Changes in the Growth of Very Preterm Infants in England 2006-2018

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ABSTRACT

Objective

To compare weight gain from birth to term equivalent age in very preterm infants in England born during two eras (2006-2011 and 2014-2018). To assess demographic and care factors influencing weight gain.

Methods

Data for infants born before 32 weeks of gestation during 2014-2018 in England were obtained (29,687 infants). Weight gain modelled using SuperImposition by Translation And Rotation (SITAR), with infants grouped by gestational week. A cohort from 2006-2011 was used for comparison (3,288 infants). Multiple linear regression was used to assess factors influencing change in weight SD score from birth to 36 weeks postmenstrual age (PMA).

Results

Weight gain velocity (termed “intensity” in SITAR models) was greater in the more recent cohort for all gestation groups born before 30 weeks of gestation. After adjustment for gestation, birthweight and other perinatal factors, care elements associated with faster weight gain included delivery in a Level 3 unit (0.09 SD less weight gain deficit, 95%CI 0.07 to 0.10) and parenteral nutrition initiation during the first day of life (0.08 SD, 95%CI 0.06 to 0.10). Factors associated with slower weight gain included early ventilation (-0.07 SD, 95%CI: -0.08 to -0.05) and less deprived neighbourhood (-0.012 SD per index of multiple deprivation decile, 95%CI: -0.015 to -0.009).

Conclusions

Weight gain for extremely preterm infants was faster during 2014-2018 than during 2006-2011. Early initiation of parenteral nutrition and birth in a level 3 unit may contribute to faster weight gain.

WHAT IS ALREADY KNOWN?

- Very preterm infants in England during 2006-2011 demonstrated a pattern of weight crossing centiles downwards.
- Poor growth during the neonatal period is associated with adverse neurodevelopmental outcomes.

WHAT THIS STUDY ADDS

- Extremely preterm infants in England gained weight faster during the period 2014-2018 compared with 2006-2011, but a fall in weight SD score between birth and 36 weeks postmenstrual age remained.
- This fall in weight SD score was smaller for infants born in a Level 3 neonatal unit and those who received early parenteral nutrition, and was greater for infants from less deprived neighbourhoods.

HOW THIS STUDY MIGHT AFFECT RESEARCH AND PRACTICE

- This study identifies care factors associated with faster weight gain in very preterm infants. Further research is required to assess their effects on important outcomes such as neurodevelopment.

INTRODUCTION

Analysis of weight trajectories of very and extremely preterm infants managed in English neonatal units during the period 2006-2011 demonstrated that downward crossing of weight centiles was common.[1] Mean growth curves of the infants fell by more than two centile spaces between birth and term equivalent age (corresponding to a fall in standard deviation score of around 1.5). This work used the SuperImposition by Translation And Rotation (SITAR) growth curve model to summarise the growth of groups of infants into a single summary curve.[2]

The extent to which this pattern of growth is physiological or desirable remains contested. Early water loss during postnatal adaptation may cause weight loss followed by growth along a lower trajectory. However, the appropriate degree of early weight loss at different gestations is difficult to define given that all very preterm infants are subject to active fluid management in neonatal units. Previous work using the SITAR method with infants born in England demonstrated a lack of early weight loss in the most preterm infants[1], whereas early weight loss was identified at all gestations in a study of a cohort of German and Canadian infants.[3]

An increasing body of evidence has demonstrated an association between faster growth during the neonatal period and improved later neurodevelopmental outcomes for preterm infants.[4-6] Work in term-born infants has identified that low birthweight followed by rapid weight gain in infancy is associated with adverse cardiometabolic outcomes.[7] Recent findings have suggested that growth during the first few weeks of life in preterm infants has little impact on metabolic health.[8,9] Taken together, these data suggest that increasing growth in the early postnatal period may improve neurodevelopmental outcomes without adversely impacting cardiometabolic health.

Since 2011 there have been changes in neonatal practice, prioritising early nutrition including the early introduction of parenteral nutrition and ongoing improved nutritional provision to preterm infants, with a recent study by our group demonstrating that early postnatal growth of infants born very preterm can be improved and brought more into line with in-utero growth.[10]

This paper has two aims: to assess changes in growth patterns of preterm infants between the 2006-2011 cohort and a later cohort born during 2014-2018; and to assess the impact of demographic features at birth, complications of prematurity and level of neonatal care unit on the growth of preterm infants.

