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Complete List of Authors:	Young, Aneurin; University Hospital Southampton NHS Foundation Trust, Department of Neonatal Medicine; University of Southampton and University Hospital Southampton NHS Foundation Trust, NIHR Southampton Biomedical Research Centre Andrews, Edward; University Hospital Southampton NHS Foundation Trust, Department of Neonatal Medicine Ashton, James; University Hospital Southampton NHS Foundation Trust, Department of Paediatric Gastroenterology; University of Southampton, Department of Human Genetics and Genomic Medicine Pearson, Freya; University Hospital Southampton NHS Foundation Trust, Department of Neonatal Medicine Beattie, R; University Hospital Southampton NHS Foundation Trust, Department of Paediatric Gastroenterology Johnson, Mark; University Hospital Southampton NHS Foundation Trust, Department of Neonatal Medicine; University of Southampton and University Hospital Southampton NHS Foundation Trust, NIHR Southampton Biomedical Research Centre
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GENERATING LONGITUDINAL GROWTH CHARTS FROM PRETERM INFANTS FED TO CURRENT RECOMMENDATIONS

Aneurin Young[a,b], MBBS, Edward Thomas Andrews[a], BM, James John Ashton[c,d], BMBS, Freya Pearson[a], MBBS, R Mark Beattie[c], MBBS, Mark John Johnson[a,b], PhD

Affiliations/Addresses: [a]Department of Neonatal Medicine, Southampton Children's Hospital, University Hospital Southampton NHS Foundation Trust, UK; [b]NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust and University of Southampton, UK; [c]Department of Paediatric Gastroenterology, Southampton Children's Hospital, University Hospital Southampton NHS Foundation Trust, UK; [d]Department of Human Genetics and Genomic Medicine, University of Southampton, UK

Corresponding Author: Aneurin Young, Neonatal Unit, University Hospital Southampton NHS Foundation Trust, Coxford Road, Southampton, SO16 5YA, UK [a.young@soton.ac.uk] 02380777222

Authors' Contributions

Dr Young made a substantial contribution to the design of the work and to the analysis and interpretation of data for the work. He drafted the work and created the web application.

Dr Andrews and Dr Ashton made substantial contributions to the conception of the work and to the acquisition of data for the work. They revised the work critically for important intellectual content.

Dr Pearson and Prof Beattie made a substantial contribution to the conception and design of the work. They revised the work critically for important intellectual content.

Dr Johnson made a substantial contribution to the conception and design of the work and to the interpretation of data for the work. He revised the work critically for important intellectual content.

All authors had final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Abbreviations:

CGA	-	Corrected gestational age
GA	-	Gestational age
HC	-	Head circumference
IQR	-	Interquartile range
MGRS	-	Multicentre Growth Reference Study
MDT	-	Multidisciplinary team
NHS	-	National Health Service
NICM	-	Newborn Infant Close Monitoring chart
RRI	-	Recommended range of intake
SDS	-	Standard deviation score
UK	-	United Kingdom
WHO	-	World Health Organization

WHAT IS KNOWN ABOUT THIS TOPIC

- Current growth charts for the preterm infant are derived from cross-sectional birthweight data, making their applicability to growing preterm infants uncertain.
- The WHO Multicentre Growth Reference Study set a new standard for the production of growth charts using longitudinally gathered repeated measurements of children.
- Despite work in the INTERGROWTH-21st project, this approach has not been fully implemented for preterm infants.

WHAT THIS STUDY ADDS

- This study presents growth charts derived from serial measurements of weight, length and head circumference.
- These charts reflect the postnatal growth of preterm infants, drawn from a real-world population fed in line with current nutritional guidelines.
- A web application has been developed to allow practitioners to plot the growth of infants under their care on these growth charts.

ABSTRACT

Objective: To use repeated measurements of weight, length and, head circumference to generate growth centile charts reflecting real-world growth of a population of very preterm infants with a well-described nutritional intake close to current recommendations.

Design: Infants born before 30 weeks gestational age (GA) were recruited. Infants received nutrition according to an integrated care pathway, with nutrient intake recorded daily, weight recorded twice-weekly and length and head circumference weekly. The LMS method was used to construct growth centile charts between 24 and 36 weeks corrected GA for each parameter.

