Growth after late-preterm birth and adult cognitive, academic, and mental health outcomes

Running title: Late-preterm birth, growth and cognition

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ABSTRACT

Background: Late-preterm birth (at $34^{0/7}$–$36^{6/7}$ weeks' gestation) increases the risk of early growth faltering, poorer neurocognitive functioning, and lower socio-economic attainment. Among early-preterm individuals, faster early growth benefits neurodevelopment, but it remains unknown whether these benefits extend to late-preterm individuals.

Methods: In 108 late-preterm individuals, we examined if weight, head, or length growth between birth, 5 and 20 months' corrected age, and 56 months, predicted grade point average and special education in comprehensive school, or neurocognitive abilities and psychiatric diagnoses/symptoms at 24–26 years of age.

Results: For every 1 SD faster weight and head growth from birth to 5 months, and head growth from 5 to 20 months, participants had 0.19–0.41 SD units higher IQ, executive functioning score, and grade point average (95% confidence intervals 0.002–0.59 SD), and lower odds of special education (OR=0.49–0.59, 95% confidence intervals 0.28–0.97), after adjusting for sex, gestational age, follow-up age, and parental education. Faster head growth from 20 to 56 months was associated with less internalizing problems; otherwise we found no consistent associations with mental health outcomes.

Conclusions: Faster growth during the critical early period after late-preterm birth is associated with better adult neurocognitive functioning, but not consistently with mental health outcomes.

INTRODUCTION

Decreasing the burden of preterm birth is a public health priority (1). Of the nearly 15 million infants worldwide who are born preterm (<37 weeks' gestation) each year (2), over 70% are born late-preterm (between 34+0 and 36+6 weeks+days' gestation) (3). The late-preterm infant is faced with a substantial risk of morbidity and mortality compared with term-born peers (4), including an increased risk of early growth faltering (5) and poorer long-term neurocognitive functioning (6) and socio-economic attainment (7). Yet, a large proportion of late-preterm individuals come to cope well, and the risk of mental disorders, for example, seems to be similar for late-preterm and term-born individuals (8).

Even though faster growth in infancy and childhood has been shown to benefit neurodevelopment in those born very preterm (<32 weeks) (9–12), early preterm (<33 weeks) (13), preterm (14), and preterm with extremely low (<1000g) (15–18) or very low (<1500g) (9,10,19–22) birth weight, in some, though not in all studies (23–25), it still remains unknown if faster early growth also benefits neurodevelopment in those born late-preterm. Accordingly, we examined if growth after late-preterm birth predicts neurocognitive functioning, academic performance, or mental health in individuals who were born late-preterm, and who participated in follow-up examinations at 5 and 20 months of corrected age (CA) and 56 months and 25 years of age.

METHODS

Participants

The *Arvo Ylppö Longitudinal Study* cohort were recruited from births in the Uusimaa region, Finland, between March 15, 1985 and March 14, 1986. Originally, we prospectively recruited infants who were admitted to a neonatal ward within 10 days of birth, and for every two hospitalized infants, we also recruited one newborn who did not require hospitalization. This cohort of 2,193 infants, described

previously in more detail, (8) included 315 late-preterm infants. At 5, 20, and 56 months, 277, 274, and 227 late-preterm individuals, respectively, participated in follow-up examinations, including anthropometric measurements.

In 2009-2012, we invited the still traceable 270 late-preterm individuals, who were living within southern Finland to a follow-up: 158 participated (58.5% of those invited; 50.2% of original participants) (Figure 1). We excluded those with intellectual developmental disability (n=4), congenital malformations or chromosomal abnormalities (n=4), or no available data on birth or childhood anthropometry (n=5), precise gestational age (n=34), or adult cognitive, school, or psychiatric data (n=3), resulting in an analytic sample of 108 late-preterm-born adults (mean age 25.2, standard deviation [SD]=0.6, range 24.5–26.7 years). The number of participants included in each of the analyses varied according to growth and outcome data availability, as shown in supplemental Tables S1-S2 (online). 101 participants (93.5% of the analytic sample) had been admitted to a neonatal ward within ten days of birth. Based on childhood records and adult self-report, none in the analytic sample had cerebral palsy or visual or hearing impairment.

The childhood study protocol was approved by the Helsinki City Maternity Hospital, Helsinki University Central Hospital, and Jorvi Hospital ethics committees, and the adulthood protocol by the Helsinki and Uusimaa Hospital District Coordinating Ethics Committee. Informed consent was obtained from parents (childhood, adulthood) and participants (adulthood).

Attrition

To test for selective attrition, we compared the analytic sample (n=108) with the attrition group (those who could not be included because of non-participation or missing data, n=188); we excluded those with intellectual developmental disability (n=8) or congenital malformations or chromosomal abnormalities

(n=11) from these comparisons. Between the analytic sample and attrition group, we found no differences in sex, gestational age, parental education, or age at childhood follow-ups; weight, length, or head circumference at birth or childhood follow-ups; maternal age, diabetes, hypertensive disorder, or smoking during pregnancy; parity or multiple pregnancy; or infant Apgar scores, ventilation treatment, septicemia, convulsions, or apnea (p-values>0.07). Compared with the analytic sample, the attrition group had mothers with higher pre-pregnancy body-mass-index (mean=23.1 vs. 21.8, n=183 vs. 108, p-value=0.002) and received less breast-feeding (22%, 48%, 30% vs. 7%, 61%, 31% never breast-fed, breast-feeding discontinued by 5 months, and breast-fed at 5 months, respectively, n=156 vs. 108, p-value=0.01). Compared with the analytic sample, the adult follow-up participants excluded because of missing data (n=42, Figure 1) were slightly older at adult follow-up (mean=25.5 vs. 25.2 years, p-value=0.048), but we found no differences in neurocognitive, school, or psychiatric outcomes or maternal mental disorder (p-values>0.15).

Body size at birth, 5 and 20 months CA, and 56 months

Experienced research nurses measured *weight,* length or height (referred to as '*length*', for simplicity), and *head circumference* at 5 and 20 months CA, and 56 months of chronological age, and we retrieved corresponding birth measurements from medical records. We converted birth sizes into *z*-scores by sex and gestational age, according to Finnish standards(26). Using the World Health Organization growth charts (27), we standardized childhood sizes by sex, and CA (5, 20 months) or chronological age (56 months).

Cognitive, academic, and mental health outcomes

We used seven subtests (Information, Similarities, Arithmetic, Digit Span, Picture Completion, Matrix reasoning, Digit Symbol Coding) of the Wechsler Adult Intelligence Scale-III (28) for estimating

Intelligence Quotient (*IQ)*, and three subtests (Logical Memory, Verbal Paired Associates, Faces) of the Wechsler Memory Scale-III (29) for estimating *General Memory*. Phonetic (words beginning with letters S and P) and Categorical (animal, and vegetable or fruit names) Verbal fluency (30), The Trail Making Test (31), and The Bohnen version of the Stroop test (32) measured executive functioning. We utilized principal component analysis with Varimax rotation to reduce the executive functioning and attention outcomes into principal components. The first component had an eigenvalue >1 and explained 56.9% of the total variance (supplemental Table S3, online), and was named *Executive functioning*: higher scores reflected better performance in Fluency, Trail Making, and Stroop tests. Participants reported grade point average (*GPA)* on their final comprehensive school diploma (usually issued the year an individual turns 16 years, in Finland), and whether they had received remedial or *special education* in comprehensive school.