Patients and Methods

Data were obtained from the National Neonatal Research Database (NNRD).[11] Weight was selected as a marker of growth as it had the most complete data entry in the database.

Data for all infants born before 32 weeks of gestation and cared for during the period from 2014 to 2018 in England were obtained from the NNRD. Data included gestation, birthweight, sex, multiplicity of pregnancy, level of neonatal unit at the place of birth, Apgar score, lower super output area (LSOA) of the mother's address, serial weight measurements, and daily ventilation and nutrition type information. The LSOA is a geographical area which is associated with an index of multiple deprivation (IMD) score in UK government publications,[12] with a higher IMD score denoting lower levels of deprivation in that neighbourhood. Weight and sex information from the published 2006-2011 cohort were used.[1,12]

Visual examination of weights revealed a handful of extreme outliers above 60,000g or below 60g which were excluded. Bands of weights far above and far below the expected range were identified as transposition errors caused by incorrect decimal places and were shifted accordingly. The data cleaning protocol is given as Supplementary File A. Upper age limits were set so that at least 10% of infants for each completed week of gestation remained in the dataset at that age, to maintain adequate data for modelling. This approach is consistent with previous reports.[1]

This project was approved by the Oxford A research ethics committee (20/SC/0073).

SITAR Analysis

Weight gain was summarised using the SITAR growth curve model with the `sitar` package in R.[13] Cleaned data from the 2006-2011 cohort were also re-analysed to compare the results for the two eras.

The SITAR model fits a shape-invariant mean growth curve which is assumed to underlie each infant's curve. Individual curves then deviate from the mean curve in terms of three random effects: *size* reflects the overall weight of the infant, *timing* is the age when the infant has the fastest weight gain velocity, and *intensity* is the overall rate of weight gain. The era of the study (i.e. 2006-2011 versus 2014-2018) was included as a fixed effect in combined models using all infants, to test its effect on size, timing and intensity.

SITAR curves were fitted for male and female infants combined as their growth patterns are known to be similar.[1,14] Separate growth curves were formed for each week of gestational age at birth, with 22 and 23 weeks of gestation combined due to small numbers. This matched the approach of the earlier cohort. Weight measurements more than four residual standard deviations from these mean growth curves were then excluded. For each individual growth curve, weight measurements were examined as triplets, velocity of weight gain was calculated for each measurement and those with an implausible velocity were excluded. Final SITAR models were formed from the resultant data.

Reanalysed UK1990 growth centiles[15,16] were illustrated using reference data within the `childsds` package for R, with the centiles for males and females averaged.[17]

Regression Analysis

Weight SD scores were calculated using the reanalysed UK1990 data, which excluded infants born prior to 23 weeks.[15] Weight SD scores were calculated at birth, at seven days of life and at 36 weeks PMA. Weight change was defined as the difference in weight SD scores between two time points.

Multiple linear regression models were used to assess demographic and clinical factors which had been identified by clinical researchers as likely to influence growth. The Bayesian information criterion (BIC) was used to assess model efficiency and to select the most appropriate variables for inclusion. For each model variable the *t*-statistic was calculated by dividing the regression coefficient by its standard error; *t*-statistics exceeding 2 in absolute value indicate statistical significance at $P < 0.05$.[18]

RESULTS

Weight data were available for 29,687 infants born 2014-2018 and 3,288 infants born 2006-2011 (161 units contributed data during 2014-2018; 40 were included in the database in 2006-2011).

SITAR Growth Curve Analysis

Figure 1A shows SITAR curves for infants born 2014-2018 grouped by completed weeks of gestation and superimposed on UK-WHO weight centiles with the sexes averaged. Figure 1B shows the same data with weight on a logarithmic scale, so that the slope of each curve represents relative weight gain (*i.e*. g/kg body weight/day).[19] Each curve is close to median weight for gestation at birth but then crosses centiles downwards.

Comparison with Data from 2006-2011

Figure 2 compares SITAR curves from the two eras, 2006-2011 and 2014-2018. For infants born from 24 to 28 weeks of gestation, weight at birth was similar. Birthweight was lower in the more recent era for infants born at 22-23 weeks, likely reflecting a trend towards initiating intensive care more commonly in the smallest and most premature infants.

For each gestation group before 28 weeks, SITAR curves for the two eras diverged slightly, with infants in the more recent era exhibiting faster weight gain signified by a steeper SITAR curve. This effect was not so apparent for infants born after 28 weeks PMA. For the more mature infants, the SITAR curve for the 2006-2011 infants demonstrated early weight loss, followed by increasing weight. This pattern was much less prominent for the 2014-2018 cohort, with very little early weight loss seen in these infants. Instead, there was a period of static weight followed by acceleration in growth velocity.

