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Postnatal growth failure in very low birthweight infants born between 2005 and 2012

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ABSTRACT

Background Postnatal growth restriction is common in preterm infants and is associated with long-term neurodevelopmental impairment. Recent trends in postnatal growth restriction are unclear.

Methods Birth and discharge weights from 25 899 Californian very low birthweight infants (birth weight 500–1500 g, gestational age 22–32 weeks) who were born between 2005 and 2012 were converted to age-specific Z-scores and analysed using multivariable modelling.

Results Birthweight Z-score did not change between 2005 and 2012. However, the adjusted discharge weight Z-score increased significantly by 0.168 Z-scores (0.154, 0.182) over the study period, and the adjusted fall in weight Z-score between birth and discharge decreased significantly between those dates (by 0.016 Z-scores/year). The proportion of infants who were discharged home below the 10th weight-for-age centile or had a fall in weight Z-score between birth and discharge of >1 decreased significantly over time. The comorbidities most associated with poorer postnatal growth were medical or surgical necrotising enterocolitis, isolated gastrointestinal perforation and severe retinopathy of prematurity, which were associated with an adjusted mean reduction in discharge weight Z-score of 0.24, 0.57, 0.46 and 0.32, respectively. Chronic lung disease was not a risk factor after accounting for length of stay.

Conclusions Postnatal, but not prenatal, growth improved among very low birthweight infants between 2005 and 2012. Neonatal morbidities including necrotising enterocolitis, gastrointestinal perforations and severe retinopathy of prematurity have significant negative effects on postnatal growth.

What is already known on this topic

- Postnatal growth in preterm infants is slower than that of the fetus of the same gestational age.
- Slower postnatal growth is associated with long-term neurodevelopmental delays.

What this study adds

- Severe retinopathy of prematurity is associated with significantly slower growth in very low birthweight (VLBW) infants.
- Chronic lung disease is not associated with significantly slower growth in this recent cohort of VLBW infants.
- Growth outcomes in VLBW infants are improving over time.

INTRODUCTION

Although there remains controversy about the optimum growth rate of preterm infants,[1–3] postnatal growth failure is very common in preterm infants[4 5] and is associated with significant neurodevelopmental impairments.[6 7]

Differences in postnatal growth rates have been associated with gender, nutritional factors, chronic lung disease and sepsis.[8–12] In the largest study to date, risk factors for postnatal growth restriction included male gender, early respiratory distress, bronchopulmonary dysplasia and postnatal steroid exposure.[13] However, those data are now almost 15 years old, and it is unclear whether similar factors remain important or whether the incidence of postnatal growth restriction has changed since that time.

Multiple definitions of postnatal growth restriction have been used, including a weight-for-age less than the 10th centile at 28-day postnatal age, at 36-week postmenstrual age, or at hospital discharge; or a fall in weight Z-score between birth and discharge >2.0, >1.0 or >0.67.[10 14] It is not known whether risk factors using one definition are similar to those using another definition.

The objectives of this study were to use a large, recent (2005–2012), dataset of very low birthweight (VLBW) infants to examine the association between common comorbidities of preterm infants and body size at hospital discharge and within-hospital growth.

SUBJECTS AND METHODS

Subject population

Data were extracted from the California Perinatal Quality Care Collaborative (CPQCC) database for the years 2005–2012 inclusive (the most recent data available). The CPQCC provides a centralised reporting mechanism for California neonatal units, with a mission to improve the quality of care provided. Currently, 132 units report data, and >90% of the VLBW infants born in the state are included in the database.

For this study, data were included for infants of birth weight 500–1500 g and gestational age 22 weeks (154 days) to 32 weeks (224 days) who were discharged home alive from their initial reporting hospital prior to 50 weeks corrected gestational age. Subjects were excluded if they had

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significant congenital abnormalities, if the birth or discharge weight was unknown or if the birth or discharge weight was more than five SDs from the expected mean for age.

Anthropometric data

Birth weight and discharge weight were converted to age-specific and gender-specific Z-scores using the 2013 Fenton dataset.[15]

Body size at discharge was assessed using two criteria:

1. The age-specific and gender-specific weight Z-score at hospital discharge.
2. Whether the weight-for-age at discharge was less than the 10th centile ($Z<-1.28$).

