as a possible indicator of acculturation. We compared differences in BMI for first and later generation California mothers with Japanese ethnicity. These factors also were compared with reference data for the BMIs of mothers of infants born in Japan.[12]

Outcomes and Risk Factors

The primary outcomes were severe IVH, mortality, and a composite outcome of severe IVH or mortality. Severe IVH was defined as grade III or IV IVH diagnosed with ultrasound examination. Mortality was defined as death in the delivery room or before discharge from the neonatal intensive care unit. The same outcome definitions are used in Japan and California.[1,2]

Maternal characteristics (**Table I**) were ascertained to account for differences in patient case mix include maternal factors such as maternal age, hypertension, chorioamnionitis, and diabetes. Infant clinical factors considered were birth weight, gestational age, birth weight small for gestational age, sex, multiple birth, cesarean delivery, antenatal steroid use, 5-minute Apgar score, outborn status, length of stay, and birth year. We assessed paternal ethnicity and maternal BMI as potential indicators of acculturation. BMIs in California mothers were calculated from height and prepregnancy weight from the birth certificate. Because BMI is not recorded in the NRNJ database, we used reported prepregnancy BMI data for Japanese women in Japan.[12]

Statistical Analyses

The association of outcomes and the selected variables were examined using descriptive analyses and χ^2 tests. Rates of outcomes were calculated among infants with known outcome status and were assessed for statistical significance between the 4 study groups using unadjusted logistic regression. We used multivariable hierarchical logistic regression models with hospital as a random effect to estimate aORs. Maternal cohort effect (exposure variable) was assessed by adjusting for temporal trends in the outcomes over time in the 4 study groups and again using 3 study groups (combining both groups of infants born in California to mothers of Japanese ethnicity). The models were estimated based on Laplace estimation. We assessed model fit by evaluating the values in −2 log likelihood, Akaike information criterion, and Bayesian information criterion between models (data available on request). The analysis was conducted in SAS 9.4 (SAS Institute, Cary, North Carolina).

We assumed that the incidences of severe IVH in Japan and in California were 5% and 10%, respectively.[10,11] Thus, we estimated that with approximately 15 000 infants with VLBW born in Japan and 150 infants with VLBW born in California to mothers with Japanese ethnicity, we would be able to see a statistical difference with 80% power and 5% type I error.

All maternal and infant information was collected anonymously, and the data were unlinked from individual

Table I. Maternal and infant characteristics in Japan and California

Characteristics	Infants born in Japan (n = 24 095)		Infants born in California to mothers with Japanese ethnicity (n = 157): Infants born to mothers who were born in Japan (n = 50)			Infants born in California to mothers with Japanese ethnicity (n = 157): Infants born to mothers with Japanese ethnicity born outside of Japan (n = 107: 103 born in the US; 4 born in other countries)				Infants born in California to non-Hispanic white mothers (n = 6173)		
Level	n/N	%	n/N	%	P value*,†	n/N	%	P value*,‡	P value*,§	n/N	%	P value*,¶
Binary variables												
Infant characteristics**												
Birth weight (g)												
≤400	271/24 095	1.1	0/50	0.0	<.01	0/107	0	<.01	NS	24/6173	0.4	<.01
401-750	6494/24 095	27.0	10/50	20.0		22/107	20.6			1179/6173	19.1	
751-1000	8012/24 095	33.3	16/50	32.0		31/107	29			1837/6173	29.8	
1001-1250	6274/24 095	26.0	13/50	26.0		30/107	28			1737/6173	28.1	
1251-1500	3044/24 095	12.6	9/50	18.0		19/107	17.8			1086/6173	17.6	
>1500	0/24 095	0.0	2/50	4.0		5/107	4.7			310/6173	5.0	
Gestational week (wk)												
24-25	5916/24 095	24.6	13/50	26.0	NS	20/107	18.7	NS	NS	1365/6173	22.1	<.01
26-27	8113/24 095	33.7	17/50	34.0		41/107	38.3			1900/6173	30.8	
28-29	10 066/24 095	41.8	20/50	40.0		46/107	43			2908/6173	47.1	
Small for gestational age infants††												
No	19 740/23 941	82.5	46/50	92.0	NS	95/107	88.8	NS	NS	5564/6173	90.1	<.01
Yes	4201/23 941	17.5	4/50	8.0		12/107	11.2			609/6173	9.9	
Male												
No	11 208/24 090	46.5	23/50	46.0	NS	43/107	40.2	NS	NS	2798/6171	45.3	NS
Yes	12 882/24 090	53.5	27/50	54.0		64/107	59.8			3373/6171	54.7	
Multiple pregnancy												
No	19 280/24 095	80.0	33/50	66.0	<.05	79/107	73.8	NS	NS	4060/6171	65.8	<.01
Yes	4815/24 095	20.0	17/50	34.0		28/107	26.2			2111/6171	34.2	
Cesarean delivery												
No	4969/23 571	21.1	12/50	24.0	NS	33/107	30.8	<.05	NS	1611/6172	26.1	<.01
Yes	18 602/23 571	78.9	38/50	76.0		74/107	69.2			4561/6172	73.9	
Antenatal steroid use												
No	9162/23 117	39.6	8/50	16.0	<.01	15/107	14	<.01	NS	750/6142	12.2	<.01
Yes	13 955/23 117	60.4	42/50	84.0		92/107	86			5392/6142	87.8	
Apgar score at 5 minutes												
0-3	1586/23 518	6.7	4/49	8.2	NS	7/107	6.5	<.01	NS	407/6142	6.6	<.01
4-7	11 116/23 518	47.3	19/49	38.8		35/107	32.7			2311/6142	37.6	
8-10	10 816/23 518	46.0	26/49	53.1		65/107	60.7			3424/6142	55.7	
Outborn infant												
No	22 679/24 095	94.1	43/50	86.0	<.01	80/107	74.8	<.01	NS	4848/6173	78.5	<.01
Yes	1416/28 095	5.9	7/50	14.0		27/107	25.2			1325/6173	21.5	
Maternal characteristics												
Age												
≤19	392/23 423	1.7	0/50	0	<.01	7/107	6.5	<.01	<.01	275/6163	4.5	<.01
20-29	7284/23 423	31.1	5/50	10		35/107	32.7			2284/6163	37.1	
30-39	14 042/23 423	60.0	28/50	56		59/107	55.1			3137/6163	50.9	
≥40	1705/23 423	7.3	17/50	34		6/107	5.6			467/6163	7.6	
Hypertension‡‡												
No	19 471/23 203	83.9	39/50	78	NS	87/106	82.1	NS	NS	4919/6153	79.9	<.01
Yes	3732/23 203	16.1	11/50	22		19/106	17.9			1234/6153	20.1	