Table 1 shows the effect of being in the 2014-2018 cohort on the size (in grams), timing (in weeks) and intensity (in percentage change) fixed effects of the SITAR models for each gestation group, with the associated *t*-statistics. The size value was generally higher (although not always significantly so). This indicates that mean weight was greater during the 2014-2018 cohort than the 2006-2011 cohort (see Figure 2). The timing parameter reflects the age at peak weight gain, and the negative effect for the later cohort indicates peak weight gain occurring earlier (although not significantly so for most groups). Intensity was significantly greater for every gestation group born before 30 weeks of gestation, indicating more rapid weight gain in the later cohort.

Table 1. The effect of birth in the 2014-2018 era (compared to the 2006-2011 era) on mean size, timing and intensity of SITAR models, grouped by gestation.

Gestation group (weeks)	Effect of later era on size, grams (95% CI)	*t*-statistic	Effect of later era on timing, weeks (95% CI)	*t*-statistic	Effect of later era on intensity, % (95% CI)	*t*-statistic
22-23	20 (-35 to 74)	0.7	-0.4 (-1 to 0.3)	-1.2	12 (5 to 19)	3.3
24	62 (31 to 93)	3.9	-0.2 (-0.6 to 0.1)	-1.3	15 (11 to 19)	7
25	11 (-17 to 40)	0.8	-0.4 (-0.7 to -0.2)	-3.2	5 (1 to 8)	2.5
26	61 (38 to 84)	5.1	-0.1 (-0.3 to 0.2)	-0.5	13 (10 to 16)	8
27	53 (33 to 73)	5.1	0.0 (-0.2 to 0.1)	-0.3	9 (7 to 12)	6.7
28	50 (32 to 68)	5.3	0.1 (-0.1 to 0.2)	1.1	6 (4 to 9)	4.8
29	24 (6 to 42)	2.6	0.1 (0 to 0.1)	2.1	5 (3 to 7)	4.3
30	11 (-7 to 29)	1.2	-0.3 (-0.6 to -0.1)	-2.8	-2 (-3 to 0)	-2.2
31	12 (-6 to 30)	1.3	-1 (-1.3 to -0.8)	-7.2	-3 (-4 to -2)	-7.4

Early Weight Loss in the 2014-2018 Cohort

Infants born at 22-23 weeks of gestation had the smallest drop in weight (mean loss 1.8%) and those at 31 weeks had the largest (mean loss 4.3%). Over the whole cohort, 49% of infants had no early weight loss.

Influences on Weight Gain in the 2014-2018 Cohort

For the analysis of influences on weight gain in the 2014-2018 cohort, infants were included who had weight measured at birth, during the second week of life and at 36 weeks PMA. Demographic details of included infants are given in Table 2. As expected, there were more infants born at later gestations (Supplementary Figure 1). The mean change in weight SD score from birth to 36 weeks PMA was -0.94. This consisted of a drop of 0.66 SD scores during the first week of life followed by a drop of 0.28 SD scores between the second week of life and 36 weeks PMA.

Table 2. Summary details of included infants

Number of infants		27505
Gestational age (weeks+days) (median (IQR))		29^{+2} (27^{+3} to 30^{+6})
Birthweight (g) (median (IQR))		1156 (895 to 1430)
Birthweight z-score (mean (SD))		-0.45 (0.90)
Small for gestational age (% (*n*))		18% (4826)
Male (% (*n*))		54% (14914)
Singleton (% (*n*))		73% (19968)
Neonatal Unit Level at Birth Centre	Level 1 (% (*n*))	9% (2423)
	Level 2 (% (*n*))	38% (10571)
	Level 3 (% (*n*))	53% (14511)
Change in Weight SD score from birth to 36 weeks PMA (mean (SD))		-0.94 (0.66)
Change in Weight SD score from birth to the second week of life (mean (SD))		-0.66 (0.39)
Change in Weight SD score from the second week of life to 36 weeks PMA (mean (SD))		-0.28 (0.62)

Table 3 summarises the multiple linear regression of weight change in the 2014-2018 cohort on selected perinatal factors. The regression coefficient column shows the effect of a one unit change in each factor on the change in weight SD score between birth and 36 weeks PMA.