We used M-CIDI interviews (33) in concordance with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, to diagnose common mental disorders (major depressive disorder, dysthymia, bipolar disorder; general anxiety disorder, social phobia, agoraphobia, panic disorder with or without agoraphobia; and alcohol or other substance use dependence or abuse disorder) within the past 12 months. The participants also completed the ASEBA Adult Self-Report (34), on which the *Total Problems* score reflects overall psychiatric symptoms and poor psychosocial adjustment, *Internalizing Problems* subscore reflects symptoms of anxiety, depression, withdrawal, and somatic complaints, and *Externalizing Problems* subscore reflects delinquent or aggressive behavior symptoms. Higher scores on all scales reflect more frequent or severe symptoms. The interviews and neuropsychological assessments were performed by eight master's level psychology students (incl. SS), trained and supervised by clinical psychologists (KH, JL, A-KP) and a psychiatrist with WHO authorization (SP), and blind to all earlier participant information.

Covariates

Gestational age was based on fetal ultrasound performed before 24+0 weeks' gestation (n=72), or last menstrual period (n=36), independently verified from medical records. From clinical pre- and postnatal records, we extracted *sex*, date of birth for calculating *age* during visits (days), and *pregnancy-related factors* (multiple pregnancy [singleton/multiple], parity [primiparous/multiparous], maternal pre-pregnancy body-mass-index [kg/m^2], age at delivery [years], and hypertensive disorders [normotension/hypertensive disorder], diabetes [no diabetes/gestational or type 1 diabetes; none had type 2 diabetes], and smoking [no/yes, at least one cigarette per day] during pregnancy). Data on *neonatal complications*, collected during daily ward visits by the pediatricians in the study (incl. AL), included 5-minute Apgar score (>7/0-7 points) and suspected septicemia, ventilation treatment, convulsions, and apnea (each no/yes). Ventilation treatment included continuous positive airway pressure and mechanical ventilation. No participants were diagnosed with intraventricular hemorrhage, necrotizing enterocolitis, or septicemia confirmed by positive blood culture. *Highest education of either parent* (basic/vocational/general upper secondary and lower tertiary/upper tertiary), and child *breast-feeding* status at 5 months CA (never breast-fed/breast-feeding discontinued/currently breast-fed) came from parental interviews during childhood. Mothers self-reported history of *maternal mental disorder* during adult follow-up.

So that missing covariate data would not affect sample size, four participants without 5-minute Apgar scores were included in the "8-10 points" category based on their high 1- and 10-minute Apgar scores and clinical descriptions; eight mothers without mention of blood pressure measurements, hypertension, or pre-eclampsia in clinical records were included in the "no hypertensive disorder" group; and 27 mothers who did not report on history of (maternal) mental disorder were considered a separate category when dummy-coding the variable.

Statistical analyses

We used linear regression models to test if growth from a) birth to 5 months CA, b) 5 to 20 months CA, and c) 20 months CA to 56 months predicted IQ, General memory, Executive functioning, GPA, and Internalizing, Externalizing, and Total psychiatric problems scores; and logistic regression analyses with special education and mental disorders as outcomes. We square-transformed IQ, General memory, and GPA, and square-root-transformed psychiatric problems scores, to attain normality, and standardized these outcomes within the sample (mean=0, SD=1) to facilitate comparison of effect sizes. So that growth period duration or earlier growth would not interfere with the interpretation of results, we used, as growth variables, standardized residual change scores from linear regression models where weight, length, and head circumference *z*-scores were regressed on corresponding measures at previous time points, creating uncorrelated residuals that reflect growth conditional on previous history (19). We considered two-tailed p-values <0.05 statistically significant.

In Model I, we adjusted for gestational age at birth, sex, age during visits (5 and 20 months CA, chronological age at 56 months and in adulthood), and parental education. In Model II, we further adjusted for pregnancy-related factors (listed above, in "Covariates"). In Model III, we adjusted for Model I-II factors, neonatal complications, and breast-feeding status at 5 months CA. In supplementary analyses with mental health outcomes (Model IV), we re-ran Model III while further adjusting for maternal mental disorder. In additional analyses, to test if associations between growth and adult neurocognitive, school, or mental health outcomes varied by birth size, we included an interaction term 'standardized birth size x corresponding growth measure' into the regression equation followed by main effects. When we observed statistically significant interactions, we divided the sample into thirds by birth size and examined the main effects separately in each group.

RESULTS

Table 1 shows body size and growth in childhood, Table 2 shows background characteristics and adult outcomes of the late-preterm participants.

Neurocognitive abilities and School Performance

We present associations between growth in weight (Figure 2), head circumference (Figure 3), and length (Figure 4), and adult neurocognitive abilities and GPA in comprehensive school, among those born late-preterm. Supplemental Table S1 (online) provides more detailed data on these associations and those between early growth and special education, across adjustment models.

Faster birth-to-5-months' weight and head growth was associated with higher IQ, Executive functioning, and GPA; and faster 5-to-20-months' head growth was associated with higher IQ and GPA. For each SD unit faster growth, these scores increased by 0.19–0.41 SD units (95% Confidence Intervals [CI] 0.002–0.59), after adjusting for sex, gestational age, age during visits, and parental education (Model I). Faster growth from birth to 5 months was also associated with lower odds of receiving special education (Model I) (odds ratio [OR]=0.59, 95% CI=0.36–0.97, and OR=0.49, 95% CI=0.28–0.88, per one SD unit faster weight and head growth, respectively).

After adjusting for pregnancy-related factors (Model II), faster birth-to-5-months' weight gain was associated with higher Executive functioning, General memory, GPA, and lower odds of special education; birth-to-5-months' head growth was associated with higher GPA and lower odds of special education; and 5-to-20-months' head growth was associated with higher IQ and GPA (effect sizes 0.22–0.43, 95% CI's 0.01–0.62; OR's 0.53–0.54, 95% CI 0.28–0.99). After further adjusting for neonatal factors (Model III), faster birth-to-5-months' weight growth was associated with higher Executive functioning and GPA; birth-to-5-months' head growth with higher Executive functioning, GPA, and

lower odds of special education; and 5-to-20-months' head growth with higher IQ and GPA (effect sizes 0.23–0.42, 95% CI's 0.002–0.62; OR 0.46, 95% CI 0.22–0.94). Although rendered below the conventional level of significance in models II and/or III, in effect size the associations between birth-to-5-months' weight gain, IQ, and special education, and birth-to-5-months' head growth, IQ, and Executive functioning changed only a little (difference in effect sizes ranged between 0.03–0.05 SD units, between significant and further adjusted non-significant models; the OR which was rendered non-significant decreased by 0.06).

We found no statistically significant associations between any neurocognitive or school outcomes and length growth, weight gain after 5 months, or head growth after 20 months (p-values>0.12, Model I).