(continued)

Table I. Continued

Characteristics	Infants born in Japan (n = 24 095)		Infants born in California to mothers with Japanese ethnicity (n = 157): Infants born to mothers who were born in Japan (n = 50)			Infants born in California to mothers with Japanese ethnicity (n = 157): Infants born to mothers with Japanese ethnicity born outside of Japan (n = 107: 103 born in the US; 4 born in other countries)				Infants born in California to non-Hispanic white mothers (n = 6173)		
Level	n/N	%	n/N	%	P value*,†	n/N	%	P value*,‡	P value*,§	n/N	%	P value*,¶
Chorioamnionitis												
No	17 200/22 318	77.0	40/50	80	NS	102/106	96.2	<.01	<.01	5562/6148	90.5	<.01
Yes	5118/22 318	22.9	10/50	20		4/106	3.8			586/6148	9.5	
Diabetes												
No	22 192/23 112	96.0	44/50	88	<.01	96/106	90.6	<.01	NS	5656/6154	91.9	<.01
Yes	920/23 112	4.0	6/50	12		10/106	9.4			498/6154	8.1	
Continuous variables	Mean ± SD	Missing	Mean ± SD	Missing		Mean ± SD	Missing			Mean ± SD	Missing	
Gestational age (wk)	26.9 ± 1.7	0	27.3 ± 1.8	0	NS	27.5 ± 1.6	0	NS	NS	27.5 ± 1.7	0	<.01
Birth weight (g)	927.1 ± 257.7	0	1012.6 ± 266.4	0	<.05	1012.8 ± 282.1	0	<.01	NS	1023.8 ± 284.9	0	<.01
LOS*,§§ (days) (n = 22 916)	105.1 ± 62.5	223	81.2 ± 34.1	0	<.05	75.4 ± 26.2	1	<.01	NS	78.5 ± 30.6	48	<.01
BMI¶¶	0	24 095	22.7 ± 4.3	3	–	26.4 ± 6.1	7	–	<.01	26.1 ± 6.6	452	–

LOS, length of stay; *NS*, not significant.
*χ^2 test or ANOVA F test for categorical variables and continuous variables.
†Comparing infants born in California to mothers who were born in Japan (first generation) with infants born in Japan.
‡Comparing infants born in California to mothers with Japanese ethnicity who were born in the US/other countries (later generation) with infants born in Japan.
§Comparing infants born in California to mothers of first generation with infants born to mothers of later generation.
¶Comparing infants born in California to non-Hispanic white mothers with infants in Japan.
**Clinical outcomes were considered from the infants who did not die in a delivery room.
††Small for gestational age was calculated using the same growth curve for Japanese and non-Hispanic white infants.
‡‡Chronic and gestational hypertension included in California cohort; gestational hypertension only in Japan cohort.
§§LOS was calculated from survivors only.
¶¶BMI not available in Japan data.

identifiers. The protocol of this study was approved by the central internal review board at Tokyo Women's Medical University, where all Japanese data were collected and stored and by Stanford University where the analyses comparing Japanese and Californian cohorts were conducted in collaboration.

Results

Figure 1 (available at www.jpeds.com) shows the flow chart of the study infants. The linkage rate to California vital records to establish ethnicity and natality was 94.6%. After application of inclusion and exclusion criteria, the final study cohort consisted of 24 095 infants born in Japan, 50 infants born in California to first-generation mothers born in Japan, and 107 infants born in California to later generation mothers with Japanese ethnicity who were born in the US (103 infants) or another country (4 infants). The comparison group included 6173 infants born in California to non-Hispanic white mothers.

Table I shows the maternal and infant risk profiles of the included infants by birthplace and maternal ethnicity. Infants born in Japan had lower birth weights and gestational ages, higher rates of cesarean delivery and 5-minute Apgar scores of <7, and lower rates of multiple births, antenatal steroid use, and outborn births. Regarding maternal factors, mothers of infants born in Japan were less likely to be teenagers, and less likely to have hypertension or diabetes compared with mothers of infants born in California. More mothers of infants born in Japan were 30-39 years of age and had chorioamnionitis. These factors were used for case mix adjustment in our logistic regression models.

Outcome Comparisons

The rates of severe IVH, mortality, or combined outcome for infants born in Japan were 5.1%, 5.0%, and 8.8%, respectively. These rates were significantly lower than rates among infants born in California to non-Hispanic white mothers (8.4%, 8.8%, and 14.6%, respectively) (Table II and Figure 2 [available at www.jpeds.com]). They also were lower than rates among infants born in California to all mothers with Japanese ethnicity regardless of maternal place of birth (12.5%, 9.7%, and 17.8%, respectively). For the California-born infants of mothers with Japanese ethnicity, rates of severe IVH, mortality, and the combined outcomes were significantly poorer for infants born to both first-generation and later generation mothers ($P < .01$) than in for infants born in Japan (Table II and Figure 2). There were no statistically significant differences between outcomes for infants born in California based on maternal ethnicity or maternal place of birth (Table II and Figure 2).