Infants with a higher Apgar score exhibited faster weight gain and those who required ventilation during the first day of life had slower weight gain, suggesting that sicker infants had slower weight gain. Birth in a level 3 unit was associated with an increase in weight SD change of 0.09 (95%CI 0.07 to 0.10), i.e. infants born in a level 3 unit gained weight faster, with a mean 0.09 SD score smaller weight gain deficit, than infants born in a level 1 or level 2 unit. Initiation of parenteral nutrition during the first day of life was also associated with greater weight gain (0.08 SD, 95%CI 0.06 to 0.10). Birth to a mother residing in a less deprived neighbourhood was associated with slower weight gain. These effects were not materially altered when weight change was calculated from the second week of life to 36 weeks PMA (Supplementary Table 1).

However the effect of birthweight was different depending on whether weight gain was calculated from birth or from the second week of life. When birth was taken as the starting point, gestational age was positively associated with weight change, and birthweight negatively, indicating that weight change was generally more positive for later born and smaller-for-dates infants. There was a positive interaction between birthweight and gestational age at birth, indicating that the effect of birthweight (i.e. faster growth for smaller-for-dates infants) was greater for more preterm infants. When weight during the second week of life was taken as the starting point, birthweight was positively associated with weight change and the interaction term was negative. This reflects greater early weight loss in larger-for-dates infants.

Table 3. Results of multiple linear regression of change in weight SD score from birth to 36 weeks postmenstrual age on factors around the time of birth

	Regression coefficient – weight change (95% CI)	***t*-statistic**
Gestational age (weeks)	0.14 (0.13 to 0.15)	23
Birthweight (kg)	-1.5 (-1.8 to -1.1)	-8
Interaction term for gestational age (weeks) and birthweight (kg)	0.02 (0.006 to 0.029)	3
Sex (female)	-0.12 (-0.14 to -0.10)	-15
IMD decile*	-0.012 (-0.015 to -0.009)	-8
Born in level 3 unit (vs born in level 1 or level 2 unit)	0.09 (0.07 to 0.10)	10
Apgar score at 5 minutes	0.005 (0.002 to 0.009)	2.1
Ventilated on day of birth (vs not)	-0.07 (-0.08 to -0.05)	-7
Parenteral nutrition during first day of life (vs not)	0.08 (0.06 to 0.10)	9
Birth year (effect of birth one year later)	0.035 (0.029 to 0.040)	12

*Index of multiple deprivation decile for mother's postcode (higher is less deprived)

Supplementary Table 1. Results of multiple linear regression of change in weight SD score from the second week of life to 36 weeks postmenstrual age on factors around the time of birth

	Regression coefficient – weight change (95% CI)	***t*-statistic**
Gestational age (weeks)	0.09 (0.08 to 0.10)	15
Birthweight (kg)	1.0 (0.7 to 1.4)	6
Interaction term for gestational age (weeks) and birthweight (kg)	-0.03 (-0.05 to -0.02)	-6
Sex (female)	-0.04 (-0.06 to -0.03)	-5
IMD decile*	-0.013 (-0.016 to -0.010)	-9
Born in level 3 unit (vs born in level 1 or level 2 unit)	0.08 (0.06 to 0.09)	10
Apgar score at 5 minutes	0.008 (0.004 to 0.013)	4
Ventilated on day of birth (vs not)	-0.08 (-0.10 to -0.06)	-9
Parenteral nutrition during first day of life (vs not)	0.04 (0.02 to 0.06)	4
Birth year (effect of birth one year later)	0.022 (0.016 to 0.027)	8

*Index of multiple deprivation decile for mother's postcode (higher is less deprived)

DISCUSSION

Changes in Weight Gain Pattern

This paper describes the weight gain pattern of very preterm infants in England born during 2014-2018. In comparison to infants born during 2006-2011, the most preterm infants (born before 30 weeks of gestation) exhibited faster weight gain. Early weight loss, which was apparent for later gestations in 2006-2011, was much less pronounced in 2014-2018, being replaced by a short period of static weight. The findings of this study are strengthened by the large number of infants included. Comparisons between the eras are limited by the inclusion of far more neonatal units in the more recent cohort. Weight data were gathered during clinical care and were not subject to standardisation or error checking. There were insufficient data to analyse linear growth or head circumference growth.