Psychiatric disorders and problems

Supplemental Table S2 (online) presents the associations between growth and mental health outcomes. Faster head growth from 20 to 56 months was associated with lower Internalizing and Total problems scores in Model I (effect sizes -0.30 and -0.28 SD, respectively, for every one SD faster growth, 95% CI -0.56 to -0.02), and Model II (effect sizes -0.34 and -0.33 SD, respectively, 95% CI's -0.63 to -0.04; also associated with lower Externalizing scores, effect size -0.32 SD, 95% CI -0.62 to -0.01). These associations were non-significant in Model III (effect sizes -0.26 and -0.27 SD, 95% CI's -0.57 to 0.02), but reached statistical significance again after further adjusting for maternal mental disorder (Model IV) (effect sizes -0.30 and -0.33 SD, 95% CI's -0.66 to -0.004). No other associations between growth and psychiatric disorders or problems were consistently significant across different adjustment models (p-values>0.09 in Model I).

Interactions between birth size and growth

We found interactions between birth head circumference and head growth from birth to 5 months, when examining GPA and General memory (p-values for interactions p=0.023 and =0.042, respectively). Faster birth-to-5-months' head growth was associated with higher GPA among those with the largest birth head circumference, i.e. highest third (effect size 0.56 SD, 95% CI 0.08–1.04) (head circumference >0.5 SD in this group, n=31), but not in the middle third (effect size 0.34 SD, 95% CI -0.04–0.73) (head circumference -0.2 to 0.5 SD, n=31) or lowest third (effect size 0.27 SD, 95% CI -0.12–0.67) (head circumference <-0.2 SD, n=29). General memory was not associated with birth-to-5-months' head growth in any tertile group (p-values>0.11). There were no other statistically significant interactions between birth size and childhood growth (model I).

DISCUSSION

In this study, in a cohort of 108 late-preterm individuals followed up to adulthood, we showed that faster growth in weight and head circumference from birth to 5 months CA was associated with higher IQ and better executive functioning in adulthood, higher GPA at the end of comprehensive school, and lower odds of having received special education in comprehensive school. Those who showed faster head growth from 5 to 20 months CA also had higher adult IQ and GPA, but growth after early infancy was otherwise not associated with neurocognitive or school outcomes. Our results also suggested that faster head growth from 20 to 56 months may be associated with fewer self-reported internalizing problems; otherwise, we found no consistent associations between growth and mental health outcomes, or growth in length and any of the studied outcomes.

For every one SD faster weight or head growth, our study participants scored 0.19–0.41 SD units higher in estimated IQ, executive functioning, and GPA, and had lower odds (OR 0.49–0.59) of having received special education. The pattern of findings, including effect sizes of the significant associations, corresponds to those previously reported for very-low-birth-weight preterm individuals (who scored

0.23–0.43 SD units higher in neurocognitive tests, per one SD faster growth from birth to term-equivalent-age, particularly in head circumference) (19,35).

To our knowledge, our study is the first to examine growth after late-preterm birth in relation to any of these outcomes. These results are mainly in line with most – but not all (23–25) – previous studies, which suggest that faster growth soon after being born very-preterm (9–12,36), early-preterm (13), preterm (14), or preterm with extremely low (15–18) or very low (9,10,19–22) birth weight may benefit neurodevelopment (9–22) and academic achievement (11,12,14,17,36), but not so much mental health (14,17,25,35). This study also supports the notion that mechanisms underlying preterm birth and neurocognitive vulnerability are at least partly different from those underlying preterm birth and mental health risk (37).

Our findings were not explained by manifest developmental disability or congenital malformations, as participants with these conditions were excluded, or by variation in gestational age or socio-economic background. The associations between faster growth and better neurodevelopment were also independent of earlier growth and no more pronounced in those with smaller birth size, indicating that environmental factors during the growth period, rather than catch-up growth after previous growth restriction, underlay the associations. Moreover, adjustment for a range of pregnancy-related and neonatal conditions produced only small changes in the regression coefficients, indicating that the reported associations were not explained by common manifest pregnancy or neonatal disorders, but were more likely to reflect a multitude of environmental conditions during the growth period.

While the mechanisms underlying these associations remain largely unknown, our results highlight the importance of the early period after late-preterm birth for neurodevelopment. At 34 weeks' gestation, the earliest limit of late-preterm birth, cortical volume is only 53% and total brain volume 65% of the term

brain, and major structural maturation is yet to occur (38). The interruption of development in the normal protective intrauterine environment during this vulnerable period may alter brain maturation and growth through an interplay of inadequate nutrition, damage to developing organs, and increased risk of infection and other neonatal complications. It has been suggested that late-preterm infants could benefit from more careful consideration of individual nutritional needs (39) and of susceptibility to complications (3), for example, but direct evidence from intervention studies aimed at improving long-term neurodevelopment after late-preterm birth is lacking. It is also worth noting that while the 12-month prevalence rates of substance use, mood, and anxiety disorders in our cohort (26%, 14%, and 8% of those who underwent psychiatric interview, respectively; 35% had at least one of these mental disorders) may seem striking, they are not characteristic of the late-preterm population in particular, (8) but rather reflect the high prevalence of mental disorders among young people (40), underlining the urgent need to identify early risk factors for mental disorders.

Our study strengths include the long follow-up of late-preterm individuals to adulthood, validated and extensive outcome data, conditional growth modeling methods, and detailed pre- and postnatal data. The main limitation of our study is the loss of follow-up. Of the original 315 late-preterm individuals, 270 could be traced and were invited. Of those invited, 158 (59%) participated in the adult follow-up. After excluding those whose gestational age, childhood anthropometry and long-term outcomes could not be reliably determined, and those whose developmental disabilities, congenital malformations or chromosomal abnormalities could have affected growth and neurodevelopment, 108 participants were included in the analytic sample (34% of original cohort, 68% of the participants of the adult-follow-up). The rate of attrition, while not exceptional for similar long-term follow-up studies which require active participation (41) calls for caution in interpreting the results. Even though those whom we excluded from the study because of missing data did not greatly differ from the analytic sample, loss of follow-up may

cause selection bias and impact generalizability of the results, especially into less healthy groups. The direction, size and confidence intervals of the reported effects did not suggest any systematic associations between growth and mental health, or growth after 20 months and neurodevelopment: while this is in line with previous studies, not finding associations does not mean that they cannot exist. Our findings encourage future studies to test these associations in larger samples, to detect potential small or, even more importantly, sub-group specific effects that were beyond the scope of this study. Other limitations include possible residual confounding. Further, study participants, born in 1985-86, may not be representative of late-preterm infants born today, and we could not address more rare mental disorders such as schizophrenia, life-long prevalence of mental disorders, or final achieved educational level.

To alter the trajectory of cognitive development, early intervention is important (42). Even though those late-preterm individuals of our cohort who grew more slowly in infancy were more likely to receive additional support in school age, they still reported poorer grades at the end of comprehensive school and showed lower general intelligence and executive abilities as adults, compared with faster-growing late-preterm peers. Future research may show whether, during this critical time period, targeted interventions could compensate for the long-lasting risks associated with late-preterm birth.

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Figure 1. Flowchart of study participation in the late-preterm cohort.

n: number of individuals

Figure 2. Growth in weight in childhood after late-preterm birth, and adult neurocognitive abilities and grade point average in comprehensive school.

1a. Growth in weight from birth to 5 months corrected age.

1b. Growth in weight from 5 to 20 months corrected age.

