Pediatric RESEARCH

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CLINICAL RESEARCH ARTICLE

Early-life growth of preterm infants and its impact on neurodevelopment

Charlotte A. Ruys[1], Jonneke J. Hollanders[2], Tinka Bröring[3], Petra E. M. van Schie[4], Sylvia M. van der Pal[5], Monique van de Lagemaat[1], Harrie N. Lafeber[1], Joost Rotteveel[2] and Martijn J. J. Finken[2]

BACKGROUND: Increasing numbers of preterm-born children survive nowadays, and improving long-term health and neurodevelopment is becoming more important. Early-life growth has been linked to neurodevelopmental outcomes. We aimed to study whether this association has changed with time.

METHODS: We studied two cohorts of preterm-born children (gestational age ≤32 weeks and/or birth weight ≤1500 g) from 1983 ($n = 708$) and 2003–2006 ($n = 138$), respectively. We distinguished four early-life growth patterns at 3 months corrected age: appropriate for gestational age (AGA) with or without growth restriction (AGA GR+/AGA GR−), and small for gestational age (SGA) with or without catch-up growth (SGA CUG+/SGA CUG−). Intelligence quotient (IQ), neuromotor function, and behavior were assessed at ages 19 and 8 years, respectively, for the cohorts.

RESULTS: In the 2003–2006 cohort, less children had early-life GR. In both cohorts, SGA CUG− subjects had unfavorable growth trajectories and neurodevelopmental outcomes (IQ β −6.5, 95% confidence interval (CI) −9.8; −3.2, $P < 0.001$; neuromotor score β −1.9%, 95% CI −3.2; −0.6, $P = 0.005$), while SGA CUG+ subjects were comparable to adequately grown subjects.

CONCLUSION: Although the incidence of adverse growth patterns decreased between the cohorts, possibly indicating improvements in care over time, the impact of these growth patterns on neurodevelopmental outcomes was not significantly different. Achieving adequate early-life growth may be crucial for improving neurodevelopmental outcomes, especially for preterms born SGA.

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INTRODUCTION

Neonatology is a rapidly evolving discipline. Throughout the years many advances have been made in both prenatal and neonatal care, including the widespread use of antenatal glucocorticoids, the introduction of synthetic surfactant, and feeding strategies aimed at the early introduction of (par)enteral feeding with high protein contents.[1,2] As a consequence, increasing numbers of extremely preterm (<28 weeks gestation) and extremely low birth weight (<1000 g) infants survive, and this may in part explain why only a modest decrease in neonatal morbidities such as sepsis and retinopathy was observed.[2,3]

Furthermore, a large proportion of preterm infants experiences intrauterine growth restriction (IUGR) and is, as a consequence, usually born small for gestational age (SGA). Preterm SGA infants typically remain smaller and lighter throughout childhood, and have poorer long-term neurodevelopmental outcomes than their appropriate for gestational age (AGA) counterparts.[4–6] In the early postnatal period, extrauterine growth restriction (EUGR) may occur, resulting in 30–95% of very low birth weight (VLBW; birth weight <1500 g) infants being growth restricted around term age or at discharge from the hospital.[7,8] Although IUGR and EUGR are considered two separate entities, both have been associated with impairments in growth and neurodevelopment.[4,9,10] After a period of growth restriction (GR), either prenatal or postnatal, most infants show catch-up growth (CUG) in weight and length during infancy and early childhood,[6] and this has been associated with favorable neurodevelopmental outcomes as compared to GR without CUG.[11] Considering the above, it is important to take both prenatal growth (represented as SGA or AGA at birth) and postnatal growth (either steady growth, GR, or CUG) into account when assessing long-term outcomes.

We aimed to study whether (1) the incidence of GR and (2) its association with childhood growth and neurodevelopmental outcomes have changed over time, by using the data of preterm-born children from two cohorts recruited 20 years apart, namely in 1983 and 2003–2006. We hypothesized that early-life GR occurs less frequent in the more recent cohort, but that growth-restricted subjects without CUG are still at a disadvantage with regard to neurodevelopmental outcomes.

[1]Department of Pediatrics/Neonatology, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands; [2]Department of Pediatric Endocrinology, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands; [3]Department of Medical Psychology, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands; [4]Department of Rehabilitation Medicine, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands and [5]TNO Child Health, PO Box 3005, 2316 ZL Leiden, The Netherlands

Correspondence: Charlotte A. Ruys (c.ruys@vumc.nl)

These authors contributed equally: Charlotte A. Ruys, Jonneke J. Hollanders

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METHODS

Population

Project On Preterm and Small for gestational age infants. The Project On Preterm and Small for gestational age infants (POPS), a nationwide cohort, consisted of almost all (94%; $n = 1338$) of the children born alive in 1983 in The Netherlands who were born either very preterm (VP; gestational age <32 weeks) and/or with a VLBW,[12] of whom 998 survived after discharge. Infants were recruited at 101 out of 115 level 1 to level 3 hospitals in The Netherlands, and no exclusion criteria were applied to the cohort. Follow-up was scheduled regularly. At age 19 years, the 959 surviving subjects were approached for follow-up, of whom 705 participated.

Study Towards the Effects of Postdischarge nutrition. For the nutritional randomized controlled trial (RCT) called "Study Towards the Effects of Postdischarge nutrition" (STEP), 152 infants born VP and/or with a VLBW between 2003 and 2006 in VU University Medical Center Amsterdam were included at birth. The Neonatal Therapeutic Intervention Scoring System (NTISS) was used as an indicator of neonatal illness severity and mortality risk. At term age, subjects were randomized to receive either a protein-enriched and mineral-enriched postdischarge formula or a standard term formula until 6 months corrected age (CA); a control group of infants fed human milk was also included. For the follow-up study at age 8 years (STEP-2), 21 subjects were excluded and 52 declined to participate or could not be traced, resulting in 79 participants.[13] At age 8 years there were no differences between the feeding groups in growth and body composition,[13] or neurodevelopmental outcomes (unpublished data).