The findings presented here are in good agreement with a recent paper using different methods to examine growth in an overlapping cohort.[23] That group found that early postnatal weight loss had decreased over time (as seen in the more mature groups in this analysis) and that subsequent weight gain was faster. Similarly to the data presented here, they identified that weight gain continues to be less than the rate needed to keep pace with the equivalent fetus in utero.

The optimal pattern of weight change during the first two weeks of life remains disputed. In term-born infants, there is a well-recognised pattern of early weight loss, caused by the term contraction of extracellular spaces (TeCES).[24] The extent to which there is a preterm correlate to this effect is unclear. Data from a cohort of preterm infants with minimal comorbidities found greater percentage weight loss in the most preterm infants than in more mature infants[3], with an average early weight loss of 11% in infants born before 30 weeks of gestation and 7% in those born at 30-34 weeks of gestation. Conversely, we found less weight loss in the most immature infants, at only 4%. The discrepancy between these results may be due to differing fluid management and nutritional strategies. Alternatively, the low mean early weight loss seen in these English data may be due to fluid overload in critically unwell infants who would have been excluded from the selective cohort of preterm infants with few complications. SITAR curves provide an objective summary of weight change over a period of time, although the smoothing process may reduce the impact of rapid weight changes, especially early weight loss.

Influences on Growth

Multiple linear regression identified demographic and care factors which were associated with changes in growth from birth to 36 weeks PMA (Table 3). The mean change in weight SD score from birth to 36 weeks PMA was -0.94, consisting of a fall in weight SD score of around 0.66 during the first week of life, followed by a more gradual drop of 0.28 between the second week of life at 36 weeks PMA (as reflected in the SITAR charts). Change in weight SD score was positively associated with later gestation, corroborating the reduced deviation from birthweight centile seen in SITAR models (Figure 2). There was also a positive association with year of birth, confirming that growth has increased over time. Birth in a hospital offering level 3 neonatal care was associated with faster weight gain, suggesting an impact of antenatal transfer to a specialised setting.[20] Early parenteral nutrition was also associated with a reduced weight gain deficit.

Conclusions

Despite modest increases in weight change in the most preterm infants, very preterm infants in England continue to exhibit a pattern of weight gain which falls short of the equivalent fetal growth pattern. Birth in a level 3 unit was associated with faster weight gain, as was early initiation of parenteral nutrition, whilst a marker of lower deprivation was associated with slower weight gain.

FIGURE LEGENDS

Figure 1. SITAR curves for weight by completed weeks of gestational age for the 2014-18 cohort superimposed on reanalysed *UK1990* centile lines (sexes averaged) plotted with **A.** an absolute weight scale; and **B.** a logarithmic scale of weight with a velocity fan demonstrating weight gain in g/kg/day.

Figure 2. SITAR curves by gestational age, comparing infants born during the era of 2006-2011 and the era of 2014-2018. Grey lines are the reanalysed *UK1990* growth chart 2nd, 50th and 98th centile lines for comparison.[15]

Supplementary Figure 1. Number of infants born at each week of completed gestation for included infants in the 2014-18 cohort.

Contributorship

Aneurin Young contributed to the conception and design of the work, analysed the data and drafted the manuscript. Tim Cole contributed to the conception and design of the work, supported data analysis and revised the manuscript. Guo Cheng contributed to the analysis of the data. Sarah Ennis, R Mark Beattie and Mark Johnson contributed to the conception of the work and revised the manuscript.

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Competing Interests

Aneurin Young and Mark Johnson occupy posts supported by NIHR Southampton Biomedical Research Centre.

Data Sharing and Data Availability

Data from the NNRD can be acquired for research upon application.

Ethics Approval Statement

This study involves human participants and was approved by the NHS HRA Oxford A Research Ethics Committee (20/SC/0073).