1c. Growth in weight from 20 months corrected age to 56 months.

The figure shows change in adult neurocognitive composite scores and grade point average in standard deviation units, per one standard deviation unit faster growth in weight during the time period in question. The growth variables are standardized residual change scores from linear regression models where weight *z*-scores were regressed on measures at previous time points, creating uncorrelated residuals that reflect growth conditional on previous history.

We adjusted for gestational age, sex, age at follow-up visit, and highest education of a parent in all analyses. Statistically significant associations ($p<0.05$) highlighted.

[a] $p<0.05$ in model II (after additional adjustments for multiple pregnancy, parity, and maternal smoking, hypertension, and diabetes during pregnancy, pre-pregnancy body-mass-index, and age at delivery).

[b] $p<0.05$ in model III (after further adjusting also for breast-feeding status at 5 months and neonatal complications including low Apgar score, apnea, convulsions, suspected septicemia, and ventilation treatment).

CI: Confidence Interval

Figure 3. Growth in head circumference in childhood after late-preterm birth, and adult neurocognitive abilities and grade point average in comprehensive school.

2a. Growth in head circumference from birth to 5 months corrected age.

2b. Growth in head circumference from 5 to 20 months corrected age.

2c. Growth in head circumference from 20 months corrected age to 56 months.

The figure shows change in adult neurocognitive composite scores and grade point average in standard deviation units, per one standard deviation unit faster growth in head circumference during the time period in question. The growth variables are standardized residual change scores from linear regression models where head circumference *z*-scores were regressed on measures at previous time points, creating uncorrelated residuals that reflect growth conditional on previous history.

We adjusted for gestational age, sex, age at follow-up visit, and highest education of a parent in all analyses. Statistically significant associations ($p<0.05$) highlighted.

[a] $p<0.05$ in model II (after additional adjustments for multiple pregnancy, parity, and maternal smoking, hypertension, and diabetes during pregnancy, pre-pregnancy body-mass-index, and age at delivery).

[b] $p<0.05$ in model III (after further adjusting also for breast-feeding status at 5 months and neonatal complications including low Apgar score, apnea, convulsions, suspected septicemia, and ventilation treatment).

CI: Confidence Interval

Figure 4. Growth in length in childhood after late-preterm birth, and adult neurocognitive abilities and grade point average in comprehensive school.

3a. Growth in length from birth to 5 months corrected age.

3b. Growth in length from 5 to 20 months corrected age.

3c. Growth in length from 20 months corrected age to 56 months.

The figure shows change in adult neurocognitive composite scores and grade point average in standard deviation units, per one standard deviation unit faster growth in length during the time period in question. The growth variables are standardized residual change scores from linear regression models where length *z*-scores were regressed on measures at previous time points, creating uncorrelated residuals that reflect growth conditional on previous history.

We adjusted for gestational age, sex, age at follow-up visit, and highest education of a parent in all analyses. Statistically significant associations ($p<0.05$) highlighted.

[a] $p<0.05$ in model II (after additional adjustments for multiple pregnancy, parity, and maternal smoking, hypertension, and diabetes during pregnancy, pre-pregnancy body-mass-index, and age at delivery).

[b] $p<0.05$ in model III (after further adjusting also for breast-feeding status at 5 months and neonatal complications including low Apgar score, apnea, convulsions, suspected septicemia, and ventilation treatment).

CI: Confidence Interval

Table 1. Body size and growth in childhood in the late-preterm cohort.

	M	(SD)	Participants
Characteristics at birth			
Weight, kg	2.7	(0.6)	108
Length, cm	47	(2.4)	108
Head circumference, cm	33	(1.6)	107
Growth from birth to 5 months CA			
Weight, kg	4.7	(0.9)	108
Length, cm	19	(2.3)	107
Head circumference, cm	10	(1.5)	106
Characteristics at the 5-month visit			
Weight, kg	7.4	(0.9)	108
Length, cm	66	(2.2)	107
Head circumference, cm	43	(1.3)	107
Corrected age, days	152	(11)	108
Growth from 5 to 20 months CA			
Weight, kg	4.5	(0.9)	103
Length, cm	19	(2.4)	97
Head circumference, cm	5.8	(0.7)	100
Characteristics at the 20-month visit			
Weight, kg	12	(1.3)	103
Length, cm	85	(3.2)	98
Head circumference, cm	49	(1.4)	102
Corrected age, days	614	(16)	106
Growth from 20 months CA to 56 months			
Weight, kg	5.9	(1.3)	86
Length, cm	23	(2.4)	79
Head circumference, cm	2.8	(0.6)	82
Characteristics at the 56-month visit			
Weight, kg	18	(2.2)	89
Length, cm	108	(4.3)	86
Head circumference, cm	52	(1.6)	88
Age, days	1721	(14)	91

CA: corrected age – cm: centimeters – kg: kilograms – M: mean – Participants: number of participants for whom data were available – SD: standard deviation

Table 2. Background characteristics and adult outcomes of the late-preterm participants.

	n	(%)	M	(SD)	Participants
Background characteristics					
Male	62	(57)			108
Gestational age in days			250	(6)	108
Highest education level of either parent					108
Basic education	11	(10)			
Vocational education	27	(25)			
General upper secondary or lower tertiary education	37	(34)			
Higher tertiary education	33	(31)			
Age at follow-up in years			25.2	(0.6)	108
Pregnancy-related factors					
Singleton	91	(84)			108
First-born	64	(59)			108
Maternal age at delivery in years			29.7	(4.8)	108
Mother smoked during pregnancy	20	(19)			108
Maternal pre-pregnancy BMI, kg/m^2			21.8	(2.4)	108
Maternal diabetes during pregnancy	12	(11)			108
Maternal hypertensive disorder during pregnancy	25	(25)			100
Neonatal complications and breast-feeding					
Apgar score at 5 minutes <8 points	7	(7)			104
Received ventilation treatment	8	(7)			108
Suspicion of septicemia	18	(17)			108
Convulsions	3	(3)			108
Apnea	3	(3)			108
Breast-feeding status at 5 months corrected age					108
never breast-fed	8	(7)			
breast-feeding discontinued	66	(61)			
currently breast-fed	34	(31)			
Maternal mental disorder					
Mother reported history of mental disorder [a]	14	(17)			81
Neurocognitive functioning in adulthood					
Intelligence Quotient score			108	(10)	103
General Memory score			103	(13)	105
Trail Making Test part A, s [b]			31	(10)	104
Trail Making Test part B, s [b]			60	(17)	104
Fluency, phonetic task raw score [b]			17	(4.6)	105
Fluency, categorical task raw score [b]			23	(5.6)	105
Stroop, baseline task, s [b]			68	(15)	102
Stroop, interference task, s [b]			120	(29)	102

Comprehensive school performance			
Grade point average, scale of 4 to 10		8.2 (0.9)	92
Received special education	35 (35)		101
Self-reported psychosocial adjustment			
Internalizing Problems T-Score		44 (12)	89
Externalizing Problems T-Score		47 (9.0)	89
Total Problems T-Score		44 (11)	89
Psychiatric interview			
Diagnosis of common mental disorder [c]	34 (35)		98

[a] Of the 14 mothers who reported mental health problems, 11 reported depression and 3 reported an anxiety disorder; none reported other psychiatric disorders.