In-hospital growth was assessed using two criteria:

1. The change in weight Z-score between birth and discharge.
2. Whether the fall in weight Z-score between birth and discharge was >1.0.

Growth velocity between birth and discharge was expressed as g/day and as g/kg/day. It was also calculated using the method of Patel[16] from the equation

$$\text{Growth velocity} = 1000 \times \text{Ln}(Wt_2/Wt_1)/(D_2 - D_1)$$

where Wt_1 and Wt_2 are the weights measured on days D_1 (Birth) and D_2 (discharge), respectively.

Antenatal data

Antenatal details[17] collected included the diagnoses of maternal hypertensive disorders, chorioamnionitis, diabetes mellitus and whether antenatal steroids had been administered.

Comorbidities

Data on postnatal comorbidities were collected using standardised definitions[17] and included data on early sepsis (bacterial sepsis prior to 3 days of age), late sepsis (bacterial or fungal sepsis after 3 days of age), chronic lung disease (the need for continuous or intermittent oxygen at 36 weeks corrected gestational age), necrotising enterocolitis (categorised into none, medical and surgical (surgery required for acute management, including explorative laparotomy or drain insertion)), severe retinopathy of prematurity (stage 3 or greater, or the needed for laser surgery or vascular endothelial growth factor inhibitor treatment), severe intraventricular haemorrhage (grade 3 or 4) and periventriular leukomalacia.

Statistical methods

Data were analysed using descriptive statistics and multivariable mixed-effects linear (for continuous outcomes) and logistic (for categorical outcomes) regression modelling. Hospital of birth was included as a random effect to adjust for residual within-hospital correlations (ie, 'cluster effects').

Growth between birth and discharge was expressed both as a continuous variable (change in weight Z-score over the period) and as a binary variable (whether the change in weight Z-score was >−1). Relative body size at birth was assessed using the weight Z-score at discharge (a continuous variable) and whether the weight Z-score at discharge was greater than the 10th centile (a binary variable). Data are considered for the entire cohort, and for four individual birthweight cohorts −500–749 g, 750–999 g, 1000–1249 g and 1250–1500 g.

The determinants of discharge weight Z-score, or of the change in weight Z-score between birth and discharge, were examined using multivariable mixed-effects linear modelling. Independent variables included gender, gestational age, birth weight, early sepsis, late sepsis (chronic lung disease, necrotising enterocolitis, severe retinopathy of prematurity, severe intraventricular haemorrhage and periventricular leukomalacia, and year of birth). Hospital of birth was included as a random effect to adjust for residual within-hospital correlations (ie, 'cluster effects'). The determinants of discharge weight Z-score above or below the 10th centile for age, or a fall in weight Z-score during admission of greater than or less than 1 were assessed using mixed-effects logistic regression models. In order to determine whether the effects of year of birth varied between the different birthweight cohorts, the interaction between birthweight cohort and year of birth was included in the multivariable models. If significant interactions with birthweight cohort were seen, analyses were carried out separately for each birthweight cohort.

Central location parameter estimates were expressed as mean (95% CI) for continuous variables and as percentages (95% CI) for categorical variables. Effect sizes were reported as regression coefficient (95% CI) for continuous variables and as OR (95% CI) for categorical variables. Effect sizes for gestational age were expressed as the coefficient per day, effects for birth weight were expressed per 100 g and those for year of birth were expressed per year. Analyses were carried out using JMP Pro 11.0 and SAS V.9.4 (both from SAS Institute, Cary, North Carolina, USA).

RESULTS

Subject demographics

Data were available on 25 899 subjects (table 1). The number of patients per year varied from 3005 in 2005 to 3309 in 2009.

Smaller infants were discharged at a later postnatal age and at a later corrected gestational age. They were heavier at discharge, but their age-specific Z-scores were lower than in infants who were heavier at birth, and their decrease in weight Z-score between birth and discharge was significantly greater (table 1).

More than half of the subjects were below the 10th weight-for-age centile at hospital discharge, and weight Z-score fell by >1.0 between birth and discharge in 41%. One-third of infants were discordant using these two definitions of growth retardation (figure 1).