Setting: A single tertiary neonatal unit in England.

Patients: 212 infants (124 male) (median GA at birth: 27.3 weeks, median birthweight: 900g).

Results: Median daily energy, protein, carbohydrate, and fat intake were within 3% of published recommendations. The total number of measurements recorded was 5944 (3431 for weight, 1227 for length and 1286 for head circumference). Centile charts were formed for each parameter. Data for male and female infants demonstrated similar patterns of growth and were pooled for LMS analysis. A web application was created and published (bit.ly/sotongrowth) to allow infants to be plotted on these charts with changes in SDS of measurements reported and graphically illustrated.

Conclusions: These charts reflect growth in a real world cohort of preterm infants whose nutrient intakes are close to current recommendations. This work demonstrates the feasibility of forming growth charts from serial measurements of growing preterm infants fed according to current recommendations which will aid clinicians in setting a benchmark for achievable early growth.

INTRODUCTION

Preterm infants are at risk of poor growth and tend to leave hospital lighter and shorter than their term-born counterparts.[1] The causes of growth failure are multifactorial and include intercurrent illnesses, complications of prematurity and the sequelae of an adverse *in utero* environment. However, nutritional intake plays a central role and changes in nutritional practice influence growth.[2] [3] Therefore, monitoring of growth against appropriate standards underpins the nutritional care of the preterm infant.

Growth is currently benchmarked against centile charts formed by taking cross-sectional weight data. Examples include the Fenton growth reference[4] which is used extensively, including in North America, and the Newborn Infant Close Monitoring chart (NICM)[5] used in the UK. In both, cross sectional birthweight data, acting as a proxy for in-utero growth, is used to create the chart. Such an approach assumes that preterm infants grow normally up until the point of delivery,[6] and does not generate a true longitudinal growth chart which follows individuals over time. Several studies have shown that, if preterm infants are followed up longitudinally, as a population they exhibit growth failure when compared to such cross-sectional charts, falling down two or more marked centile lines during the first few weeks of life and never recovering. Whether this is ‘normal preterm growth’ is uncertain.[7] [8] The pattern of growth described in these studies has led clinicians to expect and accept growth which falls well short of that demonstrated by fetuses in utero (based on growth charts derived from birthweight data).This limits the usefulness of current growth charts as significant downward deviation from centile lines is ignored or tolerated.

Recent work by our group has demonstrated that weight loss in the first two weeks and subsequent decline in centile line from birth during the initial neonatal admission is not inevitable,[9] and can be alleviated by a comprehensive approach to nutritional care including guidelines, close monitoring of growth, and regular multidisciplinary nutritional review.[2] Furthermore, growth-restricted infants subjected to this nutritional approach show a similar growth pattern to their counterparts whose growth is appropriate for their gestational age.[10]

In recent years, the WHO Multicentre Growth Reference Study (MGRS) has facilitated the generation of longitudinal growth charts, tracking the growth of term infants from six different countries between birth and 16 years of age.[11] Such standards do not exist for very preterm infants. Longitudinal charts for preterm infant growth were created for the INTERGROWTH 21st study.[12] However, it is notable that this component of INTERGROWTH data is derived from 201 infants with a mean gestation at birth of 35.5 weeks and only 28 infants (14%) born below 34 weeks GA. Therefore, data on more significantly preterm infants is mostly extrapolated and may not be representative of how such infants can or should grow, calling into question the applicability of INTERGROWTH in the most preterm populations. Furthermore, whilst there was some use of nutritional guidelines in the INTERGROWTH study, actual nutritional intakes were not reported and so the adequacy of the nutrition supplied to the infants cannot be assessed, may have been insufficient and was likely to be heterogenous across the cohort. It is therefore not clear if the INTERGROWTH infants were able to grow to their full potential.

We aimed to generate growth charts for weight, length and head circumference using data generated from a real-world population of growing preterm infants (born before 30 weeks completed gestation) who were fed to current recommendations and had close nutritional monitoring. We also created a web-based tool which can be used to plot the growth of a preterm infant on these charts.