[b] All these executive functioning test scores were available for 101 late-preterm individuals, whom we thus included in the principal component analysis.

[c] Of the 34 late-preterm participants diagnosed with at least one mental disorder, 14 were diagnosed with mood disorder, 8 with anxiety disorder, and 25 with substance use disorder.

BMI: Body-Mass-Index, kilograms per square meter – M: mean – n: number of participants – Participants: number of participants for whom data were available – s: seconds – SD: standard deviation

Figure 1

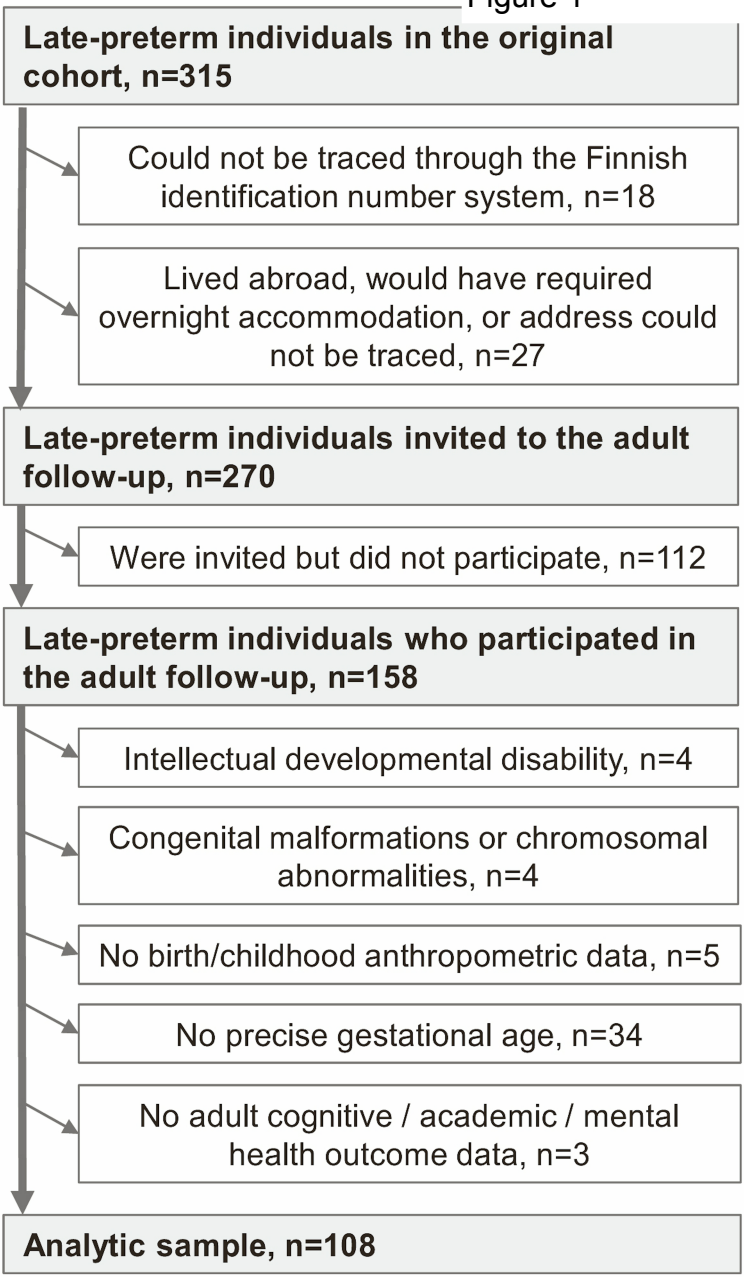
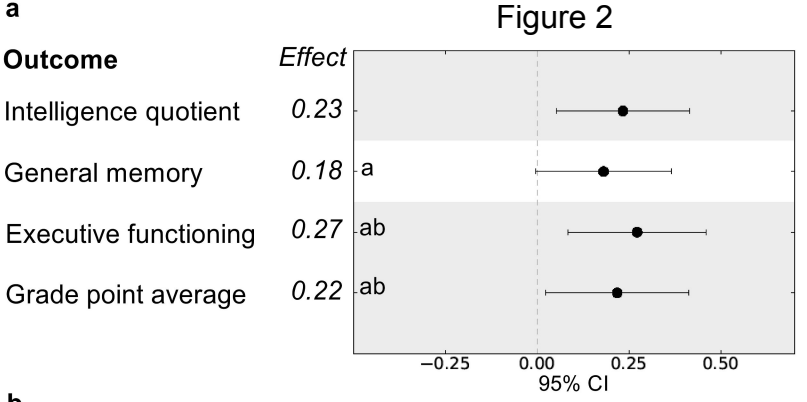
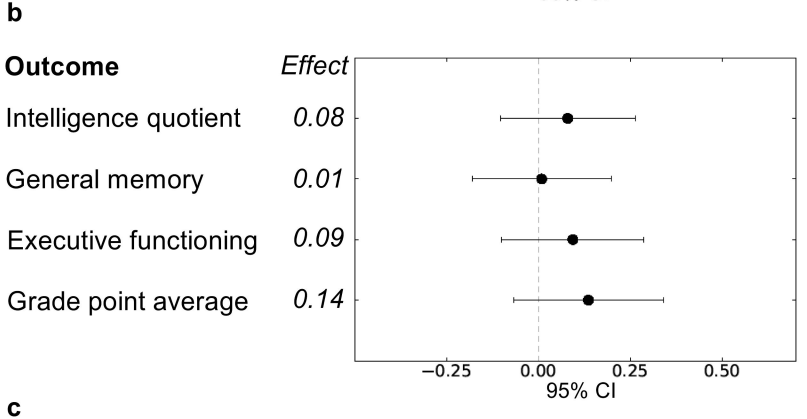

Late-preterm individuals in the original cohort, n=315
Could not be traced through the Finnish identification number system, n=18
Lived abroad, would have required overnight accommodation, or address could not be traced, n=27
Late-preterm individuals invited to the adult follow-up, n=270
Were invited but did not participate, n=112
Late-preterm individuals who participated in the adult follow-up, n=158
Intellectual developmental disability, n=4
Congenital malformations or chromosomal abnormalities, n=4
No birth/childhood anthropometric data, n=5
No precise gestational age, n=34
No adult cognitive / academic / mental health outcome data, n=3
Analytic sample, n=108

Figure 2


a
Outcome
Effect
Intelligence quotient
0.23
General memory
0.18
a
Executive functioning
0.27
ab
Grade point average
0.22
ab
−0.25
0.00
0.25
0.50
95% CI


b
Outcome
Effect
Intelligence quotient
0.08
General memory
0.01
Executive functioning
0.09
Grade point average
0.14
−0.25
0.00
0.25
0.50
95% CI