Birth weight

Small for gestational age at birth

Birth weight was below the 10th centile for age in 15.2% of subjects and was unaffected by year of birth (adjusted OR (AOR) per year 0.976 (0.943 to 1.001); figure 2A). The AOR of being small for gestational age at birth was significantly greater in males (AOR 1.677 (1.524 to 1.845); p<0.0001), those of higher gestational age (AOR per day 0.931 (0.927 to 0.935); p<0.0001) and in those whose mothers had hypertensive disorders (AOR 2.832 (2.571 to 3.120); p<0.0001). It was lower in those with chorioamnionitis (AOR 1.691 (1.261 to 2.320); p=0.0007) and not significantly affected by maternal diabetes (AOR 1.155 (0.997 to 1.341); p=0.06) or by antenatal steroid administration (AOR 1.120 (0.975 to 1.289)).

Body weight at hospital discharge

Discharge weight Z-score

Determinants of discharge weight Z-score are shown in table 2. Discharge weight Z-score was positively correlated with year of birth. Over the entire duration of the study, mean discharge weight Z-score increased by 0.168 (0.154 to 0.182) after

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Table 1 Characteristics of the study population as a whole, and for the four birthweight cohorts separately, given as per cent (95% CI) or mean (95% CI)

	Birthweight cohort				
	All infants	**500–749 g**	**750–999 g**	**1000–1249 g**	**1250–1500 g**
Birth characteristics					
Number	25 899	2941	5978	7641	9339
Male (%)	49.8% (49.2 to 50.4)	42.1% (40.3 to 43.9)	48.1% (46.9 to 49.4)	51.1% (50.0 to 52.2)	52.2% (51.2 to 53.3)
Gestational age (weeks)	28.71 (28.69 to 28.74)	25.49 (25.43 to 25.56)	27.20 (27.14 to 27.24)	29.07 (29 to 03 to 29.10)	30.41 (30.39 to 30.43)
Weight (kg)	1.11 (1.10 to 1.12)	0.65 (0.65 to 0.66)	0.881 (0.879 to 0.882)	1.127 (1.126 to 1.129)	1.376 (1.374 to 1.378)
Weight (Z)	−0.48 (−0.49 to −0.47)	−0.83 (−0.87 to −0.81)	−0.48 (−0.50 to −0.46)	−0.46 (−0.48 to −0.44)	−0.38 (−0.40 to −0.37)
SGA (%)	15.2% (14.8 to 15.6)	28.1% (26.5 to 30.0)	15.1% (14.2 to 16.0)	16.4% (15.6 to 17.3)	10.2% (9.6 to 10.9)
Discharge characteristics					
Postnatal age (days)	65.8 (65.5 to 66.2)	106.7 (105.9 to 107.6)	83.2 (82.6 to 83.8)	60.7 (60.3 to 61.2)	46.0 (45.7 to 46.3)
Postmenstrual age (weeks)	37.99 (37.94 to 38.01)	40.63 (40.50 to 40.71)	38.94 (38.89 to 39.01)	37.60 (37.56 to 37.66)	36.56 (36.80 to 36.89)
Weight (kg)	2.57 (2.57 to 2.58)	2.83 (2.81 to 28.5)	2.70 (2.69.2.72)	2.53 (2.51 to 2.54)	2.45 (2.44 to 2.46)
Weight (Z−score)	−1.40 (−1.41 to −1.39)	−1.94 (−1.98 to −1.90)	−1.55 (−1.58 to −1.52)	−1.35 (−1.38 to −1.34)	−1.17 (−1.19 to −1.16)
SGA (%)	53.3% (52.7 to 53.9)	71.6% (70.0 to 73.2)	58.8% (57.8 to 60.1)	52.7% (51.6 to 53.8)	44.4% (43.4 to 45.5)
ΔWeight (Z−score)	−0.92 (−0.93 to −0.91)	−1.10 (−1.14 to −1.07)	−1.07 (−1.09 to −1.06)	−0.90 (−0.91 to −0.88)	−0.79 (−0.80 to −0.78)
ΔWeight Z−score >1	41.4% (40.8 to 42.0)	53.6% (51.8 to 55.4)	51.7% (50.4 to 53.0)	40.8% (39.7 to 41.9)	31.4% (30.5 to 32.3)
Morbidities					
Early sepsis (%)	1.2% (1.1 to 1.3)	2.0% (1.6 to 2.6)	1.6% (1.3 to 2.0)	1.0% (0.8 to 1.2)	0.8% (0.7 to 1.0)
Late sepsis (%)	8.6% (8.3 to 8.9)	20.4% (19.0 to 21.9)	12.4% (11.6 to 13.3)	6.8% (6.3 to 7.4)	3.8% (3.5 to 4.2)
NEC (%)	3.5% (3.3 to 3.7)	6.9% (6.0 to 7.9)	5.0% (4.5 to 5.6)	2.7% (2.4 to 3.1)	2.1% (1.7 to 2.4)
– Medical (%)	2.6% (2.4 to 2.8)	4.2% (3.5 to 5.0)	3.6% (3.1 to 4.1)	2.3% (1.9 to 2.6)	1.8% (1.6 to 2.1)
– Surgical (%)	0.9% (0.8 to 1.0)	2.7% (2.2 to 3.3)	1.4% (1.2 to 1.8)	0.4% (0.3 to 0.6)	0.2% (1.6 to 3.7)
Gastrointestinal perforation (%)	1.3% (1.2 to 1.5)	4.8% (4.1 to 5.6)	2.1% (1.7 to 2.5)	0.7% (0.5 to 0.9)	0.3% (0.2 to 0.4)
Chronic lung disease (%)	23.1% (22.6 to 23.7)	60.7% (59.0 to 62.5)	37.9% (36.7 to 39.2)	16.7% (15.9 to 17.5)	7.0% (6.5 to 7.6)
Severe ROP (%)	6.3% (6.0 to 6.6)	27.7% (26.2 to 29.4)	10.6% (9.8 to 11.4)	1.5% (1.3 to 1.8)	0.3% (0.2 to 0.5)
Severe IVH (%)	4.5% (4.3 to 4.8)	11.2% (10.1 to 12.4)	7.2% (6.5 to 7.9)	3.4% (3.0 to 3.8)	1.6% (1.3 to 1.9)
PVL (%)	2.0% (1.8 to 2.2)	4.1% (3.5 to 4.9)	2.8% (2.4 to 3.2)	1.7% (1.4 to 2.0)	1.0% (0.8 to 1.2)

IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; SGA, small for gestational age.

correction for comorbidities. Discharge weight Z-score increased over the study in all birthweight strata (figure 3A).

Weight<10th centile at discharge

A weight below the 10th centile for age at discharge was more common in males, and in those with many, but not all, comorbidities of prematurity (table 2).

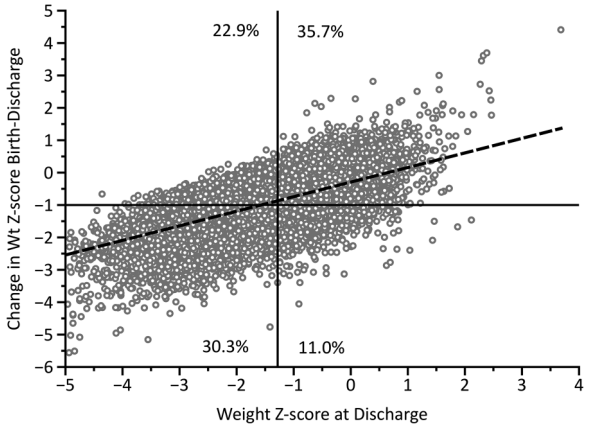

Figure 1 Scatterplot of weight-for-age Z-score at discharge against change in weight-for-age Z-score between birth and discharge (percentages do not total 100% due to rounding). The broken line represents the line of best fit.

Discharge below the 10th weight centile for age became significantly less likely in later birth years (table 2, figures 2B and 3C).

Growth between birth and discharge

Change in weight Z-score birth to discharge

Over the entire duration of the study, the mean fall in weight Z-score between birth and discharge decreased by 0.112 (0.108 to 0.116) and was significantly associated with year of birth in all birthweight cohorts (figure 3B).

The mean change in weight Z-score between birth and discharge was more negative (ie, less favourable) in infants with late sepsis, medical or surgical necrotising enterocolitis, gastrointestinal perforations, severe retinopathy of prematurity and severe intraventricular haemorrhage, and in females (table 2).

Fall in weight Z-score during admission >1.0

The odds of weight Z-score falling by >1 during hospital admission was significantly lower during later years (table 2 and figure 2C), falling from 47% in 2005 to 38% in 2012 (OR 0.76 (0.65 to 0.89)). Significant reductions were seen in all birthweight strata >1 kg (figure 3D).