Approval of the medical ethical committees of all participating centers was obtained, as well as written informed consent of (parents of) participants.

Growth parameters

Length/height, weight, and head circumference (HC) were measured using standard methods at birth, 3, 6, 12, and 24 months CA and at chronological age 5 and 19 years in the POPS cohort, and at birth, term age, 3, 6, 12, and 24 months CA and at chronological age 8 years in the STEP cohort.[14,15]

Growth data and definitions. Body mass index (BMI) was calculated as (weight (kg)/(length (m))^2) from 3 months CA onwards. Subsequently, standard deviation scores (SDS) for length/height, weight, HC, and BMI were calculated.[16,17] Using a national growth chart[17] from 3 months CA onwards was deemed most feasible for various reasons: (1) the Dutch population is much taller than other populations, (2) the period of reference data collection was best fitting for both cohorts, and (3) consistency in reporting growth data of both cohorts throughout publications. Early-life growth was defined based on the difference in weight and length SDS between birth and 3 months CA, as a proxy for term age.

To define early-life growth patterns (from birth to 3 months CA), we used the following definitions:[15]

1. AGA: Birth weight and birth length >−2 SDS.
2. AGA with or without GR (AGA GR+/AGA GR−): Weight and/or length ≤−2 SDS or weight and length >−2 SDS, respectively, at 3 months CA after being born AGA.
3. SGA: Birth weight and/or birth length ≤−2 SDS (as recommended by the International SGA Advisory Board in 2003).
4. SGA with or without CUG (SGA CUG+/SGA CUG−): Weight and length >−2 SDS or weight and/or length ≤−2 SDS, respectively, at 3 months CA after being born SGA.

The proportion of infants with a weight and/or length at birth >2 SDS (2.2% for POPS and 0.7% for STEP) was considered negligible and therefore those infants were classified as AGA.

Growth trajectories were defined as length/height, weight, HC, and BMI SDS over time (from birth until age 19 or 8 years for POPS and STEP cohorts, respectively).

Neurodevelopment

Cognitive functioning. In the POPS cohort, intelligence quotient (IQ) was measured with the Multicultural Capacity Test (MCT)—intermediate level at age 19 years.[18] The MCT has been validated for individuals from different ethnic backgrounds aged ≥16 years, with an educational level ranging from 5 years of secondary school to university level. It assesses verbal and numerical intelligence, spatial visualization, speech fluency, memory, reasoning, and speed of perception.

In the STEP cohort, cognitive functioning was assessed by a child psychologist and a trained research assistant at age 8 years. Estimated Full Scale Intelligence Quotient (eFSIQ) was assessed using a four-subtest short form of the most recent Dutch version of the Wechsler Intelligence Scales for Children-third version (WISC-III).[19] eFSIQ as measured by this short form has a high reliability ($r = .93$) and correlates strongly with FSIQ ($r = .92$).[20]

The total score of both tests was expressed on a scale with a mean of 100 and an SD of 15.

Neuromotor functioning. Neuromotor functioning was assessed with the revised version of Touwen's examination of minor neurologic dysfunction in both the POPS and STEP cohort.[21] It examines six subscales: hand function, diadochokinesis, coordination, quality of walking, posture, and passive muscle tone. Each subscale, as well as the total score, was expressed as a percentage of the maximum score.

Behavior. In the POPS cohort, parental/caregiver ratings of behavioral problems were assessed using the Young Adult Behavior Checklist (YABCL) as developed by Achenbach, which provides standardized scores on behavior, feelings, and thoughts in people aged 18 to 30 years.[22] Three problem scales were derived from eight syndrome scales: "internalizing problems" (sum of syndrome scales anxious/depressed and withdrawn behavior), "externalizing problems" (sum of syndrome scales aggressive behavior, delinquent behavior, and intrusive behavior) and "total problems" (sum of all syndrome scales).

In the STEP cohort, parental/caregiver ratings of behavioral problems were assessed using the Child Behavior Checklist (CBCL) as developed by Achenbach, which provides standardized scores on behavior and competences for children aged 6 to 18 years.[23] Three problem scales were derived from eight syndrome scales: "internalizing problems" (sum of syndrome scales anxious/depressed, withdrawn/depressed, and somatic complaints), "externalizing problems" (sum of syndrome scales rule-breaking behavior and aggressive behavior), and "total problems" (sum of all syndrome scales). Scores on the CBCL were standardized using *T*-scores with a mean of 50 and an SD of 10, where higher scores indicate higher ratings of behavioral problems.

Additionally, since deficits in attention are a known problem in preterm populations,[24] the syndrome scale "attention problems" was analyzed separately in both cohorts.

To combine behavior data from both cohorts, scores were dichotomized ("normal" vs. "(sub)clinical") based on the borderline clinical cut-off points. For the problem scales this cut-off was the 83rd percentile for the YABCL and a *T*-score ≥60 on the CBCL, and for the syndrome scales the 95th percentile for the YABCL and a *T*-score ≥65 on the CBCL.

Statistical analyses

Normally distributed variables were reported as mean ± SD and skewed variables as median (interquartile range). Subjects were

compared by early-life growth pattern using analysis of variance, χ^2/Fisher's exact, or Kruskal–Wallis as appropriate.

Growth trajectories of length/height, weight, HC, and BMI SDS from birth until 24 months CA were visualized for comparisons of the cohorts as well as the four early-life growth patterns within each cohort. The figures were constructed using longitudinal analyses (i.e., generalized estimating equations (GEEs)), where the different measurement points were used as an interaction term with the four growth pattern groups. The method described by Figueiras et al.[25] was used to calculate 95% confidence intervals (95% CIs) for every parameter at each time point.