METHODS

Eligibility Criteria

Infants born before 30 weeks gestational age were recruited from the neonatal unit of University Hospital Southampton between April 2014 and March 2019. There are over 5000 deliveries each year at University Hospital Southampton which is one of three tertiary neonatal units set within the Thames Valley and Wessex Operational Delivery Network and provides tertiary level neonatal, surgical and cardiac services to a population of over two million people in urban, suburban and rural settings.

Gestational age at birth was determined by ultrasonographic dating during the first trimester of pregnancy. Infants were recruited after parents gave informed consent in accordance with NHS Research Ethics Committee approval (Oxford A, ref 14/SC/1275). Infants were recruited within one week of birth. Patients who were transferred to the unit for gastro-intestinal or cardiac surgery, or were diagnosed with genetic syndromes known to impact on growth, were excluded. Follow-up ceased at either discharge from the recruiting neonatal unit, reaching 36 weeks corrected gestational age (CGA), or death.

Anthropometry

Infants underwent twice-weekly measurement of weight and weekly measurement of head circumference and length performed by clinical staff trained according to a standard operating procedure as part of routine clinical care.[13]

Nutritional Care

Infants were subject to a standardised nutritional approach. This approach has been previously described[2] but briefly, parenteral nutrition from the first day of life was accompanied by early trophic feeding. Enteral feeds with maternal breastmilk or preterm formula were increased at a standardised rate and breastmilk fortifier was introduced when enteral feeding reached 100-

130ml/kg/day. Weekly nutrition-focused MDT meetings addressed problems and set nutritional strategies.

Nutritional Intake

Daily nutritional intake data were calculated and stored for each infant prospectively based on the type and volume of enteral and parenteral feeds received each day, using a specially designed spreadsheet containing the nutrient content of all feeds for 33 selected nutrients. Nutrient intake is described per kilogram of body weight, based on the infant's most recent weight on that day.

Statistical Analysis

Centile charts describing the growth of infants were constructed using the LMS method.[14] This method estimates three age-specific cubic spline curves describing a Box-Cox power to remove skewness (the L curve), the median (M curve), and the coefficient of variation (S curve). Centile lines are then formed from these cubic spline curves. LMS functions of the GAMLSS package[15] were used in R[16] within the RStudio environment.[17] Data were assessed for normality using the Shapiro-Wilk test, with normal data summarised using mean and standard deviation, and non-normal data summarised using median and range. Descriptive data and nutritional intake charts were prepared using Stata 15.[18] Birthweight SDS, birth head circumference SDS and definitions of SGA and LGA were derived from the UK Neonatal and Infant Close Monitoring Growth Chart[19] constructed from reanalysed UK 1990 data.[14]

Online Package

The Shiny package[20] within RStudio was used to form a web application, published on the shinyapps.io platform (RStudio, 2017).

RESULTS

212 infants were recruited from 1st October 2014 to 31st March 2019 as part of the Growth Assessment of Preterm Infants (GAP) study (Figure 1). Table 1 shows the characteristics of the population studied. Birth characteristics were not normally distributed and are therefore reported as a median and range.

Gestational age at birth	27·29 (23 to 9·86)
Gestational age at discharge or death	36·07 (26 to 51·43)
Length of follow-up (days)	59·5 (7 to 189)
Sex (male), n (%)	124 (58·5)
Birthweight (kg)	0·90 (0·45 to 1·61)
Birthweight SDS	-0·31 (-3·61 to 2·18)
Birth HC (cm)	24·0 (19·9 to 29·0)
Birth HC SDS	-1·02 (-4·20 to 1·63)
Birth length (cm)	34·0 (26·5 to 40·2)
Small for gestational age (weight <10th centile), n (%)	48 (22·6)
Large for gestational age (weight >90th centile), n (%)	6 (2·8)

Table 1. *Demographic characteristics of preterm infants studied. HC = Head circumference; SDS = Standard deviation score. Data are median (range) unless otherwise stated.*

There were a total of 3431 weight measurements (median 18 per infant), 1227 length measurements (median 6 per infant) and 1286 head circumference measurements (median 7 per infant).