To evaluate the possibility that low rates of severe IVH and mortality in Japan were explained by a high rate of delivery room deaths, we compared delivery room deaths by

Table II. Severe IVH and mortality by cohort

Cohorts	Total infants	Severe IVH N	Severe IVH n	Severe IVH %	Severe IVH 95% CI	Delivery room mortality N	Delivery room mortality n	Delivery room mortality %	Mortality N	Mortality n	Mortality %	Mortality 95% CI	Severe IVH or mortality N	Severe IVH or mortality n	Severe IVH or mortality %	Severe IVH or mortality 95% CI	Compared with infants born in Japan*,† Severe IVH	Mortality	Severe IVH or mortality	Compared with infants born in California to non-Hispanic white mothers*,‡ Severe IVH	Mortality	Severe IVH or mortality
Infants born in Japan	24 095	23 130	1171	5.1	4.8 5.3	24 095	37	0.2	23 106	1146	5.0	4.7 5.2	23 574	2076	8.8	8.4 9.2	ref	ref	ref	*	*	*
Infants born in California to mothers with Japanese ethnicity*,§	157	152	19	12.5	7.2 17.8	157	2	1.3	154	15	9.7	5.1 14.4	157	28	17.8	11.8 23.8	*	*	*	NS	NS	NS
Mothers born in Japan (first generation)	50	49	7	14.3	4.5 24.1	50	1	2.0	49	7	14.3	4.5 24.1	50	10	20.0	8.9 31.1	*	*	*	NS	NS	NS
Mothers born in the US/other countries (later generation)	107	103	12	11.7	5.5 17.8	107	1	0.9	105	8	7.6	2.5 12.7	107	18	16.8	0.1 23.9	*	NS	*	NS	NS	NS
Infants born in California with non-Hispanic white mothers	6173	5936	498	8.4	7.7 9.1	6173	62	1.0	6087	535	8.8	8.1 9.5	6173	904	14.6	13.8 15.5	*	*	*	ref	ref	ref

ref, reference.
Mortality is death before discharge from neonatal intensive care unit, including delivery room death.
Significant test is based on logistic regression: $*P < .01$.
†All outcomes are significantly poorer for infants born in California compared with those born in Japan, except for mortality for infants born to mothers with Japanese ethnicity who were born in the US or other countries.
‡Outcomes among infants born in California to mothers with Japanese ethnicity are not significantly different from infants born to mothers with non-Hispanic white ethnicity.
§Cohort was divided based on maternal birthplace.

place of birth and ethnicity. However, rates of delivery room deaths for infants born in Japan were lower than for infants born in California to mothers with Japanese ethnicity at 0.2% (37/24 095) vs 1.3% (2/157), ($P < .01$).

Risk Profile-Adjusted Comparisons

Outcomes among the 4 study groups were analyzed with a risk profile adjustment using maternal risk factors of age, hypertension, and diabetes as well as gestational age, small for gestational age birth weight, sex, multiple birth, cesarean delivery, antenatal steroid use, 5-minute Apgar score, outborn status, and birth year.

After adjusting for differences in risk profiles, infants born in California had an increased odds of the adverse outcomes compared with infants born in Japan. This finding was true for infants born to mothers of Japanese ethnicity or non-Hispanic white ethnicity. This finding was also noted for infants born to mothers of Japanese ethnicity, regardless of whether mothers were born in Japan or in the US or other countries (**Table III**). There were no significant risk-adjusted differences between the outcomes of infants born in California to mothers with Japanese and non-Hispanic white ethnicity.

To assess the potential role of acculturation we compared the outcomes and risk profiles for California-born infants born with first or later generations of mothers with Japanese ethnicity. Observed outcomes in the 50 infants born to first-generation mothers were not significantly different from outcomes of the 107 infants born to later generation mothers (**Table II** and **Figure 2**). For infants of first-generation mothers, 24% (12/50) had fathers of Japanese ethnicity whereas for later generations, 4.7% (5/107) had fathers with Japanese ethnicity. With respect to risk profiles, infants born in California to later generation mothers with Japanese ethnicity had higher rates of teenage pregnancy and lower rates of chorioamnionitis than first-generation mothers. There were no other differences in the risk profile between first and later generation mothers (**Table I**).

The distributions of prepregnancy maternal BMIs divided into 4 categories (BMI <18.5, 18.5-24.9, >25.0, unknown) are shown in **Table IV** (available at www.jpeds.com). Overweight or obesity was present in 28.0% of first generation Japanese mothers and 51.4% of later generation mothers who gave birth in California. The overweight rate for non-Hispanic white mothers was similar to the rate for mothers of Japanese ethnicity born in the US. Although maternal BMI is not collected in the NRNJ, comparison data is included from another cohort study during 2004-2011.[12] This shows that BMI is higher in mothers residing in California than mothers in Japan.

Our analysis included only infants with VLBW born at 24-29 weeks of gestation. To assess the impact of including infants with VLBW with a gestational age >29 weeks we performed a risk adjusted sensitivity analysis. As expected, the addition of these lower risk infants with VLBW decreased all the outcome rates. However, all the statistically significant comparisons were consistent with those of our original analyses (**Table V**; available at www.jpeds.com).

Discussion

In this study, the prognosis for infants with VLBW born at 24-29 weeks of gestation in Japan was significantly better with respect to the frequency of severe IVH and/or neonatal death than for infants born to mothers of Japanese ethnicity who gave birth in California. The outcomes in Japan were also significantly better than outcomes of infants born to non-Hispanic white mothers in California. However, in California there were no significant differences in outcomes between the infants born to mothers with Japanese or non-Hispanic white ethnicity.

Based on our results, we speculate that differences in the regional perinatal transport system, social environment, and perinatal care may have a greater influence on the outcomes of high-risk infants than their genetic and epigenetic endowment. Although a detailed comparison of differences in perinatal care is beyond the scope of this analysis and our data sets do not contain sociodemographic information such as maternal education or family income, a major difference in the perinatal medical system between these 2 regions is the extent of neonatal transport. In Japan, early entry into perinatal care is almost universal in part because there are