We also used GEEs to assess mean differences over time in length/height, weight, HC, and BMI SDS between cohorts and between early-life growth patterns within each cohort. GEE accounts for missing data, provided that these data are "missing completely at random," therefore we included available growth data on all subjects in these analyses. Furthermore, GEE adjusts for grouped samples, collected from the same subject at different times, by using a correlation structure. We used an exchangeable correlation structure, in which one average within-subject correlation between samples over time is assumed. GEEs were performed with growth parameters (expressed as SDS) as continuous, dependent variables, and early-life growth pattern or cohort as categorical, independent variable. Results are presented as β (with 95% CI), which expresses the mean difference between the groups over time, taking into account the repeated measurements within subjects.

To assess the associations between early-life growth pattern and neurodevelopmental outcomes, we combined the data of the POPS and STEP cohort, and performed linear regression analyses. Interaction between cohort and early-life growth patterns was assessed by adding interaction terms (cohort $*$ early-life growth pattern) to the regression analyses. Next, the analyses were adjusted for cohort. Since differences in various perinatal and demographic characteristics were found between the POPS and STEP cohorts (Supplemental Table S1), analyses were subsequently also adjusted for the following potential confounders: sex, GA, antenatal corticosteroids, the presence of ≥1 comorbidities, and maternal education. Comorbidities (sepsis (diagnosed hematologically and/or through blood culture), intraventricular hemorrhage (diagnosed clinically and/or radiographically) and necrotizing enterocolitis (stage I or higher), and infant respiratory distress syndrome (diagnosed clinically and/or radiographically) for the POPS cohort) were tallied and dichotomized as 0 or ≥1 comorbidities. The AGA GR− group was the reference group in all analyses.

We compared the POPS and STEP cohorts on neurodevelopmental outcomes using linear and logistic regression analyses. Analyses were adjusted for cohort and subsequently for birth weight SDS in addition to the previously mentioned potential confounders.

Statistical analyses were performed with IBM SPSS Statistics version 22, and $P < 0.05$ was considered significant.

RESULTS

Population characteristics

In the POPS cohort, 21 children died between 3 months CA and age 19 years. There were no significant differences in mortality between the early-life growth pattern groups ($P = 0.102$). In the STEP cohort, none of the participants died between 3 months CA and age 8 years.

Early-life growth pattern classification was known for 708 of the 998 (71%) POPS subjects, and 138 of the 152 (91%) STEP subjects.

Early-life growth pattern and neurodevelopmental outcomes were known for 509 out of 705 (72%) participating POPS subjects at age 19 years, of whom 254 were AGA GR−, 84 AGA GR+, 117 SGA CUG−, and 54 SGA CUG+. At age 8 years, early-life growth pattern and neurodevelopmental outcomes were known for 76 of 79 (96%) STEP subjects, of whom 54 were AGA GR−, 5 AGA GR+, 9 SGA CUG−, and 8 SGA CUG+ (Supplemental Figure S1).

Baseline characteristics according to early-life growth pattern for both cohorts are shown in Tables 1a and 1b. Baseline characteristics were comparable between participants and non-participants at follow-up of both the POPS and STEP cohort, with the exception of a lower target height SDS in the non-participant group of both cohorts ($P < 0.001$ and 0.048 for POPS and STEP, respectively), and more males (69.1% vs. 45.6%) as well as less mothers with higher education (i.e., higher vocational education or university, 10.3% vs. 28.2%) in the non-participant group of the POPS cohort.

Table 1a Baseline characteristics of the POPS cohort (1983) according to early-life growth pattern

	AGA GR−	AGA GR+	SGA CUG−	SGA CUG+	*P* value
n (%)	345 (49)	114 (16)	174 (25)	75 (11)	
Male sex	172 (50)	70 (61)	94 (54)	30 (40)	0.026
Gestational age (weeks)	30.2 ± 1.6	29.5 ± 1.9	33.9 ± 2.4	34.0 ± 1.7	<0.001
Birth weight (g)	1423 ± 265	1216 ± 267	1140 ± 242	1309 ± 158	<0.001
SDS	0.0 ± 0.9	−0.4 ± 0.8	−3.2 ± 1.0	−2.6 ± 0.9	<0.001
Smoking during pregnancy	119 (35)	35 (31)	64 (37)	29 (39)	0.767
PROM	85 (25)	26 (23)	3 (2)	5 (7)	<0.001
Antenatal corticosteroids	68 (19.7)	14 (12.3)	5 (2.9)	5 (6.7)	<0.001
Born via cesarean section	121 (35)	42 (37)	144 (83)	54 (72)	<0.001
Apgar score >7 after 5 min	290 (84)	78 (68)	156 (90)	68 (91)	<0.001
Length of hospital stay (days)	59.7 ± 20.8	87.5 ± 42.3	76.1 ± 36.1	52.4 ± 12.4	<0.001
Days of ventilation	3.6 ± 6.6	7.4 ± 9.1	2.2 ± 9.6	0.4 ± 1.5	<0.001
IRDS	158 (46)	72 (63)	22 (13)	9 (12)	<0.001
Sepsis	93 (27)	40 (35)	53 (31)	18 (24)	0.285
IVH	46 (13)	31 (27)	17 (10)	5 (7)	<0.001
NEC	11 (3)	8 (7)	16 (9)	5 (7)	0.036
Target height (SD)	0.0 ± 0.8	−0.2 ± 0.9	−0.3 ± 0.8	−0.1 ± 0.8	0.002
Maternal higher education	78 (22.6)	25 (21.9)	32 (18.4)	16 (21.3)	0.707

Table 1b Baseline characteristics of the STEP cohort (2003–2006) according to early-life growth pattern