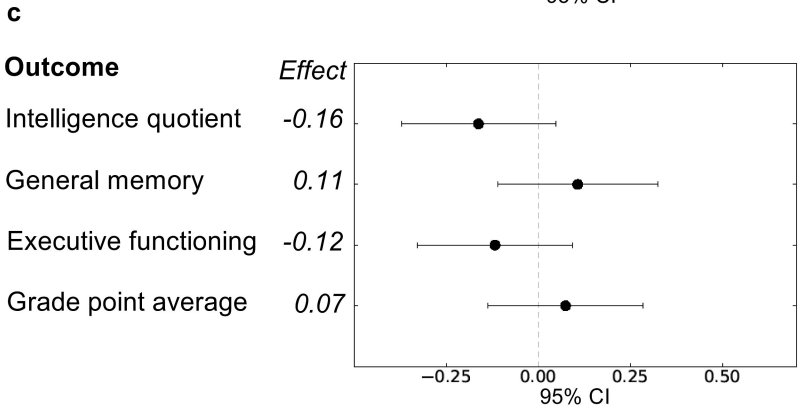

c
Outcome
Effect
Intelligence quotient
-0.16
General memory
0.11
Executive functioning
-0.12
Grade point average
0.07
−0.25
0.00
0.25
0.50
95% CI

Figure 3

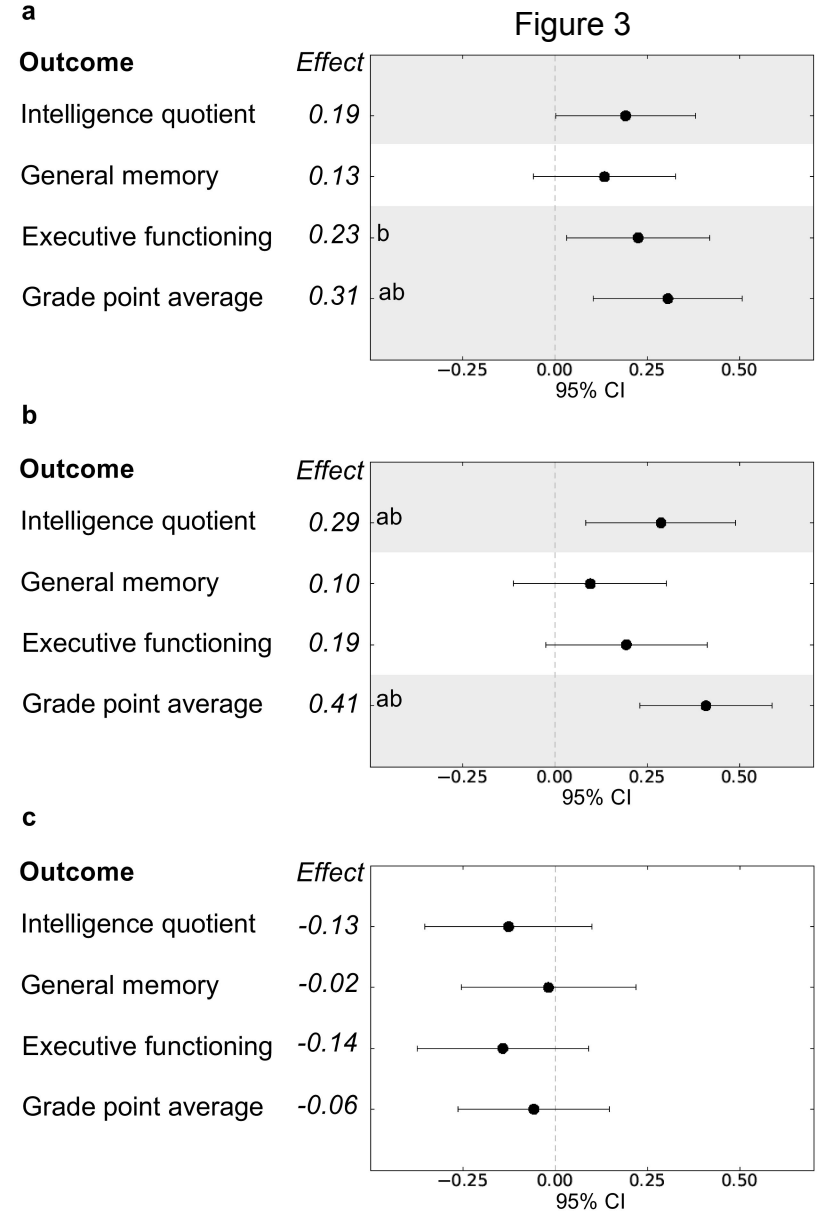
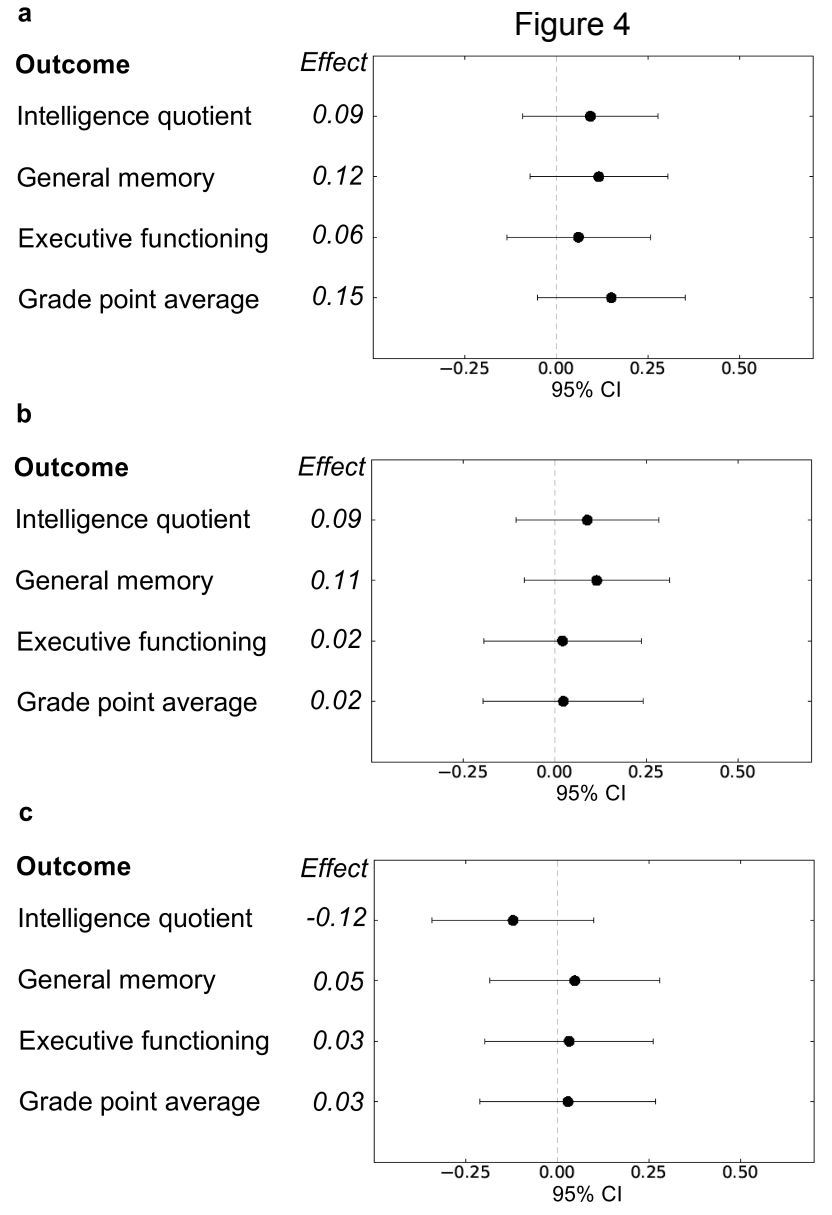

a
Outcome
Effect
Intelligence quotient
0.19
General memory
0.13
Executive functioning
0.23
b
Grade point average
0.31
ab
−0.25
0.00
0.25
0.50
95% CI
b
Outcome
Effect
Intelligence quotient
0.29
ab
General memory
0.10
Executive functioning
0.19
Grade point average
0.41
ab
−0.25
0.00
0.25
0.50
95% CI
c
Outcome
Effect
Intelligence quotient
-0.13
General memory
-0.02
Executive functioning
-0.14
Grade point average
-0.06
−0.25
0.00
0.25
0.50
95% CI