Effect of length of stay

When length of stay was accounted for in the multivariable analysis, most results were substantively unchanged. However, after correcting for length of stay, chronic lung disease was significantly associated with a higher discharge weight Z-score (effect size 0.03 (0.02 to 0.04); p<0.0001), a smaller fall in weight

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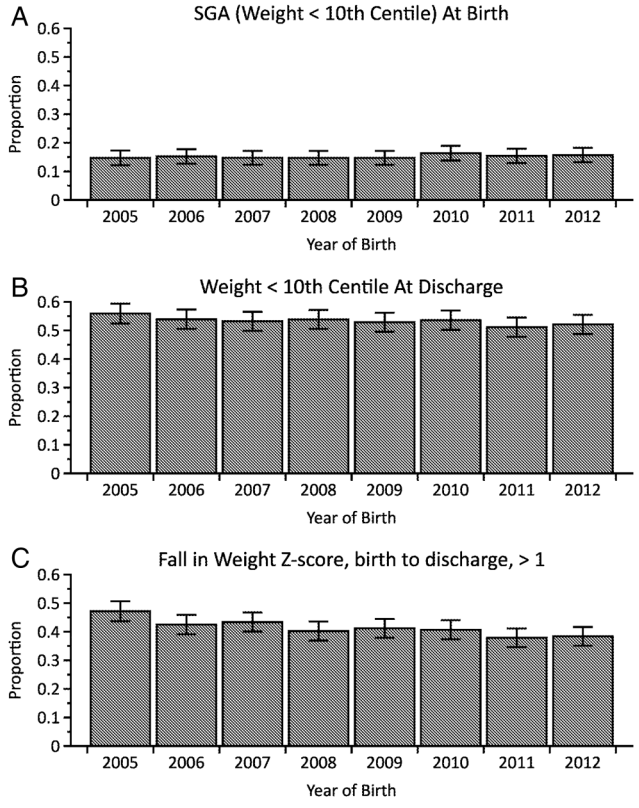

Figure 2 Incidence of small for gestational age (SGA) status at birth (A, p=not significant), weight for age below the 10th centile at discharge (B, p<0.0001)) and a fall in weight Z-score >1.0 between birth and discharge in each of the study years (C) (p<0.0001).

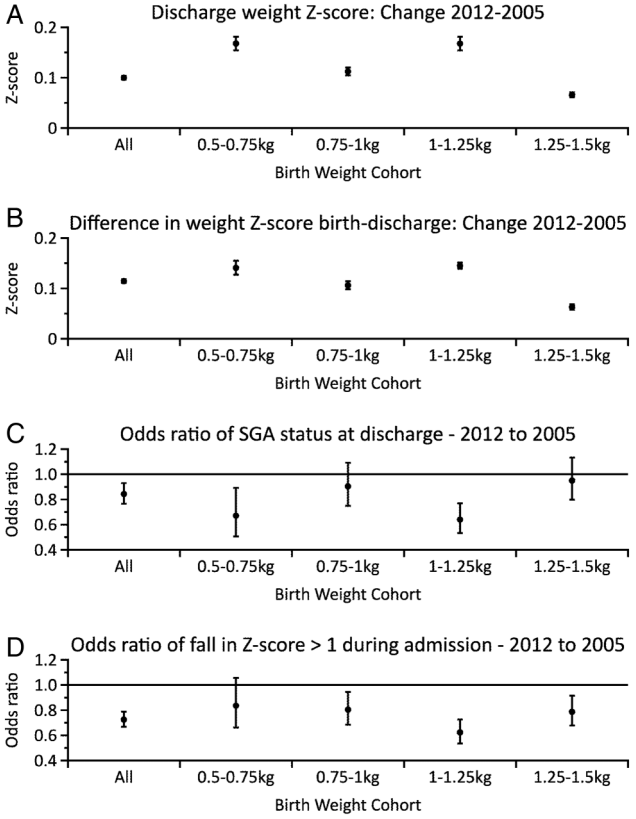

Figure 3 Effect of birthweight cohort on the change in discharge weight Z-score between 2005 and 2012 (A), the change in difference between weight Z-score and discharge weight Z-score between 2005 and 2012 (B), OR for being small for gestational age (SGA) at discharge 2005 vs 2012 (C) and OR for a fall in Weight Z-score >1.0 between birth and discharge in 2005 compared to 2012 (D). Data are shown as mean±95% CI (A and B) or as OR±95% CI (C and D).