	AGA GR−	AGA GR+	SGA CUG−	SGA CUG+	*P* values
n (%)	98 (71)	6 (4)	15 (11)	19 (14)	
Male sex	42 (43)	5 (83)	11 (73)	14 (74)	0.007
Gestational age (weeks)	30.1 ± 1.4	28.9 ± 1.9	30.8 ± 1.1	31.3 ± 1.1	<0.001
Birth weight (g)	1414 ± 271	931 ± 211	996 ± 208	1272 ± 222	<0.001
SDS	0.0 ± 0.7	−1.2 ± 0.4	−1.9 ± 0.6	−1.2 ± 0.6	<0.001
Smoking during pregnancy	12 (12)	2 (33)	3 (20)	4 (21)	0.263
PROM	14 (14)	1 (17)	—	2 (11)	0.441
Antenatal corticosteroids	50 (51)	5 (83)	10 (67)	13 (68)	0.221
Born via cesarean section	49 (50)	5 (83)	15 (100)	15 (79)	<0.001
Apgar score >7 after 5 min	71 (72)	6 (100)	13 (87)	14 (74)	0.429
Length of hospital stay (days)	48.5 ± 14.0	59.5 ± 18.8	58.1 ± 12.0	41.3 ± 13.4	0.002
Days of ventilation	8 [2–18]	20 [10–30]	19 [6–25]	4 [0–10]	0.012[a]
NTISS	21.4 ± 7.7	26.7 ± 8.1	25.1 ± 5.5	18.7 ± 7.0	0.032
IVH	12 (12)	—	3 (20)	3 (16)	0.649
Target height (SD)	−0.2 ± 0.6	−0.7 ± 0.7	−0.5 ± 0.7	−0.2 ± 0.9	0.211
Maternal higher education	40 (40.8)	1 (16.7)	6 (40.0)	6 (31.6)	0.616

Values represent mean ± SD, *n* (%), or median [IQR]. Continuous variables were compared with the one-way ANOVA test, and dichotomous variables were compared with the χ^2/Fisher's exact test

AGA appropriate for gestational age, *CUG* catch-up growth, *GR* growth restriction, *IVH* intraventricular hemorrhage, *IRDS* infant respiratory distress syndrome, *NEC* necrotizing enterocolitis, *NTISS* neonatal therapeutic intervention scoring system, *PROM* premature rupture of membranes, *SDS* standard deviation score, *SGA* small for gestational age

[a]Kruskal–Wallis test

Growth

Differences in early-life growth patterns between POPS and STEP. POPS subjects were more often born SGA compared to STEP subjects (35.2% vs. 24.6%) and these SGA subjects less often showed CUG (30.1% vs. 55.9%, $P = 0.003$). In addition, GR was seen more frequent in POPS subjects compared to STEP subjects (24.8% vs. 5.8%, $P < 0.001$).

Growth trajectories

POPS cohort: Figures 1a–d show length/height, weight, HC, and BMI SDS over time, according to early-life growth pattern group. Using GEE analyses, growth trajectories from birth to age 19 years were significantly different between all growth patterns (Table 2), except for the BMI SDS trajectory between the SGA CUG− and AGA GR+ groups ($P = 0.757$).

STEP cohort: Figures 1e–h show length/height, weight, HC, and BMI SDS over time, according to early-life growth pattern group. Using GEE analyses, the AGA GR− and SGA CUG+ groups showed similar growth trajectories from birth to age 8 years for weight, HC, and BMI ($P = 0.093$, $P = 0.639$, and $P = 0.914$, respectively), but not for length/height ($P = 0.028$). The SGA CUG− and AGA GR+ groups were significantly different from the AGA GR− group for all growth parameters (Table 2). SGA CUG− and AGA GR+ groups were comparable for all growth parameters (all $P > 0.05$).

Growth pattern and neurodevelopmental outcomes; POPS and STEP combined

No interaction was found between early-life growth pattern and cohort, and analyses were therefore not stratified (all interaction terms $P > 0.1$, data not shown).

Table 3 shows the associations between growth pattern and neurodevelopmental outcomes. Total IQ was lower in the SGA CUG− group as compared to the AGA GR− group. Scores on total neuromotor behavior as well as all subscales, with the exception of hand function, were lower in the SGA CUG− group compared to the AGA GR− group. The AGA GR+ group scored lower on the subscales diadochokinesis and coordination, while the SGA CUG+ scored lower on passive muscle tone. The odds for (sub)clinical behavioral problems were not significantly different between all four early-life growth patterns.

Most of these findings persisted in the SGA CUG− group after adjusting for cohort, while the associations in the AGA GR+ and SGA CUG+ groups disappeared.

Adjustment for potential confounders changed some of the associations as compared to the crude analyses: the AGA GR+ group no longer scored lower on the neuromotor subscales diadochokinesis and coordination (data not shown). The SGA CUG− group no longer scored lower on diadochokinesis, coordination, and walking. However, the association of the SGA CUG− group with a lower IQ became stronger (from β −6.5, 95% CI −9.8; −3.2 to β −8.2, 95% CI −11.9; −4.4), and the association with a higher odds for (sub)clinical attention problems became significant (from odds ratio (OR) 1.5, 95% CI 0.7; 3.3 to OR 3.0 95% CI 1.2; 7.9).

POPS vs. STEP

Growth during the first two years of life. Plotting the POPS and STEP growth trajectories showed significant differences for length/height, weight, HC, and BMI, with higher SDS for all growth parameters in the STEP cohort (Fig. 2). These results were confirmed by GEE analyses of all growth trajectories (Table 2). At 24 months CA, SDS for weight and length/height were significantly higher in the STEP cohort compared to the POPS cohort, while there were no differences in HC and BMI SDS (data not shown).

Neurodevelopmental outcomes. Total IQ was not significantly different between the two cohorts. Neuromotor scores were significantly higher in the STEP cohort, with the exception of the subscales hand function and walking (Table 4).