Figure 4


a
Outcome
Effect
Intelligence quotient
0.09
General memory
0.12
Executive functioning
0.06
Grade point average
0.15
−0.25
0.00
0.25
0.50
95% CI
b
Outcome
Effect
Intelligence quotient
0.09
General memory
0.11
Executive functioning
0.02
Grade point average
0.02
−0.25
0.00
0.25
0.50
95% CI
c
Outcome
Effect
Intelligence quotient
-0.12
General memory
0.05
Executive functioning
0.03
Grade point average
0.03
−0.25
0.00
0.25
0.50
95% CI

Supplemental Table S1. Growth in weight (panel I), head circumference (II), and length (III) after late-preterm birth, and adult cognitive abilities and school performance in comprehensive school.

	Model 1 *Adjusted for background characteristics* [a]			Model 2 *Adjusted for pregnancy-related factors* [b]			Model 3 *Adjusted for infancy-related factors* [c]			N
I. Weight	*β*	*OR*	*(95 % CI)*	*β*	*OR*	*(95 % CI)*	*β*	*OR*	*(95 % CI)*	
Growth from birth to 5 months										
Intelligence Quotient	0.23		(0.05, 0.42)	0.20		(-0.01, 0.41)	0.20		(-0.03, 0.42)	103
General Memory	0.18		(-0.004, 0.37)	0.22		(0.01, 0.43)	0.19		(-0.05, 0.42)	105
Executive Functioning	0.27		(0.08, 0.46)	0.30		(0.09, 0.51)	0.30		(0.08, 0.53)	101
Grade point average	0.22		(0.02, 0.41)	0.25		(0.01, 0.49)	0.36		(0.11, 0.60)	92
Received special education		0.59	(0.36, 0.97)		0.54	(0.30, 0.99)		0.53	(0.27, 1.05)	101
Growth from 5 to 20 months										
Intelligence Quotient	0.08		(-0.10, 0.26)	0.06		(-0.13, 0.25)	0.08		(-0.12, 0.28)	98
General Memory	0.01		(-0.18, 0.20)	-0.01		(-0.21, 0.19)	-0.04		(-0.25, 0.17)	100
Executive Functioning	0.09		(-0.10, 0.29)	0.11		(-0.08, 0.30)	0.12		(-0.08, 0.31)	96
Grade point average	0.14		(-0.07, 0.34)	0.11		(-0.11, 0.32)	0.14		(-0.07, 0.35)	88
Received special education		0.99	(0.61, 1.59)		1.02	(0.62, 1.68)		0.74	(0.42, 1.31)	96
Growth from 20 to 56 months										
Intelligence Quotient	-0.16		(-0.37, 0.05)	-0.12		(-0.35, 0.12)	-0.12		(-0.36, 0.11)	82
General Memory	0.11		(-0.11, 0.32)	0.15		(-0.09, 0.38)	0.15		(-0.11, 0.40)	84
Executive Functioning	-0.12		(-0.33, 0.09)	-0.03		(-0.26, 0.20)	-0.04		(-0.27, 0.19)	80
Grade point average	0.07		(-0.14, 0.29)	0.08		(-0.15, 0.31)	0.07		(-0.16, 0.30)	72
Received special education		1.14	(0.66, 1.99)		1.18	(0.63, 2.21)		1.13	(0.55, 2.33)	79

	Model 1 *Adjusted for background characteristics* [a]			Model 2 *Adjusted for pregnancy-related factors* [b]			Model 3 *Adjusted for infancy-related factors* [c]			N
II. Head circumference	*β*	*OR*	*(95 % CI)*	*β*	*OR*	*(95 % CI)*	*β*	*OR*	*(95 % CI)*	
Growth from birth to 5 months										
Intelligence Quotient	0.19		(0.002, 0.38)	0.15		(-0.06, 0.35)	0.14		(-0.09, 0.37)	101
General Memory	0.13		(-0.06, 0.33)	0.09		(-0.12, 0.30)	0.02		(-0.21, 0.25)	103
Executive Functioning	0.23		(0.03, 0.42)	0.20		(-0.004, 0.41)	0.23		(0.002, 0.45)	100
Grade point average	0.31		(0.11, 0.51)	0.26		(0.04, 0.48)	0.28		(0.05, 0.51)	91
Received special education		0.49	(0.28, 0.88)		0.53	(0.28, 0.99)		0.46	(0.22, 0.94)	100
Growth from 5 to 20 months										
Intelligence Quotient	0.29		(0.09, 0.49)	0.25		(0.03, 0.46)	0.25		(0.03, 0.48)	95
General Memory	0.10		(-0.11, 0.30)	0.10		(-0.12, 0.32)	0.08		(-0.15, 0.32)	97
Executive Functioning	0.19		(-0.02, 0.41)	0.22		(-0.01, 0.44)	0.24		(-0.001, 0.47)	94
Grade point average	0.41		(0.23, 0.59)	0.43		(0.23, 0.62)	0.42		(0.22, 0.62)	86
Received special education		0.76	(0.43, 1.32)		0.80	(0.45, 1.43)		0.65	(0.34, 1.24)	95
Growth from 20 to 56 months										
Intelligence Quotient	-0.13		(-0.35, 0.10)	-0.07		(-0.31, 0.17)	-0.07		(-0.32, 0.18)	78
General Memory	-0.02		(-0.25, 0.22)	-0.04		(-0.29, 0.21)	-0.02		(-0.29, 0.25)	80
Executive Functioning	-0.14		(-0.37, 0.09)	-0.11		(-0.35, 0.13)	-0.09		(-0.34, 0.15)	78
Grade point average	-0.06		(-0.26, 0.15)	-0.09		(-0.31, 0.14)	-0.11		(-0.34, 0.12)	69
Received special education	1.48	1.48	(0.79, 2.78)		1.48	(0.76, 2.88)		1.97	(0.85, 4.55)	77

[table S1 continued on following page]