Table III. Risk-adjusted outcomes in Japan and California

	Severe IVH				Mortality				Severe IVH or mortality			
	OR				OR				OR			
Cohorts	Estimate*1	95% CI		*P* value	Estimate*	95% CI		*P* value	Estimate*	95% CI		*P* value
Infants born in Japan	ref			-	ref			-	ref			-
Infants born in California to mothers with Japanese ethnicity†	3.31	1.93	5.68	<.01	3.73	2.03	6.86	<.01	3.26	2.02	5.27	<.01
Mothers born in Japan (first generation)	3.26	1.35	7.91	<.01	4.99	1.97	12.68	<.01	3.02	1.33	6.86	<.01
Mothers born in the US/other countries (later generations)	3.34	1.73	6.45	<.01	3.08	1.40	6.80	<.01	3.39	1.91	6.03	<.01
Infants born in California to non-Hispanic white mothers	2.01	1.65	2.45	<.01	3.12	2.58	3.78	<.01	2.41	2.05	2.83	<.01

Mortality is defined as death before discharge from neonatal intensive care unit, including delivery room death.
*Multivariable regression models were used with maternal risk factors of age, hypertension, and diabetes as well as gestational age, small for gestational age, sex, multiple birth, cesarean delivery, antenatal steroid use, 5-minute Apgar score, outborn status, and birth year.
†There were no significant increased odds of the adverse outcomes among infants born in California to mothers with Japanese and non-Hispanic white ethnicities.

minimal financial barriers. This system allows mothers to be evaluated and assigned to a facility matching their needs and, if complications arise, to be transferred before delivery to a facility whose obstetric service and neonatal intensive care unit are appropriate to their needs. A result of the success of this system is that only 5.9% of infants with VLBW were outborn, requiring transfer to perinatal centers after birth compared with 25.2% and 21.5% in our group of infants born in California. Neonatal transport of preterm infants is a major risk factor for severe IVH, even when maternal antenatal steroids are given and, in our study, this occurred 3-4 times more often in California.[13-15] Even inside Japan, neonatal transport has been reported to be a risk factor for severe IVH, necrotizing enterocolitis or focal intestinal perforation, and cognitive impairment.[16,17]

The goal of perinatal regionalization is to have mothers deliver in a facility that can meet her medical needs and those of her newborn infant. It may be difficult to predict the level of care that a mother or her infant may require. Furthermore, it is a difficult task to develop a regionalized system of care and reimbursement that facilitates early entry into prenatal care that allows time to assess the need for and to conduct the predelivery transfer of mothers to an appropriate level of care but it seems that this system has been more successful in Japan than in California. In Japan there is easy access to healthcare. Initiation of prenatal care in the first trimester is almost universal. In addition, the development of a perinatal referral system in Japan that includes emergent maternal transport on a prefectural basis began in the mid 1990s and has been highly successful in ensuring that women are cared for and deliver in a facility that is prepared to meet their level of medical needs. The precise indications for each infant's transport were not available in either database. It is noteworthy that a California study identified that 68% of neonatal transports were from community hospitals that did not have a neonatal intensive care unit and the remaining 32% of transported infants were born at facilities with a neonatal intensive care unit that could not provide the needed medical, subspecialty, or surgical care.[18] Although optimal regionalization cannot eliminate all appropriate neonatal transports, the high percentage of neonatal transports and the increased odds of severe IVH (OR, 1.56; 95% CI, 1.29-1.88) and severe IVH or the combined IVH/mortality outcome (OR, 1.22; 95% CI, 1.04-1.43) seen in the risk-adjusted analyses suggest the importance of perinatal regionalization as a focus for quality improvement in California. We suggest that promoting timely in utero maternal transfer over neonatal transport may represent an important strategy to improve outcomes among high-risk infants in California. We speculate that the benefit of maternal transfer could be more powerful than or at least offset that of antenatal steroid use, because the rate of antenatal steroid use in Japan was lower than in California (60.4% in Japan vs 87.7% in California). However, to improve the outcomes of high-risk infants, a regional comprehensive perinatal system that includes adequate prenatal care for pregnant women, appropriate maternal transport before delivery for high-risk pregnancies, and neonatal transport of high-risk infants should be considered.

Our data showed that, for mothers in our cohort with Japanese ethnicity giving birth in California, 24.0% of the mothers born in Japan and 4.7% of mothers born in the US had Japanese fathers. Changes in paternal ethnicity and increasing rates of obesity across generations have been described as indicators of acculturation.[19-21] We also observed a shift toward more obesity from the first to later generations in mothers of Japanese ethnicity. An important negative expression of obesity was the 2- to 3-fold increase in maternal diabetes, 4.0% (920/23 112) vs 10.3% (16/156). The increased neonatal morbidity for infants born in California to mothers with Japanese ethnicity may be related to rates of increased obesity and diabetes as well as to differences in perinatal care.[19] Although there is a growing literature on the negative consequences of both prepregnancy obesity and excessive weight gain during pregnancy, owing to our small sample, we were unable to identify a relationship between obesity and severe IVH or neonatal death.[22-24] We also observed an increase in teen births in California compared with Japan. Rates of teen pregnancy in Japan are quite low (1.7%) but increased with relocating to California (4.5%). Infants born to teenage mothers have been shown to be at higher risk for preterm birth and low birth weight and to have higher rates of stillbirth and neonatal mortality.[25]

Acculturation in the US has often been characterized by the adoption of less physical activity, increased rates of smoking, alcohol consumption, and obesity as well as poor access to healthcare has been associated with rates of other diseases. Previous reports on the differences between the rates of preterm birth and adult cardiac disease in the US have suggested the role of acculturation as an important driver. Rates of preterm birth have been reported as lowest in Japan, higher in mothers born in Japan who give birth in the US, and highest in mothers of Japanese ethnicity who are born in the US.[26] From our cohort, the rate of preterm birth was estimated at 4.3% in Japan, 7.4% for mothers born in Japan who gave birth in California, and 9.3% in Californians of Japanese descent (details on request). In adult medicine, rates of coronary heart disease in Japan have been reported to be lower than in the US, even after risk adjustment. Marmot and Syme reported that the most traditional group of Japanese-Americans had a rates of coronary heart disease similar to Japanese rates whereas individuals who were the most acculturated to western culture had a 3-5 excess of coronary heart disease that could not be accounted for by standard cardiac risk adjustment.[27]