For behavior, the percentages of (sub)clinical behavioral problems per cohort (POPS/STEP) were as follows: total problem 25%/20%, internalizing 28%/22%, externalizing 14%/17%, and

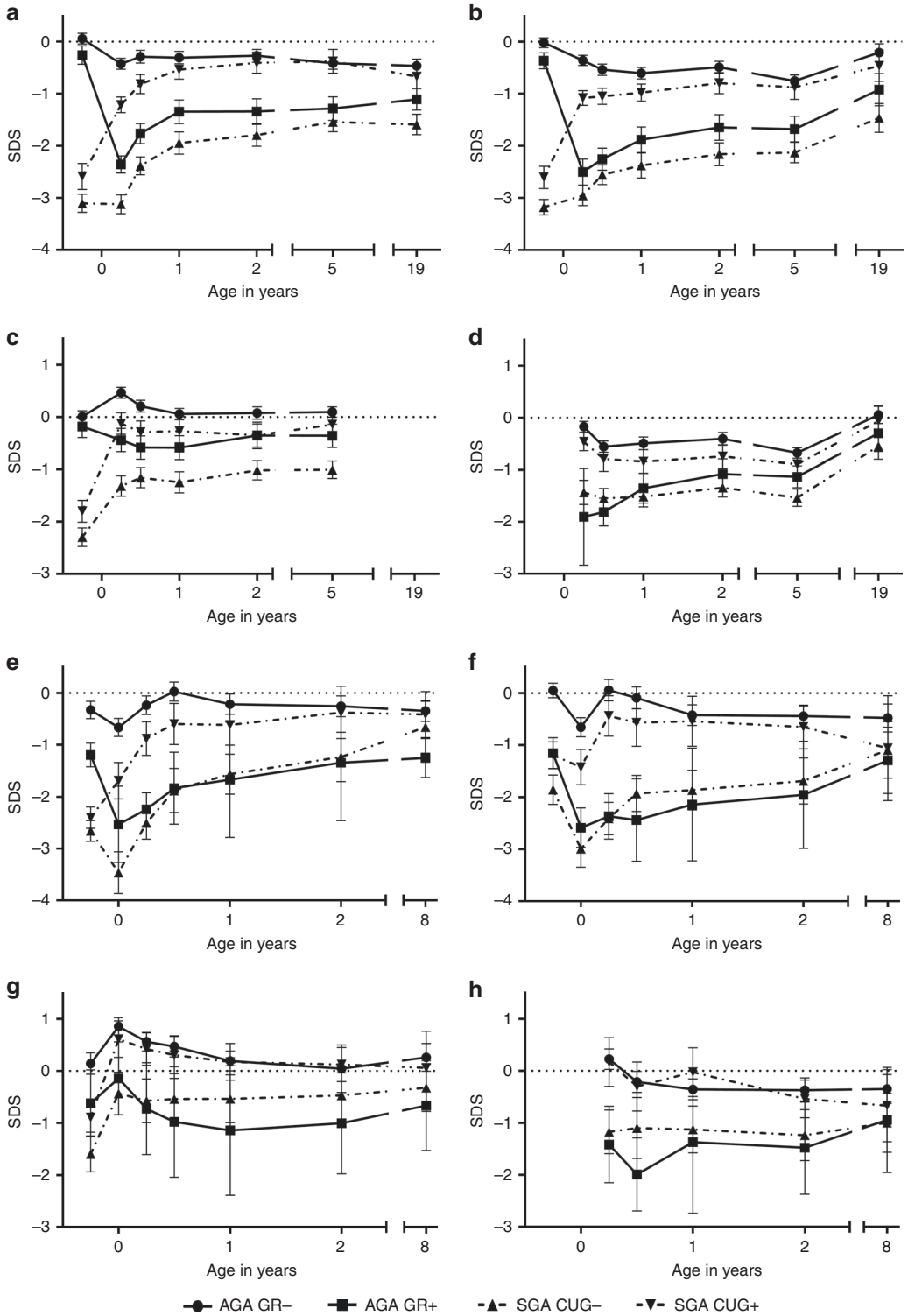

Fig. 1 Growth trajectories of **a**, **e** length/height, **b**, **f** weight, **c**, **g** head circumference, and **d**, **h** BMI according to early-life growth pattern for the POPS cohort (**a–d**) and STEP cohort (**e–h**). AGA appropriate for gestational age, CUG catch-up growth, GR growth restriction, SGA small for gestational age, SDS standard deviation score. Dotted line = reference population mean

attention 9%/13%. The odds for (sub)clinical behavioral problems were not significantly different in the STEP vs. POPS cohort (Table 4).

Adjustment for potential confounders did not change these results (data not shown).

DISCUSSION

In this historical comparison of two well-described cohorts of preterm infants, we found a decrease in prenatal and postnatal GR in the more recent cohort. This could possibly be attributed to improvements in both prenatal and postnatal care over time.

Table 2 Longitudinal analyses (GEE) of mean differences in growth trajectories between early-life growth patterns and between the POPS and STEP cohort

	Length/height (SDS)		Weight (SDS)		Head circumference (SDS)		BMI (SDS)	
	β (95% CI)	*P* value	*β* (95% CI)	*P* value	*β* (95% CI)	*P* value	*β* (95% CI)	*P* value
POPS								
AGA GR− (ref.)	—		—		—		—	
AGA GR+	−1.3 (−1.5; −1.0)	<0.001	−1.4 (−1.6; −1.2)	<0.001	−0.7 (−0.9; −0.5)	<0.001	−0.7 (−1.2; −0.3)	0.001
SGA CUG−	−1.8 (−2.0; −1.6)	<0.001	−1.8 (−2.0; −1.6)	<0.001	−1.4 (−1.6; −1.2)	<0.001	−0.8 (−1.2; −0.4)	<0.001
SGA CUG+	−0.4 (−0.6; −0.2)	0.001	−0.4 (−0.6; −0.2)	<0.001	−0.4 (−0.7; −0.2)	<0.001	−0.1 (−0.5; 0.3)	0.700
STEP								
AGA GR− (ref.)	—		—		—		—	
AGA GR+	−1.5 (−2.2; −0.8)	<0.001	−1.8 (−2.6; −1.1)	<0.001	−1.2 (−2.3; −0.2)	0.016	−1.3 (−2.1; −0.4)	0.003
SGA CUG−	−1.5 (−1.9; −1.1)	<0.001	−1.6 (−2.0; −1.3)	<0.001	−0.8 (−1.3; −0.4)	0.001	−1.0 (−1.4; −0.5)	<0.001
SGA CUG+	−0.4 (−0.8; −0.1)	0.028	−0.4 (−0.8; 0.1)	0.093	−0.1 (−0.4; 0.3)	0.639	0.0 (−0.4; 0.4)	0.914
STEP vs. POPS (ref.)	0.4 (0.2; 0.6)	<0.001	0.7 (0.5; 0.8)	<0.001	0.4 (0.2; 0.6)	<0.001	0.5 (0.4; 0.7)	<0.001