Z-score between birth and discharge (−0.04 (−0.03 to −0.05); p<0.0001) and reduced odds of being discharged below the 10th centile for age (OR 0.90 (0.82 to 0.99); p=0.0226) or a weight Z-score falling >1.0 during admission (OR 0.79 (0.73 to 0.85); p<0.0001). No other results were changed by inclusion of length of stay in the model.

Growth velocity

Unadjusted growth velocity between birth and discharge increased from 12.07 g/kg/day (11.9 to 12.15) in 2005 to 12.26 (12.20 to 12.32) in 2012. Following adjustment for confounders, the increase over the either 8-year study period was 0.25 g/day (p<0.0001). Significant differences were also seen in growth velocity in g/kg from birth to discharge (21.6 (20.0 to 23.2) in 2005 to 22.7 (21.1 to 24.3) in 2012; p<0.0001), and using the Patel formula (13.11 (13.02 to 13.20) in 2005 to 13.37 (13.30 to 13.45) in 2012; p=0.0191).

DISCUSSION

In this large cohort study of VLBW infants, we identified significant improvements in growth in hospitalised VLBW infants in California. Our outcomes are significantly better than those reported from the National Institute of Child Health and Human Development network in the 1990s, where >95% of VLBW infants were below the 10th weight-for-age centile at hospital discharge.[4 5] Although there is little comparable high-quality population-level data on recent changes in postnatal growth in preterm infants, one study from Israel has shown an improvement in growth restriction (defined as a fall in weight Z-score during admission of >1.0) from 53% in 1995–2000, to 43% in 2001–2006, to 35% in 2006–2010.[14]

These improvements may relate to changes in nutritional practices, or changes in the incidence, or severity, of conditions associated with growth restriction,[6] or non-associated improvements in growth, and decreases in the rate of these morbidities. However, there is still opportunity for improvement as another large cohort has reported even lower incidences of growth restriction.[13]

The factors most disadvantageous to growth in our study were the development of surgical or medical necrotising enterocolitis, gastrointestinal perforation and severe retinopathy of prematurity. Some of these factors have been identified previously.[10 13] The adverse growth effects of necrotising enterocolitis and gastrointestinal perforation are not[18] surprising. However, why severe retinopathy of prematurity should be associated with poorer growth is less obvious. However, there is evidence that infants with severe retinopathy of prematurity do receive lower calorie intakes than their peers,[9] and that early aggressive nutrition reduces the risk of retinopathy of prematurity.[19 20] Alternatively, early nutritional and growth factors may be involved in the pathogenesis of retinopathy of prematurity, perhaps mediated by the IGF-1/IGF-BP-3 system.[21]

Several investigators have identified early respiratory disease or oxygen requirement at 28 days as predictors of poorer growth outcomes.[10 13] We did not find a similar adverse effect of chronic lung disease in our cohort. Indeed, once the

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Table 2 Results of linear modelling and logistic modelling for growth outcomes