	Model 1			Model 2			Model 3			N
	Adjusted for background characteristics [a]			*Adjusted for pregnancy-related factors* [b]			*Adjusted for infancy-related factors* [c]			
III. Length	*β*	*OR*	*(95 % CI)*	*β*	*OR*	*(95 % CI)*	*β*	*OR*	*(95 % CI)*	
Growth from birth to 5 months										
Intelligence Quotient	0.09		(-0.09, 0.28)	0.05		(-0.14, 0.24)	0.04		(-0.16, 0.24)	102
General Memory	0.12		(-0.07, 0.30)	0.11		(-0.08, 0.31)	0.08		(-0.13, 0.29)	104
Executive Functioning	0.06		(-0.14, 0.26)	0.03		(-0.17, 0.23)	0.02		(-0.19, 0.24)	100
Grade point average	0.15		(-0.05, 0.35)	0.14		(-0.08, 0.35)	0.11		(-0.11, 0.33)	91
Received special education		0.78	(0.48, 1.26		0.81	(0.47, 1.39)		0.89	(0.51, 1.58)	100
Growth from 5 to 20 months										
Intelligence Quotient	0.09		(-0.11, 0.28)	0.04		(-0.15, 0.24)	0.01		(-0.19, 0.21)	92
General Memory	0.11		(-0.08, 0.31)	0.12		(-0.09, 0.33)	0.11		(-0.11, 0.33)	94
Executive Functioning	0.02		(-0.19, 0.24)	0.01		(-0.20, 0.23)	0.03		(-0.19, 0.25)	90
Grade point average	0.02		(-0.19, 0.24)	-0.001		(-0.23, 0.23)	0.05		(-0.19, 0.28)	83
Received special education		0.78	(0.47, 1.30)		0.79	(0.46, 1.36)		0.68	(0.37, 1.24)	92
Growth from 20 to 56 months										
Intelligence Quotient	-0.12		(-0.34, 0.10)	-0.06		(-0.30, 0.17)	-0.09		(-0.34, 0.16)	75
General Memory	0.05		(-0.18, 0.28)	0.03		(-0.23, 0.28)	-0.01		(-0.29, 0.28)	77
Executive Functioning	0.03		(-0.20, 0.26)	0.12		(-0.12, 0.36)	0.12		(-0.14, 0.37)	74
Grade point average	0.03		(-0.21, 0.27)	-0.01		(-0.27, 0.26)	-0.02		(-0.31, 0.26)	66
Received special education		1.16	(0.66, 2.04)		1.11	(0.60, 2.08)		1.11	(0.53, 2.33)	74

The table shows change in adult neurocognitive composite scores and grade point average, and odds ratio for having received special education, per one standard deviation unit faster growth from birth to 5 months of corrected age, 5 to 20 months of corrected age, and from 20 months of corrected age to 56 months.

[a] In model I, we adjusted for gestational age, sex, age at follow-up visit, and highest education of a parent.

[b] In model II, we adjusted for model I factors and for multiple pregnancy and parity, and maternal smoking, hypertension and diabetes during pregnancy, pre-pregnancy body-mass-index, and age at delivery.

[c] In model III, we adjusted for model I and II factors and for breast-feeding status at 5 months and neonatal complications including low Apgar score, apnea, convulsions, suspected septicemia, and ventilation treatment.

β: change in adult neurocognitive composite scores and grade point average in standard deviation units, per one standard deviation unit faster growth in childhood – CI: Confidence Interval – n: number of participants included in the analysis (variation according to growth and outcome data availability) – OR: odds ratio for having received special education in comprehensive school, per one standard deviation unit faster growth in childhood.

Supplemental Table S2. Growth in childhood after late-preterm birth and adult mental health.

	Weight				Head circumference				Length			
	β	*OR*	*(95 % CI)*	*N*	*β*	*OR*	*(95 % CI)*	*N*	*β*	*OR*	*(95 % CI)*	*N*
Growth from birth to 5 months												
Self-report												
Internalizing Problems Score	0.17		(-0.05, 0.39)	89 [abc]	0.02		(-0.20, 0.25)	88	0.11		(-0.10, 0.32)	88
Externalizing Problems Score	0.13		(-0.09, 0.35)	89 [bc]	0.05		(-0.17, 0.26)	88	0.11		(-0.10, 0.32)	88
Total Problems Score	0.09		(-0.13, 0.32)	89 [bc]	-0.02		(-0.25, 0.20)	88	0.08		(-0.14, 0.29)	88
Psychiatric interview												
Mental Disorder		0.75	(0.47, 1.19)	98		0.76	(0.47, 1.24)	96		0.81	(0.52, 1.28)	97
Growth from 5 to 20 months												
Self-report												
Internalizing Problems Score	-0.05		(-0.27, 0.17)	84	-0.13		(-0.37, 0.12)	83	0.08		(-0.15, 0.32)	80
Externalizing Problems Score	0.07		(-0.16, 0.30)	84	-0.06		(-0.30, 0.18)	83	0.002		(-0.25, 0.25)	80
Total Problems Score	0.02		(-0.21, 0.25)	84	-0.10		(-0.34, 0.15)	83	0.08		(-0.16, 0.33)	80
Psychiatric interview												
Mental Disorder		0.92	(0.58, 1.46)	93		0.63	(0.37, 1.08)	90		0.93	(0.56, 1.52)	87
Growth from 20 to 56 months												
Self-report												
Internalizing Problems Score	-0.11		(-0.34, 0.12)	69	-0.30		(-0.56, -0.05)	67 [ac]	0.18		(-0.05, 0.40)	66
Externalizing Problems Score	-0.18		(-0.43, 0.08)	69	-0.24		(-0.51, 0.04)	67 [a]	0.07		(-0.19, 0.33)	66
Total Problems Score	-0.14		(-0.38, 0.10)	69	-0.28		(-0.54, -0.02)	67 [ac]	0.12		(-0.12, 0.37)	66
Psychiatric interview												
Mental Disorder		0.87	(0.50, 1.53)	78		0.92	(0.53, 1.59)	74		1.31	(0.71, 2.40)	71

The table shows change in psychiatric problem scores and odds ratio for having a common mental disorder in adulthood, per one standard deviation unit faster growth from birth to 5 months of corrected age, 5 to 20 months of corrected age, and from 20 months of corrected age to 56 months.

We adjusted for gestational age, sex, age at follow-up visit, and highest education of a parent in all analyses.

[a] $p<0.05$ in model II (after additional adjustments for multiple pregnancy, parity, and maternal smoking, hypertension, and diabetes during pregnancy, pre-pregnancy body-mass-index, and age at delivery).

[b] $p<0.05$ in model III (after further adjusting for model II factors and for breast-feeding status at 5 months and neonatal complications including low Apgar score, apnea, convulsions, suspected septicemia, and ventilation treatment).

[c] $p<0.05$ in model IV (after further adjusting for model III factors and maternal mental disorder).

β: change in self-reported adult psychiatric problem scores in standard deviation units, per one standard deviation unit faster growth in childhood – CI: Confidence Interval – N: number of participants included in the analysis (variation according to data availability) – OR: odds ratio for having had a common mental health disorder (mood, anxiety, or substance use disorder) during the past 12 months, per one standard deviation unit faster growth in childhood

Supplemental Table S3. Principal component matrix. Using principal component analysis all measures of executive function (in SD units) were reorganized into one component, named Executive functioning.

	Executive functioning
Trail Making Test, part A [a]	0.67
Trail Making Test, part B [a]	0.74
Fluency, phonetic task	0.78
Fluency, categorical task	0.77
Stroop, baseline task [a]	0.78
Stroop, interference task [a]	0.80

[a] Original SD scores were multiplied by −1 so that higher scores would reflect better performance.