Further studies are needed to identify the sources of these generational changes in outcome as there may be other important factors that were not available in our datasets. Potential candidates include differences in the structure and quality of the perinatal healthcare systems, the stress of moving to another country, and the rapid integration into the behavioral and dietary lifestyle in the US. Although there are examples of racial differences being influenced by minority over-representation in low-performing hospitals, this factor does not seem to be the case for Asians who deliver in California.[28]

The primary limitation of this study is the small sample size for first-generation Japanese immigrant mothers. Although the risk-adjusted neonatal outcomes were significantly worse compared with rates for infants born in Japan, a larger sample size would be needed to identify potential differences in neonatal outcomes between mothers living in California with Japanese and non-Hispanic white ethnicity. The second limitation is a lack of data on social risk factors such as level of education, family employment, and economic status. Owing to limitations of the database, we only had information on teenage pregnancy. Third, the BMI of mothers in the NRNJ cohort was not available and it was not possible to prove a direct effect of BMI on the outcomes. We cannot rule out that the distribution of BMI and the rate of diabetes observed in the mothers born in Japan living in California was not present on arrival to California. In addition, data on the extent of acculturation, such as maternal education, prenatal care, insurance status, and income level that would allow us to assess the impact of living in California was not available in the NRNJ cohort.

The results of our study do not support the possibility that the low rates of neonatal morbidity and mortality for infants with VLBWs in Japan are due to genetic endowment. It suggests that differences in the system of perinatal care and behavioral and dietary lifestyle may be important drivers of neonatal outcome and supports the importance of the relationship between the prognosis of high-risk infants and the structure and quality of the perinatal medical system, regionalization that favors maternal over neonatal transport, and the social and living environment. Although further research in larger groups is needed, our findings provide clues to improve the prognosis of high-risk infants in the future. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *The Journal of Pediatrics*

Combating Varicella Through Drugs and Vaccination

Prager D, Bruder M, Sawitsky A. Disseminated varicella in a patient with acute myelogenous leukemia: treatment with cytosine arabinoside. J Pediatr 1971;78:321-3.

Prager et al described a 6-year old girl with newly diagnosed leukemia who then contracted disseminated chickenpox, the disease caused by primary varicella zoster virus (VZV) infection. She improved with a 7-day course of cytosine arabinoside, a pyrimidine analog with putative antiviral and antineoplastic properties. Subsequent trials demonstrated that cytosine arabinoside impairs host response to infection, thus prolonging VZV dissemination, without reaching adequate antiviral concentrations in vivo. In the mid-1970s, the introduction of acyclovir, another nucleoside analog but with selective activity against herpes simplex and VZV polymerase, opened the era of efficacious and safe antiherpetic drugs. Valacyclovir, the prodrug of acyclovir, and famciclovir, the prodrug of penciclovir, were approved by the Food and Drug Administration in the 1990s; both have antiviral activity similar to that of acyclovir but much improved bioavailability, completing an array of treatment options for herpetic infections regardless of immune status.

The control of VZV infection in children was ultimately addressed by the development of the attenuated VZV vaccine by Japanese investigators in the 1970s. Small trials in Japan indicated that immunization safely reduced infection among chickenpox contacts. Subsequent trials tested vaccine safety and effectiveness among children with leukemia, a courageous step because it involved deliberately injecting a live herpesvirus into a compromised host. The proposal to apply the VZV vaccine to American children generated several concerns, however, including the unknown rate of vaccine failure and the potential of the vaccine strain to cause early zoster. VZV vaccine champions won the day, however, and the product was incorporated into the American childhood vaccine schedule as a single dose in 1995. The concern about early zoster ultimately proved unwarranted; the potential for zoster requires dermal lesions though which the organism can enter the neuron, and because vaccinated children rarely acquired rash, immunization likely reduced, not promoted, the incidence of zoster. The issue of faulty immunity proved more troublesome. School outbreaks among immunized children continued, presumably due to primary vaccine failure. This phenomenon was largely addressed by the incorporation of a booster dose starting in 2006, completing a success story in which a ubiquitous respiratory virus was controlled through careful, scientifically sound development of therapeutics and vaccines.

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Appendix

List of additional institutions of the Neonatal Research Network of Japan and the California Perinatal Quality Care Collaborative

Neonatal Research Network of Japan participants
Sapporo City Hospital
Asahikawa Kosei Hospital
Kushiro Red Cross Hospital
Obihiro Kosei Hospital
Tenshi Hospital
Nikko Kinen Hospital
Sapporo Prefecture Medical University
Asahikawa Medical University
Aomori Prefecture Central Hospital
Iwate Medical University
Sendai Red Cross Hospital
Tohoku University
Akita Red Cross Hosptai
Tsuruoka City Shonai Hospital
Yamagata University
Yamagata Prefecture Central Hospital
Fukusima Prefecture Medical University
Takeda General Hospital
National Fukushima Hospital
Tsukuba University
Tsuchiura Kyodo Hospital
Ibaraki Children's Hospital
Dokkyo Medical University
Jichi Medical University
Ashikaga Red Cross Hospital
Gunma Prefecture Children's Hospital
Kiryu Kosei General Hospital
Gunma University
Saitama Medical University
Saitama Prefecture Children's Hospital
National Nishisaitama Central Hospital
Saitama Medical University Medical Center
Kawaguchi City Medical Center
Asahi Central Hospital
Chiba City Kaihin Hospital
Kameda General Hospital
Tokyo Women's Medical University Yachiyo Medical Center
Juntendo University Urayasu Hospital
Narita Red Cross Hospital
Tokyo Metropolitan Children's Medical Center
Tokyo Women's Medical University
Aiiku Hospital
Niho University
Tokyo Medical University
Teikyo University
Showa University
Japan Red Cross Hospital
National Center for Child Health and Development
Tokyo Metropolitan Otsuka Hospital
Tokyo University
Toho University
Tokyo Metropolitan Bokuto Hospital
Tokyo Jikei Medical University
Saint Luku Hospital
Juntendo University
Katsushika Red Cross Hospital
Yokohama Rosai Hospital
Yokohama City University Medical Center
Marianna Medical University
Kanagawa Children's Medical Center
Tokai University
Kitazato University
Odawara City Hospital
Nippon Medical School Musashi Kosugi Hospital
Yokohama City Hospital
Saiseikai Eastern Yokohama Hospital
Yamanashi Prefecture Central Hospital
Nagano Children's Hospital
Shinshu University
Iida City Hospital
Nigata University
Niigata Central Hospital
Niigata City Hospital
Nagaoka Red Cross Hospital
Koseiren Takaoka Hospital
Toyama Prefectural Central Hospital
Toyama University
Ishikawa Prefectural Central Hospital
Kanazawa Medical University
Kanazawa Medical Center
Fukui Prefectural Hospital
Fukui University
Gifu Prefectural Medical Center
National Nagara Medical Center
Seirei Hamamatsu Hospital
Shizuoka Children's Hospital
Hamamatsu Medical University
Nagoya Red Cross Daini Hospital
Nagoya University
Nagoya Red Cross Daiici Hospital
Toyohashi City Hospital
Nagoya City Seibu Medical Center
Fujita Health University
Anjokosei Hospital
Koritsu Tosei Hospital
Toyota Memorial Hospital
Okazaki City Hospital
Konankosei Hospital
Aichi Medical University
National Mie Central Medical Center
Ise Red Cross Hospital
Yokkaichi City Hospital
Otsu Red Cross Hospital
Shiga Medical University
Nagahama Red Cross Hospital