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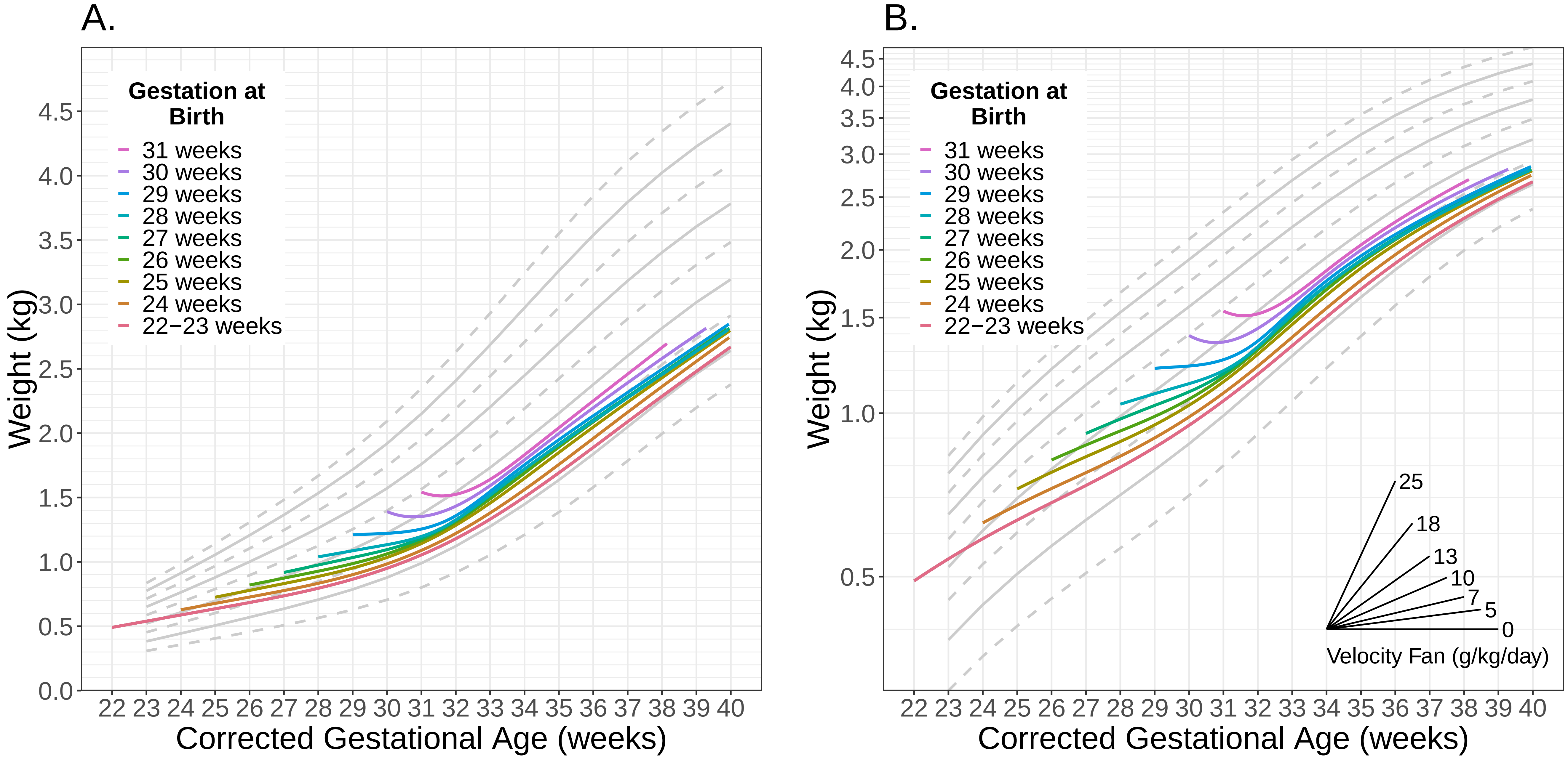