Criteria Analysis	Weight Z-score at discharge	ΔWeight Z-score birth, discharge	Weight<10th centile at discharge	ΔWeight Z-score birth discharge>1.0
Gender (female)	0.171**** (0.156 to 0.187)	−0.063**** (−0.079 to −0.048)	0.586**** (0.550 to 0.624)	1.198**** 1.137 to 1.264)
Gestational age (days)	−0.060**** (−0.060 to −0.059)	0.011**** (0.010 to 0.011)	1.187**** (1.182 to 1.193)	0.969**** (0.966 to 0.972)
Birth weight (100 g)	0.353**** (0.348 to 0.358)	−0.017**** (−0.022 to −0.012)	0.370**** (0.359 to 0.380)	1.028*** (1.012 to 1.044)
Early sepsis (yes)	0.013 (−0.058 to 0.084)	−0.013 (−0.058 to 0.085)	1.157 0.884 to 1.515)	0.987 (0.780 to 1.249)
Late sepsis (yes)	−0.154**** (−0.183 to −0.125)	−0.135**** (−0.165 to −0.106)	1.430**** (1.278 to 1.600)	1.393**** (1.265 to 1.534)
Medical NEC (vs no NEC)	−0.236**** (−0.284 to −0.187)	−0.240**** (−0.289 to −0.191)	1.675**** (1.381 to 2.031)	2.054**** (1.741 to 2.422)
Surgical NEC (vs no NEC)	−0.572**** (−0.658 to −0.486)	−0.545**** (−0.632 to −0.457)	4.562**** (3.104 to 6.707)	3.239*** (2.279 to 4.604)
Gastrointestinal perforation (yes)	−0.462**** (−0.532 to −0.392)	−0.446**** (−0.517 to −0.375)	2.587**** (1.949 to 3.434)	1.612*** (1.249 to 2.081)
Chronic lung disease (yes)	−0.029** (−0.050 to −0.007)	−0.014 (−0.007 to 0.036)	0.988 (0.911 to 1.072)	0.952 (0.888 to 1.020)
Severe ROP (yes)	−0.320**** (−0.355 to −0.283)	−0.166**** (−0.201 to −0.130)	2.489**** (2.175 to 2.847)	1.113**** (0.977 to 1.270)
Severe IVH (yes)	−0.064** (−0.104 to −0.025)	−0.064** (−0.104 to −0.025)	1.534**** (1.321 to 1.782)	1.076 (0.938 to 1.235)
PVL (yes)	−0.005 (−0.053 to 0.062)	−0.002 (−0.057 to 0.060)	0.983 (0.787 to 1.229)	1.032 (−0.850 to 1.251)
Year of birth (per year)	0.014**** (0.011 to 0.018)	0.016**** (0.012 to 0.020)	0.976*** (0.963 to 0.990)	0.955**** (0.944 to 0.967)

Effects reported as regression coefficients (95% CI) for linear modelling and as adjusted OR (95% CI) for logistic regression.
*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.
IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

increased length of stay that results from chronic lung disease was accounted for, chronic lung disease was associated with an increased body size at discharge. This result suggests that prolonged length of stay has different growth consequences in babies with chronic lung disease than in those without chronic lung disease. One might speculate that in babies without chronic lung disease, discharge is delayed, pending resolution of acute illnesses and establishment of enteral feeds, while in a baby with chronic lung disease, discharge is delayed, pending attempts to wean oxygen or arranging home oxygen supplies and those relatively stable infants have an opportunity to 'catch-up' prior to hospital discharge. Alternatively, one could speculate that the relatively better growth outcomes of babies with chronic lung disease reflect an increased awareness of the increased nutritional needs of these infants and the importance of optimising nutrition and growth to maximise their pulmonary rehabilitation.

We report associations between common morbidities and postnatal growth, but cannot prove cause and effect. It is possible that sicker infants were at an increased risk of poor growth outcomes and at higher risk of the comorbidities of prematurity, or that poorer early nutritional intakes affected both growth and the incidence of comorbidities.[22] However, not all morbidities were associated with poorer growth, and there are sound physiological reasons why some comorbidities might be the cause of poorer postnatal growth.

Our study benefits from the large size of the databases and the breadth of outcome measures and confounding data collected. More than 90% of VLBW infants born in California are covered by the database, so our results are likely to be broadly applicable. However, there are limitations to our study. Most importantly, we did not have data on specific nutritional practices, so we are unable to relate these to the improvements in growth outcomes observed.

In summary, postnatal growth restriction among VLBW infants has improved in California between 2005 and 2012. Several common comorbidities of prematurity are significantly associated with postnatal growth restriction including medical or surgical necrotising enterocolitis, gastrointestinal perforation and severe retinopathy of prematurity. These results should help clinicians to identify those infants at highest risk of adverse growth outcomes and work to further improve these outcomes.

Contributors IJG was primarily responsible for study design, data analysis, data interpretation and manuscript preparation. DJT assisted with data analysis and study design. All authors contributed to study design, data interpretation and manuscript preparation.

Competing interests None declared.

Ethics approval The protocol was reviewed by the UC Davis Institutional Review Board, which determined that neither their approval nor informed consent was required. Institutional review board approval was obtained from Stanford University.

Provenance and peer review Not commissioned; externally peer reviewed.

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