Uji Tokushukai Hospital
Japan Baptist Hospital
Kyoto University
Kyoto Red Cross Daiichi Hospital
National Maizuru Medical Center
Kyoto Prefecture Medical University
Yodogawa Christian Hospital
"Osaka Medical Center and Research Institute for Maternal and Child Health"
Osaka University
Takatuski General Hospital
Kansai Medical University
Osaka City General Hospital
Osaka City Sumiyoshi Hospital
Aizenbashi Hospital
Toyonaka City Hospital
National Cerebral and Cardiovascular Center
Kitano Hospital
Saiseikai Suita Hospital
Chifune Hospital
Bell Land General Hospital
Rinku General Hospital
Osaka Red Crsoo Hospital
Yao City Hospital
Hannan Central Hospital
Osaka City University
Kobe Children's Hospital
Kobe University
Kakogawa City Hospital
Saiseikai Hyogo Hospital
Kobe City Medical Center Central Hospital
Hyogo Medical University
Himeji Red Cross Hospital
Toyoka General Hospital
Nara Prefecture Medical University
Wakayama Prefecture Medical University
Tottori Prefectural Central Hospital
Tottori University
Shimane Prefectural Central Hospital
Matue Red Cross Hospital
Kurashiki Central Hospital
Kawasaki Medical University
National Okayama Medical Center
Hiroshima City Central Hospital
Hiroshima Prefectural Hospital
National Kure Medical Center
Yamaguchi University
Yamaguchi Prefecture Medical Center
Tokushima University
Kagawa University
Shikoku Medical Center for Children and Adults
Matsuyama Red Cross Hospital
Ehime Prefectural Central Hospital
Kochi Health Science Center
Saint Maria Hospital
National Kyushu Medical Center
Kurume University
Kitakyushu City Hospital
University of Occupational and Environmental Health Japan
Fukuoka University
Kyushu University
Iizuka Hospital
National Kokura Medical Center
National Saga Hospital
National Nagasaki Medical Center
Saseho City Hospital
Kumamoto City Hospital
Kumamoto University
Oita Prefectural Hospital
Almeida Memorial Hospital
Miyazaki University
Kagosima City Hospital
Okinawa Prefectural Nanbu Medical Center
Okinara Prefectural Central Hospital
Naha City Hospital
Okinawa Red Cross Hospital
California Perinatal Quality Care Collaborative participants
Adventist Health Bakersfield
Adventist Health Glendale
Adventist Health Ukiah Valley
Adventist Health White Memorial
Alta Bates Summit Medical Center
Anaheim Regional Medical Center
Anderson Lucchetti Women's and Children's Center
Antelope Valley Hospital
Arrowhead Regional Medical Center
Asante Rogue Regional Medical Center
Bakersfield Memorial Hospital
California Hospital Medical Center - Los Angeles
California Pacific Medical Center (CPMC)
Cedars-Sinai Medical Center
Centinela Hospital Medical Center
Children's Hospital Los Angeles
CHOC Children's at Mission Hospital
CHOC Children's Hospital
Clovis Community Medical Center
Community Hospital of San Bernardino
Community Memorial Hospital of Ventura
Community Regional Medical Center
Desert Regional Medical Center
Doctors Medical Center of Modesto
Dominican Hospital
El Camino Hospital
Emanate Health Queen of The Valley Hospital
Fountain Valley Regional Hospital & Medical Center
Garfield Medical Center
Glendale Memorial Hospital and Health Center
Good Samaritan Hospital (HCA), San Jose
Good Samaritan Hospital, Los Angeles
Grossmont Hospital, Women's Health Center
Henry Mayo Newhall Hospital
Hoag Memorial Hospital, Presbyterian
Hollywood Presbyterian Medical Center