AGA appropriate for gestational age, *CI* confidence interval, *CUG* catch-up growth, *GR* growth restriction, *SDS* standard deviation score, *SGA* small for gestational age

However, the adverse impact of early-life GR on childhood growth and neurodevelopment was not significantly different between the cohorts.

In line with other studies,[26,27] we found that early-life GR was associated with unfavorable outcomes in both cohorts. More specifically, we found that children born SGA without subsequent CUG had the greatest risk of unfavorable long-term neurodevelopmental outcomes, and that appropriate prenatal and postnatal growth were associated with favorable neurodevelopmental outcomes. Furthermore, we found similar IQ and behavioral problems in both cohorts, and better neuromotor outcomes in our more recent cohort.

As far as we know, no other study has assessed whether the association between early-life growth pattern and (neurodevelopmental) outcomes were different between cohorts recruited 20 years apart, as a proxy for changes in time. Between 1983 and 2003 perinatal care has changed dramatically. With respect to antenatal care, advances in ultrasound evaluation of fetal growth improved the possibility to identify severe IUGR and this identification may support the choice to actively induce (preterm) labor to prevent an infant from being born severely SGA.[28] In addition, the use of antenatal glucocorticoids for the induction of fetal lung maturation has become common practice, and this has been associated with a protective effect against neurodevelopmental impairment.[29] With respect to postnatal care for preterm infants, tremendous progress has been made by the use of surfactant and less invasive ventilation as well as by optimizing early nutrition.

Nevertheless, severe GR in the early postnatal period has been and still is a major concern in the care for preterm infants.[30,31] A significant part of this GR may be contributed to cumulative nutritional deficiencies acquired in the first postnatal weeks, as Embleton et al. showed that recommended daily nutritional intakes were rarely achieved.[32] This could at least in part be prevented by ensuring adequate protein and energy intake according to current guidelines, as soon as possible after birth.[1] A positive effect of providing adequate early nutritional care on later neurodevelopmental outcomes has been suggested.[31]

However, during the last two decades, the improvements in neonatal care and nutrition have not led to a clear decrease in short-term and long-term morbidities.[3,33] This may in part be attributed to the survival of children born at a lower gestational age, who generally have a more complicated neonatal course. When comparing the two cohorts, we found a decrease in the percentage of children with early-life GR. We might have expected this improvement in early-life growth to be accompanied by equally improved neurodevelopmental outcomes; however, only a modest advantage for the recent cohort in some of the neurodevelopmental outcomes was observed. This may be partly explained by the smaller sample size and the lower gestational age of the more recent cohort, or because the mean scores on neurodevelopmental outcomes in the 1983 cohort were already within the reference range. The small benefits on neuromotor functioning might partly be attributed to improvements in perinatal care and the selection of healthier preterm infants for the STEP RCT.

In the more recent cohort, unfavorable early-life growth patterns were still related to unfavorable neurodevelopmental outcomes, and therefore achieving adequate early-life growth by further optimizing early nutrition and minimizing disease burden appears to be essential to improve outcomes of preterm-born infants.[34] Although acknowledging the importance of CUG for childhood growth and neurodevelopmental outcomes, it is important to recognize the possible downside of (excessive) CUG in weight, that is, the association with an increased risk of cardiometabolic diseases at later age.[35] In addition to adequate early-life growth, interventions such as increasing parent–infant interaction, sensory stimulation, and physiotherapy during and after the neonatal intensive care unit (NICU) period could positively influence both motor and cognitive development as well, although long-term effects have to be established.[36,37]

The association between adverse early-life growth and unfavorable neurodevelopmental outcomes might either be causal or might be explained by perinatal characteristics clustering with prenatal and postnatal GR. For example, in our study, subjects with poor early-life growth had a lower birth weight and their length of hospital stay and total days of ventilation were longer, so they already seemed to be at a disadvantage compared to the subjects with appropriate early-life growth. Clustering is particularly evident in case of bronchopulmonary dysplasia, which, besides being a risk factor for postnatal GR, has been strongly associated with poor academic achievement.[38] Furthermore, the effect of severity of illness on later outcomes may be mediated by the early nutritional management.[39] The association between early-life growth and neurodevelopment might at least partly be explained by disease severity, which could actually be the underlying cause for both the adverse early-life growth and the unfavorable neurodevelopmental outcomes.