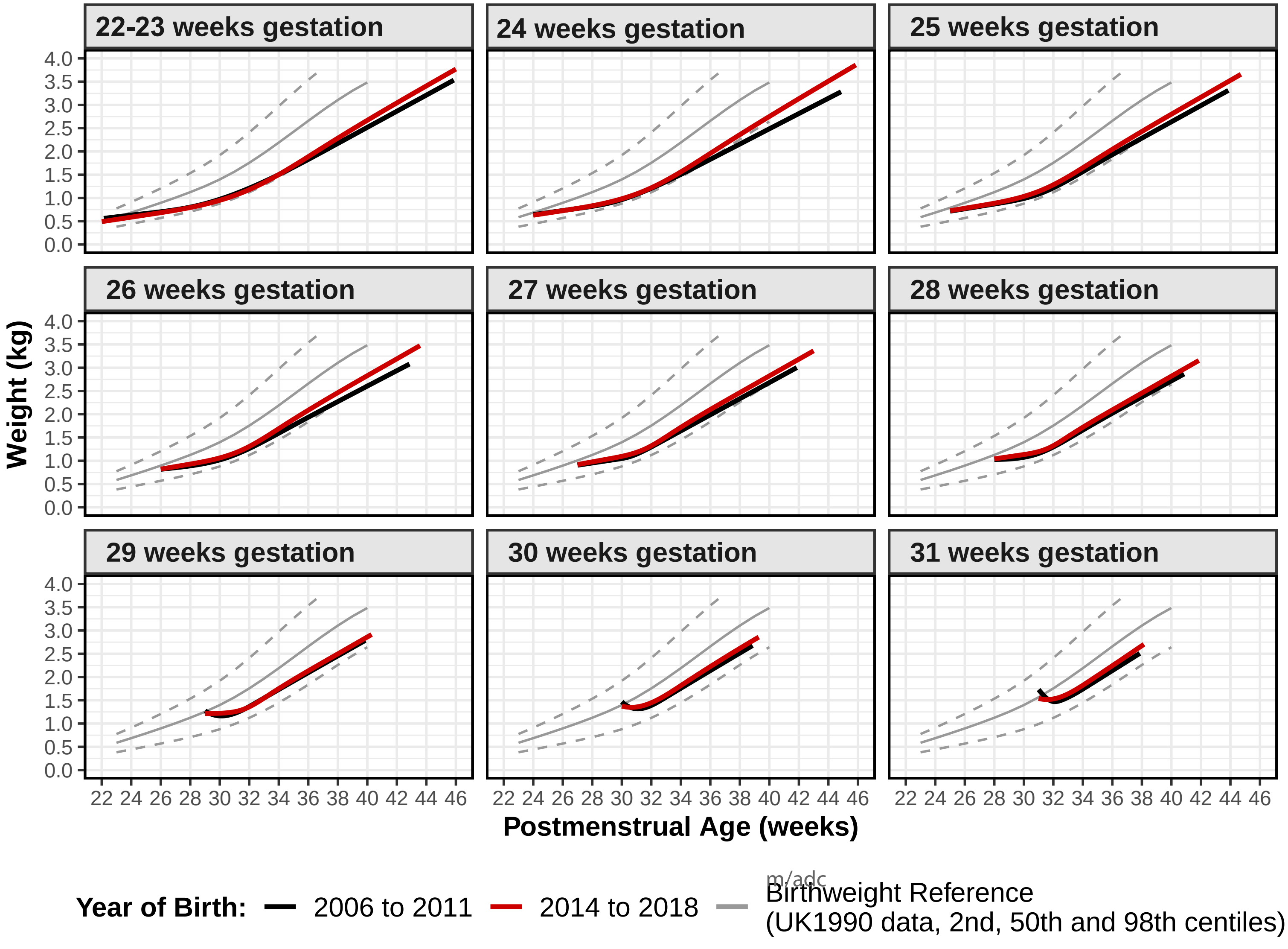
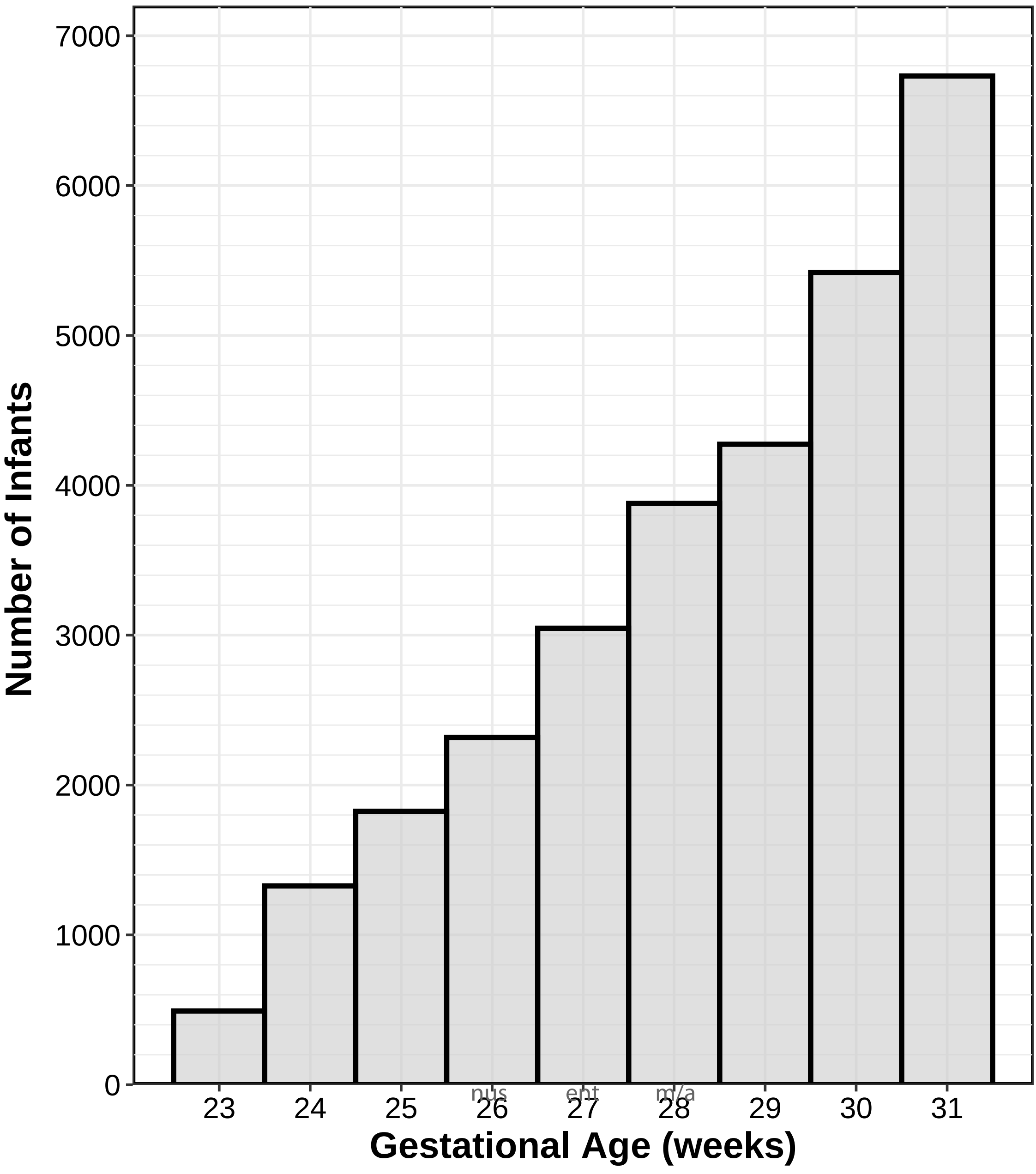