Growth Chart Creation

Centile charts for weight, length and head circumference were generated using the LMS method (Figure 2). Male and female infants were pooled for LMS analysis and growth chart creation. Visual comparison of the LMS 50th centile lines for males and females separately indicated that, although male infants were generally larger than females, patterns of growth did not substantially differ for any growth parameter (Supplementary Figure 1), meaning that changes in SDS (equivalent to downwards or upwards ‘crossing’ of centile lines) can be used to track the progress of growth regardless of sex. Further support for this approach can be found in the striking similarity of the curves at all centiles and the routine pooling of infants of different sexes in subgroup analysis of a very large cohort of preterm infants by Cole at al.[8]

Nutritional Intake

Nutritional intake data was analysed from birth to 36 weeks CGA or discharge. The median daily intake of selected key macronutrients across stay for all studied infants is set out in Table 2 and the first month of life is plotted in Figure 3.

Also shown is the current recommended range of intake (RRI) for fully enterally fed preterm infants[21] and the median daily intake as a percentage of the minimum RRI. Median daily protein intake (and protein-energy ratio) was just below the RRI. Median daily total energy and fat intakes were within the RRI and median daily carbohydrate intake was above the RRI.

Nutrient	Median Daily Intake (IQR)	Recommended Intake (RI)*	Percentage of minimum RI achieved (IQR)
Energy (kcal/kg)	120 (98-136)	110-130	109 (89-124)
Carbohydrate (g/kg)	14·5 (12·4-16·5)	11·6-13·2	125 (106-142)
Protein (g/kg)	3·40 (2·78-3·92)	3·5-4·5	97 (80-112)
Fat (g/kg)	5·45 (3·32-6·56)	4·8-6·6	114 (69-137)
Protein:Energy Ratio (g/100 kcal)	2·94 (2·65-3·10)	3·2-4·1	92 (83-97)

Table 2. *Median daily intake values for selected macronutrients from birth to 36 weeks CGA, recommended intake (RI),[21] mean daily intake as a proportion of minimum RI as % (IQR). IQR = interquartile range.*

Energy intake increased rapidly during the first week of life and then exhibited a slower rise during the remainder of the first month (Figure 3.A). Carbohydrate intake rose rapidly at first and then stabilized at a level above the recommended intake, whilst protein intake rose slowly after the first week (ultimately achieving the recommended intake range) and fat intake rose steadily during the first three weeks of life (Figure 3.B-D). This pattern led to an initial fall in protein-energy ratio followed by a gradual increase (Figure 3.E).

Online Package

An online tool illustrating the new growth charts was created and published at bit.ly/sotongrowth as the Southampton Preterm Growth Package. This tool allows users to enter weight, length and head circumference growth data for a patient and plots that data on centile charts. It also reports and graphically illustrates changes in SDS and allows the changes in weight, length and head circumference SDS to be easily compared. It also provides a basic simulation of a growing preterm infant to illustrate the application's features.

DISCUSSION

We have shown that longitudinal anthropometric data from preterm infants can be used to generate novel growth charts for weight, length and head circumference. These data are derived from a population of preterm infants for whom detailed nutritional information is available and who generally received nutritional intakes close to current recommendations. They represent a 'real-world' mixed population of preterm infants, including those with intrauterine growth restriction and those who suffered complications of prematurity, and are likely to reflect the general population of preterm infants admitted to neonatal intensive care units. They received a carefully applied protocol of nutritional care using products and strategies which are widely available in developed countries.[2]

Charts defining optimal growth would ideally be derived from a very large number of infants who were representative of the whole preterm population, received standardised care which met nutritional requirements and were free of comorbidities. Forming such a cohort is challenging. There remains substantial controversy surrounding nutritional standards. This study used the standards set out by Koletzko[21]. These standards are substantially similar to other international guidelines, including those of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[22], but some differences remain. Uauy and Koletzko define nutritional needs as "the amount and chemical form of a nutrient needed to support normal health, growth and development without disturbing the metabolism of other nutrients".[23] There is insufficient evidence available to make recommendations which fully comply with that definition. In practice, nutritional guidelines are derived from clinical trials of dietary interventions and from observed accretion rates and physiological responses to changes in diet. In the absence of certainty regarding optimal nutritional intake, there is substantial heterogeneity in the approach to nutrition between neonatal units and therefore a lack of a large cohort of infants fed similarly and to an agreed standard.