Huntington Memorial Hospital
John Muir Health, Walnut Creek Medical Center
Kaiser Foundation Hospital Baldwin Park
Kaiser Foundation Hospital Downey
Kaiser Foundation Hospital Fontana
Kaiser Foundation Hospital Los Angeles
Kaiser Foundation Hospital Modesto
Kaiser Foundation Hospital Moreno Valley
Kaiser Foundation Hospital Oakland
Kaiser Foundation Hospital Ontario Medical Center
Kaiser Foundation Hospital Orange County - Anaheim
Kaiser Foundation Hospital Orange County - Irvine
Kaiser Foundation Hospital Panorama City
Kaiser Foundation Hospital Riverside
Kaiser Foundation Hospital Roseville
Kaiser Foundation Hospital San Diego
Kaiser Foundation Hospital San Francisco
Kaiser Foundation Hospital San Leandro
Kaiser Foundation Hospital Santa Clara
Kaiser Foundation Hospital South Bay
Kaiser Foundation Hospital Walnut Creek
Kaiser Foundation Hospital West Los Angeles
Kaiser Foundation Hospital Woodland Hills
Kaweah Delta Healthcare District
Kern Medical Center
LAC/Harbor - UCLA Medical Center
LAC/Olive View - UCLA Medical Center
LAC/USC Medical Center
Loma Linda University Children's Hospital
Los Robles Hospital & Medical Center
LPCH at Sequoia Hospital
Lucile Packard Children's Hospital at Stanford
Marian Regional Medical Center
Marin General Hospital
Memorial Medical Center, Modesto
Mercy Medical Center, Redding
Mercy San Juan Medical Center
Methodist Hospital of Sacramento
Methodist Hospital of Southern California
Miller Children's and Women's Hospital at Long Beach Memorial Hospital
Natividad Medical Center
Northbay Medical Center
Northridge Hospital Medical Center
O'Connor Hospital
Orange County Global Medical Center
Parkview Community Hospital
PIH Health
Pomona Valley Hospital Medical Center
Providence Holy Cross Medical Center
Providence Little Company of Mary Medical Center - Torrance
Providence St. John's Health Center
Providence St. Joseph Medical Center
Providence Tarzana Medical Center
Rady Children's Hospital at Palomar Medical Center Escondido
Rady Children's Hospital at Scripps Mercy Chula Vista
Rady Children's Hospital at Scripps Mercy San Diego
Rady Children's Hospital San Diego
Rady Children's Hospital San Diego at Rancho Springs
Rady Children's Hospital San Diego at Scripps Encinitas
Rady Children's Hospital San Diego at Scripps La Jolla
Redlands Community Hospital
Regional Medical Center of San Jose
Riverside Community Hospital
Riverside University Health System Medical Center
Saddleback Memorial Hospital
Salinas Valley Memorial Hospital
San Antonio Regional Hospital
San Gabriel Valley Medical Center
San Joaquin General Hospital
Santa Barbara Cottage Hospital
Santa Clara Valley Medical Center
Santa Monica - UCLA Medical Center & Orthopedic Hospital
Santa Rosa Memorial Hospital
Sharp Chula Vista Medical Center
Sharp Mary Birch Hospital for Women and Newborns
Sierra Vista Regional Medical Center
St. Bernardine Medical Center
St. Francis Medical Center
St. John's Regional Medical Center
St. Joseph's Medical Center, Stockton
St. Jude Medical Center
St. Mary Medical Center
St. Mary Medical Center in Apple Valley
Sutter Roseville Medical Center
Sutter Santa Rosa Regional Hospital
Torrance Memorial Medical Center
Tri-City Medical Center
UC Davis Children's Hospital
UC Irvine Medical Center
UC San Diego Medical Center - Hillcrest
UCLA Mattel Children's Hospital
UCSD Health La Jolla - Jacobs Medical Center
UCSF Benioff Children's Hospital Oakland
UCSF Benioff Children's Hospital San Francisco
Valley Children's Hospital
Valley Children's Hospital at St. Agnes
Valley Presbyterian Hospital
Ventura County Medical Center
Washington Hospital Health Care System - Fremont
Watsonville Community Hospital
Zuckerberg San Francisco General Hospital and Trauma Center