A.
B.
Gestation at Birth
31 weeks
30 weeks
29 weeks
28 weeks
27 weeks
26 weeks
25 weeks
24 weeks
22−23 weeks
Weight (kg)
Corrected Gestational Age (weeks)
Velocity Fan (g/kg/day)
25
18
13
10
7
5
0



22-23 weeks gestation
24 weeks gestation
25 weeks gestation
26 weeks gestation
27 weeks gestation
28 weeks gestation
29 weeks gestation
30 weeks gestation
31 weeks gestation
Weight (kg)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
22 24 26 28 30 32 34 36 38 40 42 44 46
Postmenstrual Age (weeks)
Year of Birth:
2006 to 2011
2014 to 2018
m/adc
Birthweight Reference
(UK1990 data, 2nd, 50th and 98th centiles)



Number of Infants
7000
6000
5000
4000
3000
2000
1000
0
23
24
25
26
27
28
29
30
31
Gestational Age (weeks)

Supplementary File A

Data cleaning protocol

Reported weights (g) were filtered using the following protocol to correct transcription errors and discard implausible values:

If weight is greater 60000 or less than 60, discard it.
If weight is above a line defined by $\frac{2500}{11}CGA - \frac{1700}{11}$ *where CGA is the corrected gestational age in weeks, divide it by 10 (correcting for transcription errors).*
If weight is below a line defined by $\frac{125}{7}CGA - \frac{2500}{7}$*, multiply it by 10 (correcting for transcription errors).*
If weight has not been adjusted or discarded by the above steps and it lies above the line $\frac{650}{3}CGA - \frac{11500}{3}$ *or below the line* $\frac{400}{13}CGA - \frac{6700}{13}$*, discard it.*
Otherwise, retain it.

This protocol is coded as a function in R as follows:

```
function(weight,cga){
  if (weight>60000 | weight<60) NA else
  if (weight>(2500/11*cga-1700/11)) weight/10 else
  if (weight<(125/7*cga-2500/7)) weight*10 else
  if (weight>(650/3*cga-11500/3) | weight<(400/13*cga-6700/13))
NA else
  weight
}
```

SITAR models were then formed for each gestational age group using these filtered data. Weights with a standardised residual exceeding ±4 in the relevant SITAR model were excluded from the final SITAR model.