Despite the use of a nutritional care guideline, there were some deviations from recommended intakes (Table 2 and Figure 2) especially during the first days of life. Specifically, carbohydrate provision was often above the recommended range and the protein provision slightly below it, resulting in a depressed protein-energy ratio. Excess carbohydrate intake has previously been shown to be associated with increased fat storage.[24] We have previously shown that infants managed in this way mimic in utero weight gain, but increases in head circumference and length did not keep pace.[9] This has led to questioning of the quality of their growth, potential for excess adiposity and the impact of our nutritional approach on body composition.[25] Despite a standardised nutritional approach and careful nutritional care, these charts are derived from infants who may not have received optimal nutrition in every respect. Furthermore, this study is limited by the relatively small number of infants included and by its restriction to a single centre, however this did allow standardized capture of nutritional intake. Calculations of nutrient intake were reliable when parenteral nutrition or commercially available formulas are used, but values for maternal and donor breastmilk are derived from historical reference data and so may not reflect the true nutritional composition of the milk received by each individual infant.

Longitudinal charts in older children have typically been created from cohorts of individuals free from comorbidities. However, significantly preterm infants can be expected to experience some complications of their prematurity. It is not obvious how such a cohort of 'well' preterm infants could be differentiated from a 'comorbid' group for the purpose of setting growth standards. We took the approach of including all infants who had not been specifically referred to our centre for surgical care. The resultant charts represent a mixed cohort of infants fed as their clinical condition and comorbidities allowed, as opposed to optimally fed patients without comorbidities. In common with the INTERGROWTH-21st approach, infants were born and entered the study at different gestational ages, meaning that the resultant graphs form a hybrid of cross-sectional birth data and longitudinal growth data.

Tracking individual growth on a chart constructed to include a range of gestations is further complicated by expected weight loss during the first two weeks. The acceptable magnitude of this weight loss is not clear, is likely to less pronounced at earlier gestations[8] and may be preventable.[9] Innovative personalised growth trajectories may be developed to address this issue.[26]

Web-based applications are becoming increasingly popular tools for the analysis of healthcare information.[27] The package created for this project demonstrates the potential for simple web-based tools to be used to assess the growth of preterm infants, when combined with growth standards. With the increasing ubiquity of comprehensive clinical information systems in neonatal units, there is scope for such applications to be integrated into those systems and into the routine monitoring and clinical care of the growing infant.

CONCLUSIONS

We have demonstrated the feasibility of creating growth charts using longitudinal measurements of preterm infants with known nutritional intake. Current charts are based on cross-sectional data and clinicians tolerate downward deviation through the centiles. In contrast, charts created using the approach used in the present study with larger cohorts (and extending into later growth) may allow clinicians to feel a greater confidence that growth along a centile line represents an achievable target, improving the clinical usefulness of growth charts in the preterm population. Web apps can be created from such charts and may provide a tool to promote their implementation in clinical care.

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DATA SHARING STATEMENT: We will share individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices). along with the study protocol and analytic code to researchers who provide a methodologically sound proposal beginning three months and ending five years following article publication. Proposals should be directed to a.young@soton.ac.uk.

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LEGENDS

Figure 1. Recruitment flow chart.

Figure 2. Centile charts for: A) weight, B) length and C) head circumference from 24 to 36 weeks corrected gestational age. Centile lines are marked on the right. Points are individual measurements.

Figure 3. Median (±IQR) daily intake for all infants from first full day of life to 28th day of life of: A) energy, B) carbohydrate, C) protein, D) fat, and E) protein-energy ratio, with recommended intake range indicated by red box.

Supplementary Figure 1. 50th centile lines for male (dashed line) and female (solid line) infants generated using LMS for A) weight, B) length and C) head circumference.