Table 3 Association between early-life growth pattern and neurodevelopmental outcomes in the POPS and STEP cohort combined

	AGA GR− (ref.) ($n = 443$)	AGA GR+ ($n = 120$)		SGA CUG− ($n = 189$)		SGA CUG+ ($n = 94$)	
	Mean (95% CI)	β (95% CI)		β (95% CI)		β (95% CI)	
		Crude	Adjusted[a]	Crude	Adjusted[a]	Crude	Adjusted[a]
Total IQ	102.1 (100.3; 103.9)	−3.1 (−7.0; 0.8)	−3.1 (−7.0; 0.9)	−6.5 (−9.8; −3.2)*	−6.5 (−9.8; −3.2)*	−0.9 (−5.3; 3.5)	−0.8 (−5.2; 3.6)
Neuromotor behavior—% of maximum score							
Total score	94.4 (93.6; 95.1)	−0.9 (−2.4; 0.6)	−0.3 (−1.8; 1.2)	−1.9 (−3.2; −0.6)**	−1.4 (−2.7; −0.1)**	−1.0 (−2.8; 0.8)	−0.7 (−2.5; 1.0)
Hand function	96.8 (96.1; 97.6)	−1.0 (−2.5; 0.6)	−1.5 (−3.0; 0.1)	−1.3 (−2.6; 0.1)	−1.7 (−3.1; −0.4)**	−0.2 (−2.0; 1.6)	−0.5 (−2.2; 1.2)
Diadochokinesis	90.1 (88.8; 91.3)	−2.8 (−5.5; −0.2)**	−1.8 (−4.3; 0.8)	−2.6 (−4.9; −0.3)**	−1.7 (−3.9; 0.6)	−1.7 (−4.7; 1.3)	−1.1 (−4.0; 1.8)
Coordination	93.4 (92.5; 94.3)	−2.3 (−4.2; −0.4)**	−1.7 (−3.6; 0.1)	−1.9 (−3.5; −0.3)**	−1.4 (−3.0; 0.2)	0.1 (−2.0; 2.2)	0.4 (−1.6; 2.5)
Walking	96.9 (95.9; 98.0)	−0.7 (−2.8; 1.5)	−0.4 (−2.6; 1.7)	−2.3 (−4.1; −0.4)**	−2.1 (−4.0; −0.2)**	0.9 (−1.5; 3.3)	1.0 (−1.4; 3.5)
Posture	95.6 (94.5; 96.6)	−1.0 (−3.2; 1.2)	−0.1 (−2.2; 2.1)	−3.8 (−5.8; −1.8)*	−3.0 (−5.0; −1.1)**	−2.2 (−4.9; 0.6)	−1.9 (−4.5; 0.8)
Passive muscle tone	91.2 (89.8; 92.6)	−0.9 (−3.8; 2.0)	0.4 (−2.4; 3.3)	−5.7 (−8.2; −3.1)*	−4.5 (−7.0; −2.0)**	−3.7 (−7.0; −0.4)**	−2.9 (−6.1; 0.3)
		OR (95% CI)		**OR (95% CI)**		**OR (95% CI)**	
		Crude	**Adjusted[a]**	**Crude**	**Adjusted[a]**	**Crude**	**Adjusted[a]**
Behavior—dichotomized[b] (normal/(sub)clinical)							
Total problem	—	1.2 (0.6; 2.2)	1.2 (0.6; 2.2)	1.4 (0.8; 2.5)	1.4 (0.8; 2.4)	1.0 (0.5; 2.0)	1.0 (0.5; 2.0)
Externalizing	—	0.6 (0.3; 1.4)	0.6 (0.3; 1.5)	1.6 (0.9; 3.0)	1.7 (0.9; 3.1)	1.2 (0.5; 2.6)	1.2 (0.5; 2.6)
Internalizing	—	1.5 (0.8; 2.6)	1.4 (0.8; 2.5)	1.4 (0.9; 2.4)	1.4 (0.8; 2.3)	1.0 (0.5; 1.9)	0.9 (0.5; 1.9)
Attention	—	0.8 (0.3; 2.3)	0.9 (0.3; 2.5)	1.5 (0.7; 3.3)	1.6 (0.8; 3.5)	1.4 (0.5; 3.7)	1.4 (0.6; 3.8)

Results of linear and logistic regression analyses, represented as β (95% CI) and OR (95% CI), respectively. The AGA GR− group was used as reference group (ref.)
AGA appropriate for gestational age, *CI* confidence interval, *CUG* catch-up growth, *GR* growth restriction, *OR* odds ratio, *SGA* small for gestational age
*P 0.001, **P 0.05
[a]Linear/logistic regression analyses adjusted for cohort
[b]Behavioral scores were dichotomized using the "borderline clinical cut-off points"