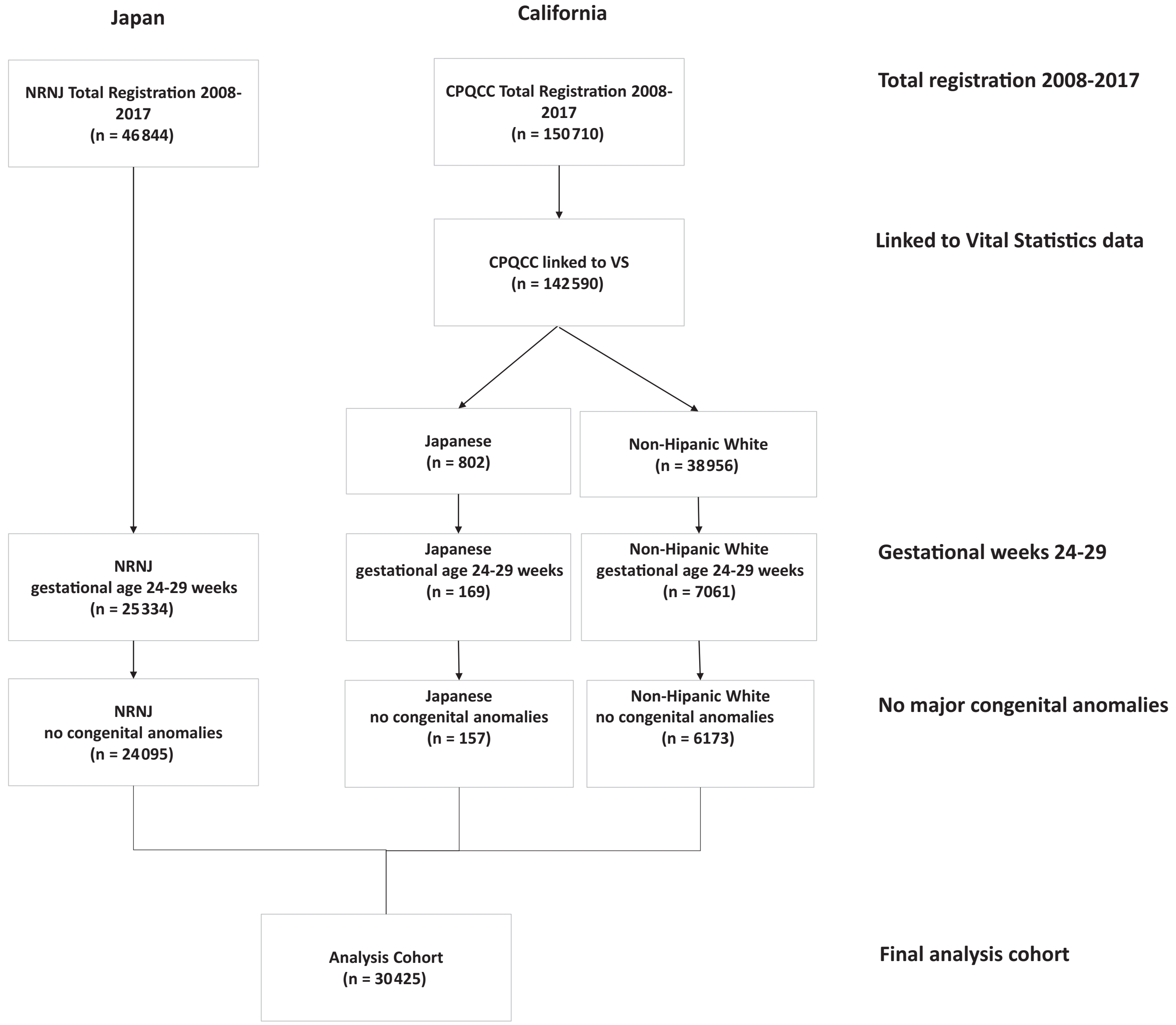

Figure 1. Patient flow chart. *VS*, vital statistics.

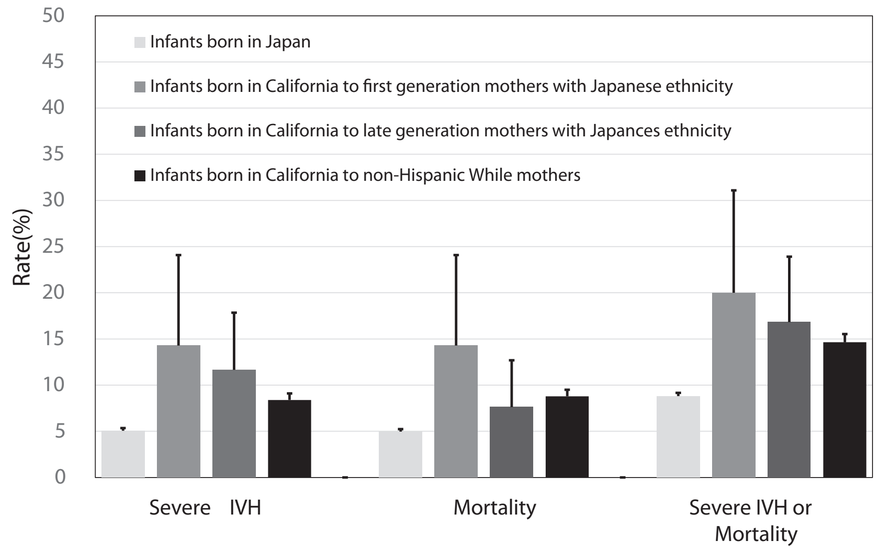

Figure 2. Comparison of outcomes among 4 different cohorts. The rates and 95% CI for severe IVH, mortality, and the combined outcome of severe IVH or mortality of the study groups. Risk-adjusted rates of adverse outcomes were lower for infants born in Japan than for infants in all other groups ($P < .01$). For all outcomes, there were no significant differences between the 3 groups of infants born in California. First-generation mothers are mothers born in Japan. Late generation mothers are mother born in the US or another country with Japanese ethnicity. Mortality is defined as death before discharge from neonatal intensive care unit including delivery room death.

Table IV. Prepregnancy BMI of the study patients and a reference group

		BMI							
		<18.5		18.5-24.9		≥25			
Study groups	n	Underweight		Normal		Overweight		Unknown	
Prepregnancy reference data for BMI for women in Japan*	104 070	19 311	18.6%	80 494	77.3%	4265	4.1%	0	0.0%
Mothers in California born in Japan (first generation)	50	7	14.0%	26	52.0%	14	28.0%	3	6.0%
Mothers in California born in the US/other countries (later generation)	107	5	4.7%	39	36.4%	55	51.4%	8	7.5%
Non-Hispanic white mothers in California	6173	244	4.0%	2892	46.8%	2585	41.9%	452	7.3%

*The BMIs of Japanese mothers in Japan were referred from reference 12.

Table V. Sensitivity analysis using all infants with VLBW in Japan and California

Cohorts	Total infants	Severe IVH					Delivery room mortality			Mortality					Severe IVH or mortality					Compared with infants born in Japan*			Compared with infants born in California to non-Hispanic white mothers†		
		N	n	%	95% CI		N	n	%	N	n	%	95% CI		N	n	%	95% CI		Severe IVH	Mortality	Severe IVH or mortality	Severe IVH	Mortality	Severe IVH or mortality
Infants born in Japan	40 709	39 009	1277	3.3	3.1	3.5	40 709	49	0.1	39 078	1288	3.3	3.1	3.5	39 762	2315	5.8	5.6	6.1	ref	ref	ref	‡	‡	‡
Infants born in California to mothers with Japanese ethnicity§	273	247	20	8.1	4.7	11.5	273	2	0.7	270	15	5.6	2.8	8.3	273	29	10.6	7.0	14.3	‡	‡	‡	NS	NS	NS
Mothers born in Japan (first generation)	100	90	7	7.8	2.2	13.3	100	1	1.0	99	7	7.1	2.0	12.1	100	10	10.0	4.1	15.9	‡	‡	¶	NS	NS	NS
Mothers born in the US/other countries (later generation)	173	157	13	8.3	4.0	12.6	173	1	0.6	171	8	4.7	1.5	7.8	173	19	11.0	6.3	15.6	‡	NS	‡	NS	NS	NS
Infants born in California to non-Hispanic white mothers	9971	9289	542	5.8	5.4	6.3	9971	65	0.7	9976	571	5.8	5.3	6.2	9971	983	9.9	9.3	10.4	‡	‡	‡	ref	ref	ref

NS, not significant; *ref*, reference.
Mortality is defined as death before discharge from neonatal intensive care unit, including delivery room death.
Significant test is based on logistic regression: ¶$P < .05$, ‡$P < .01$.
*All outcomes are significantly poorer for infants born in California compared with those born in Japan, except for mortality for infants born to mothers with Japanese ethnicity who were born in the US or other countries.
†Outcomes among infants born in California to mothers with Japanese ethnicity are not significantly different from infants born to mothers with non-Hispanic white ethnicity.
§Cohort was divided based on maternal birthplace.