Figure 1

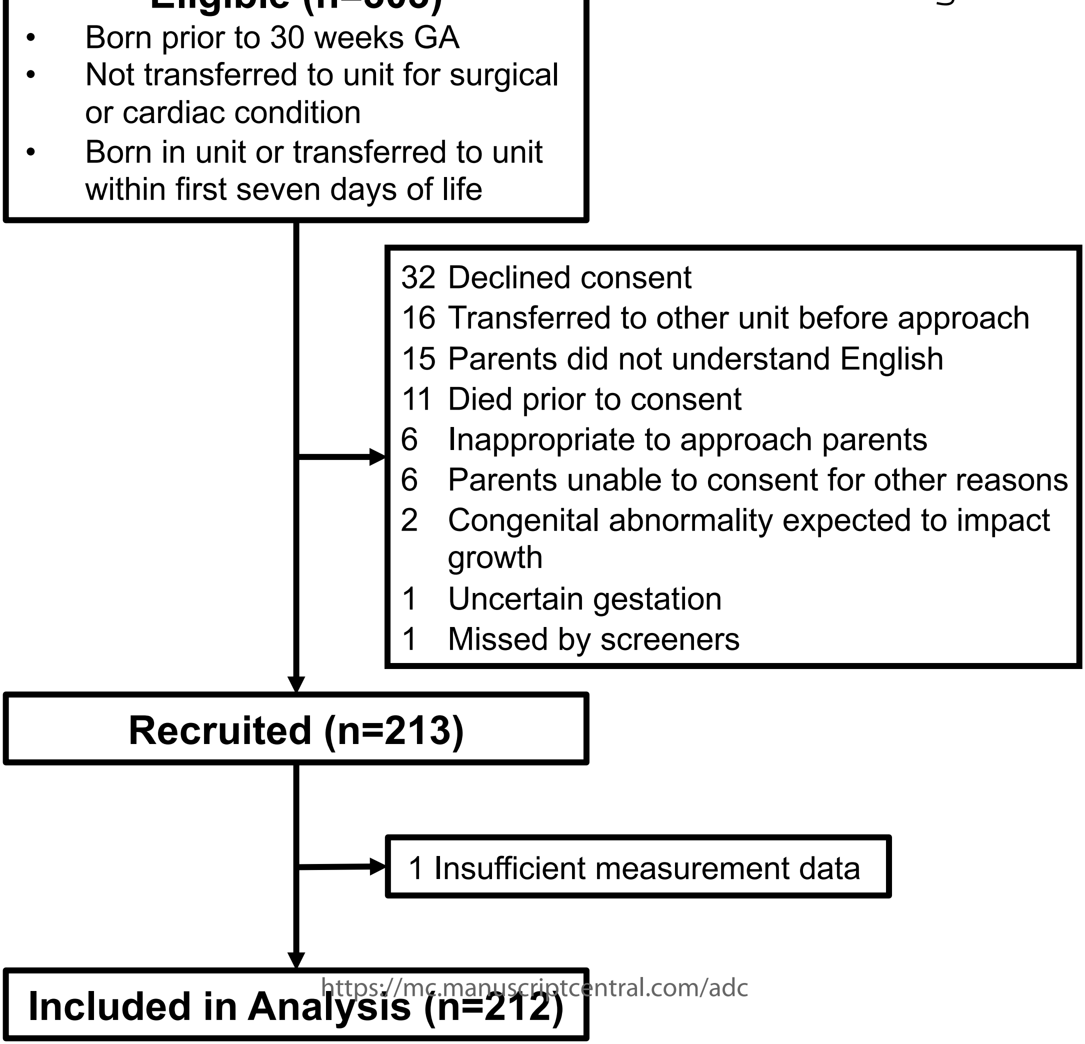

Eligible (n=303)
• Born prior to 30 weeks GA
• Not transferred to unit for surgical or cardiac condition
• Born in unit or transferred to unit within first seven days of life
32 Declined consent
16 Transferred to other unit before approach
15 Parents did not understand English
11 Died prior to consent
6 Inappropriate to approach parents
6 Parents unable to consent for other reasons
2 Congenital abnormality expected to impact growth
1 Uncertain gestation
1 Missed by screeners
Recruited (n=213)
1 Insufficient measurement data
Included in Analysis (n=212)