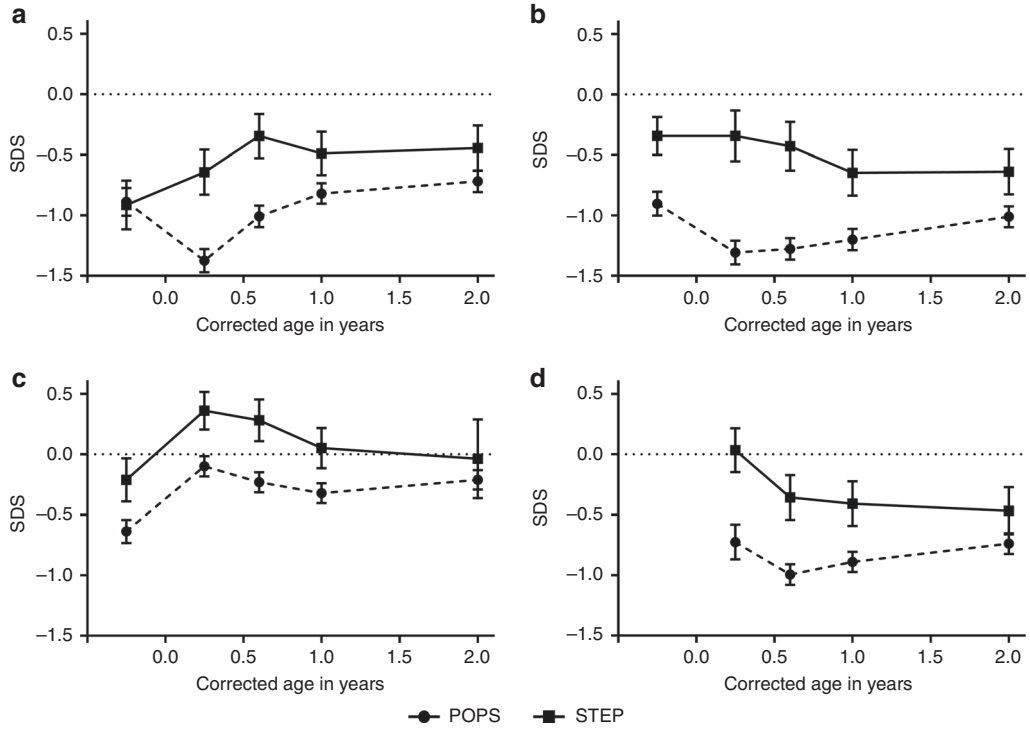

Fig. 2 Growth trajectories of **a** length/height, **b** weight, **c** head circumference, and **d** BMI until 2 years corrected age, compared between the POPS and STEP cohorts. SDS standard deviation score. Dotted line = reference population mean

Table 4 Comparison of neurodevelopmental outcomes between the POPS and STEP cohort

Cohort	POPS (ref.) ($n = 509$) Mean (95% CI)	STEP ($n = 76$) β (95% CI)[a]	*P* value
Total IQ	100.2 (99.0; 101.5)	0.3 (−3.4; 4.1)	0.873
Neuromotor function (%)			
Total score	92.7 (92.2; 93.2)	3.4 (2.1; 4.7)	<0.001
Hand function	93.8 (96.2; 97.3)	−3.1 (−4.6; −1.6)	<0.001
Diadochokinesis	87.5 (86.6; 88.3)	7.9 (5.4; 10.3)	<0.001
Coordination	91.8 (91.2; 92.4)	3.6 (1.9; 5.3)	<0.001
Walking	96.1 (95.5; 96.8)	1.3 (−0.7; 3.3)	0.188
Posture	93.1 (92.4; 93.9)	6.1 (4.2; 8.0)	<0.001
Passive muscle tone	87.2 (86.3; 88.1)	9.8 (7.1; 12.5)	<0.001
	STEP vs. POPS (ref.)OR (95% CI)[b]		P value
Behavior—dichotomized (normal/(sub)clinical)[c]			
Total problem	0.8 (0.4; 1.5)		0.446
Externalizing	1.2 (0.6; 2.5)		0.545
Internalizing	0.7 (0.4; 1.3)		0.285
Attention	1.5 (0.7; 3.3)		0.327

CI confidence interval, *OR* odds ratio, *ref.* reference group
[a]Unadjusted linear regression analyses,
[b]Unadjusted logistic regression analyses
[c]Behavioral scores were dichotomized using the "borderline clinical cut-off points"

Strengths and limitations

Our study has several strengths and limitations. The major strength of our study is that we had the unique opportunity to compare extensive data from two cohorts with a long-term follow-up. Our study has several limitations, which could offer an alternative explanation for the results of our study. A selection bias might be present due to the original RCT design of the STEP cohort compared to the observational design of the POPS cohort, as well as due to recruiting from a single center vs. multiple centers. The change in the incidence of adverse early-life growth patterns could also be attributed to these factors. Additionally, the sample size of the STEP cohort at follow-up was very small, with

<10 subjects for three out of four early-life growth pattern groups, and the power to detect changes in neurodevelopmental outcomes between the two cohorts might therefore be too limited. Moreover, comparing IQ measured at age 8 and 19 years may ignore the possibility of changes in neurodevelopmental outcomes over time within a preterm-born population. Current literature is inconclusive as to how cognitive performance develops from school age onwards in a preterm population, with studies showing stable,[40] improved,[41] and worsened[42] results within the same cohort. It has also been suggested that executive functioning and academic performance have worsened with time when comparing sequential cohorts.[43] Furthermore, although pre-discharge and postdischarge growth appears to impact neurodevelopment differently,[44] the lack of anthropometric data at term age for the POPS cohort forced us to use the CA of 3 months to define early-life growth patterns. Methodologically our study was limited as well: both the age at testing and the instruments used to assess neurodevelopment differed between our cohorts. However, the tests were both conceptually and methodologically similar enough for a pooled data analysis using standardized scores (i.e., by using predefined cut-offs instead of raw scores). The use of parental reports on behavioral problems might lead to an overestimation of behavioral problems, although parents of preterm subjects appear to appraise their child's health quite accurately.[45] We decided to use the parental report because almost 82% of the POPS subjects were still living at home at the time of follow-up, suggestive of a reliable parental report. Moreover, parent reports were available for both cohorts, enabling comparison. Lastly, we acknowledge that, as with any historical cohort, generalizability to current NICU populations may be hampered because of ongoing changes in perinatal care policies.

CONCLUSION

The incidence of adverse early-life growth patterns is significantly lower in our cohort from 2003 compared to our cohort from 1983, possibly indicating improvements in care over time. However, the impact of adverse early-life growth on neurodevelopment was not significantly different between the cohorts. Children born SGA without CUG remain vulnerable and should be followed closely with regard to the timely detection of neurodevelopmental problems during childhood. Children born SGA with CUG had outcomes similar to adequately grown children. Ongoing attention for adequate early-life growth is needed, and interventions to support neurodevelopment, specifically in infants with early-life GR, should be considered.

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AUTHOR CONTRIBUTIONS

We confirm that all authors met the *Pediatric Research* author requirements. Substantial contributions to conception and design: M.v.d.L., H.N.L. (STEP) and S.M.v.d.P., M.J.J.F. (POPS); acquisition of data: C.A.R., T.B., P.E.M.v.S., S.M.v.d.P., M.v.d.L., M.J.J.F.; or analysis and interpretation of data: C.A.R., J.J.H., J.R., M.J.J.F.; drafting the article: C.A.R. and J.J.H.; revising the article critically for important intellectual content: all authors; final approval of the version to be published: all authors.

ADDITIONAL INFORMATION

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