Figure 2

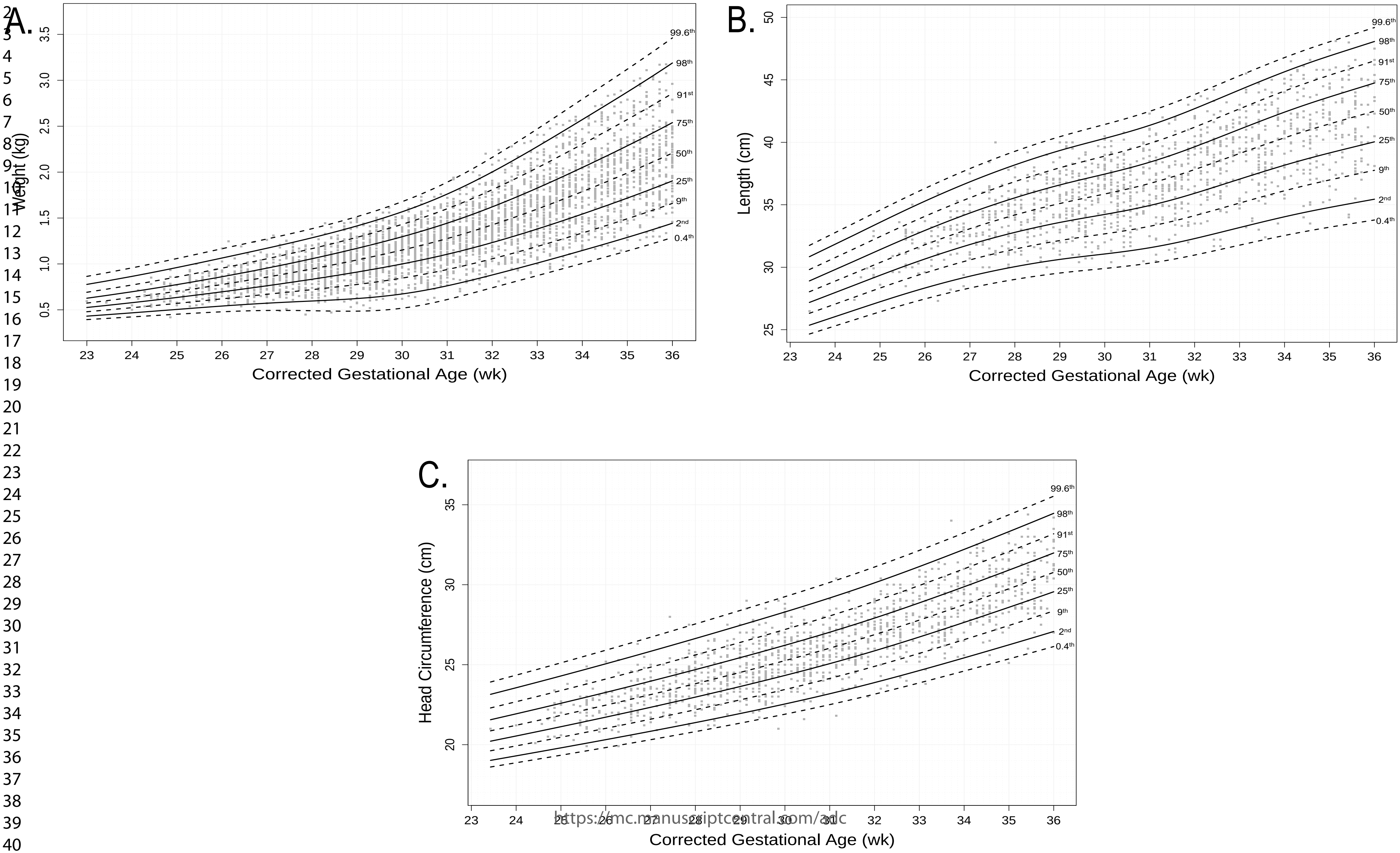
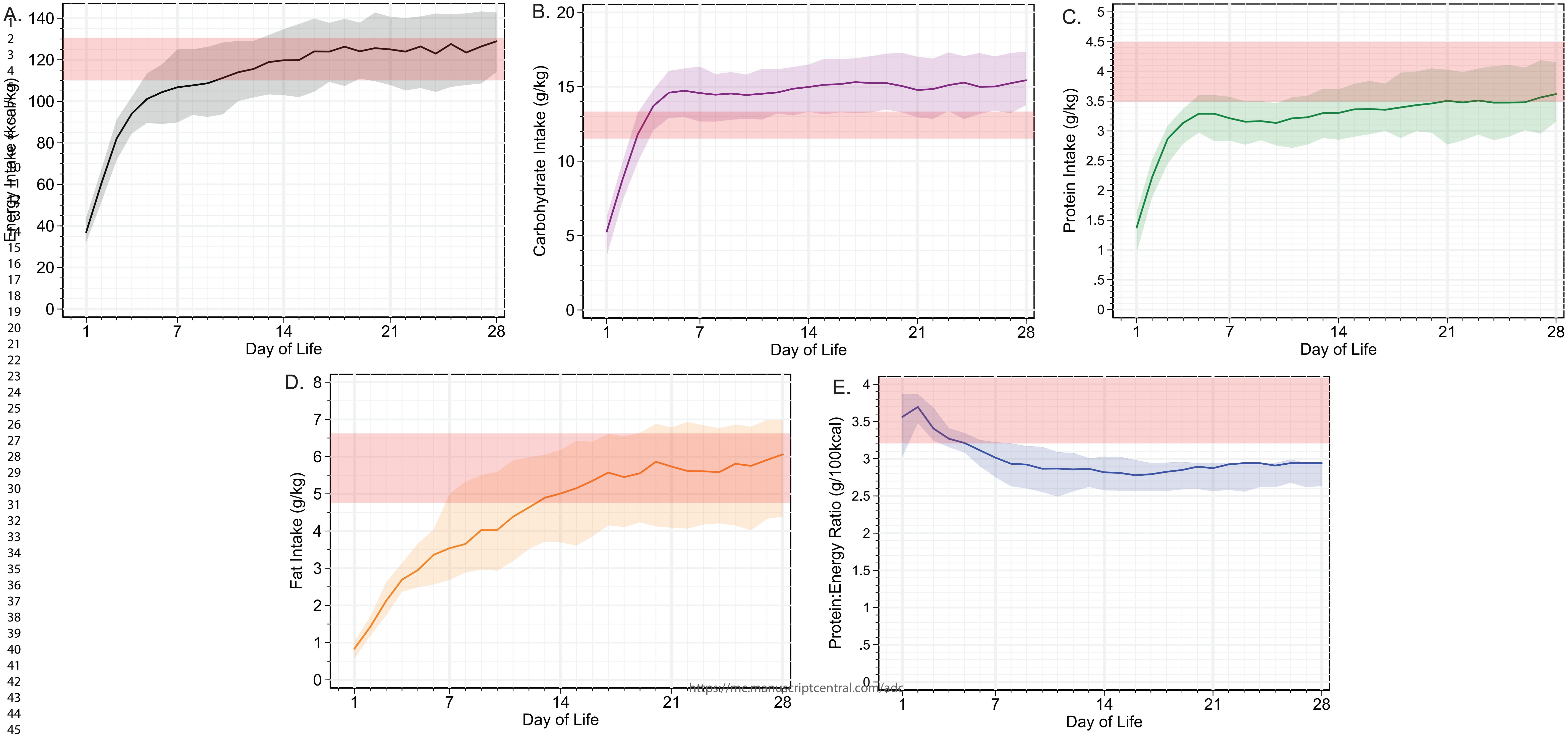

A.
Weight (kg)
Corrected Gestational Age (wk)
99.6th
98th
91st
75th
50th
25th
9th
2nd
0.4th
B.
Length (cm)
Corrected Gestational Age (wk)
99.6th
98th
91st
75th
50th
25th
9th
2nd
0.4th
C.
Head Circumference (cm)
Corrected Gestational Age (wk)
99.6th
98th
91st
75th
50th
25th
9th
2nd
0.4th

Figure 3


A.
Energy Intake (kcal/kg)
Day of Life
B.
Carbohydrate Intake (g/kg)
Day of Life
C.
Protein Intake (g/kg)
Day of Life
D.
Fat Intake (g/kg)
Day of Life
E.
Protein:Energy Ratio (g/100kcal)
Day of Life

Supplementary Figure 1